**Lecanemab: A Targeted Approach to Beta Amyloid Reduction in Alzheimer’s Disease**

**ABSTRACT:**

Alzheimer's disease is a progressive neurological disorder that primarily affects older adults and is the most common cause of dementia. It involves the degeneration of brain cells, leading to memory loss, cognitive decline, and changes in behavior and personality. Worldwide, an estimated **50 million people** are living with dementia, and Alzheimer's disease accounts for approximately **60-70%** of these cases and by 2050 the number of people with Alzheimer's is expected to triple, reaching about **150 million** globally, primarily due to the aging population. Currently available treatments only halts the symptoms of the disease, and the underlying pathology remains untouched; thus, there is progressive deterioration due to the intact pathology. Various drugs are being researched to address the complex neuropathology of AD. The FDA's approval of lecanemab marks a significant advancement in Alzheimer's disease treatment, as it targets the underlying pathology of the disease rather than just alleviating symptoms. This shift in focus from symptomatic treatments to addressing the root cause is exemplified by lecanemab's ability to reduce amyloid-beta (Aβ) plaques, and its clinical properties highlight its potential for improving patient outcomes.

This paper provides a thorough review of the efficacy and safety of lecanemab, a monoclonal antibody, with an emphasis on its binding properties and clinical trial data. Lecanemab stands out from other monoclonal antibodies due to its remarkable affinity for hazardous Aβ protofibrils. Clinical trials have yielded promising outcomes, including lower amyloid load, improved cognitive assessments, and a slower rate of cognitive decline.

This review article aims to provide a comprehensive overview of Alzheimer’s disease, focusing on its epidemiology, risk factors, pathophysiology, and the emerging role of lecanemab as a potential disease-modifying therapy. By comparing lecanemab with existing symptomatic treatments that primarily address symptoms rather than underlying pathology, this review emphasizes the importance of targeting the fundamental mechanisms of AD for improved patient outcomes. Furthermore, it underscores the necessity for continued research to refine treatment strategies and enhance our understanding of this complex disease to better serve affected individuals and their families.

**Keywords:** Alzheimer’s Disease, Neurological disorder, Memory loss, Cognitive decline, Dementia

**INTRODUCTION:**

More than 50 million people worldwide suffer from Alzheimer’s disease (AD), a neurodegenerative condition marked by a persistent or progressive decline in cognitive function. It is the **most common type of dementia**, accounting for **60–80% of dementia cases**. Dementia is an **umbrella term** for a group of neurological conditions characterized by **progressive cognitive decline** that interferes with daily life. While there are different types of dementia, Alzheimer’s is **distinct** due to its **specific pathological hallmarks** and **progressive nature**. In 2020 and 2021, it was formally ranked as the seventh most common cause of death. In 2019, Tiwari et al. in his study found that early signs include mood swings, decreased judgement, linguistic problems, recent memory loss, and a gradual shift in personality **[1].** The person fails to learn new information and recall (encoding, storage, and recall) over its unrelentingly progressive path. In addition to developing sphincteric incontinence and severe motor weakness, the person’s behavioural issues of wandering, anger, hostility, and bewilderment worsen, and they end up bedridden and completely dependent on everyday tasks **[2].** AD throws a great deal of strain on the family and has a significant impact on caregivers. Age is a significant risk factor; in the 65–69 age range, up to 10% of people get AD, while in the 85+ age range, over 50% of people have AD **[3],[4].** The Mini-Mental Scale Examination (MMSE) shows a loss of about 3.5 points every year. According to the theory, AD has a very long preclinical phase known as mild cognitive impairment (MCI), during which time the hallmark neuropathological alterations gradually but steadily accumulate and cause memory loss. There are two forms of MCI: The majority of people with amnestic MCI go on to develop full-blown AD. Non-amnestic MCI is characterized by a deterioration in non-memory cognitive abilities like language, executive and spatial function. Amnestic MCI is characterized by memory impairment with intact cognitive skills in other domains. AD is separated into phases:

**Table 1:** Stages of Alzheimer’s disease. The table outlines the five stages of Alzheimer's disease, from the earliest preclinical phase to the severe final stage. Each stage is described with key characteristics, symptoms, and the impact on a person's daily life. **[75]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Stage** | **Description** | **Symptoms** | **Impact on Daily Life** |
| **Stage 1:**  Preclinical Alzheimer’s | No outward signs; brain abnormalities start appearing. | Presence of tau tangles and amyloid plaques in the brain. | No impact on daily life. |
| **Stage 2:**  Mild Cognitive Impairment (MCI) | Early memory and cognitive problems, but they don’t significantly impact functioning | Early memory problems, cognitive difficulties, but day-to-day life remains largely unaffected. | Minimal impact on daily life, but some difficulty with memory or cognitive tasks. |
| **Stage 3:**  Moderate Alzheimer’s Disease | Noticeable memory loss and disorientation affecting daily tasks. | Difficulty recalling recent events, significant memory loss, disorientation, trouble with money management. | Impairs daily activities like managing finances, recalling recent events. |
| **Stage 4:**  Mild Alzheimer’s Disease | Substantial cognitive decline that makes daily tasks difficult. | Severe memory loss, confusion about time and place, difficulty identifying loved ones, language issues, mood swings, anxiety. | Difficulty with personal care, substantial memory loss, need for assistance with daily activities. |
| **Stage 5:**  Severe Alzheimer’s Disease | Cognitive and physical capacities significantly deteriorate; full-time care required. | Loss of ability to recognize family members, difficulty swallowing and moving, increased susceptibility to infections. | Requires full-time care for basic activities like eating, moving, and communicating. |

**Alzheimer’s disease staging:**

**Figure 1:** Staging of Alzheimer’s disease.

AD throws a great deal of strain on the family and has a significant impact on carers. Age is a significant risk factor; in the 65–69 age range, up to 10% of people get AD, while in the 85+ age range, over 50% of people have AD **[5].**

**THE CAUSES AND CONTRIBUTING VARIABLES OF ALZHEIMER’S DISEASE**

Examining the genetic, environmental, behavioural, and acquired risk factors that influence the development and course of Alzheimer’s disease is essential to comprehending its aetiology.

