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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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EFFECTIVENESS OF LECANEMAB AND DONANEMAB TREATMENT FOR EARLY ALZHEIMER'S DISEASE

Maria Ufniarska *(Corresponding Author, Email: marykle99@gmail.com)*
Saint Adalbert Hospital in Gdańsk, aleja Jana Pawła II 50, 80-462 Gdańsk, Poland
ORCID ID: 0009-0008-5927-4811

Tomasz Ufniarski
University Clinical Centre in Gdańsk, Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0008-6555-3403

Aleksandra Piech
Clinical Provincial Hospital No. 2 in Rzeszow, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0001-4485-2200

Karolina Pasierb
The University Hospital in Krakow, Jakubowskiego 2, 30-668 Kraków, Poland
ORCID ID: 0009-0006-5806-3508

Karol Poplicha
National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warszawa, Poland
ORCID ID: 0009-0005-3835-9777

Martyna Grodzińska
Lower Silesian Oncology, Pulmonology and Hematology Center, pl. Ludwika Hirszfelda 12, 53-413 Wrocław, Poland
ORCID ID: 0009-0004-1001-6484

Bartłomiej Siuzdak
Clinical Provincial Hospital No. 2 in Rzeszów, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0003-8691-6617

Justyna Moszkowicz
Clinical Provincial Hospital No. 2 in Rzeszow, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0009-2582-6187

Piotr Sobkiewicz
Lower Silesian Oncology, Pulmonology and Hematology Center, pl. Ludwika Hirszfelda 12, 53-413 Wrocław, Poland
ORCID ID: 0009-0007-6610-440X

Patrycja Kardasz
Saint Adalbert Hospital in Gdańsk, aleja Jana Pawła II 50, 80-462 Gdańsk, Poland
ORCID ID: 0009-0006-8137-9789

Marta Jutrzenka
Szpital Praski p.w. Przemienienia Pańskiego Sp. z o.o., Aleja Solidarności 67, 03-401 Warszawa, Poland
ORCID ID: 0000-0001-7266-1586

Patrycja Ucieklak
District Hospital in Zawiercie, ul. Miodowa 14, 42-400 Zawiercie, Poland
ORCID ID: 0009-0002-3681-1051

ABSTRACT

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by amyloid-beta (Aβ) plaques, tau neurofibrillary tangles, and other pathological factors like neuroinflammation and oxidative stress. This review discusses the effectiveness of Lanacemab and Donanemab - new anti-amyloid monoclonal antibodies- for the treatment of early Alzheimer's Disease. While no cure exists, current symptomatic treatments are complemented by emerging disease-modifying therapies (DMTs). Recent breakthroughs with anti-amyloid monoclonal antibodies, Lecanemab and Donanemab, show promise in slowing disease progression. Clinical trials like CLARITY-AD for Lecanemab and TRAILBLAZER-ALZ 2 for Donanemab demonstrated significant reductions in brain amyloid and a slowed cognitive and functional decline in early AD. Lecanemab selectively targets Aβ protofibrils, while Donanemab targets N-terminally truncated Aβ in plaques, both facilitating amyloid clearance. These DMTs, though associated with side effects like ARIA, mark a pivotal shift towards targeting underlying AD pathology, offering hope for more effective interventions and potentially preventive strategies, such as those explored in the TRAILBLAZER-ALZ 3 trial.

KEYWORDS

Lecanemab, Donanemab, β-amyloid, Alzheimer's Disease Treatment, CLARITY-AD Trial, TRAILBLAZER-ALZ 2 Trial

CITATION

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Objective

This analysis examines the function of Lecanemab and Donanemab in the management of Alzheimer's disease, concentrating on its mechanism of action, clinical effectiveness, and safety profile. The objective is to evaluate its potential as a substitute therapy for the current existing drugs.

Introduction

Dementia is a broad term for a notable drop in mental abilities that impacts daily life. Alzheimer's disease (AD) is the most common form, affecting at least two-thirds of people over 65. It's a brain disease that worsens slowly, gradually impairing memory, understanding, language, attention, reasoning, and judgment. Alzheimer's disease is identified by the buildup of abnormal protein clumps called neuritic plaques and twisted fibers known as neurofibrillary tangles. These form because of the accumulation of amyloid-beta peptide (Aβ) and hyperphosphorylated Tau protein (pTau), primarily in the medial temporal lobe and neocortical structures, which are the most affected areas of the brain **(1-2)**. However, in addition to neurotoxicity connected with Aβ peptide and pTau, other key factors of the neurodegenerative process such as neuroinflammation, mitochondrial abnormalities, excitotoxicity, and oxidative stress (OS) need to be included in the list of the main causative factors of AD. OS is regarded as a bridge that connects the hypotheses and mechanisms of Alzheimer's disease as it is a part of various pathways affecting brain homeostasis. While Alzheimer's disease itself isn't a direct cause of death, it significantly increases the risk of other issues that can be fatal. Nowadays there's still no cure for Alzheimer's disease (AD), current treatments focus on alleviating and managing its symptoms. Recently, there have been exciting breakthroughs in medications designed to slow down the disease's progression, particularly with the discovery of new disease biomarkers **(3-4)**.

