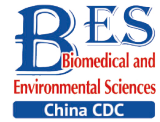## Letter to the Editor

Lecanemab Unveiled: Exploring Alzheimer's Treatment Advancements, Assessing Strengths, Limitations, and Its Therapeutic Landscape Position

VICTOR Abiola Adepoju[1], OKECHUKWU Innocent Onyezue[2], SAFAYET Jamil[3], OLALEKAN John Okesanya[4,#], and DON Eliseo Lucero-Prisno III[5]

In the ever-evolving landscape of Alzheimer's treatment, lecanemab (Leqembi) has emerged as a promising drug. Unlike conventional therapies that merely alleviate symptoms, lecanemab is a humanized monoclonal antibody with a distinct focus. It targets protofibrils, insoluble fibrils, amyloid oligomers, and soluble amyloid-beta protofibrils, which are known to be especially damaging to neurons, with high accuracy. Lecanemab is a possible game-changer in a field where scientific advances are anticipated, providing a window into the future in which Alzheimer's disease (AD) treatment not only ameliorates symptoms but also fundamentally changes the course of the disease[1] Given that approximately 55 million individuals suffer from dementia worldwide, there is an urgent need for successful treatment. In 2023, the US Food and Drug Administration (FDA) granted accelerated approval for lecanemab, an anti-amyloid antibody that affects biological markers and clinical outcomes in early AD. Regulatory reviews are currently underway in Europe[2]. While this drug shows promise in helping people with early stages of AD in delaying mental decline for a longer period, it is important to consider both the strengths and limitations of this treatment, as well as its potential place in the current landscape of Alzheimer's therapies. One strength of Leqembi is its targeted approach to reducing beta-amyloid plaques, a protein believed to contribute to the progression of AD. In an 18-month phase 3 trial of lecanemab conducted by van Dyke et al. (2023), involving participants experiencing the early stage of AD, patients treated with Leqembi showed a reduction in brain amyloid concentrations. Additionally, they exhibited a moderately lower decline in psychological assessments of cognitive function compared to those in the placebo group, as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[1]. It was found that there was a treatment difference of 0.373 points on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score, favoring lecanemab over placebo. The medication was highly selective for aggregated Aβ species, specifically targeting the most dangerous forms. The amyloid sub-study revealed that the lecanemab group had a mean amyloid level that was lower than the positive threshold. Lecanemab reduced amyloid, tau, neurodegeneration, and neuroinflammation indicators more effectively than the placebo. The experiment exceeded expectations, with a treatment difference of 0.373 points in the CDR-SB score. Ongoing safety and efficacy data for children beyond 18 months of age will be provided in an open-label extension study. Limitations include the absence of a cure, associated risks such as brain swelling, and its high costs, which pose accessibility challenges[1,3,4].

Lecanemab has several risks and adverse effects, including headaches, dizziness, vision abnormalities, and increased disorientation, all of which can influence daily life. Notably, there is a danger of significant consequences such as brain edema, hemorrhage, and shrinking, with a few cases of death described. Nearly one-third of the patients develop infusion responses, which can include changes in blood pressure, respiration, skin, fever, and chills, although the majority of these responses are manageable. Amyloid-related imaging abnormalities (ARIA), such as brain hemorrhage and edema, affect approximately two of every ten

people, with symptoms occurring in one of every five instances. Apolipoprotein E-epsilon 4 (APOE-ε4) carriers have a higher risk of developing ARIA and associated consequences. However, it is important to note that Leqembi is not a cure for AD and does not stop or reverse the disease. It is also associated with risks, including the potential for brain swelling and small brain bleeding, which may require frequent MRI monitoring[1]. Additionally, the high cost of Leqembi (over $25,000 per person) may render it inaccessible to many patients[2]. This highlights the need for more affordable treatment options for AD and other forms of dementia. However, this is a significant improvement over previous Alzheimer's drugs, which have had limited success in improving symptoms. Lecanemab, adducanumab, and donanemab used to treat early AD are exclusively accessible in the United States, but are yet to be licenced for use in Europe and other parts of the world[4].