**Genetic components**

1. **Deterministic genes:** Alzheimer’s disease is directly caused by some genetic alterations, especially in cases that start early in families. Important genes consist of:

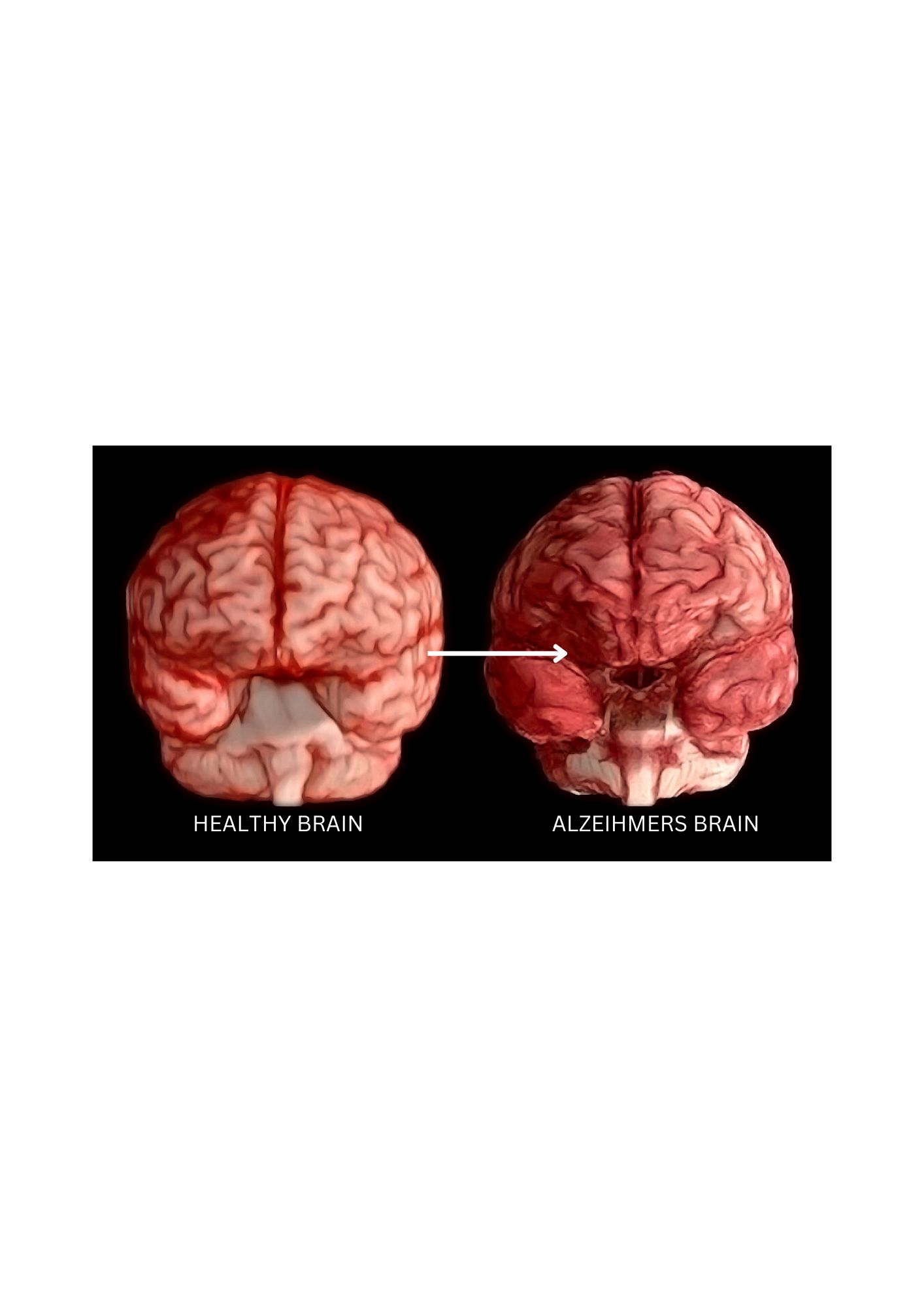
* **Amyloid precursor protein (APP):** This protein is mutated to produce more amyloid-beta peptides, which aid in the development of plaque in the brain. **Located on chromosome 21, this gene encodes the APP protein.** Mutations in APP can lead to increased production of **Aβ42**, a highly aggregation-prone form of beta-amyloid. APP mutations are found in **early-onset familial AD (FAD)** cases.
* **Presenilin 1 (PS1) and presenilin 2 (PS2):** The enzymatic digestion of APP is mediated by the genes presenilin 1 (PS1) and presenilin 2 (PS2). About 5% of familial AD is caused by mutations in these genes, which also result in increased production of amyloid beta (Cleveland clinic). These genes encode components of **gamma-secretase**, an enzyme complex that cleaves APP. Mutations in **PSEN1 and PSEN2 lead to an altered cleavage of APP, producing more Aβ42**, which aggregates into plaques. PSEN1 mutations are responsible for the majority of **early-onset AD cases**, while PSEN2 mutations are rarer but still pathogenic.