Methodology

A literature review was conducted using PubMed, GoogleScholar and clinical trial registries. Key words included "Lecanemab", "Donanemab", "β-amyloid" and "Alzheimer's Disease treatment", prioritizing randomized controlled trials, meta-analyses and observational studies.

1. Diagnostic Criteria

The diagnosis of Alzheimer's Disease (AD) presents a significant challenge due to its pathobiological heterogeneity (e.g., severity, location, and composition) with further complications such as diverse genetic predispositions, differential brain resilience, and the resultant spectrum of distinct clinical phenotypes (logopenic variant of primary progressive aphasia (lvPPA), posterior cortical atrophy (PCA), corticobasal syndrome (CBS), and frontal AD). Alzheimer's disease pathology can frequently co-occur with other neurodegenerative and vascular diseases, particularly in the aging brain. A patient during diagnostics of AD is presented with dementia confirmed by neuropsychological tests, progressive memory loss, impaired daily-life activity, and symptoms like aphasia, apraxia, and agnosia. Although the stated above cannot confirm the presence of AD, they are considered to be the first step in determining the presence of the disease. The next steps include the findings of specific biomarkers which can be divided into pathophysiologic biomarkers and topographic biomarkers. The first group includes amyloid positron emission tomography (PET), cerebrospinal fluid (CSF) concentrations of amyloid and tau proteins, and plasma concentrations of amyloid, tau, and other protein biomarkers. The second group lists biomarkers related to the regional consequences of AD pathology, such as regional hypometabolism on fluorodeoxyglucose (FDG)-PET, tau PET, and regional/local atrophy on structural magnetic resonance imaging (MRI) **(5-6)**.

2. Pathophysiology

Alzheimer's disease (AD) is classified as a protein-conformational disease (PCD). This means it primarily arises from the improper processing and polymerization of normally soluble proteins. Essentially, due to factors like genetic mutations, environmental influences, or age-related protein misfolding, typically soluble proteins within neurons adopt abnormal shapes which leads to dysfunctional neurons and, ultimately, neuronal loss. **(7)**

- **Amyloid Plaques:** In a healthy individual, β-amyloid exists as a small, water-soluble peptide. It's produced when the amyloid precursor protein (APP), a large glycoprotein found in cell membranes (including neurons), is sequentially cleaved by α-secretase, β-secretase, and γ-secretase. However, if this normal processing of APP is disrupted, often due to mutations, it leads to the formation of toxic oligopeptides, ranging from 39 to 43 amino acids in length, which can include protofibrils and fibrils that then aggregate to form deposits. The resulting β-amyloid fragments, particularly the Aβ-42 isoform, are highly cytotoxic, especially to neurons. This toxicity promotes the generation of oxygen radicals, which are harmful to nerve cells, causing their death **(8-10)**.

- **Tau Protein:** It is a factor that promotes the process of the correct assembly of the tubulin protein. Tubulin, in its physiological state, undergoes polymerization to form microtubules. These dynamic cytoskeletal structures are crucial for shaping the intracellular transport pathways, along which cellular motor proteins translocate, and also play a pivotal role in cell division by forming the mitotic spindle. Hyperphosphorylation of the Tau protein directly facilitates the aberrant assembly of tubulin protein and the deposition of neurofibrillary fibers, which is said to be one of the causes of Alzheimer's disease. The neurotoxicity of the Tau protein is based on two main pathways: the loss of its physiological function, which causes the destabilization of microtubules, or the gain of toxic function, which leads to apoptosis of neurons **(11)**.

- **Oxidative Stress:** Because of its membrane composition, the brain is particularly vulnerable to free radicals which are formed during oxidative stress. Those free radicals attack polyunsaturated fatty acids, initiating lipid peroxidation reactions. Beyond just lipids, the oxidation of brain proteins by free radicals or their byproducts is a major concern in Alzheimer's disease (AD). This is because these oxidative changes promote Amyloid plaques deposition, Tau hyperphosphorylation, and the subsequent loss of synapses and neurons **(12)**.

- **Cholinergic Changes:** Cholinergic neurotransmission, which relies on the neurotransmitter acetylcholine (ACh), is involved in various disease conditions. Given ACh's critical role in cognitive processes, the cholinergic system is considered a key player in many types of dementia, including Alzheimer's disease. Deficiencies in cholinergic transmission can potentially impact all facets of cognition and behavior, including how information is processed in the cortex and hippocampus. Research has shown, that cholinergic synapses are particularly affected by β-amyloid oligomers early neurotoxicity and the synaptic loss is linked with cognitive impairment. In fact, the severity of memory problems and brain damage seen in AD patients directly correlates with changes in hippocampal synaptic transmission **(13)**.

