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Lilly's Donanemab: US FDA's Questions Focus On Patient Selection, Dose Cessation

by Sue Sutter

Given the frequent occurrence of ARIA and an imbalance of deaths in the pivotal TRAILBLAZER-ALZ 2 study, the agency also will ask the Peripheral and Central Nervous System Drugs Advisory Committee whether there are patient subgroups where the benefit-risk is more or less favorable.

Basing the efficacy of *Eli Lilly and Company*'s Alzheimer's treatment donanemab on patients' tau levels and translating the pivotal trial's stopping rules for dosing into clinical settings will be among the key focus areas for a US Food and Drug Administration advisory committee.

The Peripheral and Central Nervous System Drugs Advisory Committee will meet 10 April to discuss the product, an anti-amyloid agent proposed for treatment of early symptomatic Alzheimer's disease.

Although plans for an advisory committee meeting were announced late in the biologics license application's review, causing the FDA to miss the user fee goal date, the agency's briefing *document* released on 6 April appears to raise no major red flags that would suggest approval is unlikely. (Also see "*Lilly's Donanemab Delay: Labeling, Real-World Operationalization May Be Reason For Adcomm*" - Pink Sheet, 8 Mar, 2024.)

Rather, the agency seeks the committee's views on the appropriate patient population because the Phase III trial excluded patients with no or very low tau levels.

The pivotal trial's dose-cessation rules, which were driven by the amount of amyloid reduction, also have the agency

Key Takeaways

- The FDA seeks advisory committee input on the appropriate patient population for donanemab given the pivotal trial

asking whether there are clinical or scientific considerations that may factor into a decision to stop giving donanemab.

In addition, the agency seeks discussion of donanemab's risks, which include amyloid-related imaging abnormalities (ARIA) and an imbalance in deaths in the pivotal trial. FDA officials also want recommendations on whether there are certain subgroups with a more or less favorable benefit-risk assessment.

The agency will pose two voting questions for the committee: whether efficacy has been demonstrated and for whom; and the overall benefit-risk assessment.

excluded patients with no or very low tau levels.

- The panel also will be asked whether and how the pivotal trial's dose cessation rules should extend to clinical practice.
- The frequent occurrence of ARIA in the Phase III trial, along with an imbalance in deaths, will inform the benefit-risk assessment.

Pivotal Trial Results Follow CRL

Donanemab is in its second review cycle. The initial BLA submission requested accelerated approval on the basis of amyloid plaque reduction in a Phase II study. That filing resulted in a January 2023 complete response letter because the safety database was insufficient to characterize long-term safety. (Also see "*US FDA Rejects Lilly's Bid For Donanemab Accelerated Approval In Early Alzheimer's*" - Pink Sheet, 19 Jan, 2023.)

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The BLA was resubmitted on 12 June 2023 with results from the pivotal TRAILBLAZER-ALZ 2 trial, also known as Study AACI. Lilly seeks regular approval.

In Study AACI, 1,736 patients with early symptomatic AD were randomized 1:1 to donanemab or placebo infusion every four weeks. The primary endpoint was the change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks. Secondary endpoints included the change from baseline in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) and the two components of the iADRS, the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog 13) Subscale and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL) subscale.

Study AACI originally was designed with the CDR-SB as the primary endpoint. The endpoint was changed to the iADRS while the study was underway, a decision with which the FDA disagreed.

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Novel Trial Design Features

Two key features of Study AACI distinguish it from those that supported marketing of the two anti-amyloid monoclonal antibodies that preceded donanemab: *Biogen, Inc.*'s Aduhelm (aducanumab-avwa), which received accelerated approval in June 2021, and *Eisai Co., Ltd.* and Biogen's Leqembi (lecanemab-irmb), which received accelerated approval in January 2023 and regular approval six months later. (Also see "*Eisai/Biogen's Leqembi: US FDA's Full Approval Comes With A Boxed Warning On ARIA Risk*" - Pink Sheet, 6 Jul, 2023.)

Study AACI used brain tau PET imaging as an enrichment strategy to increase the proportion of patients who were likely to progress during the placebo-controlled period. Study participants were required to have tau on PET imaging based on quantitative assessment and topographic deposition. Two primary analysis populations based on tau PET imaging were prespecified: a low/medium tau level population, and the overall population comprising low/medium plus high tau levels.

