

Prescribing Aducanumab in the Face of Meager Efficacy and Real Risks

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The US Food and Drug Administration (FDA) approved aducanumab on June 7, 2021, using an accelerated approval mechanism, based on evidence that aducanumab reduced brain β -amyloid ($A\beta$) peptide.¹ The FDA press release stated that the effect on the surrogate end point “is reasonably likely to predict a clinical benefit to patients...” at some point in the future. As clinical neurologists, we should understand the evidence for this approval and whether this justifies prescribing this medication.

The saga of aducanumab’s journey is convoluted.²⁻⁴ Two phase III studies were initiated in August 2015. They were constructed and executed in an identical manner. In March 2017, the sponsor revised the protocol to allow all participants assigned to the high-dose arm to receive 10 mg/kg. The sponsor conducted a preplanned futility analysis, which led to termination of both studies in March 2019. Three months later, in a surprise press release, the company stated that subsequent analyses with another 3 months of data led them to conclude that there was a sufficient clinical efficacy signal to pursue a new drug application. In follow-up post hoc analyses conducted by the sponsor, one trial (EMERGE or 302) showed statistically significant effects in the high-dose group on several clinical outcome measures; the other study (ENGAGE or 301) showed no benefits.^{2,3,5,6}

We as neurologists need a strategy to advise our patients in this unusual situation where the drug was approved without evidence of consistent clinical benefits. Based on the prescribing information,⁷ the sponsor shows data from only the positive trial and fails to provide the negative trial’s cognitive and functional outcomes. Neurologists should have access to all of the relevant data in these clinical trials; however, they will have to go elsewhere to find it.^{2,3,5,6} Even choosing to focus on the one trial with the favorable outcome in the high-dose group and ignoring the negative trial, the clinical benefits are decidedly small. The drug never produced substantial improvements. The clinical benefit amounted to about 3 months’ worth of delay in decline over a year (annualized Clinical Dementia Rating Scale sum of boxes 0.26 rating points reduction in decline with high-dose aducanumab in the setting of 1.17 points annualized decline in the placebo group). Because our field has not established what constitutes clinical meaningfulness, this benefit could be perceived as having value by some patients and their families. However, this range of delay and progression is well within the untreated variability of groups of patients with mild cognitive impairment (MCI) or dementia due to Alzheimer disease (AD).⁸ The negative trial, which cannot be brushed under the rug, raises questions about the reliability and reproducibility of any such claimed benefits. The sponsor’s presentation at the FDA hearing on November 6, 2020, proposed several post hoc explanations to account for the negative results; however, subjecting the positive trial to post hoc analyses introduced substantial bias and raised serious questions about dose effects and effects on subgroups, as pointed out by the FDA’s statistician.⁹ Combining the results from the 2 trials found no statistically significant clinical benefit for high-dose aducanumab.⁶ As part of this accelerated approval, the FDA requires Biogen to conduct another prospective clinical trial over the next 9 years to determine whether this drug produces clinical benefit.

The FDA focused on an alternative outcome measure to justify accelerated approval of aducanumab. Rather than relying on a failed clinical end point, the FDA pointed out that the drug lowered brain $A\beta$, using this biomarker as a surrogate end point. A surrogate outcome measure is reasonable if it predicts clinical benefit. However, no data from either trial or any other source indicate that lowering

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Page 517

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Page 543

From the Department of Neurology (D.S.K.), Mayo Clinic, Rochester, MN; and Department of Neurology (J.S.P.), Washington University School of Medicine, St. Louis, MO. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

brain A β provides clinical benefit to individuals with AD or when such benefit would occur, if it does. In fact, over the 18-month clinical trials with aducanumab, the FDA explicitly acknowledged no consistent clinical benefit occurred. Several studies demonstrated that lowering A β in the brain by inhibition of β - or γ -secretases made patients cognitively worse.¹⁰ Furthermore, the change in cognitive performance with aducanumab in the two phase 3 trials did not correlate with the reductions in brain A β , as analyzed the FDA's own statistician. In the cardiovascular world, there are many examples of claims based on "sure-thing" biomarker changes that failed to predict eventual clinical benefits.¹¹ Nevertheless, without evidence, lowering A β can only hope to be disease-modifying.

