MEMORANDUM FOR CYNTHIA CARLSSON, M.D.

DATE: May 24, 2024

FROM: Robert M. Califf, M.D.
Commissioner
Food and Drug Administration (FDA)

Signed on 05.24.24

SUBJECT: Waiver to allow participation in a Food and Drug Administration advisory committee meeting, under Title 18, Section 208(b)(l) of the United States Code

The criminal conflict of interest statute, 18 U.S.C. § 208(a), prohibits a federal executive branch employee from participating personally and substantially in any particular matter that will have a direct and predictable effect on the employee's financial interests or on the financial interests of certain other persons whose financial interests are imputed to the employee. Under 18 U.S.C. § 208(b)(l), however, the employee's appointing authority, or his or her delegate, may permit an employee to participate in a matter in which he or she has an otherwise disqualifying financial interest, if a waiver is issued based on a determination that the financial interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from the employee. As discussed below, I have decided to issue a conflict of interest waiver to permit you to participate in a certain particular matter as described below.[1]

Nature of the Particular Matter

You have been invited to serve as a temporary voting member of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) meeting on June 10, 2024, to evaluate and discuss biologics license application (BLA) 761248, for donanemab solution for intravenous infusion, submitted by Eli Lilly and Company, for the treatment of early symptomatic Alzheimer's disease (AD). The topic of this advisory committee meeting is a particular matter involving specific parties.

Employee's Position, Duties and Role

[1] You are a federal government employee with the Department of Veteran Affairs. Therefore, SGE waiver authority at 18 U.S.C. § 208(b)(3) is not applicable. This waiver is being issued pursuant to 18 U.S.C. § 208(b)(l).

You are a federal government employee with the Department of Veteran Affairs. You are also employed by the University of Wisconsin School of Medicine and Public Health where you serve as Director of the Wisconsin Alzheimer's Institute, Professor of Medicine (with Tenure) in the Department of Medicine of the Division of Geriatrics and Gerontology, and Clinical Core Leader of the Wisconsin Alzheimer's Disease Research Center.

Nature of Disqualifying Financial Interest

The disqualifying financial interests at issue arise from the imputed interests of your employer, University of Wisconsin, and its participation in three studies evaluating the safety and efficacy of other potential or alternative treatments for early Alzheimer's disease that may, if subsequently approved by FDA, compete with the Eli Lily biologic to be discussed during the June 10 PCNS meeting. The first study is sponsored by Eisai, Inc. and has some overlap with the topic before the advisory committee. The second study is sponsored by Cognition Therapeutics and involves the same patient population as the indication coming before the committee. The third study is sponsored by Bristol Myer Squibb and also involves the same patient population as the indication coming before the committee.

Relevant Factors Considered under 18 U.S.C. § 208(b)(1)

In determining whether a waiver may be issued to allow your official participation in the particular matter described above, I have considered each of the factors described in 5 C.F.R. § 2640.301(b), including the nature of the disqualifying financial interest as described below. I have carefully considered the following factors.

Type, Nature and Magnitude of the Financial Interest:

Your employer, University of Wisconsin, is participating in a multi-site study titled *AHEAD 3-45 Study: A Placebo-Controlled, Double-Blind, Parallel-Treatment Arm, 216 Week Study to Evaluate Efficacy and Safety of Treatment With BAN2401 in Subjects With Preclinical Alzheimer's Disease and Elevated Amyloid (A45 Trial) and in Subjects With Early Preclinical Alzheimer's Disease and Intermediate Amyloid (A3 Trial)* NCT04468659, sponsored by Eisai, Inc. This study combines two studies, the A3 Study and A45 study. The study began on March 1, 2020, with an anticipated end date of (b) (4). University of Wisconsin anticipates receiving a maximum future potential payment of between $1,000,000 and $2,000,000. You serve as Site Principal Investigator. Payments from Eisai, Inc. do not include salary support and you will not receive any personal remuneration for your role in the study.

Secondly, your employer, University of Wisconsin, is participating in a study titled *Synaptic Therapy Alzheimer's Research Trial (START): A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial to Evaluate the Safety and Efficacy of CT1812 in Early Alzheimer's Disease Over 18 Months* NCT05531656, sponsored by Cognition Therapeutics.

The overall study began on June 28, 2023 with an anticipated end date of April 2027, however, the study has not started at the University of Wisconsin yet. If all study requirements are met, the potential payment to your employer will be between $1,000,000 to $2,000,000, including 1% salary support. You will not receive any personal remuneration for the study.