In terms of its role in the current landscape of Alzheimer's therapies, Leqembi belongs to a class of drugs known as monoclonal antibodies, which are designed to target specific proteins in the brain that are believed to be involved in the progression of AD. Aducanumab (Aduhelm) is another drug in this class that was approved by the FDA in 2021[4]. However, 86% (184/214) of the clinicians declined to administer or prescribe aducanumab to patients with AD[5]. Solanezumab has shown mixed results in clinical trials, and donepezil (Aricept) has comparable or more effective cognitive and behavioral effects than anti-Aβ antibody[6]. The mechanism of action of Leqembi is similar to that of these drugs in that it targets beta-amyloid plaques, but appears to be more effective at reducing cognitive decline. The drug's effectiveness, when compared with other anti-amyloid drugs, stems from its ability to target certain Aβ species, particularly those considered highly pathologic and lethal. APOE genotype influences drug efficacy. APOE-ε4 carriers have lower treatment efficiency and are more susceptible to ARIA. A meta-analysis by Qiao et al. (2023) indicated consistent efficacy and direction for decreasing Aβ amyloid and slowing cognitive deterioration. However, safety issues include a higher incidence of ARIA-E and ARIA-H, as well as possible gastrointestinal and neurological side effects[7]. This finding is also supported by the outcome of a meta-analysis by Lacorte et al. (2022), which included data from multiple clinical trials of monoclonal antibodies for Ads[8]. A meta-analysis found that treatment with monoclonal antibodies

was associated with a statistically significant improvement in cognitive function compared with placebo, with the largest effect observed in studies of Leqembi. The Institute for Clinical and Economic Review (ICER) recently assessed the financial viability, health-related outcomes, and financial consequences of lecanemab among individuals with early AD. They concluded that the current scientific evidence is insufficient to prove that the cumulative health advantage of lecanemab, when combined with supportive care therapy, is more effective than that achieved through supportive medical care therapy alone[9].

Lecanemab is administered intravenously once every two weeks without titration, with patients receiving a dosage of 10 mg/kg of total body mass. The drug is administered at doses of 500 mg/5 mL (100 mg/mL) and 200 mg/2 mL (100 mg/mL). Lecanemab is added to a disposable infusion container containing 250 mL of 0.9% saltwater injection and administered via an intravenous line equipped with a low-protein affinity 0.2 micron compatible filtering system. Patients are monitored for potential reactions, and follow-up may involve shorter observation intervals if no reactions occur[3]. It is recommended that patients meet the diagnostic criteria for mild cognitive impairment (MCI) due to AD or mild AD dementia, with MMSE scores ranging from 22 to 30, as supported by biomarker evidence such as amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF), before considering lecanemab therapy for AD. APOE-ε4 carriers should undergo genetic testing before using lecanemab. Age constraints (50–90 years) and exclusion criteria for immunological disorders, unstable health problems, recent epileptic attacks, pregnancy or breastfeeding, depressive disorders, and BMI are critical for patient selection[5,6]. Individuals should not receive treatment if they have a history of seizures or cerebral amyloid angiopathy-related inflammation/amyloid beta-related angiitis (CAA-ri/ABRA) because these conditions increase the risk of ARIA. Lecanemab should also not be administered to patients taking warfarin, vitamin K antagonists, or direct oral anticoagulants, or those with MRI evidence of underlying CAA-ri/ABRA or conditions that predispose them to ARIA[9]. Prior to treatment initiation, eligible patients underwent MRI screening within 12 months. Routine MRI was performed after the fifth, seventh, and fourteenth infusions. For APOE4 carriers and those exhibiting ARIA evidence, follow-up MRI after week 52 is advised. However, lecanemab therapy is not available to patients who

cannot undergo MRI because of certain medical conditions[2,3]. Lecanemab trials have permitted the concurrent use of indicative anti-dementia medications, such as cholinesterase inhibitors and memantine, as long as the patient's medical history and doses remain constant. Aducanumab, a different anti-amyloid monoclonal antibody used to treat early AD, belongs to the same family but is administered differently with titration and magnetic resonance imaging (MRI) surveillance. Lecanemab should not be administered if the patient is already receiving aducanumab or has severe or persistent amyloid-related imaging abnormalities while using aducanumab. These strict requirements guarantee the safety and effectiveness of lecanemab in clinical settings, whereas medical judgement is employed in individual circumstances to consider the impact of these criteria[3].