- **Genetic Factors:** Alzheimer's Disease can be inherited as an autosomal dominant disorder with almost complete penetrance. It is linked to mutations in 3 genes: the AAP gene on chromosome 21, Presenilin 1 (PSEN1) on chromosome 14, and Presenilin 2 (PSEN2) on chromosome 1. APP mutations can result in an increased production and accumulation of β-amyloid protein, while PSEN1 and PSEN2 mutations interfere with the processing of gamma-secretase, which leads to the aggregation of β-amyloid in the brain. While these genetic mutations are uncommon, contributing to only about 5% to 10% of all Alzheimer's disease cases, they are highly linked to early-onset forms of the illness. Among these, the PSEN1 mutation is the most frequently observed, accounting for roughly 5% of all AD diagnoses. Apolipoprotein E (APOE) is a lipid metabolism regulator with an affinity for beta-amyloid protein. There are three common alleles of the APOE gene: ε2, ε3, and ε4. The ε4 allele of the APOE gene is a major genetic risk factor for Late-Onset Alzheimer's Disease (LOAD). Individuals who inherit one copy of the ε4 allele (heterozygous carriers) have a three times higher risk of developing AD, while those with two copies (homozygous carriers) face a striking 15 times increased risk. For patients with Early-Onset Alzheimer's Disease (EOAD), the risk associated with the ε4 allele is even more pronounced, especially in homozygous ε4 carriers and heterozygous ε4 carriers who have a family history of AD **(14-16)**.

3. Epidemiology

Alzheimer's Disease is primarily a condition affecting older individuals. The global prevalence of dementia was stated to be 20.3 million in 1990, with a significant increase to 43.8 million in the year 2016, representing a dramatic increase of 116%. From 1990 to 2019, the rate of new cases of Alzheimer disease and other dementias jumped by 147.95% and 160.84%, respectively. Current projections are even more concerning, estimating that the number of individuals affected by dementia will reach 150 million by 2050, representing a fourfold increase from current figures.

The risk of developing Alzheimer's disease (AD) dramatically increases with age. Specifically, the incidence of AD doubles every five years after the age of 65. This translates to a significant jump in age-specific incidence rates: from less than 1% annually before 65 to 6% per year after 85. Similarly, prevalence rates also climb sharply with age, increasing from 10% after age 65 to 40% after age 85. Furthermore, women exhibit slightly higher incidence rates of Alzheimer's disease, a difference that becomes particularly pronounced after the age of 85 **(17-18)**.

4. Stages of Alzheimer's Disease

Alzheimer's disease (AD) unfolds through distinct clinical phases, each marked by specific cognitive and functional changes.

1. Pre-Clinical (Pre-Symptomatic) Stage

This initial stage can span many years and is characterized by subtle mild memory loss and early pathological changes in the cortex and hippocampus. Crucially, individuals at this stage experience no functional impairment in daily activities and show no overt clinical signs or symptoms of AD.

2. Mild (Early) Stage

As AD progresses, several symptoms become noticeable. Patients may start experiencing difficulties with daily tasks, including loss of concentration and memory, disorientation of place and time, mood changes, and the development of depression.

3. Moderate Stage

In the moderate stage, the disease spreads to broader areas of the cerebral cortex. This leads to more significant memory loss, making it difficult for patients to recognize family and friends. Individuals may also experience a loss of impulse control and increased challenges with reading, writing, and speaking.

4. Severe (Late) Stage

The final, severe stage of AD involves the widespread dissemination of the disease throughout the entire cortical area. This results in a severe accumulation of neuritic plaques and neurofibrillary tangles, leading to profound functional and cognitive impairment. Patients may no longer recognize their family and can become bedridden, struggling with basic functions like swallowing and urination. Ultimately, complications arising from these impairments lead to the patient's death **(19-21)**.

5. Current Treatment of Alzheimer's Disease

Traditionally, there hasn't been a cure for Alzheimer's disease (AD), so everyday clinical practice primarily focuses on symptomatic treatment. Currently, two main types of medications are approved to treat AD: cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists **(22)**.

1. Cholinesterase Inhibitors

Cholinesterase inhibitors work by boosting the levels of acetylcholine, a crucial neurotransmitter that facilitates communication between nerve cells. Acetylcholine is vital for processes like learning, memory, and overall cognitive function. The FDA has approved three drugs in this class for treating Alzheimer's disease: Donepezil, Rivastigmine, and Galantamine **(23)**.

- Donepezil

Donepezil is a widely used, second-generation acetylcholinesterase inhibitor (AChEI) and is considered a primary treatment for Alzheimer's disease (AD). This drug works by reversibly binding to and inhibiting acetylcholinesterase, an enzyme that breaks down acetylcholine (ACh). By doing so, it leads to a higher concentration of ACh in the synapses, improving communication between nerve cells. Donepezil is generally well-tolerated, with mild and temporary side effects primarily affecting the gastrointestinal and nervous systems. It's important to note that donepezil helps manage AD symptoms, such as improving cognition and behavior, but it does not alter the progression of the disease itself. It is a drug of choice for AD with mild dementia with once-daily dosing in the evening **(24)**.

