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Review

Donanemab: A comprehensive review of mechanism, clinical efficacy, and safety in early stage Alzheimer's disease therapy

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease and the main cause of dementia worldwide. It affects cognitive decline, functional impairment and a significant burden on socjety. For many years, available treatments focused on reducing symptoms and did alter the underlying neurodegenerative process. Recent advances in drug develepment show that there are real possibilities for disease-modifying therapies that will target pathomechanisms such as β-amyloid deposition.

The following review narrates the current knowledge about donanemab, a humanized monoclonal antibody targeting N-terminal pyroglutamate-modified amyloid-β, focusing on its mechanism of action, pharmacokinetics, clinical efficacy, and safety profile. The review was based on published results of clinical trials and review articles identified in medical databases. Donanemab promotes microglia-mediated clearance of amyloid plaques by binding to dense-core amyloid plaques. Additionally, it reduces plasma concentrations of phosphorylated tau 217 and glial fibrillary acidic protein (GFAP). Pharmacokinetic studies show predictable, dose-dependent exposure after intravenous administration. In Phase II and III clinical trials donanemab treatment resulted in significant reduction in cognitive and functional decline. Positron emission tomography (PET) imaging showed substantial amyloid reduction and changes in plasma and cerebrospinal fluid biomarker levels. The most common adverse event was amyloid-related imaging abnormalities (ARIA), but most cases were asymptomatic and resolved after treatment adjustment.

Compared with other anti-amyloid monoclonal antibodies, donanemab achieves more rapid and complete amyloid clearance than aducanumab and shows similar disease-modifying activity to lecanemab. Ongoing research on emerging therapies for Alzheimer's disease may lead to further breakthroughs in disease treatment.

KEYWORDS

Alzheimer's disease, donanemab, monoclonal antibody, amyloid, disease-modifying therapy,

Introduction

Alzheimer's disease characteristics and pathophysiology

In 2021, dementia affected about 57 million people worldwide. Alzheimer's disease (AD) is one of the most common causes of dementia, estimated for approximately 60-70% of cases [1]. AD is characterized by progressive cognitive and functional decline, memory loss, impaired thinking and behavioral changes. Patients affected by this disease need help with daily activities, which can ultimately lead to complete loss in independence and even death [2]. It poses a socioeconomic challenge for the individual, family, and the entire society and system [3].

Pathophysiologically, AD develops due to excessive accumulation of extracellular amyloid-β (Aβ) plaques and the deposition of phosphorylated tau protein, which forms neurofibrillary tangles within neurons. As the neurodegenerative process progress, it leads to a loss of synaptic connections and neuronal atrophy [4]. Neuroinflammation also occurs, meaning excessive activation of microglial cells and release of inflammatory mediators, which disrupts glial cell function and triggers synaptic and neuronal phagocytosis [5].

Alzheimer's disease therapeutic strategies

Previous therapeutic approaches for Alzheimer's disease have focused mainly on symptomatic treatment with cholinesterase inhibitors such as donepezil and rivastigmine, as well as memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist. These agents provide modest improvements in cognitive function, but do not influence the underlying neurodegenerative process that is the main cause of the disease [6]. For approximately two decades, no significant breakthroughs were achieved in disease-modifying or causal treatment of Alzheimer's disease [7]. Among the early therapeutic strategies that failed to demonstrate clinical benefit was an active β-amyloid vaccine (AN1792); its clinical development was discontinued due to an increased risk of meningoencephalitis [8]. Further efforts focused on inhibiting the production of β-amyloid from amyloid precursor protein (APP) by targeting key enzymes involved in this process such as γ-secretase and β-secretase (BACE1). However, these approaches proved unsuccessful in clinical trials, due to limited efficacy and poor safety profile [9].

