

**Evaluation of Aducanumab for Alzheimer Disease**

A US Food and Drug Administration (FDA) advisory committee met on November 6, 2020, to discuss the effectiveness and safety of aducanumab, a human IgG1 anti-A monoclonal antibody specific for -amyloid oligomers and fibrils involved in the pathogenesis of Alzheimer disease. 1 Given the value of drug discovery for this common and frequently fatal condition, the abandonment of previous monoclonal antibodies targeting -amyloid, and the health, regulatory, and commercial implications that approval of aducanumab may have, there has been a lot of concern in the production and regulatory analysis of aducanumab.

Two almost identically planned phase 3, double-blind, placebo-controlled randomized clinical trials (RCTs) of high- and low-dose aducanumab were intended to provide primary efficacy proof for aducanumab. The experiments were launched after a phase 1b safety and dose-finding analysis showed that the drug was safe. A proposed interim review exceeded prespecified futility requirements approximately halfway through the phase 3 tests, and the trials were terminated in March 2019.

Considerations of the Safety of Aducanumab. Ultimately, any determination of readiness for market must also consider a drug’s overall benefit-risk balance. The pivotal trials of aducanumab were carefully designed to minimize the potential harms from amyloid-related imaging abnormalities (ARIA). The FDA’s statistical review suggested evidence of potentially greater falls among individuals treated with high dose aducanumab, which as with many of the other symptoms of ARIA, are especially complicated clinically because of their potential overlap with underlying disease progression. While briefing materials suggested risk of ARIA can be mitigated by monitoring via imaging and dosing management,[1](https://jamanetwork.com/journals/jama/fullarticle/2778191#jvp210039r1)(p118) it is unclear how consistently and comprehensively this could be performed in clinical practice.

Looking Forward. As compelling public testimony during the FDA’s advisory committee meeting made clear, Alzheimer disease poses a major burden on millions of people and their families, and there is an overwhelming demand for safe and effective new treatments. In light of this, the sponsor of aducanumab deserves recognition for a development program that included the design and conduct of 2 well-controlled, randomized, potentially pivotal trials that should be published in the peer-reviewed literature. However, considering that these efficacy trials were stopped for futility, there is no reason to favor the trial with the positive signal in 1 of 2 treatment groups over the trial with the negative outcome in both treatment groups, and there is no persuasive evidence to support approval of aducanumab at this time.