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# A TIMELINE OF THE ADUCANUMAB FDA APPROVAL PROCESS

This memorandum provides a timeline and overview of the events leading up to the U.S. Food and Drug Administration's (FDA) approval of aducanumab, a monthly intravenous infusion medication intended to treat Alzheimer's disease, which afflicts about six million people in the United States. Aducanumab is the first drug approved to treat Alzheimer's disease itself and not just symptoms of dementia. The drug's manufacturer, Biogen, markets it under the brand name Aduhelm. After the FDA approved aducanumab, several medical experts expressed concern over the approval process, the drug's effectiveness, and the fiscal ramifications for Medicare.

## August-September 2015

- Biogen began two Phase 3 trials of aducanumab involving 3,825 participants. Phase 3 trials generally provide data on safety and benefits for the intended patient group.

## March 21, 2019

- Biogen discontinued the Phase 3 trials at fifty percent completion because there was little evidence of benefit. About one-third of the trials' participants were not able to complete the regimen due to the cancellation.

## June 14, 2019

- The FDA recommended to Biogen that the company and the agency further analyze the Phase 3 trial data.

## October 22, 2019

- Biogen announced that, after consulting with the FDA, it was applying for FDA approval of aducanumab. Biogen reanalyzed data from patients in one of the trials who had continued the treatment. The data showed a high dose of aducanumab delayed cognitive decline by 22 percent over 18 months. However, high and low doses in the other Phase 3 trial showed no statistically significant decline.

- Phase 3 trial data also showed some risk to participants. About 40 percent of Phase 3 participants who received a high dose of the drug experienced brain swelling or bleeding. Most of those participants were asymptomatic or experienced headaches, but six percent of high-dose participants left the trial as a result of side effects.

**November 6, 2020**

- Following a joint presentation by FDA staff and Biogen to a body of experts outside the agency, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee (Committee) voted against recommending aducanumab for approval. While the FDA's Office of Neuroscience director stated in a presentation that the "evidence supporting [aducanumab's] approval appears strong," a member of the panel said he or she could not understand "how the FDA could conclude that there is substantial evidence of effectiveness." The FDA is not required to follow the recommendations of its advisory panels.

- The FDA informed the Committee that, even though data on the drug showed a reduction in amyloid beta proteins that are associated with cognitive decline, the agency would not rely on that data for final approval of aducanumab. In clinical trials of other drugs intended to reduce amyloid beta protein levels, those medications failed to reduce cognitive decline in patients. However, scientists have shown that the buildup of these proteins is a common "biomarker" of Alzheimer's disease.

**June 2, 2021**

- The American Geriatrics Society issued a statement calling the FDA's review of aducanumab "premature" due to the "lack of sufficient evidence to support that aducanumab reduces progression of Alzheimer's disease."

**June 7, 2021**

- The FDA approved aducanumab through the agency's accelerated approval process, which the FDA says is designed "to provide earlier access to potentially valuable therapies for patients with serious diseases where there is an unmet need, and where there is an expectation of clinical benefit despite some residual uncertainty regarding that benefit."

- In its approval, the FDA cited data showing the drug successfully reduced amyloid beta proteins in trial participants' brains, though the FDA had previously stated the agency would not use amyloid data as justification for approval. The proteins are believed to kill brain cells, according to FDA officials, and a drug-induced reduction in protein levels would be "reasonably likely" to help patients with Alzheimer's disease. The director of the FDA's Center for Drug Evaluation and Research's Office of New Drugs stated that "[b]ecause amyloid is a hallmark of the disease through its entire course, the expectation is that this drug will

provide benefits across that spectrum." The FDA approved the drug for anyone with Alzheimer's disease, though the clinical trials tested the medication only on patients in the early stage of the disease.

- Since the FDA approved Aduhelm through its accelerate process, the agency will require Biogen to conduct another clinical trial (Phase 4) on the drug's effectiveness. Biogen has until 2030 to complete the trial. During that time, Aduhelm will still be available to patients. The FDA is not required to revoke approval should the new trials fail to prove the drug's effectiveness.

- Biogen announced the list price for Aduhelm will be $56,000 a year. This figure does not include the additional costs of diagnostic testing and brain imaging that would accompany the drug treatment. Since many people are expected to take the drug, and potentially for many years, experts predict the cost to Medicare will be very high.

**June 9, 2021**

- Three members of the FDA's Peripheral Central Nervous System Drugs Advisory Committee resigned over the approval of Aduhelm. One of the committee members who resigned told the FDA, "While I realize that the committee is advisory, the approval of aducanumab appears [to] have been foreordained." He disagreed with the FDA's decision to approve the drug based on the apparent reduction in amyloid proteins rather than "consistent clinical benefit."

**June 25, 2021**

- The U.S. House Committee on Oversight and Reform and the U.S. House Committee on Energy and Commerce announced they would investigate the FDA's approval of Aduhelm.

**July 8, 2021**

- The FDA amended the target group for Aduhelm to only those with mild memory problems. The new recommendation likely shrinks the number of eligible patients from 6.0 million to 1.5 million. Even with the new guidance, doctors can still prescribe Aduhelm to patients with moderate to severe Alzheimer's disease.

**July 9, 2021**

- The FDA asked the U.S. Department of Health and Human Services (HHS) to investigate the lead-up to the approval of Aduhelm. According to a letter, the FDA acting commissioner asked HHS to focus on "interactions" between Biogen and FDA officials during the approval process.

- The U.S. Centers for Medicare and Medicaid Services (CMS) announced the start of a review of coverage standards for Aduhelm. The “national coverage determination” will depend on whether CMS believes Aduhelm is a “reasonable and necessary” treatment for Alzheimer’s disease. If CMS extends national coverage to the drug, Medicare will be required to pay for it, though CMS could also decide against coverage or leave the decision up to individual Medicare contractors. A final decision is expected in early 2022.

**July 14, 2021**

- The Cleveland Clinic and the Mount Sinai Health System, two of the largest medical complexes in the United States, announced they would not administer Aduhelm to their patients. In a statement, the Cleveland Clinic announced, “[b]ased on the current data regarding its safety and efficacy, we have decided not to carry aducanumab at this time.” In response to the two announcements, Biogen stated that it “continues to stand 100 percent behind Aduhelm and the clinical data that supported approval.”