Only in recent years have research efforts begun to show more promising results, offering hope for disease-modifying therapies by targeting pathomechanisms such as β-amyloid deposition, tau pathology, neuroinflammation, and oxidative stress. Monoclonal antibodies directed against β-amyloid have now entered clinical practice. Nevertheless, not all drugs in this class have demonstrated clinical efficacy; phase III trials show no significant cognitive or functional benefit for solanezumab [10] and bapineuzumab [11]. The first monoclonal antibodies with documented clinical efficacy and acceptable safety profile approved by the U.S. Food and Drug Administration (FDA), were aducanumab (Aduhelm) [12] and lecanemab (Leqembi) [13], both co-developed by Biogen and Eisai. More recently, donanemab (Kisunla), developed by Eli Lilly, has also received regulatory approval and continues to be investigated to further characterize its efficacy and safety profile [14].

Material and methods

A narrative review was conducted using PubMed and ClinicalTrials.gov databases to identify relevant literature and studies on donanemab. The search included articles and trials published up to October 2025, using combinations of the terms "donanemab", "donanemab trial", "donanemab Alzheimer's" "TRAILBLAZER-ALZ" and "amyloid-beta antibody". Studies discussing the donanemab mechanism of action, pharmacokinetics, clinical efficacy, safety and comparison to

other anti-amyloid antibodies were included. Both original research and review papers were considered. Non-English publications, conference abstracts, and studies without an accessible full text were excluded. Reference lists of key articles were also screened to capture additional relevant sources.

Mechanism of action

Donanemab (LY3002813) is a humanized IgG1 monoclonal antibody directed specifically against the N-terminal pyroglutamate-modified amyloid-β peptide (N3pG-Aβ or $A\beta_{p3-42}$), an epitope found mostly in the dense-core amyloid plaques that accumulate in the brain and are characteristic of AD. Upon binding to this modified form of Aβ, donanemab facilitates the clearance of insoluble plaque deposits through mechanisms such as microglia-mediated phagocytosis, complement activation, and Fcγ receptor engagement. It also promotes the removal of Aβ–antibody complexes across the blood–brain barrier, as well as via perivascular pathways and the glymphatic system [15]. Moreover, post hoc analyses demonstrated that treatment with donanemab led to a significant reduction in plasma levels of phosphorylated tau protein 217 (p-tau217) and glial fibrillary acidic protein (GFAP) compared with placebo, suggesting a beneficial effect on tau pathology and astrocyte activity [16].

The mechanism of action of donanemab indicates the possibility of reducing synaptic dysfunction, neuroinflammation, neuronal destruction, and consequently slowing down the progression of cognitive deficits in patients with early AD [17]. However, it should be emphasized that the N3pG-Aβ epitope arises at a later stage, typically in symptomatic patients, suggesting that targeting this epitope may be less effective during the asymptomatic phase of AD when this form of amyloid has not yet developed [18].

Pharmacokinetic profile

In the Phase I trial, donanemab's pharmacokinetic (PK) and pharmacodynamic (PD) profiles and safety were evaluated in amyloid-positive participants with mild cognitive impairment (MCI) or mild to moderate AD dementia [19,20,21]. PK analyses showed linear dose-proportional increases in both maximum serum concentration (C_{max}) and area under the curve (AUC) following intravenous administration. The terminal elimination half-life was approximately 11.8 days in patients with Alzheimer's disease. Body weight and antidrug antibody (ADA) titre were identified as covariates affecting drug exposure in a population pharmokinetic model including participants from Phase 1b and the TRAILBLAZER-ALZ study. However, they did not result in clinically meaningful changes in the pharmacodynamic response. Maintaining serum donanemab concentrations above approximately 4.43 μg/mL was associated with achieving amyloid plaque clearance (95% confidence interval (CI), 0.956–10.4 μg/mL) in that model [22]

In another Phase 1 study conducted in healthy adults in China, participants received single intravenous doses of 350, 700, and 1400 mg of donanemab. Similar clearance values were observed

across the dose groups, with a dose-dependent decline in serum concentrations. The drug was generally well tolerated in all cohorts [23].

Clinical efficacy

The clinical effects of donanemab have been reported in several studies evaluating its safety, tolerability, pharmacokinetic profile, and clinical efficacy in patients with early-stage Alzheimer's disease. [20,21,24,25,26,27,28].