**Table 2:** The table categorizes the **acquired risk factors** that contribute to the development and progression of **Alzheimer’s disease (AD)**. It is divided into three main sections: **cerebrovascular diseases, metabolic and lifestyle-related factors, and cognitive/behavioral influences**.

|  |  |  |  |
| --- | --- | --- | --- |
| **CATEGORY** | **RISK FACTORS** | **MECHANISM OF CONTRIBUTION TO ALZHEIMER'S DISEASE** | **REFERENCES** |
| **Cerebrovascular Diseases** | Ischemic infarcts | Both minor and major infarcts contribute to dementia by impairing cerebral blood flow. | Love & Miners (2016) [6] |
|  | Vasculopathies | Vascular changes and white matter damage increase AD risk; amyloid buildup and cerebral health are linked. | Love & Miners (2016) [6] |
| **Hypertension** | High blood pressure | Causes vascular damage, ischemia, and increased amyloid-beta accumulation. | Skoog & Gustafson (2006) [7] |
| **Type II Diabetes** | Insulin resistance | Enhances amyloid-beta synthesis by affecting insulin signaling. | Li et al. (2015) [8] |
|  | Chronic inflammation | Leads to vascular inflammation and neuronal damage. | Li et al. (2015) [8] |
|  | Advanced glycation end products (AGEs) | Promotes amyloid-beta accumulation and neuronal death. | Li et al. (2015) [8] |
| **Obesity** | Middle-age obesity | Increases AD risk due to metabolic instability and inflammation. | Anstey et al. (2011) [9] |
|  | Late-life obesity | Conflicting results—some studies suggest an inverse relationship with dementia risk. | Anstey et al. (2011) [9] |
| **Dyslipidemia** | High cholesterol | Leads to increased amyloid-beta deposition, neuroinflammation, and blood-brain barrier dysfunction. | Xue Shan et al. (2016) [10] |
| **Lifestyle & Environmental Factors** | Age | Biggest non-modifiable risk factor; risk doubles every 5 years after age 65. | Xu W, TanL, Wang HF et. al [11] |
|  | Family history | Higher risk if multiple relatives are affected. | Xu W, TanL, Wang HF et. al [11] |
|  | Cardiovascular health | Conditions like hypertension, diabetes, and hyperlipidemia impair cerebral blood flow, increasing AD risk. | Xu W, TanL, Wang HF et. al [11] |
|  | Head injury | Severe or repeated trauma increases AD risk. | Xu W, TanL, Wang HF et. al [11] |
|  | Physical inactivity | Sedentary lifestyles are linked to cognitive decline. | Xu W, TanL, Wang HF et. al [11] |
|  | Smoking | Promotes vascular damage and inflammation, increasing AD risk. | Xu W, TanL, Wang HF et. al [11] |
|  | Diet | Diets high in sugar and saturated fats increase risk, while omega-3 and antioxidants are protective. | Xu W, TanL, Wang HF et. al [11] |
| **Cognitive & Behavioral Factors** | Cognitive engagement | Learning and problem-solving improve cognitive reserve and delay AD onset. | Williams KN, Kemper S. et. al[12] |
|  | Social interaction | Strong social networks are linked to better cognitive outcomes. | Williams KN, Kemper S. et. al[12] |

1. **Risk genes:**

* **Apolipoprotein E (ApoE):**  is the most prominent risk gene; in particular, the e4 allele considerably increases the chance of developing AD. The disease is three times more likely to strike someone with one e4 allele and 6.5 times more likely to strike someone with two e4 alleles. The ApoE €4 allele is present in at least one copy in almost 50% of AD patients.



**Figure 2:** Demonstration of Healthy Individual Brain and Alzheimer’s disease Brain

**EPIDEMIOLOGY OF ALZHEIMER DISEASE**

The primary characteristic of dementia, a multifaceted illness, is the steady decline of cognitive abilities across multiple domains, which hinders daily functioning in social, physical, and occupational domains **[13].** Currently, dementia affects over 35.6 million individuals globally, with 7.7 million new cases recorded each year **[14].** According to recent projections, the “baby boomer” phenomenon will cause Europe’s population to increase by 87% between 2010 and 2050 **[15].** Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease, accounting for 60–80% of dementia cases reported. It significantly burdens national and worldwide healthcare systems **[16].**

Unlike AD, which has increased by 68% in the past ten years, other health disorders, such as cardiovascular disease, have shown a decline in the modern age **[17].** According to studies on AD, the incidence rate is 6.3 per 100,000 and the yearly prevalence is roughly 24.2 per 100,000 among those aged 45–64 **[18]**. Nonetheless, the disease is much more common in people over 65, and the likelihood of developing AD increases exponentially. **[19].**

### **TREATMENT MODALITIES FOR ALZHEIMER’S DISEASE**

Currently, Alzheimer’s disease (AD) has **no cure**, but various treatment modalities are available to **manage symptoms and slow progression**. These include **pharmacological treatments**, **non-pharmacological approaches**, and **emerging disease-modifying therapies**.

1. **Pharmacological Treatments (Symptomatic Management)**

Traditional drug therapies primarily focus on **symptom relief** by **enhancing neurotransmitter activity** in the brain.