- Rivastigmine

Rivastigmine works as a slow reversible inhibitor of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). It prevents the breakdown of acetylcholine (ACh) by binding to two specific sites on the AChE enzyme. While BuChE is mainly found in glial cells and accounts for only about 10% of AChE activity in a healthy brain, its activity significantly increases in the Alzheimer's disease (AD) brain, rising to 40-90%. At the same time, AChE activity decreases. This suggests that elevated BuChE activity could be a marker for moderate to severe dementia in AD **(25)**.

Rivastigmine is prescribed for mild to moderate Alzheimer's disease and has been shown to enhance cognitive functions and improve daily living activities. While taken orally, the drug can cause side effects like nausea, vomiting, indigestion, weakness, loss of appetite, and weight loss. These adverse effects often lead patients to stop taking the medication. However, with continued use, these side effects can lessen, making the drug more tolerable over time. To address these issues and improve patient experience, rivastigmine is also available as transdermal patches. These patches provide a controlled and continuous delivery of the drug through the skin, which significantly improves tolerability and leads to greater caregiver satisfaction. Patches can also deliver a lower dose compared to pills, further reducing side effects. Given that many AD patients experience memory loss and difficulty swallowing, which can hinder their ability to take oral medications regularly, transdermal patches are often the most suitable delivery method for this patient population **(26-28)**.

- Galantamine

Galantamine is a common first-line treatment for mild to moderate Alzheimer's disease. This drug is a unique tertiary isoquinoline alkaloid that works in two ways: it acts as a competitive inhibitor of acetylcholinesterase (AChE) and it can allosterically bind to and activate the alpha-subunit of nicotinic

acetylcholine receptors. Similar to other AChE inhibitors, it effectively improves behavioral symptoms, daily life activities, and cognitive performance. While Galantamine is generally well tolerated, it exhibits most common side effects of cholinesterase inhibitors which are gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Due to an increase in vagal tone, these medications can be the cause of bradycardia, cardiac conduction defects, and syncope. The drug is available as a twice-daily tablet or once-daily extended-release capsule. It is contradicted in individuals with end-stage renal disease or severe liver dysfunction due to the decrease of clearance of the drug. In mild renal and liver impairments the dose of galantamine should be reduced and not exceed 16mg daily **(29-30)**.

2. Partial N-Methyl D-Aspartate (NMDA) antagonist- Memantine

Memantine is a medication that acts as a low-affinity uncompetitive antagonist of the NMDA receptor (NMDAR). The NMDAR is a type of glutamate receptor and by blocking it, memantine helps prevent the over-activation of the glutaminergic system, which is implicated in the neurotoxicity seen in Alzheimer's disease (AD). It's approved by the FDA for treating moderate to severe AD. Common side effects include dizziness, body aches, headache, and constipation. Memantine can also be used in combination with cholinesterase inhibitors like donepezil, rivastigmine, or galantamine, particularly for individuals with moderate to severe AD **(31-32)**.

6. Lecanemab and Donanemab - mechanism of action

6.1 Lecanemab

Lecanemab, also known as BAN2401, is a modified human antibody derived from the mouse antibody mAb158. It is an immunoglobulin G1 monoclonal antibody which primarily targets soluble Aβ protofibrils and also shows activity against insoluble fibrils. What sets Lecanemab apart from other anti-amyloid monoclonal antibodies (mAbs) is its targeted action primarily against Aβ protofibrils, which proves it to be revolutionary in treatment of early onset Alzheimer's Disease **(33,34)**.

Aβ protofibrils are large, soluble Aβ aggregates that exhibit neurotoxicity disrupting the electrical signaling in the brain crucial for memory. The presence of the Arctic APP mutation accelerates the formation of these protofibrils, and this mutation is linked to early-onset Alzheimer's disease (AD), strongly suggesting a role for Aβ protofibrils in AD development. Studies have further indicated that intermediate-sized Aβ oligomers and protofibrils are the most harmful forms of amyloid-beta. This insight led to the design of lecanemab, specifically to target these large, soluble protofibrils (which are over 1000 times bigger than individual Aβ molecules). Lecanemab also interacts with the insoluble fibrils that make up the bulk of amyloid plaques in the brain, with its development being shaped by insights gained from understanding the mechanisms by which the Arctic APP mutation leads to early-onset Alzheimer's disease **(35-36)**.

6.2 Donanemab

Donanemab is an immunoglobulin G1 (IgG1) monoclonal antibody specifically engineered to recognize and bind to an insoluble, N-terminally truncated, and modified form of β- amyloid that is selectively present within cerebral amyloid plaques. Upon binding to this specific Aβ species, Donanemab facilitates the microglial-mediated phagocytosis and subsequent clearance of these pathological plaque aggregates from the brain parenchyma **(37)**.