Participants enrolled were generally aged 60–85 years and presented with early symptoms of Alzheimer's disease, defined as mild cognitive impairment (MCI) or mild dementia due to AD, verified by PET imaging with ^{18}F-florbetapir demonstrating amyloid-β and tau pathology. Inclusion criteria also required a Mini-Mental State Examination (MMSE) score ranging from 20 to 28. Major exclusion criteria across the trials included clinically significant cardiovascular disease, central nervous system disorders other than AD that could interfere study participation or completion, prior treatment with anti-amyloid immunotherapy and the presence of extensive microhemorrhages or superficial siderosis on baseline MRI [17,20,21,29].

In the phase 1b TRAILBLAZER-ALZ trial, the first dose-dependent effects of donanemab on amyloid plaque reduction were observed. At week 24, the mean changes from baseline in amyloid PET Centiloid values for single intravenous doses were −16.5 (SE = 11.22) for 10 mg/kg, −40.0 (SE = 11.23) for 20 mg/kg, and −49.6 (SE = 15.10) for 40 mg/kg. Among participants receiving multiple doses, mean Centiloid changes were −55.8 (SE = 9.51) for 10 mg/kg every 2 weeks (Q2W), −50.2 (SE = 10.54) for 10 mg/kg every 4 weeks (Q4W), and −58.4 (SE = 9.66) for 20 mg/kg every 4 weeks (Q4W). In single-dose cohorts, mean amyloid levels remained below baseline up to 72 weeks. In the multiple-dose cohorts, continued reduction in florbetapir PET signal were observed compared with single dosing. Both in single- and multiple-dose cohorts no notable reaccumulation was observed. Moreover, six out of 28 patients reached complete amyloid clearance within 24 weeks [21].

The first larger, multicenter Phase 2 trial, TRAILBLAZER-ALZ, was conducted from 2017 to 2021 and further assessed the efficacy of donanemab [28]. Participants in the treatment group received intravenous donanemab every four weeks, beginning with three doses of 700 mg, followed by 1,400 mg up to week 72.

The study confirmed donanemab's effectiveness in reducing amyloid burden, as measured by amyloid PET imaging, with an adjusted mean difference of 85 centiloids between the donanemab and placebo group at 76 weeks [30].

Participants underwent regular assessments of cognitive and functional performance throughout the study. The primary outcome was the change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) score (range 0–144, with lower scores indicating greater cognitive and

functional decline). Secondary outcomes also included iADRS as well as the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) and the Mini-Mental State Examination (MMSE).

At baseline, both groups had a mean iADRS score of 106. By week 76, the mean change from baseline was −6.86 in the donanemab group and −10.06 in the placebo group (95% CI, 0.12–6.27; p = 0.04) [29], corresponding to approximately a 32% slowing of decline [31]. A post hoc analysis further demonstrated a significant reduction in p-tau217 levels by 23% and GFAP levels by 12% from baseline in participants treated with donanemab. In contrast, the placebo group showed increases of 6% and 15% in p-tau217 and GFAP levels, respectively [32].

The following TRAILBLAZER-ALZ 2 phase 3 trial confirmed these results in a larger population. In addition, the patient cohort was divided into two subgroups: those with low/medium tau protein levels and those with high tau protein levels. Classification into these groups was based on ^{18}F-flortaucipir PET imaging.

After 76 weeks of treatment, the least squared mean (LSM) change in the iADRS score was −6.02 (95% CI: −7.01 to −5.03) for participants receiving donanemab and −9.27 (95% CI: −10.23 to −8.31) for those on placebo, representing a difference of 3.25 (95% CI: 1.88–4.62; P < 0.001) in the group with low/medium tau levels. In the overall study population, the corresponding changes were −10.2 (95% CI: −11.22 to −9.16) with donanemab and −13.1 (95% CI: −14.10 to −12.13) with placebo, making a difference of 2.92 (95% CI: 1.51–4.33; P < 0.001). Similar statistically significant changes from baseline were observed in CDR-SB scores when comparing the placebo and donanemab groups.

