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

DATE: March 21, 2022

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 Standing Voting Member: **Dr. Ranjana Advani, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: April 22, 2022

Description of the Particular Matter to Which the Waiver Applies:

Ranjana Advani, M.D., is a standing 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.

On April 22nd, the committee will discuss supplemental new drug application (sNDA) 213176/S-002, for Ukoniq (umbralisib) tablets, and biologics license application (BLA) 761207, for ublituximab injection, both submitted by TG Therapeutics, Inc. The proposed indication (use) for these two products is in combination for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. In addition, the committee will also discuss the existing umbralisib indications in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma under 21 CFR 314.500 (subpart H, accelerated approval regulations). The matters under review by the advisory committee are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Advani is currently employed by Stanford University (Stanford). The technology for a competing product, magrolimab, originated from Stanford University and it was licensed from Stanford by Forty Seven (a Stanford spin off) before it was acquired by Gilead Sciences, with

royalties to Stanford. She is not aware of the details or royalties to Stanford for their involvement. Dr. Advani states that she does not personally receive royalties from Stanford University for her involvement with magrolimab.

Dr. Advani's employing institution, Stanford University, is participating in a study titled *A Phase 1b/2 Trial of Hu5F9-G4 (magrolimab) in Combination With Rituximab or Rituximab + Chemotherapy in Patients With Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma,* NCT02953509*,* sponsored by Gilead. The study population overlaps with the indications coming before the advisory committee, specifically Follicular Lymphoma. The study began in March 2017 and is projected to end in March 2023. Dr. Advani is the Site-Principal Investigator for the study. Stanford University receives between $400,000 and $500,000 per year from Gilead for its participation in this study. She receives (b) (6)% salary support for her effort in the study; between (b) (6) received per year to date.

Dr. Advani's employer is also participating in a study titled: *An Open-Label, Multi-Center Phase 1 Study to Investigate the Safety and Tolerability of REGN1979 (odronextamab, an Anti-CD20 x Anti-CD3 Bispecific Monoclonal Antibody), in Patients With CD20+ B-Cell Malignancies Previously Treated With CD20-Directed Antibody Therapy (ELM-1), NCT02290951,* sponsored by Regeneron. The study population overlaps with the indications coming before the advisory committee, specifically Chronic Lymphocytic Leukemia and Follicular Lymphoma. The study began in December 2014 and is projected to end in December 2022. Dr. Advani is Site-Principal Investigator for the study. Stanford University receives between $100,000 and $200,000 per year from Regeneron for its participation in this study. She receives (b) (6)% salary support for her effort in the study; between (b) (6) received per year to date.

Basis for Granting the Waiver:

Dr. Ranjana Advani has unique qualifications and specialized expertise needed for this particular matter.

Dr. Ranjana Advani is the Saul Rosenberg Professor of Lymphoma and Professor of Medicine, Oncology at Stanford University Medical Center. She serves as the Physician Leader of the Lymphoma Clinical Care Program.

Dr. Advani completed her medical education at Bombay University in India and completed her residency at Stanford University followed by a Hematology and Oncology Fellowship at Stanford University. She specializes in research and treatment of Hodgkin and non-Hodgkin lymphomas (NHL) and has developed a broad collaborative investigative program, encompassing clinical trials and translational correlates. She is the Principal Investigator on numerous clinical trials. She currently serves on the National Comprehensive Cancer Network (NCCN) non Hodgkin and Hodgkin Lymphoma (vice chair) guidelines panel, Lymphoma Core Committee of the Eastern Cooperative Oncology Group (ECOG) and the National Cancer Institute Lymphoma Steering Committee. She is the author of over 240 peer-reviewed publications, 42 reviews, 13 book chapters, and 190 abstracts (since 2015).

The committee will discuss umbralisib (Ukoniq) and ublituximab in combination for the treatment

of adult patients with CLL or SLL. In addition, the committee will discuss the existing umbralisib indications for relapsed or refractory follicular lymphoma and marginal zone lymphoma. According to the review division responsible for review of the application at issue for this meeting, multiple hematologist/oncologists are needed at the meeting to assess the overall survival and safety concerns along with concerns for support for the selected doses of the combination require expertise to contextualize the dosing considerations.