1. **Cholinesterase Inhibitors** (For Mild to Moderate AD)

These drugs **increase acetylcholine levels**, which is essential for memory and cognitive function.

**Commonly used drugs:**

1. **Donepezil** (Aricept) – Approved for all stages of AD. (Birks & Harvey, 2018)**[64]**
2. **Rivastigmine** (Exelon) – Available in oral and transdermal forms. (Tian et al., 2019)**[65]**
3. **Galantamine** (Razadyne) – Also has nicotinic receptor-modulating properties. (Wilkinson et al., 2018) **[66].**
4. **NMDA Receptor Antagonists** (For Moderate to Severe AD)

These drugs **regulate glutamate activity**, preventing excessive neuronal damage.

1. **Memantine** (Namenda) is the primary drug in this class. It is often used alone or in combination with cholinesterase inhibitors. (Howard et al., 2012) **[67]**
2. **Combination Therapy**
3. **Donepezil + Memantine** (Namzaric) is a combination therapy for moderate-to-severe AD, providing both **cholinergic support and NMDA antagonism**. (Schneider et al., 2011) **[68]**.
4. **Other Symptomatic Medications**
5. **Antidepressants (e.g., SSRIs like sertraline, citalopram)** – Help manage depression and anxiety. (Sepehry et al., 2012) **[69]**.
6. **Antipsychotics (e.g., risperidone, olanzapine)** – Used in extreme cases of agitation or psychosis but with caution due to risk of stroke. (Maher et al., 2011) **[70]**.

#### **Non-Pharmacological Approaches**

#### **Cognitive Behavioral Therapy (CBT)** – Helps improve coping mechanisms. (Teri et al., 2005) **[71]**.

#### **Physical & Occupational Therapy** – Maintains independence in daily activities. (Heyn et al., 2004) **[72]**.

#### **Dietary Modifications** – Mediterranean and MIND diets may slow cognitive decline. (Morris et al., 2015) **[73]**.

#### **Social & Cognitive Engagement** – Stimulating activities like puzzles, music therapy, and social interaction improve quality of life. (Livingston et al., 2020) **[74]**.

#### **LECANEMAB - A New Approach in Disease Modification**

IgG1 monoclonal antibody lecanemab, sometimes referred to as BAN2401 or Leqembi, is a drug intended to bind to and interact with soluble amyloid-beta clumps, specifically oligomers and protofibrils **[20].** At Bio Arctic Neuroscience, where this drug was first created, it was discovered that the Amyloid Precursor Protein (APP) has a mutation **[21]**. People with the mutation and Alzheimer’s disease have high levels of amyloid-protofibrils and no amyloid plaques **[22].** Targeting APP (Amyloid Precursor Protein) with the Arctic mutation E693G, lecanemab is a humanized IgG1 monoclonal antibody that has been demonstrated to primarily bind to soluble amyloid beta protofibrils **[23].**Several preclinical studies have demonstrated that lecanemab preferentially reduces amyloid beta protofibrils and pathogenic amyloid beta levels in the brains of mice genetically engineered to produce human amyloid precursor protein with two specific mutations: Swedish (KM670/67INL) and Arctic (E693G) **[24]**.Based on the findings of first- and second-phase clinical trials, lecanemab has garnered a lot of attention as a possible treatment for AD and has spurred additional research to ascertain its effectiveness **[25].** And positive preclinical results. Interestingly, it has recently been demonstrated that lecanemab lowers blood levels of P-Tau181**[26]**. This discovery, together with the data from the first and second phases, motivated the DINA trial unit team to investigate the first double adaptive tau-amyloid-beta treatment, which included combining Lecanemab with Eisai’s anti-tau antibody E2814 **[27]**.People with a family history of AD due to a particular inherited genetic variation (in genes called APP, presenilin 1, and presenilin 2) are given a test to check for the presence of abnormal protein deposits in the brain called amyloid-cognitive symptoms as part of a novel prevention clinical trial called DIANTU**[28]**. Between 1% and 5% of all cases of Alzheimer’s disease are caused by this kind of genetic variation **[29]**. To find out how well lecanemab affected cognition in early Alzheimer’s disease, a phase III randomized, placebo-controlled, double-blind study compared it to a placebo **[30].**

Among these Mabs, lecanemab exhibits encouraging outcomes when used to treat AD. It functions by lessening the buildup of amyloid beta in the brain, which is a defining feature of the illness. Cognitive decline has improved as a result of this decrease in amyloid beta, and the occurrence of the adverse consequence known as ARIA has also been comparatively rare. According to research, lecanemab, when given by intravenous infusion once every two weeks at a dosage of 10 mg/kg, is safe and has a minor therapeutic effect. To prove lecanemab’s safety and effectiveness, more research is required **[31]**.

**MOA OF LECANEMAB**

Lecanemab is a monoclonal antibody developed to treat Alzheimer’s disease. The major mechanism of action (MOA) targets amyloid-beta (Aβ) protofibrils, which are linked to Alzheimer’s disease.

1. **Targeting Aβ protofibrils:**

 Alzheimer’s disease is distinguished by the presence of amyloid plaques in the brain, which are clumps of misfolded amyloid beta peptides. These plaques are thought to affect cell function and cause neurodegeneration.

