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Aduhelm's Goodbye: ENVISION Confirmatory Study To End In May, With BLA Withdrawal In November

by Sue Sutter

Biogen faces complex logistics in shutting down a multinational trial with more than 200 sites and approximately 1,000 patients enrolled; company also is facing calls to publish data collected from the unfinished study as well as other aducanumab trials.

Biogen, Inc.'s decision to discontinue development and commercialization of the Alzheimer's drug Aduhelm (aducanumab-avwa) means its ENVISION confirmatory trial will end much the way it began – surrounded in controversy and questions.

The sponsor is facing the complex logistics of shutting down a multinational trial in which approximately 1,000 subjects have been enrolled, and it already is facing calls to publish the data collected from the unfinished study as well as other aducanumab trials.

The biologics license application for Aduhelm will be withdrawn effective 1 November 2024, Biogen told the *Pink Sheet*.

Key Takeaways

- The multi-month wind-down of Aduhelm's confirmatory study underscores the complexity of the partially enrolled international trial.
- HHS Inspector General expects to publish the second report in its series on the accelerated approval pathway by September 2024.

"After November 1, it will no longer be on the market," the company said. "Patients on commercially available Aduhelm will have the option to continue their treatment until that

date, which was to help support patient continuity."

All participants in ENVISION have the choice to continue in the study through 1 May, Biogen said. "After that date, they should work with their physician to develop next steps in their treatment plans." Since Aduhelm will not be available after 1 November, there will not be an expanded access program.

- Advisory committee members continue to press Biogen to publish data, especially safety results.
- The product will remain a touchstone for agency critics.

Aduhelm undoubtedly will be viewed as one of the greatest commercial failures in biopharma history – an outcome attributable to efficacy data widely viewed as less than robust, a controversial FDA accelerated approval, an over-reach by Biogen in setting the initial annual price tag of $56,000, and the Centers for Medicare and Medicaid Services' coverage decision limiting reimbursement to patients who are in clinical trials. (Also see "*An Elegy For Aduhelm*" - Pink Sheet, 1 Feb, 2024.)

However, the drug has had a substantial impact on policy and legislation on several fronts, particularly use of the accelerated approval pathway and the timing of confirmatory trials.

The drug's review and approval spurred an internal FDA evaluation and congressional investigation of the agency's interactions with Biogen. (Also see "*US FDA's Post-Aduhelm Reforms Include Updated Alzheimer's Development Guidance, Record-Keeping On Sponsor Meetings*" - Pink Sheet, 2 Jan, 2023.)

It also led to a review of the accelerated approval program by the Department of Health and Human Services' Office of Inspector General. (Also see "*Beyond Aduhelm: OIG Review Will Put FDA's Entire Accelerated Approval Program Under Microscope*" - Pink Sheet, 4 Aug, 2021.)

The OIG's initial report focused on delayed confirmatory trials. (Also see "*OIG Accelerated Approval Report Spotlights Financial Costs Ahead Of Congressional Debate*" - Pink Sheet, 29 Sep, 2022.) OIG expects to publish the second report in its series on the accelerated approval pathway by September 2024.

Confirmatory Trial Controversial From The Start

Biogen said it decided to discontinue the development and commercialization of Aduhelm and terminate the ENVISION trial after failing to identify potential strategic partners or external financing for the anti-amyloid antibody. (Also see "*Biogen Closes The Book On The Aduhelm Saga*" - Pink Sheet, 31 Jan, 2024.)

During this strategic review, the company considered the time and investment required for the ENVISION study as well as the likely advances in the field by the time Aduhelm potentially could receive regular approval.

The confirmatory trial was a source of controversy from the start, beginning with the Center for Drug Evaluation and Research's surprise decision in June 2021 to allow aducanumab to come to market under the accelerated approval pathway. (Also see "*Aducanumab Accelerated Approval Reflects US FDA Flexibility But Raises Doubts About Confirmatory Trial*" - Pink Sheet, 7 Jun, 2021.)