In a comprehensive assessment of the impact of non-pharmacological interventions and societal factors on implementing lecanemab for AD, the study discovered that those treated with lecanemab alongside the standard of care (SoC) acquired an extra 0.62 years of lifespan over the course of their lives, in contrast to patients treated with SoC alone. This resulted in higher QALYs and lower overall costs per patient from both the payer and societal perspectives. Scenario analyses were performed to examine the effects of different demographic groupings, timespans, treatment doses, and ending rules. This study demonstrated the potential economic benefit of lecanemab in delaying the onset of AD, emphasizing the necessity of early detection and treatment. The study recognizes uncertainties and the need for additional validation based on real-world evidence as lecanemab becomes more extensively used after approval[7]. In addition, the progression of AD and the effectiveness of drug treatments can be influenced by non-pharmacological therapies, which have demonstrated a wide range of techniques with different efficacies. Exercise has shown the potential to improve daily living activities and MMSE scores, whereas cognitive therapies, such as emotional, physical, and social engagement, caregiver training programs, emotion-based interventions, and rehabilitation, have improved MMSE scores. Dietary changes appear promising for lowering the progression of AD; however, there is no scientific evidence. Repetitive transcranial magnetic stimulation has neuroprotective and pro-cognitive benefits, whereas acupuncture therapy improves cognitive function and ADL. However, music therapy

has not demonstrated substantial efficacy. One meta-analysis found low evidence quality, emphasizing the need for more studies and necessitating the need for individualized, professionally managed approaches. The combination of pharmacological and non-pharmacological approaches could lead to more effective treatment strategies. Addressing broader social and economic factors, such as access to care, support for caregivers, and increased funding for research and resources is crucial for addressing the burden of the disease[10].

Clinicians should be educated on cognitive assessment, AD, infusion methods, ARIA diagnosis, amyloid confirmation, patient communication, and APOE genotyping. They should create standard guidelines for managing severe ARIA, conduct regular assessments of individuals with MCI or dementia, and explore lecanemabs for early AD. Regular MRI, quick accessibility to MRI studies, and communication channels for ARIA symptoms are required. The effectiveness of lecanemab was supported by a lower-than-expected drop in rating instruments. Trust-building and transparent communication between clinicians and patients are critical for productive and sustainable lecanemab administration in real-world therapeutic settings[3]. In conclusion, Leqembi, a potential treatment for AD, requires careful consideration for its long-term effectiveness and safety. The historical context of Alzheimer's drug development, including the controversy surrounding Aduhelm, and further research are needed to address the gaps in the current knowledge. Other approaches to treating AD include cholinesterase inhibitors approved by the FDA for mild, moderate, and severe AD, and memantine for moderate to severe AD.

Ethical Approval   There is no ethical issue.

Competing Interest   The authors declare no conflicts of interest.

Author Contributions   VICTOR Abiola Adepoju, OKECHUKWU Innocent Onyezue, SAFAYET Jamil, and OLALEKAN JohnOkesanya conceived and designed the study, conducted the research, provided research materials, collected and organized the data, and analyzed and interpreted the data. VICTOR Abiola Adepoju, OKECHUKWU Innocent Onyezue, SAFAYET Jamil, OLALEKAN JohnOkesanya, and DON Eliseo Lucero Prisno III wrote the initial and final drafts of the article, and DON Eliseo Lucero Prisno III provided logistical support. All authors critically reviewed and approved the final draft and are responsible for the content and similarity index of

the manuscript.

#Correspondence should be addressed to OLALEKAN John Okesanya, E-mail: okesanyaolalekanjohn@gmail.com Tel: 2348130307211.

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