 Lecanemab specifically targets soluble Aβ protofibrils, which are intermediate-sized aggregates generated during the transition from monomeric Aβ to insoluble amyloid plaques. Proteins are regarded as particularly hazardous since they are soluble and can alter synaptic function, resulting in cognitive impairment and neuronal damage **[32].**

1. **Reduction of Amyloid Plaques:**

Lecanemab reduces amyloid plaques by binding to Aβ protofibrils and preventing further aggregation.

Lecanemab binds to Aβ protofibrils, promoting their clearance by the brain’s immune system. This procedure is expected to lessen the total load of amyloid plaques in the brain.

 Lecanemab may block the seeding and spreading of new amyloid plaques by lowering the number of protofibrils, potentially reducing disease progression.

1. **Microglial activation and clearance:**

 Lecanemab binds to protofibrils, allowing microglia, the brain’s immune cells, to recognize them more easily.

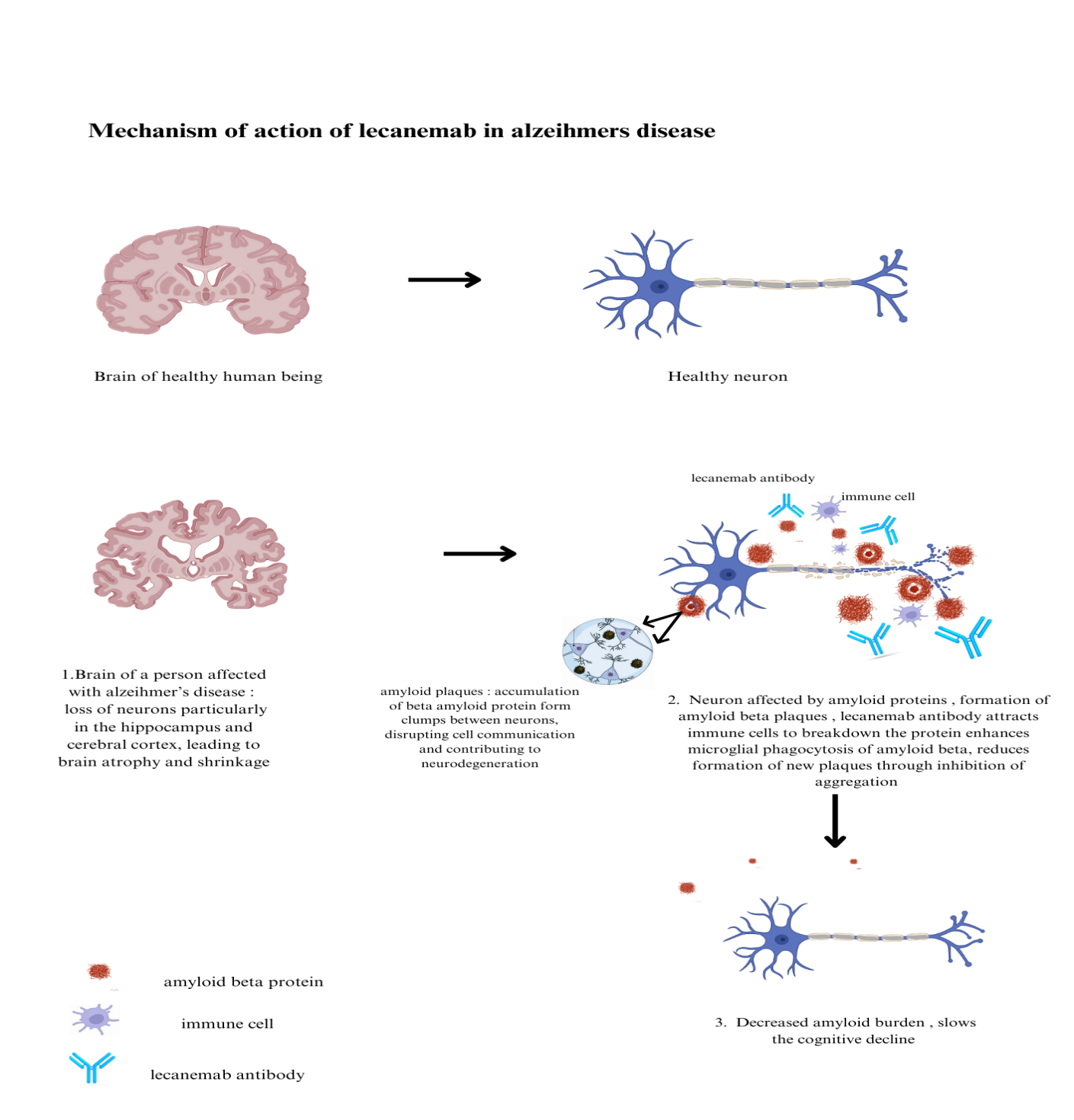
Microglia help remove cellular waste and misfolded proteins. Lecanemab-bound protofibrils activate microglia, which engulf and degrade Aβ aggregates, removing the dangerous substance from the brain. Immune-mediated clearance reduces neuroinflammation caused by amyloid accumulation and may have a neuroprotective impact.

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1. **Impact on Disease Progression:**

By targeting amyloid pathology, lecanemab hopes to alter the underlying disease process rather than just alleviating symptoms.