The difference in LSM change for P-tau217 biomarker was -0.25 (95% CI, −0.28 to −0.22; P < 0.001) in the low/medium tau population and −0.22 (95%CI −0.24 to −0.20; P < .001) in the combined population at 76weeks. Over the same period, individuals in the low/medium tau group treated with donanemab showed an 88.0 Centiloid reduction in brain amyloid plaques (95% CI, -90.20 to -85.87), whereas those receiving placebo exhibited an increase of 0.2 Centiloids (95% CI, -1.91 to 2.26). In the combined cohort, amyloid levels decreased by 87.0 Centiloids (95% CI, -88.9 to -85.17) with donanemab and by 0.67 Centiloids (95% CI, -2.45 to 1.11 in the placebo group [17].

In post-hoc analysis, 1,582 patients were included and assigned to deciles based on their posttreatment amyloid PET values. The results showed that almost all participants in the lowest 3 deciles (472 out of 474; 99.6%) were treated with donanemab. In contrast, deciles characterized by higher post-treatment amyloid levels included a larger percentage of placebo-treated participants (449 out of 474; 94.7%) and were associated with greater clinical decline. Similar relationships were found for the AD biomarkers p-Tau217 and GFAP [33].

The main characteristics of the donanemab clinical trials are summarized in Table 1, while Table 2 compares the results of its clinical efficacy.

Table 1. Summary of donanemab study characteristics

Study	Type of study	Status	Baseline Participants	Study duration	Main inclusion criteria	
NCT01837641 I5T-MC-AACC [34]	Phase 1 Randomized, Parallel Assignment, Double-Blinded, Placebo-Controlled Trial	Completed (2013-2016)	63 (donanemab = 51/placebo = 12)	16 weeks	**Healthy participants**	**Participants with MCI*/AD***
					Overtly healthy** 18-40 years old 18.0-30.0 kg/m^2 BMI*	≥ 50 years old MCI due to AD or mild/moderate AD Positive florbetapir scan
NCT05533411 I5T-MC-AACK [24]	Phase 1 Randomized, Parallel Assignment, Double-Blinded, Placebo Controlled Trial	Completed (2022-2023)	36 (donanemab = 30 / placebo = 6)	85 days	18-40 years old Overtly healthy Native Chinese (with both parents and all four grandparents Chinese origin) 18.0-28.0 kg/m^2 BMI	
NCT05567159 I5T-MC-AACP [35]	Phase 1, Open-Label Single Group Assignment Trial	Completed (2022-2023)	42 (all donanemab)	22 weeks	18-40 years old Overtly healthy 19.0-32.0 BMI score	
TRAILBLAZER-ALZ NCT03367403 I5T-MC-AACG [28]	Phase 2 Randomized, Parallel Assignment, Double-Blinded Placebo-Controlled Trial	Completed (2017-2021)	256 (donanemab = 131/ placebo = 126)	72 weeks	60-85 years old Gradual and progressive change in memory function (≥ 6 months) MMSE* score 20-28 or positive flortaucipir PET* scan within 6 months prior to baseline Positive 18^F-flortaucipir PET scan (meeting criteria)	
TRAILBLAZER-ALZ 2 NCT04437511 I5T-MC-AACI [25]	Phase 3 Randomized, Parallel Assignment, Double-Blinded Placebo-Controlled Trial	Active, Not Recruiting (2020-)	1736 (donanemab = 860/ placebo = 876)	76 weeks	60-85 years old Gradual and progressive change in memory function (≥ 6 months) MMSE score 20-28 Positive 18^F-flortaucipir PET scan	
TRAILBLAZER-ALZ EXT NCT04640077 I5T-MC-AACH [26]	Phase 2 Non-Randomized, Sequential Assignment, Open-Label Trial	Completed (2020-2024)	95 (55 received donanemab in part B)***	72 weeks	60-90 years old Previous participation in a double-blind treatment period of a sponsor-approved originating donanemab trial Stable AD and cognition-affecting medications ≥30 days before baseline	
TRAILBLAZER-ALZ 3 NCT05026866 I5T-MC-AACM [36]	Phase 3 Randomized, Parallel Assignment, Double-Blinded, Placebo Controlled Trial	Active, Not Recruiting (2021-)	2996 (Estimated Enrollment)	182 weeks	65-80 years old Intact cognitive functioning in TICS-M* P-tau result consistent with the presence of amyloid and early-tau pathology	