The FDA granted accelerated approval despite the lack of an ongoing, or even planned, confirmatory trial, an action that ran counter to the agency's longstanding view that confirmatory trials should usually be underway at the time of approval. (Also see "*US FDA Has History Of Pushing Sponsors On Confirmatory Trials … Sometimes*" - Pink Sheet, 25 Jan, 2023.)

Furthermore, the agency gave Biogen nearly nine years to complete a confirmatory trial, a jaw-dropping amount of time in the view of many observers. (Also see "*3,189 Days: Aduhelm Phase IV Timeline Is Long Among Alzheimer's Drugs And Other Accelerated Approvals*" - Pink Sheet, 12 Jul, 2021.)

Both the FDA and Biogen came in for criticism over the long study timelines. Biogen accelerated the study's pace such that it was on target for completion in October 2026, almost three years ahead of the 2029 milestone in the FDA's approval letter. (Also see "*Biogen Pushes Ahead With Aduhelm Confirmatory Trial As CMS Final Decision Looms*" - Pink Sheet, 27 Jan, 2022.)

The outcry related to the generous timelines for the Aduhelm trial led, in part, to accelerated approval reforms enacted as part of omnibus government funding legislation in December 2022. The Food and Drug Omnibus Reform Act gave the FDA authority to require that confirmatory trials be underway at the time of approval and to specify conditions for such studies, including enrollment targets, the study protocol and milestone dates. (Also see "*Accelerated Approval Reforms Give US FDA More Power And Flexibility – With Some Gaps*" - Pink Sheet, 20 Dec, 2022.)

Where Things Stand Now

ENVISION began enrolling on 2 June 2022, according to ClinicalTrials.gov, which lists more than 200 trial sites, including more than 80 in the US, as currently recruiting.

Biogen said ENVISION has enrolled about two-thirds of the target 1,512 patients.

The primary endpoint – change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) – is measured at week 78, meaning that these assessments would have begun in December 2023 at the earliest.

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It is unclear how many subjects will have had primary endpoint assessments before the trial ends or if Biogen will publish any data from the study.

“We have learned significantly from the research completed as part of the Aduhelm program,” the company said. “We have published a number of publications and will be evaluating opportunities to continue to share learnings from the program.”

Adcomm Members Weigh In

The commercial demise of Aduhelm, and the early termination of its confirmatory trial, provides an “I told you so” moment to critics of the FDA’s initial approval decision, who had questioned the robustness of the efficacy data, safety concerns including amyloid-related imaging abnormalities (ARIA), and the close working relationship between some members of the FDA review team and Biogen.

“The FDA should never have approved aducanumab,” Robert Steinbrook, director of Public Citizen’s Health Research Group, said in a statement.

“Biogen’s announcement that it will abandon the drug underscores the folly of the agency’s efforts to steamroll the product onto the market. It is a telling reminder of the pernicious effects of the inappropriately close collaboration between Biogen and the FDA before and after the company’s marketing application, which compromised the integrity of the approval process. Fortunately, very few patients were prescribed aducanumab.”

"Of greater concern” is *Eisai Co., Ltd.* and Biogen’s Alzheimer’s drug Leqembi (lecanemab-irmb), Steinbrook said. Leqembi received accelerated approval in January 2023 on the basis of amyloid plaque reduction following the regulatory path traveled by aducanumab. However, unlike aducanumab it had a completed confirmatory trial at the time of accelerated approval, and the FDA granted regular approval in July 2023. (Also see "*FDORA Effect? For Accelerated Approval Class Of 2023, Most Confirmatory Trials At Least Underway*" - Pink Sheet, 29 Jan, 2024.)

“Lecanemab received full approval, despite the evidence that the drug’s clinical benefits did not outweigh its substantial health risks,” Steinbrook said. “The prescribing information for lecanemab includes a black box warning for brain swelling and bleeding risks. Although patients with Alzheimer’s disease and their families are desperate for better treatments, neither aducanumab, and now lecanemab, are the answer.”