Neurologists must also consider the risks, especially in light of the low potential for benefit. Patients with an excess of cortical microbleeds and those on most anticoagulants should not receive aducanumab. Infusion of the recommended monthly doses of aducanumab comes with safety concerns, especially in the form of amyloid-related imaging abnormalities—edema or hemorrhage. With a rate of 40%, and higher in *APOE* $\epsilon 4$ carriers,⁵ safety monitoring must be integrated into management. Patients must be able to undergo MRI scans and *APOE* genotyping for safety reasons. Skilled neuroradiology is also a necessity.

With the above caveats, neurologists then need to determine which patients may be appropriate for aducanumab. With the above caveats, neurologists then need to determine which patients may be appropriate for aducanumab. The original prescribing information⁷ was revised by the sponsor with approval by the FDA on July 8, 2021 from an apparently very broad indication of "Alzheimer's disease" to a much smaller group of "patients with mild cognitive impairment and mild dementia... the population in which treatment was initiated in clinical trials."¹² The sponsor acknowledged that there is no evidence for treating patients with aducanumab who are either milder than mild cognitive impairment or more impaired than mild dementia, nor is there safety information in those groups. The revised approved indication guides neurologists to avoid prescribing aducanumab to more severely affected patients. There is no evidence for treating patients whose cognitive disorder is jointly attributed to AD and another etiology. Because aducanumab's target is elevated brain A β , neurologists must have the available technology to verify that a candidate for aducanumab has elevated brain A β . Clinical diagnoses alone are insufficient to verify elevated A β .

Aducanumab's approval raises expectations for treatments for patients with symptomatic AD. On the one hand, neurologists want to offer hope. Yet, aducanumab's benefits are meager, if even present,¹³ and there are nontrivial risks of side effects. These issues place a substantial burden on neurologists to take the time and effort to counsel patients and families on expectations for aducanumab treatment. Neurologists will have to manage therapeutic perceptions by presenting patients and families with unbiased information about the benefits and risks. This is even more challenging as no peer-reviewed publication is available.

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Disclosure

D.S. Knopman serves on a Data Safety Monitoring Board for the DIAN study; serves on a Data Safety Monitoring Board for a tau therapeutic for Biogen but receives no personal compensation; is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California; has served as a consultant for Roche, Samus Therapeutics, Third Rock, and Alzeca Biosciences but receives no personal compensation; and receives funding from the NIH. J.S. Perlmutter has received research funding from the NIH (NS075321, NS103957, NS107281, NS092865, U10NS077384, NS097437, U54NS116025, U19NS110456, AG050263, AG-64937, NS097799, NS075527, ES029524, NS109487, R61 AT010753 [NCATS, NINDS, NIA], RO1NS118146, R01AG065214), Department of Defense (DOD W81XWH-217-1-0393), Michael J Fox Foundation, Barnes-Jewish Hospital Foundation (Elliot Stein Family Fund and Parkinson disease research fund), American Parkinson Disease Association (APDA) Advanced Research Center at Washington University, Greater St. Louis Chapter of the APDA, Paula and Rodger Riney Fund, Jo Oertli Fund, Huntington Disease Society of America, Murphy Fund, and CHDI; has received honoraria from CHDI, Huntington Disease Study Group, Parkinson Study Group, Beth Israel Hospital (Harvard group), University of Pennsylvania, and Stanford University; is co-director for the Dystonia Coalition, which has received the majority of its support through the NIH (grants NS116025, NS065701 from the National Institutes of Neurological Disorders and Stroke and TR 001456 from the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences); serves as Director of Medical and Scientific Advisory Committee of the Dystonia Medical Research Foundation, Chair of the Scientific Advisory Committee of the Parkinson Study Group, Chair of the Standards Committee of the Huntington Study Group, member of the Scientific Advisory Board of the APDA, Chair of the Scientific and Publication Committee for ENROLL-HD, and member of the Education Committee of the Huntington Study Group; and has provided medical legal consultation to Wood, Cooper and Peterson, LLC, and Simmons and Simmons LLP. D.S. Knopman and J.S. Perlmutter were members of the Peripheral and Central Nervous System Advisory Committee of the Food and Drug Administration but resigned on June 7 and 9, respectively. J.S. Perlmutter participated in the Advisory Committee meeting of November 6, 2020, but D.S. Knopman had been recused from that meeting because he was a site investigator in the aducanumab ENGAGE study. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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David S. Knopman, MD	Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content
Joel S. Perlmutter, MD	Washington University School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content

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