On the molecular level, plaque clearance may eliminate the cause of synaptic pathology and reduce neuroplasticity, which are key components of total cognitive impairment in the disease. At a genetic level, Donanemab's action may also influence the downstream signaling of APP processing, potentially altering the amyloid cascade that leads to tau hyperphosphorylation and neurofibrillary tangles, which are other key markers of AD pathology. By removing amyloid, this drug also reduces the overall amyloid concentration in the brain. This lessens the toxic effects of amyloid that occur later in the disease process, including reducing plaque-induced inflammation, protecting neurons from further damage, and possibly halting or slowing the deterioration of cognitive abilities associated with AD. Furthermore, a reduction in amyloid plaques could stabilize or even improve synaptic function, which would tackle the fundamental cause of the illness, moving beyond simple symptom management, which represents a major leap forward in developing successful therapies for Alzheimer's **(38,39)**.

7. Clinical Trials

Main clinical trials for drugs:
- CLARITY-AD trial for Lecanemab published in November 2022
- TRAILBLAZER-ALZ 2 trial for Donanemab published in August 2023

Overall, the study results were positive, indicating a clinical benefit. Both trials successfully met their main and secondary goals, showing that the treatment slowed down cognitive and functional decline. This was accompanied by the expected reductions in Alzheimer's disease (AD) biomarkers **(40)**.

As a brief overview of the similarities and differences in trial designs, both studies tracked participants for about 18 months and included individuals with mild cognitive impairment (MCI) or mild dementia caused by Alzheimer's disease (AD). The reason participants with early-stage AD were chosen for treatment is because evidence indicates that intervening earlier with disease-modifying therapies (DMTs) shows the most promise in creating a biological impact that can be seen through clinical improvements. There were notable differences in the trial designs, particularly concerning dosing frequency and the primary cognitive assessment scales utilized. Lecanemab was administered as biweekly infusions, while Donanemab was given monthly. Regarding cognitive assessment, the CLARITY-AD trial used the Clinical Dementia Rating–Sum of Boxes (CDR-SB), where scores from 0 to 18 indicate increasing impairment (a higher score is worse). In contrast, the TRAILBLAZER-ALZ 2 trial employed the integrated AD rating scale (iADRS), with scores ranging from 144 down to 0, where lower scores signify greater cognitive decline **(41-43)**.

7.1 Lecanemab

7.1.1 Overview of the clinical trial

The CLARITY-AD trial was an 18-month, phase 3, multi-center study designed as a double-blind, placebo-controlled, parallel-group investigation, focusing on individuals with early Alzheimer's disease. Participants were randomly assigned in 1:1 ratio to receive either intravenous Lecanemab (10 mg per kilogram every two weeks) or a placebo. This randomization process considered several factors to ensure balanced groups, including:

- Their clinical subgroup (mild cognitive impairment due to AD or mild AD-related dementia).
- Whether they were already taking approved medications for AD symptoms (like acetylcholinesterase inhibitors or memantine) at the start of the study.
- Their apolipoprotein E (ApoE) ε4 status (carriers or non-carriers).
- Their geographic location.

Throughout the trial, participants had regular blood tests to monitor plasma biomarkers. They also had the option to join three additional sub-studies that assessed changes over time in:

- Brain amyloid burden using positron-emission tomography (PET).
- Brain tau pathology also using PET.
- Cerebrospinal fluid (CSF) biomarkers related to Alzheimer's disease **(44)**.

7.1.2 Selection of participants in the trial

The study enrolled individuals between 50 and 90 years old who had either mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or mild AD-related dementia, as defined by the National Institute on Aging–Alzheimer’s Association criteria. To confirm AD pathology, all participants showed amyloid positivity, determined by either PET imaging or measurement of Aβ1–42 in cerebrospinal fluid (CSF). Additionally, all participants exhibited an objective deficit in episodic memory, indicated by a score at least one standard deviation below the age-adjusted mean on the Wechsler Memory Scale IV–Logical Memory II. The primary efficacy end point was the change in the score on the Clinical Dementia Rating (CDR)–Sum of Boxes (CDR-SB) from baseline at 18 months **(44)**.

7.1.3 Division of participants

Out of 5,967 individuals screened, 1795 were randomly assigned to either the Lecanemab group (898 participants) or the placebo group (897 participants). This took place across 235 sites in North America, Europe, and Asia between March 2019 and March 2021. For the primary outcome, data was available from 729 (81.2%) Lecanemab recipients and 757 (84.4%) placebo recipients who completed the trial. The analysis for treatment effectiveness included 1734 participants (859 in the Lecanemab group and 875 in the placebo

group), while the safety analysis covered all 1795 randomly assigned participants. Additionally, 698 participants were enrolled in a substudy examining amyloid burden via PET, 257 in a substudy on tau pathology via PET, and 281 in a substudy analyzing CSF biomarkers of Alzheimer's disease **(44-45)**.

7.1.4 Results of the clinical trial

At the beginning of the study, both the Lecanemab and placebo groups had an average CDR-SB score of approximately 3.2. This finding is typical for early Alzheimer's disease, which generally ranges from 0.5 to 6. After 18 months, the Lecanemab group's average CDR-SB score increased by 1.21 points from baseline, while the placebo group's score increased by 1.66 points. This represents a statistically significant difference of -0.45 points (95% confidence interval, -0.67 to -0.23; P<0.001) in favor of the Lecanemab group, indicating a slower rate of decline.

