From: Patrizia Cavazzoni, MD, Director, Center for Drug Evaluation and Research (CDER)/FDA

BLA # 761178
Applicant: Biogen Inc.
Proprietary Name: Aduhelm
Established or Proper Name: Aducanumab-avwa

This memo documents my concurrence with the decision of the Office of Neuroscience (ON) in the Office of New Drugs (OND) to approve BLA 761178 for Aduhelm (aducanumab-avwa) injection for the treatment of Alzheimer's disease.

Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. It is estimated that 6.2 million Americans age 65 and older are currently living with AD dementia, and AD is the sixth leading cause of death in the United States. There is an urgent and unmet medical need for effective treatments for AD, and a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of AD.

Biogen, Inc. (Biogen) submitted this BLA to FDA on July 7, 2020. As part of its BLA, Biogen submitted, among other things, the results of a Phase 2 dose-range-finding trial (Study 103) and two Phase 3 clinical trials (Studies 301 and 302). This BLA, including the data and information submitted to FDA by Biogen, has been the subject of intense public interest, due in part to the unmet medical need and the population potentially eligible for treatment. This BLA has also been the subject of rigorous scientific discussion and deliberation within FDA, including within the review team for this application.

The review team for this BLA, with the exception of one office, is aligned that the application should be approved. In its decisional Summary Review memorandum, ON summarized the review team's review of the relevant sections of the application and documented ON's determination that the BLA has met the requirements for accelerated approval, including ON's conclusion that Biogen has provided substantial evidence of effectiveness on the surrogate endpoint of reduction in brain amyloid plaque and that the surrogate endpoint is reasonably likely to predict clinical benefit. (*See ON Summary Memorandum, Drs. Buracchio, Yasuda, Bastings, and Dunn.*) In its integrated clinical pharmacology review, the Office of Clinical Pharmacology (OCP) within the Office of Translational Sciences (OTS) documented, among other things, its pharmacometrics analyses that supported effectiveness of aducanumab; OCP recommended approval of the application. (*See OCP Integrated Clinical Pharmacology Review, Drs. Wang and Mehta.*) The other review disciplines also documented their respective reviews and recommendations that the application be approved.

In its biostatistics review, the Office of Biostatistics (OB) within OTS provided documentation for its recommendation that substantial evidence of effectiveness had not been provided in the application. OB's recommendation was based, in part, on inconsistencies in the data. (*See Biostatistics Review, Dr. Massie, concurrence from Drs. Jin, Wang, Hung.*) OB does not support approval of the application. For additional information on OB's analyses and recommendations, see OB's biostatistics review.

Having reviewed and considered the relevant information, and consistent with the analysis set forth in the ON decisional Summary Review memorandum and the concurrence memo from Dr. Peter Stein,

Director, OND, I disagree with OB's recommendation that the application should not be approved. I concur with ON that the BLA has met the requirements for accelerated approval, including with ON's conclusion that Biogen has provided substantial evidence of effectiveness on the surrogate endpoint of reduction in brain amyloid plaque and that the surrogate endpoint is reasonably likely to predict clinical benefit, for the reasons set forth in ON's summary memorandum. (*See, e.g., ON Summary Memorandum (section 6 – clinical/statistical – efficacy), Drs. Buracchio, Yasuda, Bastings, and Dunn; Concurrence Memorandum, Dr. Stein.*) I also concur with the analysis from Dr. Peter Stein set forth in his concurrence memo, which outlines his further support for the approval of this BLA under the accelerated approval pathway. (*See Concurrence Memorandum, Dr. Stein.*) Based on the foregoing, I concur with the decision of ON and the rest of the review team to approve BLA 761178 for Aduhelm (aducanumab-avwa) injection.

Patrizia A. Cavazzoni -S

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