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aducanumab, they should certainly publicly release information that has been gathered to date through their confirmatory trial." – Johns Hopkins University's Caleb Alexander

Caleb Alexander, an internist and epidemiologist at Johns Hopkins University, was a member of the Peripheral and Central Nervous System Drugs Advisory Committee that rendered an overwhelmingly negative verdict on aducanumab in November 2020 when the drug was being considered for regular approval. (Also see "*Biogen's Aducanumab Falls Hard At Panel Review, Leaving US FDA In A Tight Spot*" - Pink Sheet, 7 Nov, 2020.)

Alexander said he did not think anyone was surprised by Biogen's announcement about the drug's discontinuation. "Perhaps the most surprising thing is that it didn't come sooner, although there remains a lot of enthusiasm for anti-amyloid therapies and it is an incredibly active area of drug development."

"The problem to date is that the therapies – even lecanemab – have incredibly modest efficacy with a non-trivial risk of serious adverse events – and that is a tough combination to navigate, especially when, due to their nature, the adverse events may be difficult to quickly identify and manage," he said.

"While Biogen may wish to turn the page on the case of aducanumab, they should certainly publicly release information that has been gathered to date through their confirmatory trial," Alexander said.

Madhav Thambisetty, senior investigator and chief of the Clinical and Translational Neuroscience Section at the National Institute on Aging, also sat on the aducanumab advisory committee and was critical of then-Office of Neuroscience Director Billy Dunn's characterization of the efficacy data as robustly positive and a home run. (Also see "*What Did US FDA Do Wrong In Its Review Of Aducanumab? AdCom Members Have A List*" - Pink Sheet, 7 Nov, 2020.)

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Institute on Aging's Madhav Thambisetty

In response to questions from the *Pink Sheet*, Thambisetty said termination of ENVISION is disappointing, especially because the trial had sought to enroll 18% of participants from Black/African American and Latinx populations.

"Enhancing diversity and equal access to clinical trials in Alzheimer's disease for patients from under-represented minorities is a critical need and a moral imperative," Thambisetty said. "Although the prior Phase III trials of aducanumab (ENGAGE and EMERGE) enrolled more than 3,200 patients across trial sites in 20 countries, only six Black patients were randomized to the high dose arm of the drug, i.e. the dosage that was eventually approved by the FDA under the accelerated approval pathway."

"The termination of ENVISION is yet another stark reminder that ensuring diversity in, and equitable access to, dementia clinical trials for minority participants remains a distant dream," he said.

Safety Concerns Warrant Publication Of Data

Furthermore, Biogen's decision to discontinue development and commercialization highlights the need to ensure that pre-specified analyses proposed as part of the earlier Phase III trials are completed and fully reported in a timely manner, Thambisetty said. "This is especially important when results might suggest risk of harm from the drug."

Thambisetty said that in the publication of the Phase III trial results, Biogen noted that analyses of MRI changes revealed an increase in a "measure of neurodegeneration" – specifically, expansion of the fluid space, or lateral ventricle volume – in the brains of patients who received the drug.

"It is a glaring omission that no further results have been reported until now on whether these changes were also associated with worsening memory or functional abilities in these patients," Thambisetty said. "It is essential to fully understand whether patients treated by the drug who showed these changes on their brain scans had a worsening of their disease course. The fact that these results remain unreported since accelerated approval of aducanumab in 2021 is a grave concern to me as a practicing physician."

Thambisetty noted that lecanemab and *Eli Lilly and Company*'s donanemab, which is under FDA review, have also showed brain volume loss, or atrophy, in trials, but the related clinical

outcomes have not been reported for those drugs either.

The FDA declined to answer questions about Biogen's announcement on the Aduhelm withdrawal and termination of the ENVISION study. "The FDA is generally unable to discuss existing or potential applications. That is confidential commercial information."