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

DATE: April 4, 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: **David N. Assis, M.D.**

Committee: Gastrointestinal Drugs Advisory Committee

Meeting date: May 19, 2023

Description of the Particular Matter to Which the Waiver Applies:

Dr. David N. Assis is a standing voting member of the Gastrointestinal Drugs Advisory Committee (GIDAC). The committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of gastrointestinal diseases and make appropriate recommendations to the Commissioner of Food and Drugs.

On May 19, 2023, the committee will discuss new drug application 212833, obeticholic acid 25 mg oral tablets, submitted by Intercept Pharmaceuticals, Inc., for the treatment of pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis (NASH). The topic of this meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Assis reported that his employer, Yale School of Medicine, was awarded a study titled *A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis* (REGENERATE trial, NCT02548351), sponsored by Intercept Pharmaceuticals. The study enrollment began on April 28, 2016, and enrollment was closed on June 17, 2019. The study is in long-term follow up phase and is estimated to end in [redacted] (b) (4). Dr. Assis is not involved in the study.

The Yale School of Medicine to date has received between [redacted] (b) (4) and anticipates receiving between $[redacted] (b) (4) in total for the study. The estimated funding amount per year is between $[redacted] (b) (4). Dr. Assis does not receive salary support or personal remuneration from this funding.

Basis for Granting the Waiver:

Dr. David N. Assis has unique qualifications and specialized expertise needed for this particular matter.

Dr. Assis received his medical degree from Jefferson Medical College followed by a residency internship and residency at Thomas Jefferson University Hospital in Philadelphia, where he was also Chief Resident. He completed training in a gastroenterology and hepatology fellowship under the T32 research track at Yale followed by a transplant hepatology fellowship also at Yale. Dr. Assis is currently Assistant Professor of Medicine, Internal Medicine, Yale School of Medicine.

Dr. Assis' clinical and research interests are focused on autoimmune and cholestatic liver diseases. Specifically, he treats patients with autoimmune hepatitis, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) at his clinic. He performs translational and basic research on autoimmune hepatitis, PSC, and PBC using human biospecimens in addition to work with animal models. He is investigating the link between the pro-inflammatory cytokine macrophage migration inhibitory factor and autoimmune hepatitis, and the effect of psychological stress on autoimmune hepatitis. He is also studying human bile-derived organoids, and their interaction with T-cells, to elucidate the pathophysiology of PSC and identify novel therapeutic approaches. He is active in the American Association for the Study of Liver Disease as co-chair of the writing group on Guidance for PSC and Cholangiocarcinoma, and former member of the writing group on Guidelines for autoimmune hepatitis.

The particular matter is considered sensitive.

This topic is considered to be sensitive, as the FDA Division with responsibility for review of this product expects the meeting may receive significant public interest and non-trade press interest. Fatty liver disease has been prominent in the press and obeticholic acid is the first drug seeking approval for this disease.

Dr. Assis' expertise in this particular matter is necessary in the interest of public health.

Nonalcoholic fatty liver disease (NAFLD), a condition in which excess fat is stored in the liver, is one of the most common causes of liver disease in the United States (U.S.). It's estimated that about 25 percent of adults in the U.S. have NAFLD and of those about 20 percent have NASH (5% of adults in the U.S.). The reason some people with NAFLD have simple fatty liver and others get NASH is not known, although research suggests that certain genes may play a role.

NASH is the more severe form of NAFLD in which an individual has inflammation of the liver and liver cell damage, in addition to fat in the liver. Inflammation and liver cell damage can also

cause fibrosis which leads to permanent liver damage, cirrhosis, and its outcomes. The presence of metabolic syndrome (obesity, dyslipidemia, hypertension, and glucose intolerance) increases the likelihood that a patient has NASH rather than simple steatosis. The pathogenesis of NAFLD is poorly understood but seems to be linked to insulin resistance (e.g., as in obesity or metabolic syndrome). Obeticholic acid is the first drug seeking approval for NASH in the U.S.

In the interest of public health, it is important that the Agency has available the unique expertise that Dr. Assis 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. Assis' expertise in this matter.

Dr. Assis is a hepatologist with extensive clinical and research experience in liver and digestive diseases. Given his past and present professional and research experiences, Dr. Assis' participation in the committee's discussions will provide necessary expertise for this important discussion. Dr. Assis' participation in the past GIDAC meetings has been very helpful. He has unique, applicable experience reviewing obeticholic acid for GIDAC in 2016, when it was discussed for another indication (primary biliary cholangitis). Given the safety concerns that have been identified by the Division in this application, Dr. Assis' will provide necessary expertise for this important risk-benefit discussion.

Accordingly, I recommend that you grant Dr. David N. Assis, voting member of the Gastrointestinal 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):

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_____

_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S
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May 1, 2023

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

Date