The information being discussed relates to safety and efficacy outcomes in patients with hematologic malignancies, diseases of the blood, bone marrow, and/or immune system, which can have unique safety and efficacy considerations given the underlying disease and the treatments administered to these patients. Hematologists with knowledge of the treatment landscape and the safety and efficacy of treatments administered to patients with NHL are needed to provide context to the data and information presented at the ODAC. Multiple hematologists/oncologists were invited but either declined due to schedule conflicts or had financial interests creating more significant conflicts. Dr. Advani possesses the expertise to provide context to the safety and efficacy data being discussed, which will allow her to provide valuable insight and understanding to the issues brought to the committee

The particular matter is sensitive.

The FDA Division responsible for review of umbralisib and ublituximab does expect the matter coming before the committee to 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. The Division seeks ODAC input on the risk-benefit of the combination in the proposed indication and how the current information impacts the existing indications under accelerated approval.

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

Non-Hodgkin lymphoma is one of the most common cancers in the United States, accounting for about 4% of all cancers. The American Cancer Society's estimates for Non-Hodgkin Lymphoma in 2022 are about 80,470 people (both adults and children) will be diagnosed with NHL and about 20,250 people will die from this cancer. There are an estimated 672,980 people living with or in remission from non-Hodgkin lymphoma. Indolent lymphomas are slow-moving and tend to grow more slowly and have fewer signs and symptoms when first diagnosed. Slow-growing or indolent subtypes represent about 40 percent of all NHL cases. Indolent NHL subtypes include but are not limited to Follicular lymphoma (FL), which is the most common subtype of indolent NHL, followed by Marginal Zone Lymphoma (MZL) and Chronic Lymphocytic Leukemia or Small-Cell Lymphocytic Lymphoma (CLL/SLL).

Chronic lymphocytic leukemia or small lymphocytic lymphoma is an indolent malignancy characterized by increased production of mature but dysfunctional B lymphocytes. CLL comprises 25 to 30% of total leukemias in the United States. According to the American Cancer Society, in 2021 there were an estimated 21,250 new CLL cases and about 4,320 deaths from CLL. Patients with CLL or SLL are not cured with conventional therapy, and most will relapse eventually.

There are many current first-line treatment options for CLL or SLL. Active treatment is started if the patient begins to develop disease-related symptoms or there are signs that the disease is progressing based on testing during follow-up visits. The choice of treatment depends on the stage of the disease, the patient's symptoms, the age and overall health of the patient, and the benefits versus side effects of treatment. The treatment landscape has also expanded with the development of targeted agents, in addition to the traditional chemotherapy agents. For relapsed or refractory disease, treatment may incorporate one or more of the following targeted agents, often administered as combinations: Bruton tyrosine kinase inhibitors, phosphoinositide 3'-kinase (PI3K) inhibitors, BCL2 inhibitors and anti-CD-20 monoclonal antibodies.

For lymphoma, about 1 out of 5 lymphomas in the United States is a follicular lymphoma. FL is the second common form of NHL in the U.S with an estimated incidence of six new cases/ 100,000 persons/year. The vast majority of patients treated for FL will have an initial response to therapy with 40 to 80 percent demonstrating a complete response, depending on the initial regimen used. However, conventional therapy for FL is not curative and most of these patients will ultimately develop progressive disease. In addition, less than 10 percent of patients treated with initial chemoimmunotherapy will not respond to treatment (ie, refractory disease). Marginal zone lymphomas account for about 5% to 10% of lymphomas. MZL is the second most common indolent non-Hodgkin's lymphoma which accounts for approximately eight percent of all NHL cases. Although conventional first-line treatment options are proved beneficial, many the patients become resistant to or experience a relapse following treatment.

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

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

Dr. Advani is uniquely qualified by having the specialized knowledge and research experiences in Hodgkin disease, non-Hodgkin lymphomas, and clinal trial conduct. Her expertise in hematologic malignancies will be helpful in understanding the issues around safety and efficacy with the umbralisib and ublituximab combination, the assessment of benefit and risk, and the implications for the currently approved indications for umbralisib being discussed. Her professional experiences combined with experiences with treating these patients will be invaluable to a robust and productive discussion on the issues coming before the committee.

Accordingly, I recommend that you grant Dr. Ranjana Advani, a standing 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):

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_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S Date: 2022.04.05 10:09:42 -04'00'

April 5, 2022

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

Date