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

DATE: March 22, 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 Temporary Voting Member: **Louis Diehl, M.D.**

Committee: Oncologic Drugs Advisory Committee

Meeting date: April 22, 2022

Description of the Particular Matter to Which the Waiver Applies:

Louis Diehl, 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 use in the treatment of cancer and make appropriate recommendations to the Commissioner of Food and Drugs.

On April 22, 2022, 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 a specific party.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Diehl's employing institution, Duke University (Duke), is participating in the following studies that potentially can be affected by the particular matters before the advisory committee. He advised

that Duke puts all clinicians as investigators on all study protocols so that they can talk to patients about the studies and refer patients to the coordinators. In July 2017, Dr. Diehl was appointed as Chair of the Duke Investigational Review Board (IRB). Since his appointment as IRB Chair, Dr. Diehl was removed as investigator from all studies. Dr. Diehl has confirmed that he has not been involved in any of the studies mentioned below and will not be involved in the future. As Chair of the IRB, Dr. Diehl does not have direct involvement with these studies, and he is not aware of the funding amounts awarded to his institution. Dr. Diehl does not receive any personal remuneration or salary support from the funding.

- Study titled *A Phase 3, Randomized Study to Assess the Efficacy and Safety of Ublituximab in Combination With TGR-1202 Compared to Obinutuzumab in Combination With Chlorambucil in Patients With Chronic Lymphocytic Leukemia (UTX-TGR-304, UNITY-CLL),* NCT02612311, sponsored by TG Therapeutics, a party to the matter. The study began on August 29, 2016. It was closed to patient accrual on October 18, 2017, but is not closed for Duke IRB.

- Study titled *A Multi-Center, Open-Label, Study to Evaluate the Safety and Efficacy of Ublituximab (TG-1101) in Combination With TGR-1202 for Patients Previously Enrolled in Protocol UTX-TGR-304 (UTX-TGR-204),* NCT02656303, sponsored by TG Therapeutics, a party to the matter. The study was approved by the IRB in October 2017 and is ongoing at his institution.

- Study titled *An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma,* NCT03336333, sponsored by BeiGene, a competing firm. The study began on April 12, 2018, and is ongoing at his institution.

- Study titled *An Open-Label, Phase 1/2 Study of JCAR017 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma,* NCT03331198, sponsored by Celgene, a competing firm. The study began on May 28, 2019, and is ongoing at his institution.

Basis for Granting the Waiver:

Dr. Louis Diehl has unique qualifications and specialized expertise needed for this particular matter.

Louis Diehl, M.D. is Professor of Medicine, Chair of the Institutional Review Board and a Board Member of the Pharmacy and Therapeutic Agents Committee at the Duke University Medical Center. He is also the Co-Chair of the Data Safety Monitoring Board at the National Heart, Lung and Blood Institute at National Institutes of Health. His research interests include Hodgkin disease, non-Hodgkin lymphomas, chronic lymphocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, and myelodysplasia. His research centers on the optimal application of existing treatments and the development of new treatments for all forms of lymphoma and leukemia. The goal of his research is to bring together all of the treatment options, including

pathway directed medications, and biological and immunological approaches, in order to maximize the quality and length of life of patients.

Dr. Diehl received his medical degree from the Georgetown University School of Medicine and completed an Internal Medicine Residency and a Hematology-Oncology Fellowship at the Walter Reed Army Medical Center. He is the author of 79 research publications, 60 abstracts, and three book chapters.

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. Dr. Diehl is uniquely qualified by having the specialized knowledge and experience to treat these patients and he would provide important insight and feedback essential for assessing discussion topics.

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. Louis Diehl's expertise in this particular matter is necessary in the interest of public health.

Non-Hodgkin lymphoma (NHL) 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% 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 6 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% 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% 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 8% of all NHL cases. Although conventional first-line treatment options are proved beneficial, many of 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. Diehl 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. Louis Diehl's expertise in this matter.

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. Multiple PI3K inhibitors have been approved for the treatment of patients with hematologic malignancies. 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. Diehl is uniquely qualified by having the specialized knowledge and research experiences in Hodgkin disease, non-Hodgkin lymphomas, chronic lymphocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, and myelodysplasia. His 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. His 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. Louis Diehl, 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: 2022.04.05 10:12:15 -04'00'

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

April 5, 2022
Date