In a key substudy that measured amyloid burden using PET scans (a crucial secondary outcome) and included 698 participants, the average amyloid level at the start of the study was roughly 77.92 centiloids in the Lecanemab group and 75.03 centiloids in the placebo group. After 18 months, the Lecanemab group showed a significant average decrease of -55.48 centiloids from their baseline amyloid levels, whereas the placebo group saw a slight average increase of 3.64 centiloids. This translates to a statistically significant difference of -59.12 centiloids between the groups (95% CI, -62.64 to -55.60; P<0.001), proving Lecanemab's effectiveness in reducing brain amyloid **(44, 46-48)**.

7.1.5 Tolerability of Lecanamab and adverse effects observed during the trial

Lecanemab was generally well-tolerated in the CLARITY-AD trial. There were no deaths directly linked to Lecanemab during the main study. In the open-label extension (OLE), there were 9 deaths, with 4 potentially related to the study treatment. Across both the core study and OLE, a total of 24 deaths occurred. Of these, 3 were due to intracerebral hemorrhage (ICH): one in the placebo group during the core study, and two in the Lecanemab OLE group (one of whom was on tissue plasminogen activator and another on anticoagulant therapy).

The most common side effects observed in the Lecanemab group (affecting over 10% of participants) during the entire study period (Core + OLE) included:

- Infusion-related reactions (24.5%)
- Amyloid-related imaging abnormalities (ARIA) with hemosiderin deposits (ARIA-H) microhemorrhages (16.0%)
- COVID-19 (14.7%)
- ARIA with edema (ARIA-E) (13.6%)
- Headache (10.3%)

It's worth noting that ARIA-E and ARIA-H were mostly mild to moderate when viewed on scans. ARIA-E typically appeared within 3 to 6 months of starting treatment and was more prevalent in individuals who carried the ApoE ε4 gene (16.8%), especially those with two copies of the gene (homozygous participants, 34.5%) **(49-51)**.

7.1.6 BAN2401-G000-201 (Study 201)- the prequel of CLARITY-AD trial

This was the Phase 2b proof-of-concept clinical trial for Lecanemab. BAN2401-G000-201 aimed to establish the effective dose 90% (ED90), defined as the simplest dose that achieves at least 90% of the maximum treatment effect. The primary measure for this was a Bayesian analysis of the Alzheimer's Disease Composite Score (ADCOMS) after 12 months, aiming for an 80% probability of at least a 25% reduction in clinical decline compared to placebo for the ED90 dose. Key secondary objectives included both Bayesian and frequentist analyses at 18 months, evaluating:

- Brain amyloid reduction using positron emission tomography (PET)
- Clinical decline as measured by ADCOMS
- The Clinical Dementia Rating-Sum-of-Boxes (CDR-SB)
- The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14)
- Changes in cerebrospinal fluid (CSF) biomarkers
- Total hippocampal volume (HV) measured by volumetric magnetic resonance imaging (MRI)

In the study, 854 participants were randomly assigned to treatment groups (609 received Lecanemab, and 245 received placebo) **(52-53)**. At the 12-month mark, the target dose of 10 mg/kg biweekly Lecanemab had a 64% chance of showing at least a 25% improvement on the ADCOMS score compared to placebo. This

fell short of the 80% probability required to meet the primary goal. However, by 18 months, the 10 mg/kg biweekly Lecanemab treatment significantly reduced brain amyloid levels (by -0.306 SUVr units). Furthermore, analyses (both Bayesian and frequentist) showed that active treatment with Lecanemab resulted in a better outcome compared to placebo:

- ADCOMS: 27% (Bayesian) and 30% (frequentist) reduction in decline
- ADAS-Cog14: 56% (Bayesian) and 47% (frequentist) reduction in decline
- CDR-SB: 33% (Bayesian) and 26% (frequentist) reduction in decline
- Changes in cerebrospinal fluid (CSF) biomarkers also supported a positive treatment effect

Lecanemab was generally well-tolerated, with amyloid-related imaging abnormalities-edema/effusion (ARIA-E) occurring in 9.9% of participants receiving the 10 mg/kg biweekly dose.

While BAN2401-G000-201 did not meet the 12-month primary endpoint, its 18-month results showed significant reduction in brain amyloid and consistent reduction in clinical decline, which led to the introduction of CLARITY-AD – a larger phase 3 study build of the findings of study 201 **(54-55)**.

7.2 Donanemab

7.2.1 Overview of the clinical trial

The TRAILBLAZER-ALZ 2 study was an 18-month, phase 3 clinical trial conducted across 277 medical research centers and hospitals in 8 countries. This multicenter, randomized, double-blind, placebo-controlled study enrolled 1,736 participants between June 2020 and November 2021. The main goal of the study was to measure the change in the integrated Alzheimer Disease Rating Scale (iADRS) score from the start of the study to 76 weeks (with scores ranging from 0 to 144, where lower scores mean more severe impairment).