TRAILBLAZER-ALZ 4 NCT05108922 I5T-MC-AACN [37]	Phase 3 Randomized, Parallel Assignment, Open-Label Trial	Completed (2021-2023)	148 (aducanumab = 69 / donanemab = 71)	18 months	50-85 years old Gradual and progressive change in memory function (≥ 6 months) Positive 18^F-flortaucipir PET scan (meeting criteria) 20-30 MMSE score 0.5 or 1 CDR* score
TRAILBLAZER-ALZ 5 NCT05508789 I5T-MC-AACO [38]	Phase 3 Randomized, Parallel Assignment, Double-Blinded Placebo Controlled Trial	Ongoing (2022 -)	1500 (Estimated Enrollment)	76 weeks	60-85 years old Gradual and progressive change in memory function (≥ 6 months) 20-28 MMSE score Meeting amyloid PET scan criteria
TRAILBLAZER-ALZ 6 NCT05738486 I5T-MC-AACQ [27]	Phase 3b Randomized, Parallel Assignment, Double-Blinded, Placebo-Controlled Trial	Active, Not Recruiting (2023 -)	842	76 weeks	60-85 years old Gradual and progressive change in memory function (≥ 6 months) 20-28 MMSE score Positive amyloid PET scan

*Abbreviations: MCI - mild cognitive impairment, AD - Alzheimer's disease, BMI - body mass index, PET - positron emission tomography, MMSE - Mini Mental State Examination, TICS-M - A Telephone Interview for Cognitive Status, CDR - Clinical Dementia Rating Scale

**determined by medical history and physical examination, willing to use a reliable method of birth control and will not donate sperm during the study

***in TRAILBLAZER-ALZ EXT study 55 participants who had received placebo in originating trials were administrated by donanemab in part B of the trial

Table 2. Summary of donanemab Phase II and III results

Study	Primary Outcome	Secondary Outcome	
TRAILBLAZER-ALZ (references: [29])	**iADRS*** LSM* change from baseline donanemab group -6.86 placebo group -10.06 difference 3.20 (95% CI*, 0.12 to 6.27; P = 0.04)	CDR-SB* LSM change from baseline difference (SD) -0.36 (−0.83 to 0.12)	
		ADAS-Cog13* LSM change from baseline difference (SD) −1.86 (−3.63 to −0.09)	
		ADCS-iADL* LSM change from baseline difference (SD) 1.21 (−0.77 to 3.20)	
		MMSE* LSM change from baseline difference (SD) 0.64 (−0.40 to 1.67)	
TRAILBLAZER-ALZ 2 (references: [17])	iADRS LSM change from baseline (SD) *low/medium tau group* donanemab group −6.02 (−7.01 to −5.03) placebo group −9.27 (−10.23 to −8.31) difference 3.25 (1.88 to 4.62; P < 0.01) *combined population* donanemab group −10.19 (−11.22 to −9.16) placebo group −13.11 (−14.10 to −12.13) difference 2.92 (1.51 to 4.33; P < 0.01)	CDR-SB LSM change from baseline difference (SD; P value; % slowing of clinical progression)	
		low/medium tau group −0.67 (−0.95 to −0.40; P < 0.001; 36.0%)	*combined population* −0.70 (−0.95 to −0.45; P < 0.001; 28.9%)
		ADAS-Cog13 LSM change from baseline difference (SD; P value; % slowing of clinical progression)	
		low/medium tau group −1.52 (−2.25 to −0.79; P < 0.001; 32.4%)	*combined population* 1.33 (−2.09 to −0.57; P < 0.001; 19.5%)
		ADCS-iADL LSM change from baseline difference (SD; P value; % slowing of clinical progression)	
		low/medium tau group 1.83 (0.91-2.75; P < 0.001; 39.9%)	*combined population* 1.70 (0.84 to 2.57; P < 0.001; 27.8%)

