## New Options for Alzheimer's Disease

On January 6, 2023, the FDA approved Eisai/Biogen's Leqembi™ (lecanemab-irmb) for the treatment of Alzheimer's disease (AD). It is administered every other week via IV infusion. Leqembi is the second anti-amyloid monoclonal antibody to be approved by the FDA for the treatment of AD, after Biogen's Aduhelm® (aducanumab) in 2021. The medication works by selectively binding to neutralize and eliminate soluble amyloid-beta (Aβ) plaques that are thought to contribute to the progression of Alzheimer's disease. It is estimated that more than 6 million Americans may have dementia caused by Alzheimer's disease.

Leqembi was approved under the FDA's accelerated approval pathway. This allows for earlier approval of medications that treat serious conditions and fill an unmet medical need while the medication continues to be studied in larger and longer trials. Leqembi's approval was based on efficacy data from a Phase 2 trial (Study 201) which was an 18 month, double-blind, placebo-controlled, dose-finding study of 856 patients with Alzheimer's disease. Treatment was initiated in patients with mild cognitive impairment or mild dementia and confirmed presence of amyloid-beta pathology. Five dosing arms were established in the trial. The primary endpoint, to determine the most effective dose that had 80% probability of ≥25% reduction in clinical decline compared to placebo at 12 months, was not met. If the primary endpoint had been achieved, more patients would have been changed to the most effective dose at 12 months. As a result, full dose randomization continued as scheduled for the total 18-month duration of the trial. Ultimately, the most effective dose was determined to be 10mg/kg biweekly based on the Alzheimer's Disease Composite Score (ADCOMS), which measures outcomes among patients with mild cognitive impairment and mild dementia due to AD. Results from prespecified key secondary endpoint analyses demonstrated that lecanemab reduced brain amyloid and showed early and sustained activity for the 10 mg/kg biweekly lecanemab dose across the 18-month treatment period for several clinical measures of AD. For example, patients receiving the treatment demonstrated a reduction of amyloid beta plaque from baseline to Week 79 as compared to the placebo arm, which had no reduction of amyloid beta plaque. In addition, lecanemab reduced clinical decline on the Alzheimer's Disease cognitive subscale (ADAS-Cog14) over 18 months, with 47% ($P$ =0.017) less decline compared to placebo. The amyloid hypothesis suggests that amyloid plaques, the hallmark of AD, is a primary cause of the loss of brain cells that lead to declines in memory and thinking. However, thus far, there is no direct correlation with AD progression and amyloid beta plaques. In addition, the clinical trials that have been conducted to support Aduhelm and Leqembi's approval, success was measured not by cognitive improvement but by slowing in the rate of cognitive and functional decline. Brain impairment still occurred despite the modest decrease in amyloid beta plaque.

Leqembi is not indicated for all types of AD. The approved labeling states that treatment with Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was studied in clinical trials. Patients should also have confirmed presence of amyloid beta pathology prior to starting treatment. The labeling does state that there is no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. However, the label does recommend a baseline magnetic resonance imaging (MRI) to look for pre-existing ARIA and again prior to the 5$^{th}$, 7$^{th}$, and 14$^{th}$ infusion to monitor for changes.

The prescribing information for Leqembi includes a warning for amyloid-related imaging abnormalities (ARIA), which are known to occur with antibodies of this class. ARIA usually does not have symptoms,

although serious and life-threatening events rarely occur. ARIA most commonly presents as temporary swelling in areas of the brain and usually resolves over time. It may be accompanied by small spots of bleeding in or on the surface of the brain, though some people may have symptoms such as headache, confusion, dizziness, vision changes, nausea, and seizure. Another warning for Leqembi is the risk of infusion-related reactions, with symptoms such as flu-like symptoms, nausea, vomiting and changes in blood pressure. The most common side effects of Leqembi were infusion-related reactions, headache, and ARIA.