The trial also included 24 additional outcomes (covering primary, secondary, and exploratory measures). Among these, a key secondary goal was to assess the change in the Clinical Dementia Rating Scale (CDR-SB) sum of boxes score (which ranges from 0 to 18, with higher scores indicating greater impairment) **(37)**.

7.2.2 Selection of participants in the trial

All participants had early symptomatic Alzheimer's disease (meaning they had either mild cognitive impairment or mild dementia) and also showed evidence of amyloid pathology along with low, medium, or high levels of tau pathology, as determined by positron emission tomography (PET) imaging **(37)**.

7.2.3 Division of participants

Participants were divided in 1:1 ratio with 860 receiving Donanemab and 876 receiving a placebo. Both treatments were administered intravenously every four weeks with the dosage of Donanemab being 700 mg for the first 3 doses, then 1400 mg for up to 72 weeks. Blinded dose-reduction evaluations occurred at 24 and 52 weeks based on amyloid clearance. Participants in the Donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met **(37)**.

7.2.4 Results of the clinical trial

Out of 1736 randomized participants 1320 (76%) finished the trial. Of the 24 planned outcomes, 23 showed statistically significant results. For the primary outcome (iADRS score) at 76 weeks:

- In the low/medium tau population, the average change in iADRS score was -6.02 for the Donanemab group and -9.27 for the placebo group. This represents a statistically significant difference of 3.25 points in favor of Donanemab (P<.001), indicating less decline.
- In the combined (low/medium and high) tau population, the average change was -10.2 for the Donanemab group and -13.1 for the placebo group. This also showed a statistically significant difference of 2.92 points favoring Donanemab (P<.001), again indicating slower decline.

Regarding the secondary outcome of CDR-SB score at 76 weeks:

- In the low/medium tau population, the average increase in CDR-SB score was 1.20 for the Donanemab group, compared to 1.88 for the placebo group. This statistically significant difference of -0.67 points (P<.001) indicates less decline for those on Donanemab.
- In the combined (low/medium and high) tau population, the average increase was 1.72 for Donanemab versus 2.42 for placebo. This also showed a statistically significant difference of -0.7 points (P<.001) favoring Donanemab, signifying a slower rate of functional decline **(37, 56-58)**.

7.2.5 Tolerability of Donanemab and adverse effects observed during the trial

In the Donanemab group, amyloid-related imaging abnormalities (ARIA) with edema or effusion were observed in 205 participants (24.0%), with 52 of these individuals experiencing symptoms. In contrast, only 18 participants (2.1%) in the placebo group developed ARIA, none of whom were symptomatic during the study period. Infusion-related reactions were also more common with Donanemab, occurring in 74 participants (8.7%), compared to just 4 participants (0.5%) in the placebo group. Three deaths in the Donanemab group and one in the placebo group were deemed to be related to the study treatment. Even though this drug has an over 10% higher ARIA risk then Lanacemab, it is considered to have a favorable tolerability profile when compared to other drugs that target β- amyloid based on the fact that the side effects are usually manageable by monitoring the patients and intervening appropriately **(59,60)**.

7.2.6 TRAILBLAZER-ALZ- the prequel of TRAILBLAZER-ALZ 2 trial

TRAILBLAZER-ALZ was a randomized, double-blind, placebo-controlled phase 2 study conducted from 18 December 2017 to 4 December 2020, at 56 sites in the US and Canada. The study enrolled 272 participants between the ages of 60 and 85 who had been diagnosed with early symptomatic Alzheimer's disease (AD), specifically those in the prodromal stage or with mild dementia. All included individuals met criteria for elevated amyloid and intermediate tau pathology as confirmed by PET scans, and their Mini-Mental State Examination (MMSE) scores ranged from 20 to 28.

In this analysis, participants were divided into two equal groups: one receiving intravenous Donanemab and the other receiving a placebo every four weeks, for a maximum of 72 weeks. Initially, the Donanemab dose was 700 mg for the first three administrations, after which it was increased to 1400 mg. A key aspect of the trial design involved a blinded dose adjustment at weeks 24 and 52, based on the results of amyloid PET scans. If a participant's amyloid levels, as measured by a single scan, fell between 11 and 25 Centiloids (CL), their Donanemab dose was reduced to 700 mg. Furthermore, if amyloid levels were below 11 CL on a single scan, or consistently below 25 CL on two consecutive scans, Donanemab administration was halted, and these participants were switched to receive placebo **(41)**.

The effect of Donanemab on brain amyloid and tau pathology was assessed using the specific PET tracers 18F-florbetapir (detecting amyloid plaque at baseline and weeks 24, 52, and 76), and 18F-flortaucipir (detecting tau neurofibrillary tangles at baseline and week 76). Plasma samples were collected at baseline and weeks 12, 24, 36, 52, 64, and 76.