"The applicant hypothesized that a treatment effect might be more difficult to demonstrate in participants with high tau levels due to their more advanced disease stage," the agency's briefing document states. "The applicant did not propose a requirement for confirmation or quantification of tau pathology in the prescribing information despite excluding participants with no or very low tau from the controlled portion of Study AACI and prioritizing a low/medium tau population in the statistical analysis."

The low/medium tau population accounted for 68% of randomized participants in Study AACI. Subjects with no or very low tau levels were excluded from the placebo-controlled trial, but were eligible to enroll in the Study AACI Safety Addendum.

The trial also instituted treatment stopping rules, allowing for cessation of donanemab dosing guided by amyloid PET levels measured at 24, 52 and 76 weeks after the start of treatment. If the amyloid plaque level was <11 Centiloids on a single PET scan, or 11 to <25 Centiloids on two consecutive PET scans, the subject was eligible to switch to placebo.

Hitting All Endpoints

On the primary efficacy endpoint, donanemab demonstrated a statistically significant treatment effect on the iADRS at week 76 compared to placebo in both the low/medium tau group (3.3, 95% CI: 1.9, 4.6; p<0.001) and the overall population (2.9; 95% CI: 1.5, 4.3; p<0.001). Although the subgroup of patients with high tau levels was not powered to detect a treatment effect, the results on the primary endpoint in this group numerically favored donanemab.

Statistically significant treatment effects also were demonstrated for the ADAS-Cog13 and ADCS-iADL components of the iADRS, and on the CDR-SB in the low/medium tau population and the overall population.

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Donanemab demonstrated a statistically significant effect on change from baseline to week 76 in brain amyloid plaque in the low/medium tau and overall populations, with the result indicating a time-dependent relationship.

Donanemab also was associated with a decrease in whole brain volume and an increase in ventricular volume.

"Similar changes have been observed with other monoclonal antibodies that target amyloid," the agency said. "Although decreases in brain volume can reflect atrophy or neurodegeneration, the physiologic or pathologic changes that underly the observed changes in brain volume with monoclonal antibodies targeting amyloid are unclear."

The clinical relevance of these changes also is unclear, "particularly in light of the favorable results on clinical endpoints observed in Study AACI," the agency said. "It will be important to collect longer-term data in a large number of patients to further understand the clinical implications, if any, of these observations."

Closer Look At Tau Subgroups

The agency said further consideration of efficacy across the spectrum of baseline tau levels is relevant because tau PET imaging was used as an enrichment strategy in the pivotal study, and Lilly did not propose a labeling requirement for confirmation or quantification of tau pathology.

Although participants with no or very low tau were excluded from Study AAIC, there are biomarker data on approximately 200 such individuals who were enrolled in the single-arm safety addendum.

"Compared to participants with low/medium or high tau enrolled in Study AACI, participants with no or very low tau had lower baseline levels of brain amyloid, plasma p-tau 217 and [glial fibrillary acidic protein], consistent with their earlier disease stage," the agency said. "Reductions in amyloid, plasma p-tau 217 and GFAP from baseline were generally similar in the two populations."

Patients with a higher tau burden would be expected to have a greater extent of neurodegeneration, potentially limiting the benefit of anti-amyloid therapy in this population relative to patients with low tau burden, the FDA said.

"It may be reasonable to generalize the efficacy results from the

population studied in Study AACI across the spectrum of tau burden, including patients with very low or no tau." – FDA

"The primary results of Study AACI in the low/medium and overall populations appear to support the expectation of a larger magnitude of treatment effect (% slowing) in patients earlier in the disease," the agency said. "The prespecified subgroup analyses by baseline tau tercile also suggest that a treatment effect was observed across the range of baseline tau levels included in Study AACI, including in participants with high tau levels."

As an anti-amyloid antibody, donanemab does not require the presence of tau to exert its pharmacologic effect, and there is no *a priori* reason to believe that a certain tau level needs to be present for the drug to be effective. A negative tau PET scan with flortaucipir also does not preclude the presence of tau pathology, the agency said.

Nevertheless, whether the reduction in amyloid plaque in patients with no or minimal tau has the same effect on clinical endpoints has not been established, the agency said.