Leqembi is expected to be available by the end of January 2023. Eisai has stated that it will be priced at $26,500 per year, based on an average patient weight. This price is just under Aduhelm's current price of $28,200 per year and above the Institute for Clinical and Economic Review's (ICER's) suggested cost-effective annual list price of $8,500 to $20,600. Utilization of Leqembi is expected to be low until the Centers for Medicare & Medicaid Services (CMS) modifies the National Coverage Determination (NCD) that was outlined in April 2022. Unconvinced by the evidence of Aduhelm and due to its accelerated approval, CMS restricted coverage of Aduhelm and other AD medications like it to patients currently participating in a clinical trial. Because lecanemab was granted accelerated approval, it falls under CMS's existing NCD. If lecanemab subsequently receives a traditional FDA approval, CMS would likely provide broader coverage in a variety of treatment settings. According to CMS, an FDA traditional approval indicates the drug has demonstrated evidence of efficacy from a direct measure of clinical benefit.

On the same day that Leqembi received accelerated approval, Eisai announced that it submitted the supplemental Biologics License Application (sBLA) to the FDA to convert Leqembi to a traditional approval based on data from the confirmatory Phase 3 CLARITY AD clinical trial. This phase 3 trial was an 18-month, multicenter, double-blind study in early Alzheimer's patients with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. A total of 1,795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The primary end point was the change from baseline at 18 months in score on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). The range of rating is 0 to 18 with higher scores indicating greater impairment. The mean CDR-SB score at baseline was approximately 3.2 in both groups. Lecanemab reduced clinical decline on the CDR-SB scale compared with placebo at 18 months by 27%, which represents a treatment difference in the score change of -0.45 (p=0.00005). In a sub study involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo. Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%. A decision on Leqembi's traditional approval is expected in late 2023.

Recently, the FDA denied the accelerated approval of donanemab, a third potential antibody by Eli-Lilly, for AD. Donanemab is administered once monthly via IV infusion and works by targeting a modified form of deposited beta amyloid (Aβ) called N3pG. This pathological form of Aβ is highly prone to aggregate, depositing in the core of all amyloid plaques, but is found nowhere else in the brain. In November 2022, Lilly announced that donanemab met all primary and secondary endpoints for the 6-month primary outcome analysis in the Phase 3 TRAILBLAZER-ALZ 4 study. The main purpose of the study was to compare donanemab to Aduhelm on amyloid plaque clearance in participants with early AD. Brain amyloid plaque clearance was achieved in 37.9% of donanemab-treated participants (25 of 66) compared with 1.6% of Aduhelm-treated patients (1 of 64) at 6 months. In a key secondary outcome, donanemab reduced brain amyloid levels versus baseline by 65.2% compared with 17.0% for Aduhelm at 6 months. ARIA was the most common adverse event in both groups. In the Aduhelm group,

the incidence of total ARIA was 26.1% with 4.3% being symptomatic. In the donanemab group, the incidence of total ARIA was 25.4% with 2.8% being symptomatic. Treatment with donanemab led to greater amyloid clearance than Aduhelm, however it was not associated with a higher rate of ARIA. Eli-Lilly will continue the phase 3 trial and seek traditional approval later this year. The pricing for donanemab is anticipated to be comparable to Aduhelm and Leqembi.

Treatment of Alzheimer's disease has always been a highly challenging area. Until Aduhelm's approval in 2021, the FDA had not approved a drug treatment for AD in more than 17 years. In addition, Aduhelm's approval was controversial based on less than convincing trial results. Lecanemab offers another treatment option that reduces markers of amyloid and appears to modestly reduce cognitive decline when compared to placebo. However, it was only studied in mild forms of AD and did not demonstrate any evidence of direct disease modification. Now donanemab has the potential to be the third anti-amyloid antibody treatment available for AD. Early studies indicate it may be more effective that Aduhelm at clearing amyloid plaque and reducing levels of amyloid in the brain. It has not been compared or studied versus Leqembi. However, despite their potential benefit, Aduhelm, Leqembi, and donanemab all have the potential to cause serious and life-threatening ARIA that can result in small brain bleeds, edema, or effusions. While Alzheimer's patients and their caregivers are extremely thankful to have additional treatments available for this devastating disease, longer trials are warranted that demonstrate their direct effect on the course of AD progression, various stages of AD and to continue to determine their true efficacy, safety and ultimate place in therapy.

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