TRAILBLAZER-ALZ 4 (references: [39])	Amyloid PET* clearance (< 24.1 CL*) at 6 months (% of participants who reached AP clearance) donanemab vs aducanumab *overall population* 37.9% vs 1.6% (P < 0.001) *low–medium tau subpopulation* 38.5% vs 3.8% (P = 0.008)	Amyloid PET clearance (< 24.1 CL) using florbetapir PET at 12 and 18 months donanemab vs aducanumab *overall population* At 12 months 70.0% vs 24.6% (P < 0.001) At 18 months 76.8% vs 43.1% (P < 0.001) *low/medium tau group* At 12 months 76.0% vs 18.5% (P < 0.001) At 18 months 72.0% vs 43.5% (P = 0.022)
TRAILBLAZER-ALZ 6 (references: [40,41])	ARIA-E* frequencies at 24 weeks (standard vs modified titration, dose skipping, and Cmax) 23.7% vs 13.7%, 18.6%, and 18.3% Modified titration met the 24-week primary outcome with 94% probability of achieving ≥ 20% RRR*	ARIA-E frequencies by 76 weeks (standard vs modified titration, dose skipping, and Cmax) 24.2% vs 15.6 %, 18.6 %, and 19.2 % (P = 0.028) ARIA-H *frequencies by 76 weeks (standard vs modified titration) 27.5% vs 25.5% Microhemorrhage frequencies (standard vs modified titration) no significant difference Cortical superficial siderosis frequencies (standard vs modified titration) 15.0% vs 9.0%

*Abbreviations: iADRS - Integrated Alzheimer's Disease Rating Scale, LSM - least square mean, CI – confidence Interval, CDR-SB – Clinical Dementia Rating Scale Sum of Boxes, ADAS-Cog13 - Alzheimer's Disease Assessment Scale-cognitive subscale, ADCS-iADL - Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory instrumental subscale, MMSE - Mini-Mental State Examination, R - Spearman rank correlation, RRR - relative risk reduction, ARIA-E – amyloid-related image abnormalities associated with edema or effusion, ARIA-H – amyloid-related image abnormalities associated with hemosiderin deposits

Safety and adverse events

Amyloid-related imaging abnormalities (ARIA)

In all trials, amyloid-related imaging abnormalities (ARIA) were the most common adverse event [42]. ARIA (amyloid-related imaging abnormalities) are vascular or parenchymal abnormalities detectable on MRI, associated with antibody therapies targeting amyloid-β. Although the exact pathophysiological mechanism of ARIA remains unclear, it is hypothesized that antibody interaction with amyloid-β deposits in cerebral parenchyma and vasculature leads to disruption of vascular wall integrity. This disruption results in increased vascular permeability and fluid leakage into the surrounding tissues [43]. ARIA are classified into two main types: vasogenic edema or effusion (ARIA-E) and abnormalities associated with hemosiderin deposits (ARIA-H) resulting from microhemorrhages or superficial siderosis. Most of these findings are typically asymptomatic or transient; however, they require close radiological monitoring due to potential risk of neurological symptoms [44].

In the TRAILBLAZER-ALZ Phase 2 trial, ARIA-E occurred in 26.7% of participants treated with donanemab, while 23.7% had ARIA-H. Symptomatic ARIA-E was observed in 6.1% of participants. The majority of cases were mild to moderate and resolved after dose interruption or after treatment discontinuation [17,29,42]. The frequency of ARIA was higher in APOE ε4 carriers, which is explained by the role of these alleles in amyloid deposition and cerebrovascular amyloid angiopathy. This contributes to increased vascular vulnerability and a higher risk of treatment-related abnormalities [45]. The TRAILBLAZER-ALZ 2 study [17] found similar results, showing ARIA-E in 24% and ARIA-H in 31% of participants.