Thirdly, your employer, University of Wisconsin, is negotiating to participate in a study titled *A Randomized, Double-blind, Placebo-controlled, Global, Study to Evaluate the Efficacy, Safety, and Tolerability of BMS-986446, an Anti-MTBR Tau Monoclonal Antibody, in Participants With Early Alzheimer's Disease (TargetTau-1)* NCT06268886, sponsored by Bristol Myers Squibb. The nationwide start date was March 20, 2024, with an anticipated end date of November 16, 2027, however, the study has not started at the University of Wisconsin yet. Payment to your employer is under negotiation but is likely to include 1- 5% in salary support. You will not receive any personal remuneration for the study.

Because your employer's interests are imputed to you under 18 U.S.C. § 208, the waived financial interest for each of these three studies is the University of Wisconsin's contractual interest in receiving the money they are owed under the contract for the University's participation in each study. Specifically, the University's financial interest is limited to its interest in the corporate sponsors' ability or willingness to perform under the respective contracts governing each study. Eisai, Inc. is the U.S. subsidiary of a multinational pharmaceutical firm with a large number of drugs in the market. For this reason, we have determined there is a low risk that the outcome of this meeting will affect Eisai, Inc.'s ability or willingness to perform on its contractual obligations. Similarly, Bristol Meyers Squibb is a large multinational pharmaceutical firm manufacturing, marketing, and/or distributing over 30 drugs within the United States and over $45 billion in revenue in 2023. Accordingly, the outcome of this meeting has a low risk of affecting Bristol Meyers Squibb's ability or willingness to meet its contractual obligations to your employer due to its broad product lines and sources of revenue. Cognition Therapeutics is a clinical-stage neuroscience firm with four active studies regarding its CT1812 product for different conditions (Lewy Body dementia, Alzheimer's Disease, and Dry Age-related Macular Degeneration). Although CT1812 appears to be its only product in development, its work with CT1812 involving other medical conditions indicates there is limited risk the outcome of the June 10 PCNS meeting will affect Cognition Therapeutics' ability or willingness to meet its contractual obligations. Nevertheless, because the confidential nature of study contracts precludes our analysis of the specific financial details of the contracts supporting these studies, we are issuing this waiver out of an abundance of caution and in the interest of disclosure.

Although your employer receives or may receive salary support from the funding for two of the studies, you have a base salary that is covered through a variety of grants and institutional mechanisms and your job performance is evaluated on a variety of elements related to the quality of the work you perform. Additionally, in January, the University of Wisconsin announced that it has been awarded $150 million from the National Institutes of Health for the study of

Alzheimer's Disease, unrelated to the studies discussed here. Therefore, even if the studies above were to shut down or close, it would not impact the payment of your salary. As such, we do not find that you have any personal financial interest in these studies.

The nature and importance of your participation, and the need for your services on the matter.

The advisory committee meeting that you will be participating in is focused on discussion of biologics license application (BLA) 761248, for donanemab solution for intravenous infusion, submitted by Eli Lilly and Company, for the treatment of early symptomatic Alzheimer's disease (AD).

AD is a fatal illness that causes progressive decline in memory and other aspects of cognition. Dementia due to AD is the most common form of dementia, accounting for 60 to 80 percent of all cases. AD involves parts of the brain that control thought, memory, and language and can seriously affect a person's ability to carry out daily activities. AD is the most common cause of dementia among older adults, one of the top 10 leading causes of death in the United States, and the 5th leading cause of death among adults aged 65 years or older. The number of people living with the disease doubles every 5 years beyond age 65. In 2010, the costs of treating AD were projected to fall between $159 and $215 billion. By 2040, these costs are projected to jump to between $379 and more than $500 billion annually. There's no cure for AD, but certain medications and therapies can help manage symptoms temporarily. There are two classes of FDA-approved drug treatments for AD: (1) drugs that change disease progression and (2) drugs that treat cognitive symptoms (memory and thinking). Instead of only treating the symptoms, donanemab targets the fundamental pathophysiology of AD. It is an investigational antibody designed to clear amyloid plaque from the brain. As an immunoglobulin G1 monoclonal antibody directed against insoluble, modified, N-terminal truncated form of β-amyloid present only in brain amyloid plaques, donanemab binds to N-terminal truncated form of β-amyloid and aids plaque removal through microglial-mediated phagocytosis.