The medicine is used in the early stages of Alzheimer’s disease, such as moderate cognitive impairment (MCI) or mild dementia caused by Alzheimer’s, when amyloid pathology is still building and intervention may be most beneficial **[33].**

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**Figure 3:** Mechanism of Action of Lecanemab in Alzheimer’s disease

**PHARMACOKINETICS:**

1. **Absorption and Distribution**: Intravenous (IV) administration of lecanemab ensures full bioavailability. Lecanemab has a limited diffusion outside of the vascular compartment, as evidenced by its distribution capacity of about 3.8 liters.
2. **Metabolism:** Lecanemab is a monoclonal antibody that, like natural immunoglobulins, is broken down by proteolysis into smaller peptides and amino acids. It is not metabolized by the system of cytochrome P450 enzymes**.**
3. **Elimination:** Lecanemab has an elimination half-life of roughly 5 to 7 days, which permits dosing every two weeks. Since its excretion is not heavily dependent on renal excretion, clearance is around 0.225 L/day, and no dose modification is necessary for renal or hepatic impairment **[34]**.
4. **Special Populations:** Mild to moderate renal or hepatic impairment does not substantially change the pharmacokinetics in Alzheimer's patients. Pharmacokinetics have not been found to alter based on gender **[35].**

**PHARMACODYNAMICS**

Lecanemab may decrease the progression of Alzheimer’s disease and enhance cognitive performance in those who are affected by it by lowering Aβ aggregation and toxicity **[36]** Lecanemab may be a useful treatment for Alzheimer’s disease since it targets and removes harmful Aβ oligomers from the brain, according to its overall pharmacodynamics **[37]**. To completely understand lecanemab’s therapeutic potential in the treatment of this debilitating neurological disease, more clinical research is required **[38].**

**CLINICAL EVIDENCE FOR THE USE OF LECANEMAB**

**Preclinical**

In 2001, Nilsberth et al.identified preclinical Aβ protofibrils as a pathogenic mechanism for AD after observing a unique APP mutation called "Arctic" that accelerated the development of Aβ protofibrils and caused early-onset AD symptoms in mutation carriers**[39]**. According to an in vivo study conducted in transgenic mice that expressed the Swedish and Arctic APP mutations (also known as "ArcSwe"), mAb158, which was initially created to detect Aβ protofibrils, decreased both soluble and insoluble Aβ plaques when given early in the course of the disease. The humanized BAN2401 was developed as a result of research on human post-mortem AD brains, which revealed that mAb158 bound to comparable soluble Aβ protofibrils (about 80–500 kDa) in the human samples **[40].**

**Phase I**

In order to evaluate lecanemab’s safety, PK, and impact on plasma and CSF biomarkers, the phase I clinical trial (NCT01230853) recruited 80 subjects [20]. The MMSE scores of 16–28 and the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer’s Disease and Related Dementias Association (NINCDS-ADRDA) criteria indicated that the eligible participants had mild to moderate AD. Six lecanemab and two placebos per cohort were randomly assigned to single and multiple ascending dose arms. 0.1, 0.3, 1, 3, 10, and 15 mg/kg were included in the SAD trial, and 0.3, 1, and 3 mg/kg were included in the MAD study. Given every four weeks and every two weeks at a dose of 10 mg/kg. SAD And MAD were performed with staggered parallel cohorts; MAD was initiated once the dose was established as well tolerated inthe SAD cohort. Lecanemab was well tolerated in both dosage arms. PK analyses indicated lecanemab had a dose-proportional response and a 7-day serum half-life with doses ≥10 mg/kg. There was no observed ARIA-E; ARIA-H was observed in two cases in the SAD cohorts (one symptomatic) and six cases (all without symptoms) in the MAD cohorts (with one being placebo). Biomarker changes observed were limited to a mild increase in plasma Aβ1–40 **[41].**

**Phase II**

Phase II The phase IIb trial of lecanemab (NCT01767311) was an 18-month study that enrolled 856 subjects to determine the dose and efficacy of the treatment **[42].** Participant eligibility Required Aβ pathology confirmed by PET or CSF Aβ1-42 measurement, an MMSE ≥22 (22–28 in participating EU nations), and objective memory impairment (Weschler Memory Scale IV–Logical Memory II [WMS-IV LMII]) criteria. A unique Bayesian adaptive dose-finding trial design was used for the first 12 months to assess the primary endpoint, the change from baseline on the AD Composite Score (ADCOMS). For a dose arm to be successful at the 12-month objective, it had to have an 80% chance of decreasing the decline on the ADCOMS by 25% more than a placebo. 196 of the 854 participants in the trial were randomized to receive a placebo (n = 56) and five distinct dosage arms (2.5, 5, and 10 mg/kg every two weeks, and 5 and 10 mg/kg every month, n = 28 each cohort). Following that, each cohort's ADCOMS performance was used to randomly assign each of the 50 participants to the dose arms. At 12 months, the trial's main goal was not met, even though the biweekly dose of 10 mg/kg had a 64% chance of delaying the fall in ADCOMS by 25% more than the placebo. Up until month 18, the trial was double-blind.