In TRAILBLAZER-ALZ 6 , donanemab demonstrated significant efficacy in reducing brain amyloid levels, achieving approximately a 71 Centiloid decrease over 76 weeks while maintaining a manageable safety profile. A modified dosing schedule gradual titration significantly lowered the incidence of ARIA-E from 24.2% to 15.6%, while also decreasing both the severity of ARIA-E and the number of symptomatic cases, all without affecting treatment efficacy. Furthermore, this titration method resulted in 38.8% decrease in cortical superficial siderosis, indicating additional safety benefits [40,41].

Other adverse events

Across the conducted trials, no statistically significant differences were observed between the donanemab and placebo groups regarding the incidence of death or serious adverse events, except for the previously mentioned amyloid-related imaging abnormalities (ARIA) [17,46]. Injection-related reactions were reported in 7.6% of participants receiving donanemab and in none of those receiving placebo in the TRAILBLAZER-ALZ study, while in TRAILBLAZER-ALZ 2 these occurred in 8.7% and 0.5% of participants, respectively [17,29]. Other adverse events observed in two largest trials are summarized in Table 3.

Table 3. Comparison of other adverse events reported in TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 [17,29]

Adverse Event	TRAILBLAZER-ALZ (Donanemab N = 131 / Placebo N = 125)	TRAILBLAZER-ALZ 2 (Donanemab N = 853 / Placebo N = 874)
Death	1 (0.8%) / 2 (1.6%)	1.9% / 1.1%
Serious adverse events	23 (17.6%) / 22 (17.6%)	17.4% / 15.8%
Discontinuation due to adverse events	20 (15.3%) / 6 (4.8%)	112 (13.1%) / 38 (4.3%)
COVID-19	Not reported	136 (15.9%) / 154 (17.6%)
Fall	17 (13.0%) / 19 (15.2%)	114 (13.4%) / 110 (12.6%)
Dizziness	11 (8.4%) / 15 (12.0%)	53 (6.2%) / 48 (5.5%)
Headache	10 (7.6%) / 15 (12.0%)	119 (14.0%) / 86 (9.8%)
Arthralgia	Not reported	49 (5.7%) / 42 (4.8%)
Urinary tract infection	13 (9.9%) / 5 (4.0%)	45 (5.3%) / 59 (6.8%)
Diarrhea	11 (8.4%) / 5 (4.0%)	43 (5.0%) / 50 (5.7%)
Infusion-related reaction	10 (7.6%) / 0 (0%)	74 (8.7%) / 4 (0.5%)
Upper respiratory tract infection	9 (6.9%) / 9 (7.2%)	Not reported
Pneumonia	7 (5.3%) / 5 (4.0%)	Not reported
Depression	6 (4.6%) / 8 (6.4%)	Not reported
Fatigue	Not reported	42 (4.9%) / 45 (5.1%)
Vomiting	7 (5.3%) / 3 (2.4%)	Not reported
Anxiety	7 (5.3%) / 2 (1.6%)	Not reported
References	[29]	[17]

Comparative efficacy of donanemab and other anti-Aβ monoclonal antibodies

In the phase 3 open-label study TRAILBLAZER-ALZ 4 comparing donanemab and aducanumab, donanemab achieved substantially greater and more rapid clearance of amyloid plaques: at 6, 12 and 18 months 37.9%, 70.0% and 76.8% of donanemab-treated participants reached the predefined threshold (<24.1 Centiloids) versus only 1.6%, 24.6% and 43.1% in the aducanumab group ($p <$

0.001). Median time to clearance was 359 days for donanemab versus 568 days for aducanumab ($p < 0.001$). The frequency of ARIA events was consistent with previous reports, with amyloid-related imaging abnormality–edema/effusion (ARIA-E) observed in 23.9% of participants treated with donanemab and in 34.8% of those receiving aducanumab. The authors suggest that the differences in clearance speed and magnitude may reflect donanemab's distinct binding profile (targeting N-terminal pyroglutamate-modified Aβ in dense cores) and the dosing regimen used, resulting in faster and deeper plaque removal [39].