There was a significant decrease in both plasma pTau217 and GFAP levels in patients receiving Donanemab compared with placebo group levels. The changes were observed after 12 weeks and continued throughout the 76 weeks of study:

- Decrease in mean plasma PTau217 level by 23% in patients with Donanemab with an increase of plasma level by 6% in the placebo group
- Decrease in mean plasma GFAP level by 12% in patients with Donanemab with an increase of plasma level by 15% in the placebo group

There was a positive correlation between the change in plasma pTau217 levels and the percentage change in amyloid plaque (measured in Centiloids) observed at 76 weeks (R=0.484; 95% CI, 0.359-0.592; P<.001). Similarly, the change in plasma GFAP levels also showed a positive correlation with the percentage change in amyloid plaque at 76 weeks (R=0.453; 95% CI, 0.306-0.579; P<.001).

The TRAILBLAZER-ALZ study demonstrated that Donanemab treatment led to a reduction in the rate of cognitive and functional decline, which led to the introduction of TRAILBLAZER-ALZ 2– a larger phase 3 study build of the findings of the phase 2 study **(61,62)**.

7.2.7 The future of Donanemab- the TRAILBLAZER-ALZ 3 study

The TRAILBLAZER-ALZ 3 trial is designed to determine if Alzheimer's disease (AD) can be delayed or prevented in individuals who are currently cognitively healthy but have developed amyloid plaques. This study is part of a larger initiative to explore strategies for intervening at very early stages of the disease. The trial is expected to yield vital information on how effective amyloid-targeting treatments are during the preclinical phase of AD. TRAILBLAZER-ALZ 3 underscores a growing focus on early detection and intervention in AD management.

If the trial is successful, it would support using Donanemab not just to treat early symptomatic AD, but also as a preventive therapy for individuals at high risk. This could fundamentally change clinical practice, shifting it towards more proactive management strategies that prioritize biomarker screening and early

therapeutic intervention. The ultimate goal is to delay or prevent the onset of AD symptoms, which could significantly lessen the overall impact of the disease **(56)**.

8. Results

Recent clinical trials, specifically the CLARITY-AD and TRAILBLAZER-ALZ 2 studies, have confirmed that Lecanemab and Donanemab are effective in treating the early stages of Alzheimer's Disease. These drugs significantly slowed disease progression and reduced β-amyloid plaque in the brain, offering a new treatment option for patients who cannot tolerate or do not respond to traditional therapies. The new drugs have a favorable tolerability profile, representing a significant advance in AD management. Future research, including the TRAILBLAZER-ALZ 3 study, will investigate their long-term effectiveness and potential for use in combination therapies.

9. Discussion

In summary, recent clinical trials for Lecanemab and Donanemab have demonstrated their efficacy in slowing the progression of early-stage Alzheimer's disease (AD). Both drugs, which are monoclonal antibodies targeting β-amyloid plaques, significantly reduced the amount of these deposits in the brain and were associated with a slower rate of cognitive and functional decline. This provides a promising new therapeutic avenue for patients who may not respond to or tolerate traditional AD treatments like Donepezil. The results underscore a significant shift from purely symptomatic management to disease-modifying therapies, marking a major step forward in the treatment of AD.

10. Conclusions

The findings from recent clinical trials support the efficacy of Lecanemab and Donanemab in the treatment of early stages of Alzheimer's Disease. Both of the drugs can be proposed to patients who are presented with an intolerability to Donepezil or who lack response to traditional therapies. Compared to placebo, Lecanemab and Donanemab were associated with a significant slowdown in the progression of AD as well as a reduction in the β-amyloid amount deposited in the brain. Both of the 18-month studies: CLARITY-AD trial for Lecanemab and TRAILBLAZER-ALZ 2 trial for Donanemab confirm the effectiveness of the new generation AD drugs as well as prove their favorable tolerability profile when compared to other drugs that target β- amyloid. Moreover, the ongoing TRAILBLAZER-ALZ 3 study for Donanemab is expected to provide information on how effective amyloid-targeting treatments are during the preclinical phase of AD, which may be revolutionary in the prevention of the onset of AD symptoms, and therefore provide the patients with an unchanged quality of life. Future research of both of the drugs should focus on long-term effectiveness and potential combination therapies to further optimize Alzheimer's Disease management.

Disclosures

Author's contribution:
Conceptualization: Maria Ufniarska, Tomasz Ufniarski
Methodology: Aleksandra Piech, Karolina Pasierb
Software: Karol Poplicha, Martyna Grodzińska
Check: Bartłomiej Siuzdak, Justyna Moszkowicz, Piotr Sobkiewicz
Formal Analysis: Patrycja Kardasz, Marta Jutrzenka, Patrycja Ucieklak
Writing – Rough Preparation: Maria Ufniarska, Tomasz Ufniarski, Karol Poplicha
Writing – Review and Editing: Aleksandra Piech, Karolina Pasierb, Martyna Grodzińska
Visualization: Bartłomiej Siuzdak, Justyna Moszkowicz, Piotr Sobkiewicz
Supervision: Patrycja Kardasz, Marta Jutrzenka, Patrycja Ucieklak

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