On the ADCOMS and ADAS-Cog, frequentist analyses showed statistically significant differences favouring lecanemab. In 81% of participants, amyloid PET showed Aβ plaque reduction below the detection threshold. The combined biweekly and monthly 10 mg/kg lecanemab arm had increased Aβ1-42 and reduced P-tau at 18 months compared with placebo in an optional substudy of CSF biomarkers. Because APOE ε4 carriers are the most at risk for ARIA, a significant change to the trial required that they be removed from the 10 mg/kg biweekly arm as directed by a regulatory body. The trial's high-dose arm had fewer APOE ε4 allele carriers as a result of this adjustment. Infusion responses were the most frequent adverse effects (AEs), other from ARIA which responded to prophylactics or treatment and were often mild or moderate **[43].**

**Phase III**

 1795 patients were recruited for "CLARITY AD" (NCT03887455), and they were randomized 1:1 to either the placebo arm (n = 897) or the 10 mg/kg biweekly Lecanemab arm (n = 898**).**Age (50–90 years), a diagnosis of mild AD or MCI (National Institute on Aging–Alzheimer’s Association [NIA-AA] criteria), a 1 SD decline in objective episodic memory below the age-adjusted mean (WMS-IV LMII), and Aβ positivity by PET or CSF Aβ1–42 measurement were the criteria used to determine eligibility. The change from baseline on the CDR-SB at 18 months was the main endpoint for CLARITY AD. In comparison to a placebo, lecanemab delayed the decline on the CDR-SB by 0.45 points (+1.21point change) (+1.66point change). Other cognitive measures in the lecanemab arm (ADAS-Cog, ADCOMS, ADCS-ADL-MCI) had significantly slower decline than placebo at 18 months. Amyloid PET plaque levels were reduced on lecanemab (−55.48 centiloid change) versus placebo (+3.64 centiloid change). All CSF and plasma biomarkers favoured lecanemab over placebo except for neuroflament light (NfL), which showed no Drug-placebo difference. Infusion-related reactions (26.4%), ARIA-H (17.3%), and ARIA-E (12.6%) were the most com-Mon AEs in the lecanemab dosage arm. Non-carriers of The APOE ε4 allele in the lecanemab arm had the lowest Incidence of ARIA-H (11.9%) and ARIA-E (5.4%); ε4 het-Erozygotes had a higher incidence of both (ARIA-H: 14%; ARIA-E: 10.9%). APOE ε4 homozygotes had an incidence of ARIA-H and ARIA-E in 39% and 32.6%, respectively. Because lecanemab's Aβ decrease in the phase IIb trial was thought to be a relatively good indicator of clinical effect, the FDA (Food and Drug Administration) gave it fast approval. Based on the findings of CLARITY AD, the FDA gave lecanemab standard approval **[44].**

**LECANEMAB'S EFFECTIVENESS AND SAFETY IN AD**

Lecanemab, an anti-amyloid monoclonal antibody, has shown promise in treating Alzheimer's disease (AD) by focusing on amyloid-beta (Aβ) plaques, which are a major feature of the disease. Depending on the stage of AD, its effectiveness varies; early-stage treatments have the strongest evidence.

**1. Alzheimer's disease in its early stages (mild AD and mild cognitive impairment)**

**Effectiveness:** In early-stage AD, lecanemab has shown notable effectiveness in reducing cognitive and functional deterioration, particularly in mild AD or moderate cognitive impairment (MCI). According to clinical research, including the Phase 3 Clarity AD trial, lecanemab-treated patients had a 27% lower rate of decline than placebo-treated patients, as determined by the Clinical Dementia Rating-Sum of Boxes (CDR**-**SB) **[45].**

**Mechanism:** When used early in the course of the disease, lecanemab is believed to be crucial in slowing the progression of the condition because it targets and reduces the accumulation of Aβ plaque **[46].**

**2. Alzheimer's disease that is moderate**

**Efficacy:** Since most studies focus on patients in the early stages of AD, there is little information available on lecanemab's effectiveness in this condition. According to the underlying mechanisms, amyloid-targeting therapies such as lecanemab may be less effective in moderate stages of neurodegeneration, when tau tangles and extensive brain cell loss are present in addition to amyloid plaques. Proof from Additional Anti-Amyloid Treatments: In moderate stages of AD, when interventions frequently fail to reverse significant neurodegeneration, similar amyloid-targeting therapies have demonstrated limited benefit **[47].**

**3. Alzheimer's disease that is severe**

**Efficacy:** Patients with severe AD are not usually tested for lecanemab. Because of the severe neurodegeneration and diminished significance of amyloid plaque as a determinant in the progression of the illness, anti-amyloid treatments are typically less successful in advanced stages of AD. As a result, early intervention is emphasized in current treatment guidelines and trials.

**Risk and Safety:** Lecanemab frequently causes amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhages, particularly in patients with a higher amyloid burden, which is frequently seen in moderate-to-severe AD **[48].** The limited significance of amyloid-targeting medicines in later stages of AD is supported by this study, despite its focus on another anti-amyloid drug.

**RISKS AND ADVERSE EFFECTS RELATED TO LECANEMAB**

Evaluating possible adverse effects and medication risks is crucial while contemplating a course of treatment for any ailment. Better prognostic prognosis, patient compliance, and management are made possible by this understanding. Headaches, light-headedness, and nausea were the most frequent side effects linked to Lecanemab infusions. These side effects were more common in the higher-dose group and were typically mild to moderate in intensity **[49, 50].** Death was observed in 0.8% of the placebo group and 0.7% of lecanemab patients. Brain parenchymal edema, superficial siderosis, and cerebral micro haemorrhages are frequently linked to amyloid-related imaging abnormalities (ARIA)] **[50]**. Anti-Aβ antibodies, which may bind to cerebral amyloid antipathy (CAA) or increase CAA production, are frequently found to have this type of ARIA **[51]**. Higher medication dosages and the presence of the ApoE4 genotype were associated with a higher prevalence of ARIA in patients **[52].** Given that genetic investigations are rarely conducted in clinical practice before beginning treatment, it is alarming that patients who are ApoE4 carriers unexpectedly displayed improvement in cognitive deterioration **[53].** However, lecanemab may cause clinical deterioration in AD patients who are ApoE4 carriers. When compared to other medications used to treat AD, such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), these side effects are specific to monoclonal antibodies**[54].**