You are Director at Wisconsin Alzheimer's Institute and Professor of Medicine (with Tenure) in the Department of Medicine of the Division of Geriatrics and Gerontology, and Clinical Core Leader at Wisconsin Alzheimer's Disease Research Center at University of Wisconsin School of Medicine and Public Health. You are also Staff Physician at Veteran's Affairs (VA) Memory Assessment Clinic at William S. Middleton Memorial Veterans Hospital. You are a member of the National Institutes of Health/National Institute on Aging (NIH/NIA) Alzheimer's Disease Centers Clinical Core Steering Committee and Clinical Task Force and chair several NIH/NIA research review committees.

You earned your medical degree from University of Michigan Medical School and completed your residency at the University of Wisconsin Hospital and Clinics/William S. Middleton Memorial Veterans Hospital where you further completed fellowships in Geriatric Medicine and

Older Women's Health. You then completed your Masters in Population Health Sciences at the University of Wisconsin Medical School. You are board certified in Internal Medicine and Geriatric Medicine. Your research focuses on the effects of vascular risk factors and their treatments on cognition and biomarkers for AD in persons at risk for dementia. You are extensively published in your field and have served in numerous committees, taskforces, and data safety monitoring boards.

The advisory committee will discuss the efficacy and safety of donanemab solution for intravenous infusion for the treatment of early symptomatic AD. The meeting discusses the data from a Phase 3 study of donanemab in AD, and focuses on issues with study design, safety, and the overall benefit-risk assessment. A productive discussion of the issues would depend upon having strong experts in AD and other neurodegenerative diseases, and the perspectives of multiple physicians who treat these diseases will be critical for the thorough evaluation of the data related to the use of donanemab in the treatment of early symptomatic AD. The Agency conducted an extensive search for potential candidates with your qualifications and expertise in the clinical care of people with AD, the conduct of clinical trials in AD, and the evaluation and interpretation of scientific research and data from clinical trials. It is challenging to identify experts with these qualifications who do not have conflicts of interest as pharmaceutical companies also seek the same qualifications for consultants on their drug development programs. The Agency contacted many experts in AD and other neurodegenerative diseases who could not be considered due to direct financial relationships. Having multiple physicians on the advisory committee with expertise in AD will inform the discussion on the condition of interest, the current treatment armamentarium, and how results of the clinical studies may translate to the clinical experience. Inclusion of multiple physicians with expertise in AD and other neurodegenerative diseases will increase the likelihood that these issues are fully explored during the discussion.

You have expertise in the clinical care of people with AD, the conduct of clinical trials, and the evaluation and interpretation of data from clinical trials demonstrating your knowledge on the current state of the science in AD research. The other AD experts who are slated to attend are either neurologists or neuropathologists have either no or very limited experience in the conduct of clinical trials. You also bring a unique perspective as a geriatrician who has expertise in the clinical care of aging patients and, in particular, the challenges of the implementation of new treatment strategies for AD in the clinical care setting.

Sensitivity of the matter.

This topic is considered to be sensitive, as the FDA Division with responsibility for the review of this product expects the matter coming before the committee to garner significant public interest, (non-trade) press interest, significant congressional interest, or considered highly controversial.

U.S. FOOD & DRUG ADMINISTRATION

Determination

Based on my evaluation of the factors in 5 C.F.R. 2640.301(b), I have determined that your financial interests are not so substantial as to be deemed likely to affect the integrity of the services that the federal Government may expect from you. For the specific reasons detailed above, I am granting you a waiver under 18 U.S.C. 208(b)(1) to permit you to participate in the advisory committee meeting described herein. This waiver is based on your full disclosure of your financial interests and consideration of the nature of the particular matter that you will be involved in as an FDA employee. This waiver only applies to the conflicts of interest described herein and for the June 10, 2024, meeting of the PCNS.

The Office of Government Ethics will be notified concerning the issuance of this waiver, as specified in 5 C.F.R. § 2640.303, and the HHS Designated Agency Ethics Official has reviewed this document, as required by the Delegation of Authority by the Secretary to the Heads of Operating and Staff Divisions to Grant Conflict of Interest Waivers under 18 U.S.C. §§ 203(d), 205(e), and 208(b), dated January 16, 2009, and has concluded that this waiver adequately addresses the requirements for such waivers as set forth in OGE regulations at 5 C.F.R. § 2640.301.

Please sign below indicating your agreement to the terms of this waiver and return the signed original to Rachel Bressler, Director (acting), Advisory Committee Oversight and Management, Office of the Chief Scientist, FDA, and retain a copy for your own records.

CYNTHIA CARLSSON Digitally signed by CYNTHIA CARLSSON Date: 2024.05.24 10:11:29 -05'00'

Cynthia Carlsson, M.D. Date

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