"There were no notable differences in safety between individuals with very low or no tau and individuals with higher tau burden," the FDA said. "Based on these considerations, it may be reasonable to generalize the efficacy results from the population studied in Study AACI across the spectrum of tau burden, including patients with very low or no tau."

Questions Remain On Dose Cessation

Under the pivotal study's dose cessation guidelines, at Weeks 24, 52, and 76 the proportion of participants in the donanemab treatment arm who met dose-stopping criteria based on amyloid PET results was 17%, 42%, and 60%, respectively.

Lilly assumed that dosing cessation once brain amyloid on PET fell below a specific threshold would not adversely affect clinical outcomes, the FDA said.

"Payers, including the Centers of Medicare and Medicaid Services (CMS), have also expressed a great deal of interest in the potential for limited-duration dosing, as this may significantly lower the cost

of care in comparison to chronically dosed medications." – Eli Lilly

"Although this assumption is reasonable, it was not verified by including an arm with continuous donanemab dosing," the agency wrote in briefing documents. "There is also uncertainty regarding the optimal Centiloid threshold value for dose cessation. Data from the ongoing long-term extension portion of the study may provide insight into the persistence of effect."

The agency also said it is uncertain whether there would be a need to restart donanemab based on reaccumulation of amyloid.

In its briefing *document*, Lilly said the limited duration dosing approach studied in AACI could be implemented in routine practice, and clinicians and patients should have the option to consider stopping treatment once amyloid clearance is achieved.

"Lilly has received consistent feedback from patients, caregivers, and health care professionals that this approach has the potential to decrease treatment burden, an important consideration for this vulnerable and elderly population," the company said. "Payers, including the Centers of Medicare and Medicaid Services (CMS), have also expressed a great deal of interest in the potential for limited-duration dosing, as this may significantly lower the cost of care in comparison to chronically dosed medications."

ARIA Risk And Deaths

Consistent with labeling for the class of anti-amyloid drugs, the primary safety issues for donanemab in Study AACI were ARIA, cerebral hemorrhage, infusion-related reactions and hypersensitivity, including anaphylaxis, the FDA said.

Overall, the incidence of ARIA was 36% in the donamemab arm of Study AACI versus 14% in the placebo arm. The incidences of ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H) were 24% and 31% in donanemab-treated patients, respectively. The risk of ARIA increased in ApoE ε4 carriers and the majority of ARIA cases were asymptomatic.

An imbalance of deaths also was reported in the donanemab arm at 76 weeks, 17 (2.2%) compared to 10 (1.2%) in the placebo arm.

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The FDA requested Lilly retrieve additional mortality information for participants who discontinued Study AACI prior to week 76.

However, a higher dropout rate in the donanemab arm complicated the mortality analysis. Among randomized participants, 25.9% in the donanemab group discontinued the study early compared with 19.5% on placebo. Vital status at week 76 was not captured for those individuals.

"This lack of vital status information collected during the conduct of AACI adds uncertainty to mortality analysis results … for which there was an imbalance in deaths observed with donanemab relative to placebo," the agency said. "With high rates of missing vital status at week 76 and its potential impact on the assessment of mortality, the agency requested that the applicant retrieve additional mortality information among participants who discontinued the AACI study prior to week 76 and for whom the vital status was not available."

A third-party vendor found the vital status for 184 of the 352 participants who were missing week 76 vital status using publicly available records and databases, social media and traditional media. Among these individuals, two participants randomized to donanemab and five participants randomized to placebo died within 76 weeks.

"Inclusion of these retrieved deaths reduced the imbalance in deaths observed from the deaths observed during Trial AACI," with 19 deaths in the donanemab arm versus 16 on placebo. "However, it is worth noting that approximately 10% of subjects still have missing vital status information (data could not be obtained in some subjects due to regulatory and/or legal requirements in other countries) and the retrieved vital status information lacks information on cause of death," the FDA said.

In the placebo-controlled portion of Study AACI, there were three ARIA-related deaths in the donanemab group and none on placebo.

"Other than ARIA-related deaths, the remaining deaths did not appear to be causally related to donanemab and there was no unusual grouping of deaths that would suggest a causal relationship," the agency said.