DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring MD 20993

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

DATE: June 1, 2016

TO: Jill Hartzler Warner, J.D.
Associate Commissioner for Special Medical Programs, FDA

THROUGH: Division of Ethics and Integrity
Office of Operations

Michael F. Ortwerth, Ph.D.
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson. BSPharm., J.D.
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Member: Marvin Konstam, M.D.

Committee: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

Meeting date: June 28, 2016

Description of the Facts on Which the Waiver is Based:

Type, Nature, and Magnitude of the Financial Interests:

Marvin Konstam, M.D., is a Trustee/Board Member for the Tufts Medical Center. He is also the Director of the Cardiovascular Center at Tufts Medical Center.

Dr. Konstam (b) (4) The study began in (b) (4) and is expected to continue through (b) (4) The goal of this study is to assess whether (b) (4)

(b) (4) Dr. Konstam is not an investigator for the study and he has no direct involvement or managerial oversight over the study. (b) (4) is a competing product to the topic of this Advisory Committee meeting. Issues related to renal and vascular protective effect will be discussed at this meeting.

The funding to (b) (4) from the sponsor of (b) (4) is anticipated to be between $0 – 50,000 per year. Dr. Konstam does not receive any salary support or personal remuneration; this study is being conducted in the (b) (4), which is not in his area of oversight.

Description of the Particular Matter to Which the Waiver Applies:

On June 28, 2016, the committee will discuss supplemental new drug application (sNDA) 204629 for empagliflozin (Jardiance) tablets and sNDA 206111 for empagliflozin and metformin hydrochloride (Synjardy) tablets. Both sNDAs are sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., and are for the proposed additional indication of adult patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death and to reduce the risk of cardiovascular death or hospitalization for heart failure. The topic of this meeting is a particular matter involving specific parties.

Basis for Granting the Waiver:

Marvin Konstam, M.D., is a cardiologist and Director of the Cardiovascular Center, Tufts Medical Center. He received his medical degree from Columbia University in 1975. He is an expert in cardiology with a subspecialty in advanced heart failure and transplant cardiology. It is important to have cardiologists at this meeting to provide input into the discussions concerning the indication to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death and to reduce the risk of cardiovascular death or hospitalization for heart failure in adult patients with type 2 diabetes mellitus and high cardiovascular risk. The discussions for the meeting will focus on trial design, objectives and findings. Dr. Konstam's clinical experience, clinical research and regulatory experience will help to ensure that the Agency can carry out a successful advisory committee meeting.

The committee will discuss the findings from the EMPA-REG OUTCOME trial. The EMPA-REG OUTCOME trial was a cardiovascular outcomes trial of empagliflozin compared to placebo added to usual care in patients with type 2 diabetes mellitus and increased cardiovascular risk. The results of this trial have been submitted to support supplemental new drug applications 204629/S-8 and 206111/S-4. The trial was primarily designed to evaluate cardiovascular risk but the final results suggest empagliflozin, a member of the sodium glucose co-transporter 2 inhibitor (i.e., SGLT-2i) class, may reduce deaths from cardiovascular causes in adults with type 2 diabetes at risk for new onset or recurrent atherosclerotic cardiovascular disease. According to the reported trial results, patients who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome, cardiovascular death and death from any cause when these interventions were added to standard care. The new efficacy claim sought is related to cardiovascular disease and based on these findings.

The trial itself is complex, as interim results from this trial were used to examine cardiovascular safety for the purpose of drug approval; the trial was primarily designed as a safety trial, and the observed drug effect on cardiovascular outcomes was not entirely consistent with the effect anticipated (i.e., reduction in macrovascular disease outcomes). Interpretation of the findings, for the purpose of assistance with reaching a regulatory decision, requires input from experts in cardiology, and in particular experts with cardiovascular clinical research and cardiovascular outcomes trial expertise. It is anticipated that there will be discussion of the diabetic nephropathy findings from the EMPA-REG study.

The trial is not a "typical" diabetes or cardiovascular disease trial that would be conducted for an efficacy claim. The primary purpose of the trial was to assess the drug's atherosclerotic cardiovascular safety. A secondary objective of the trial was to assess the drug's efficacy on atherosclerotic cardiovascular disease only if safety objective had first been met. The trial reported a beneficial effect on a cardiovascular outcome that is different from a macrovascular disease outcome (heart attacks, strokes and cardiovascular deaths resulting from these). The unusual aspect of the trial, the reported findings results and thus the applications, raise issues regarding the robustness of the findings that require a public discussion. Experts with various types of cardiology expertise, including heart failure expertise, are needed to weigh in on the trial findings, the level of evidence provided by this single trial and the clinical meaningfulness of the results.

The various cardiology experts who were invited to attend this meeting have different and varied expertise. Some experts are sub-specialized within the field of cardiology, in macrovascular disease (i.e., heart attack, etc.), and others are sub-specialized in heart failure. Some experts have conducted and analyzed large outcomes trials. These experts understand issues of trial conduct and analysis which could impact interpretability of final results. Some other experts have extensive regulatory experience through their service on this or other committees; others are familiar with the Agency's current policy for cardiovascular safety for anti-diabetic drugs. A broad cardiology expertise is needed for this advisory committee meeting to ensure the committee's success.

Dr. Konstam is an expert in heart failure and an expert in conducting clinical trials in heart failure. He is familiar with the Agency's cardiovascular safety guidance for anti-diabetic products and is familiar with the regulatory requirements for demonstrating effectiveness of new products. His expertise in all these domains will be called upon at this meeting and will help to ensure a successful and productive advisory committee meeting. In the interest of public health it is critical for the agency to review products that can potentially provide treatment for patients with diabetes that have an increased cardiovascular risk. A large percentage of older adults with diabetes die from some form of heart disease. Adults with diabetes are more likely to have heart disease than adults without diabetes. Dr. Konstam's knowledge in the area of cardiology and heart failure will provide necessary expertise for this important discussion.

Accordingly, I recommend that you grant a waiver for Dr. Marvin Konstam, a temporary voting member of the Endocrinologic and Metabolic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

___x_____ 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.

/S/ 6/17/2016

Jill Hartzler Warner, J.D.
Associate Commissioner for Special
Medical Programs

Date