

Memorandum

Date: June 7, 2021

To: Nathan Fountain, M.D., Peripheral and Central Nervous System Drugs Advisory Committee Chairperson

From: Billy Dunn, M.D.

Subject: Accelerated Approval of Aducanumab NDA for Alzheimer's disease

The U.S. Food and Drug Administration (FDA) would like to extend our gratitude for the committee's participation in the Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee in November 2020.

The candid discussion and feedback at this meeting provided FDA with important insight into the unique challenges faced by Alzheimer's disease patients, their families and caregivers, and health care professionals. This input was invaluable and supports the Agency's mission to protect the health of the American public.

Today, we granted an accelerated approval for aducanumab to treat patients with Alzheimer's disease. As you know, this approval represents the first new treatment for Alzheimer's disease since 2003 and is the first approved therapy targeting a defining pathophysiological feature of Alzheimer's disease, amyloid beta. I am writing to provide you with the rationale for our regulatory decision.

On November 6, 2020, BLA 761178 was brought to the PCNS committee to discuss aducanumab for the treatment of Alzheimer's disease. The committee was asked to discuss the evidence of effectiveness to support approval of aducanumab based primarily upon the evidence of clinical benefit from Study 302, with support from the evidence of clinical benefit in Study 103, and considering the analyses that evaluated potential explanations for the discordant results of Study 302 and Study 301 on the primary endpoint of the two studies. The committee was also presented with the pharmacodynamic data from the program, including the effects on markers of amyloid plaque, tau, and neurodegeneration.

After a robust and informative discussion, the committee voted, with 10 members against and 1 member uncertain, that it was not reasonable to consider the evidence of clinical benefit from Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease, with the vote largely based upon the conflicting results of Study 302 and Study 301.

Following the advisory committee meeting, further discussion within FDA considered the uncertainty introduced by the conflicting results of Study 302 and Study 301 and the committee's discussion of that uncertainty. Our discussions raised further consideration of the accelerated approval pathway; a topic discussed earlier in the development program but not directly discussed during the advisory committee meeting given the focus at that meeting on the evidence of clinical benefit. As you may be aware, the accelerated approval pathway is for drugs to treat serious diseases that are expected to provide a meaningful advantage over available therapy, but where there is residual uncertainty regarding the drug's ultimate clinical benefit. To be approved

under this pathway, there must be substantial evidence of the drug's effectiveness on a surrogate endpoint—usually an endpoint that reflects the underlying disease pathology (accelerated approval can also use an intermediate clinical endpoint). An effect on this surrogate endpoint must be shown to be reasonably likely to predict clinical benefit. We concluded that these requirements were met for aducanumab, with substantial evidence that the drug reduces amyloid beta plaque, and that this reduction is reasonably likely to predict clinical benefit. For drugs approved using the accelerated approval pathway, further study is required to verify anticipated clinical benefits.

We recognize that there has been tremendous public interest in aducanumab and differing viewpoints on the extensive and complicated data supporting the application for aducanumab. Our discussions leading up to the decision to grant an accelerated approval for aducanumab considered a wide range of views, both external and internal to FDA. We appreciate the comments from the advisory committee members and can assure you that we listened carefully and viewed the meeting proceedings as an important source of input as we discussed the appropriate action. Ultimately, the decision on whether aducanumab will be used for treatment will be made by patients, their families and caregivers, and health care professionals. The public can be confident that the Agency used a rigorous, science-based approach to assess this therapy, considering all of the evidence in the application, and also the tremendous unmet medical need for the many patients living with this disease.

Sincerely,

Billy Dunn, M.D., Director, Office of Neuroscience, CDER