Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: January 23, 2023

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

FROM: Byron Marshall
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Meeting Voting Member: **Robert C. Alexander, M.D**.

Committee: Peripheral and Central Nervous System Drugs Advisory Committee

Meeting date: March 22, 2023

Description of the Particular Matter to Which the Waiver Applies:

Robert C. Alexander, M.D., is a standing voting member of the Peripheral and Central Nervous System Drugs Advisory Committee. The committee's function is to review and evaluate data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of neurologic diseases and make appropriate recommendations to the Commissioner of Food and Drugs.

On March 22nd, the committee will discuss new drug application (NDA) 215887, for tofersen (BIIB067) intrathecal injection, submitted by Biogen Inc., for the treatment of amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene. The topic of this meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Alexander reported a financial interest in stocks in (b) (6), a competing/affected firm. The value of his stock holdings in (b) (6) is between $100,000 and $150,000.

Under a regulatory exemption (5 CFR § 2640.202(b)(2)) issued by the Office of Government Ethics, an employee may participate in any particular matter involving specific parties in which the disqualifying financial interest arises from the ownership by the employee, his spouse, or minor children of securities issued by one or more entities that are not parties to the matter but that are

affected by the matter if the aggregate market value of the holdings of the employee, his spouse and minor children in the securities of all the affected entities does not exceed $25,000. Because Dr. Alexander's financial interest in stocks in a competing/affected entity exceed that amount, he has a disqualifying financial interest.

Basis for Granting the Waiver:

Dr. Robert C. Alexander has unique qualifications and specialized expertise needed for this particular matter.

Dr. Robert C. Alexander is a psychiatrist and the Chief Scientific Officer of the Alzheimer's Prevention Initiative, led by Banner Alzheimer's Institute. Dr. Alexander is also the Research Professor at the Department of Psychiatry at the University of Arizona College of Medicine.

Dr. Alexander received his undergraduate and medical degrees from the University of Chicago. He completed an internal medicine internship at the New England Deaconess Hospital and a residency in Adult Psychiatry at McLean Hospital/Harvard Medical School. Following residency, Dr. Alexander was a fellow in the Neuropsychiatry Branch of the National Institute of Mental Health (NIMH) and then at Columbia University (in Medical Genetics). He has been in medical practice for more than 20 years. In recent years, he has focused on neurodegeneration in both Alzheimer's and Parkinson's disease. He also has extensive experience in both early-and late-stage drug development and medical governance. Dr. Alexander was the medical leader of the AstraZeneca team that developed the beta-secretase inhibitor that delivered the phase 1 package and started phase 2/3 in only 21 months – the fastest development time in the class. Since then, he guided the early clinical development of a number of treatments targeted toward Alzheimer's disease and other neurodegenerative disorders, including small molecules, antibodies, antisense oligomers and gene therapies. Dr. Alexander is uniquely qualified by having the specialized knowledge and experiences in neurodegenerative disorders.

The committee will discuss tofersen (BIIB067) for the treatment of ALS associated with a mutation in the SOD1 gene. Currently, there is no cure for ALS and no effective treatment to halt or reverse the progression of the disease. The issue for the committee is to consider the strength of the evidence supporting the application for approval of tofersen for the treatment of ALS associated with a mutation in the SOD1 gene. Because of Dr. Alexander's knowledge and his experiences and research in Alzheimer's Disease and other neurodegenerative disorders, his participation in the committee's discussion is essential to providing expert advice and recommendations to the Agency.

The particular matter is considered sensitive.

The FDA Division responsible for the review of this product does expect the matter coming before the committee to garner public interest. It is considered a highly controversial issue with expected interest coming from non-trade press, congress, and the public.

Dr. Robert C. Alexander's expertise in this particular matter is necessary in the interest of public health.

ALS, commonly known as Lou Gehrig's disease, is a rare, rapidly progressive, and fatal neuromuscular disease that primarily affects the nerve cells (neurons) responsible for controlling voluntary muscle movement like chewing, walking, and talking. ALS can be categorized as familial or sporadic disease which accounts for the majority of patients, depending on whether the patient has a family history of the disease or not. Familial ALS accounts for approximately 10% of cases, and among these, *C9ORF72* and *SOD1* are the two most common causative genes. *SOD1* encodes for superoxide dismutase, a mutated protein which has been associated with the degeneration of motor neurons. SOD1-ALS is the second most common form of familial ALS. There are approximately 16,000 people living with ALS in the United States, with an estimated prevalence of 5 patients per 100,000 population, and with 5,000 new cases diagnosed each year. Most cases of ALS are sporadic; 5-10% of ALS cases are familial and associated with approximately 50 different genes. Familial ALS generally has an earlier onset (by about 10 years) than sporadic ALS. Most patients with ALS die from respiratory failure, usually within 3 to 5 years from when the symptoms first appear. Approximately 10% of people with ALS survive for 10 or more years. There are no effective treatments to halt or reverse the progression of the disease. The product at issue for the March 22nd meeting is tofersen (BIIB067) intrathecal injection for the treatment of ALS associated with a mutation in the SOD1 gene.

In the interest of public health, it is important that the Agency has available the unique expertise that Dr. Alexander will provide for the discussion of the particular matter before the committee.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Alexander's expertise in this matter.

Dr. Alexander is highly respected internationally for his deep insights and broad perspectives, and he has been highly valued as a member of the Peripheral and Central Nervous System Drugs Advisory Committee. Few neuropsychiatrists possess his broad perspectives, clinical acumen, public health focus, and wealth of experience in clinical trial design and analysis, and few individuals would be able to disentangle the difficult issues raised by this NDA. For these reasons, the expertise of Dr. Alexander will be invaluable to a robust and productive discussion on the application coming before the committee. Further mitigating the risk is the fact that (b) (6) has hundreds of pharmaceutical products in development and on the market, meaning that the potential for this particular matter to substantially affect the stock price is reduced.

Accordingly, I recommend that you grant Dr. Robert C. Alexander, a standing voting member of the Peripheral and Central Nervous System Drugs Advisory Committee, a waiver from the conflict-of-interest prohibitions of 18 U.S.C. § 208(a).

Certification:

✓ The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee's or Special Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

_____

_____

_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S Date: 2023.02.16 12:35:29 -05'00'

February 16, 2023

Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

Date