When comparing donanemab and lecanemab, recent literature highlights the efficacy of both antibodies in reducing amyloid deposition in the brain, as confirmed by PET imaging, as well as their beneficial effects on cognitive function assessed through standardized scales such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog14) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) [47,48]. Lecanemab has shown a greater improvement in scores on the Alzheimer's Disease Composite Score (ADCOMS) and ADAS-Cog14, while donanemab demonstrates more rapid amyloid clearance compared with other anti-amyloid antibodies, as confirmed by recent studies [7,47].

In terms of safety profile, donanemab is associated with a higher incidence of amyloid-related imaging abnormalities with edema or effusion (ARIA-E), particularly in APOE ε4 carriers, compared to lecanemab, which exhibits a comparatively lower ARIA-E risk but still requires vigilant monitoring [47,49].

Ongoing clinical trials are currently investigating novel agents with mechanisms of action similar to donanemab — including ABBV-916 (which binds N-terminal truncated, pyroglutamate-modified Aβ pE3 in dense-core plaques) [50], ACU193 (which selectively binds soluble Aβ oligomers with high affinity) [51], trontinemab (a bispecific antibody engineered for transferrin-receptor-mediated brain shuttle plus Aβ binding to enhance CNS delivery) [52] and remternetug (which targets pyroglutamate Aβ42 similarly to donanemab) [53,54]. However, the results of these ongoing trials need to be awaited in order to enable a meaningful comparison of their therapeutic effects with those of currently approved monoclonal antibodies.

Conclusions

Due to the high prevalence of Alzheimer's disease in the general population, the development of disease-modifying therapies represents an important step toward improving patients' quality of life and slowing the progression of dementia. Until recently, treatment with cholinesterase inhibitors and memantine was limited to symptomatic relief and did not affect the underlying neurodegenerative process. Among newest therapeutic approaches, monoclonal antibodies targeting amyloid-β have become particularly important and represent a major advance in slowing cognitive and functional decline.

Donanemab is one of the most recently FDA-approved drugs for the treatment of Alzheimer's disease. By targeting the N-terminal pyroglutamate-modified amyloid-β epitope, it promotes the removal of β-amyloid plaques from the brain. Clinical trials results have shown that this effect is associated with a significant slowing of cognitive and functional decline in patients with early Alzheimer's disease, especially in those with low to intermediate tau pathology on PET imaging. Post hoc analyses also demonstrated reductions in biomarker plasma levels such as phosphorylated tau protein (p-tau217) and glial fibrillary acidic protein (GFAP).

In terms of safety, the most commonly reported adverse effect of donanemab is the occurrence of amyloid-related imaging abnormalities (ARIA) visible in the MRI assessment. Although ARIA were relatively frequent, most cases were asymptomatic and resolved after treatment modification. Recent clinical trial results showed that a gradual dose-titration strategy reduced both the frequency and severity of ARIA without affecting clinical efficacy. When compared with other anti-amyloid antibodies, donanemab demonstrated greater efficacy than aducanumab and comparable efficacy to lecanemab in reducing amyloid plaque burden and improving cognitive and functional outcomes, as assessed by scales such as ADAS-Cog14 or CDR-SB. However, due to its more rapid amyloid plaque clearance, the incidence of ARIA was higher in participants treated with donanemab than other agents.

A remaining limitation is that the N3pG-Aβ epitope usually appears in symptomatic patients with AD. Therefore, donanemab may be less effective when used in individuals with confirmed Alzheimer's disease who have not yet developed clinical symptoms. Ongoing studies are expected to provide further information on the drug's efficacy and to better define its safety profile. Continued research into new Alzheimer's disease therapies remains essential, as novel agents may lead to further advances in the treatment of this condition.

Authors' contribution

Conceptualization: J.C; resources: J.C, M.Z., P.S., M.Kot., M.Koc., A.Z.; writing—original draft preparation: J.C, M.Z, P.S.; writing—review and editing: M.B., J.K.; All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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