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

DATE: September 20, 2021

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 Temporary Voting Member: **Gita Thanarajasingam, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: October 28, 2021

Description of the Particular Matter to Which the Waiver Applies:

Gita Thanarajasingam, M.D., is a temporary voting member of the Oncologic Drugs Advisory Committee (ODAC). The committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for the use in the treatment of cancer and make appropriate recommendations to the Commissioner of Food and Drugs.

The committee will discuss new drug application (NDA) 214383, Pepaxto (melphalan flufenamide) for injection submitted by Oncopeptides AB, approved under 21 CFR 314.500 (subpart H, accelerated approval regulations), in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.
The committee will hear an update where the confirmatory trial demonstrated a worse overall survival in the melphalan flufenamide treatment arm compared to the control arm. Confirmatory studies are post-marketing studies to verify and describe the clinical benefit of a drug after it receives accelerated approval. Based on the update provided, the committee will have a general discussion focused on next steps for the product including whether the indication should remain on the market while additional trial(s) are conducted. The topic of the meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Thanarajasingam's employing institution, the Mayo Clinic, is participating in the study titled *A Phase 1/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 701 Monotherapy, or in Combination With Pomalidomide, With and Without Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (ParadigMM-1B),* sponsored by Amgen. The study contract began on December 20, 2018, and the estimated study completion date is (b) (4). As a Co-Investigator on the trial, Dr. Thanarajasingam can enroll patients; however, she advised that she has not enrolled any patients on the trial.

The Mayo Clinic anticipates receiving between $100,000 and $500,000 per year, from Amgen, for its participation in this study. Dr. Thanarajasingam does not receive salary support or personal remuneration from this funding.

Her employer is also participating in a study titled *A Phase 1a/1b Dose Escalation and Expansion Trial of TTI-621, a Novel Biologic Targeting CD47, in Subjects With Relapsed or Refractory Hematologic Malignancies and Selected Solid Tumors,* sponsored by Trillium. The study contract began in May 2016 and the estimated study completion date is (b) (4). As a Co-Investigator on the trial, Dr. Thanarajasingam can enroll patients; however, she advised that she has not enrolled any patients on the trial.

The Mayo Clinic anticipates receiving a total of between $100,000 and $500,000 from Trillium for its participation in this study. Dr. Thanarajasingam does not receive salary support or personal remuneration from this funding.

Lastly, the Mayo Clinic is participating in a study titled *A Multi-Center, Open Label Phase 1/2 Study of CYT-0851, an Oral RAD51 Inhibitor, in Patients With Relapsed/Refractory B-Cell Malignancies and Advanced Solid Tumors,* sponsored by Cyteir. The study contract began on September 7, 2020, and the estimated study completion date is (b) (4). As a Co-Investigator on the trial, Dr. Thanarajasingam can enroll patients; however, she advised that she has not enrolled any patients on the trial.

The Mayo Clinic anticipates receiving a total of between $100,000 and $500,000 from Cyteir for its participation in this study. Dr. Thanarajasingam does not receive salary support or personal remuneration from this funding.

Basis for Granting the Waiver:

Dr. Gita Thanarajasingam has unique qualifications and specialized expertise needed for this particular matter.

Dr. Gita Thanarajasingam is Assistant Professor of Medicine, Mayo Clinic College of Medicine and Sciences and Consultant, Division of Hematology, Department of Internal Medicine, Mayo Clinic. She is a lymphoma clinician and health outcomes researcher at Mayo Clinic and serves as

a Co-Investigator on most lymphoma protocols so that she may enroll her patients.

Dr. Thanarajasingam earned a Bachelor of Science in Research Intensive: Molecular, Cellular, & Developmental Biology from Yale University. She earned her medical degree from Mayo Medical School, Mayo Clinic College of Medicine, and completed her Internal Medicine Residency at Brigham and Women's Hospital, Harvard Medical School. She further completed a Hematology/Oncology Fellowship Program and an Advanced Hematology Fellowship - Lymphoma with Mayo Clinic, Rochester, Minnesota. She is board certified in Internal Medicine, Hematology and Medical Oncology.

Dr. Thanarajasingam's research interests are in Hodgkin and non-Hodgkin lymphoma, adverse event analysis in cancer clinical trials, patient-oriented outcomes research as well as therapeutic and cancer control clinical trials. While she is a lymphoma clinician, she also focuses on translation health outcomes research to improve patients' experience of cancer treatment. As part of her fellowship, she developed a novel, longitudinal statistical approach to evaluating the toxicity of cancer therapy called Toxicity over Time (ToxT). She expanded this work to also include patient-reported toxicity data. Dr. Thanarajasingam is a recognized leader in advocating for a more compressive approach to analysis of adverse events. In 2018, she led an international *Lancet Haematology* Commission to generate awareness and action around the world.

According to the FDA division responsible for the review of the application, a productive discussion of the issues depends upon having multiple experts in the field of hematology/oncology at the meeting. Changes in the treatment landscape of Multiple Myeloma and the safety results with Overall Survival detriment in patients with relapsed/refractory MM requires specialized knowledge of the impact of these changes and are necessary for the assessment of the role for melphalan flufenamide in the relapsed/refractory patient population.

The particular matter is sensitive.

The matter coming before the committee will garner public interest as it relates to the regulatory pathway of accelerated approval which was promulgated in 1992. This pathway has been used extensively in oncology approvals to bring new therapies to patients in an expedited fashion.

Dr. Gita Thanarajasingam's expertise in this particular matter is necessary in the interest of public health.

Multiple myeloma (MM) is a systemic malignancy of plasma cells that typically involves multiple sites within the bone marrow. According to the American Cancer Society, the estimated number of new cases of MM in the United States in 2021 is 34,920 while the estimated number of deaths is 12,410. Median survival times have improved with the introduction of newer therapies. Despite the improvement, relapse of MM and disease progression is common even after the achievement of a complete remission. Relapsed/refractory MM (RRMM) is defined as a disease which becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy. Despite the availability of new treatments, most patients with multiple myeloma will relapse and some patients may become refractory to the therapies that currently comprise the hematologic

standard of care for the malignancy, including proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. Evidence from literature suggests that outcomes are poor for patients whose multiple myeloma has become refractory to proteasome inhibitors, immunomodulatory agents, and anti-CD38 antibodies. Three therapies are currently approved for patients who are relapsed/ refractory to proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. The product at issue for the October 28 meeting is Oncopeptides' Pepaxto (melphalan flufenamide) indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.

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

Dr. Thanarajasingam's expertise in assessing safety and analysis of safety in hematologic malignancies and her expertise in Multiple Myeloma are very important to assess the results that will be reported at the meeting. According to the review division, multiple drugs are approved for the treatment of patients with RRMM. Although approved for specific lines, the therapies can be used in later line settings and patients can be retreated with therapies that they have failed previously. Dr. Thanarajasingam's knowledge of the treatment landscape and safety and efficacy of multiple myeloma therapies in different lines is needed to provide context to the results presented at the ODAC.

Accordingly, I recommend that you grant Dr. Gita Thanarajasingam, a temporary voting member of the Oncologic 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: 2021.10.08 13:58:47 -04'00'

October 8, 2021

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

Date