In a phase 3 trial for preclinical AD patients who received solanezumab also experienced side effects like ARIA with microhemorrhages, hemosiderosis, or edema, and even aducanumab **[55]**. Overall, lecanemab's safety profile was favorable, and the Phase III trial revealed no new safety concerns. The findings indicate that lecanemab has a manageable safety profile and that the treatment's advantages outweigh its risks **[56].**

In Alzheimer's disease studies, monoclonal antibodies targeting Aβ peptides, oligomers, fibrils, and amyloids reduced brain amyloid deposits observed by PET imaging.   
  
They have not slowed the cognitive decline. However, their use has frequently resulted in major health problems due to adverse events induced by amyloid-related imaging abnormalities (ARIA) as observed on MRI images. They can cause life-threatening cerebral oedema and haemorrhages.17-23 In the lecanemab trial, the most common adverse events were infusion-related reactions (26.4% with lecanemab and 7.4% with placebo), ARIA-H with microhemorrhages, macrohemorrhages, or superficial siderosis (17.3% with lecanemab and 9.0% with placebo), and ARIA-E with brain oedema (12.6% with lecanemab and 1.7% with placebo).

**COMPARISON WITH ALTERNATIVE THERAPIES FOR AD**

Cholinesterase inhibitors, which raise acetylcholine levels, are among the few known treatments for AD at the moment. These include galantamine, rivastigmine, and donepezil. Memantine, an NMDA receptor antagonist that controls glutamate activity, is the alternative. These medications do not alter the course of the disease; they merely relieve its symptoms **[57]**. Therefore, the alleviation is only momentary and disappears when the prescription is stopped because it offers no real benefit. There is no attention being paid to the main pathophysiology underlying AD. Conversely, lecanemab, which is currently FDA-approved, helps to reduce disease by addressing the main amyloid pathology in the brain, which delays cognitive loss and slows the progression of the disease. However, the patient not only experiences symptomatic relief, However, the primary pathology is being addressed in order to fully eradicate the illness **[58].**

**THE EFFECTIVENESS OF OTHER MONOCLONAL ANTI-AMYLOID Aβ ANTIBODY MEDICATIONS**

Two noteworthy phase III clinical trials, "ENGAGE" (NCT02477800) and "EMERGE" (NCT02484547), were conducted on aducanumab [24]. The outcomes of both trials were nearly identical to those of the placebo**.** Biogen after that due to interim post hoc assessments demonstrating futility, both studies were terminated. Additionally, the FDA continues to approve the drug June 2021 **[59].** However, there are serious doubts about its effectiveness and usefulness. In AD, gantenerumab has also demonstrated some promise. Doses as high as 1200 mg when given subcutaneously showed a significant decrease in Aβ in people with prodromal to mild AD once every four weeks **[60].** Phase III trials and additional research are needed to demonstrate its effectiveness and win FDA approval. In the EXPEDITION 1 and 2 phase 2 studies, solanezumab reduced beta-amyloid levels; however, this effect was limited to mild AD and did not ameliorate moderate AD. The outcomes were nearly identical to a placebo, even in patients with moderate AD **[61].** Even in EXPEDITION 3, the main goal of reducing cognitive decline was not achieved in a solanezumab Phase 3 trial that was started in a cohort of patients with moderate AD. Solanezumab was preferred in a number of secondary clinical endpoints, such as cognitive and functional assessments, but the benefit was essentially non-comparable **[62].**

**CONCLUSION**

Alzheimer’s disease possesses a profound challenge to global health affecting millions of people worldwide and it significantly impacting families and caregivers. Examination of Lecanemab’s ability to bind, its effectiveness in clinical settings, and its safety record offers a positive outlook on its potential contribution to the therapy of Alzheimer’s disease (AD). Overall, although Lecanemab demonstrates potential in specifically targeting Aβ protofibrils and producing favorable clinical results, more investigation and a comprehensive evaluation of its safety and long-term efficacy are essential for determining its function in treating Alzheimer’s disease. The discourse surrounding Lecanemab highlights the necessity of a well-rounded comprehension of its ad-vantages and possible obstacles to guarantee informed decision-making in treating Alzheimer’s disease. The results of this study have the potential to inform clinical guidelines and benefit healthcare professionals, caregivers, and researchers in their efforts to improve the treatment of AD. This review is a crucial step in addressing the growing challenge of AD and enhancing the well-being of affected individuals and their families. While lecanemab presents a favourable safety profile, it is associated with amyloid-related imaging abnormalities (ARIA). Unlike symptomatic treatments, lecanemab addresses the disease’s underlying pathology, marking a significant advancement in AD therapy.

Lecanemab is a significant development in the treatment of Alzheimer's disease, as it is one of the first FDA-approved monoclonal antibodies designed to target amyloid plaques in the brain, a hallmark of the disease. By binding to and helping clear these plaques, Lecanemab has shown potential to slow cognitive decline in patients with early Alzheimer's, offering hope for more effective treatments. Its approval marks a step forward in Alzheimer's research, signaling that disease-modifying therapies are becoming a reality. Ultimately, Lecanemab's significance lies in its potential to improve quality of life for patients and their families, changing the landscape of Alzheimer's treatment**[63].**

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