LOI DECISION LETTER

DDTBMQ000077

December 4, 2018

Peter William Nickerson, MD, FRCPC
Distinguished Professor of Internal Medicine and Immunology
Vice Dean Research, Rady Faculty of Health Sciences, University of Manitoba
Room A203 Chown Building
753 McDermot Avenue
Winnipeg, Manitoba Canada R3E 0T6

Dear Dr. Nickerson:

We are issuing this Letter of Intent (LOI) Decision Letter to notify you of our decision on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your LOI submission of August 13, 2018, and have concluded to **Accept** it into the CDER BQP.[1] We support and encourage your ongoing study and use of this promising prognostic biomarker.

You have proposed qualification of the HLA-DR/DQ Molecular Eplet Mismatch Score as a tool to determine a transplant recipient's category of potential risk for de novo donor specific antibody formation (DSA), transplant rejection and graft failure for use in enrichment or stratification of risk in phase 2 and 3 clinical drug development trials. As this biomarker development effort is refined in subsequent BQP submissions, the submitted data, the specifics of your context of use (including the target patient population), the specific analytics and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below may be the most applicable to your qualification effort.

Based on our review of the LOI, we agree there is an unmet need and the development of HLA-DR/DQ Molecular Eplet Mismatch Score as a prognostic biomarker, used in conjunction with other established transplant donor/recipient compatibility testing, to categorize a kidney transplant patient's potential risk (low, intermediate and high) of de novo DSA formation, graft rejection and graft failure may be helpful for enrichment or stratification of risk in clinical drug development trials.

When you are prepared to make a submission to the next stage in the 507 DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical and software validation of the

[1] In December, 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned, please include detailed study protocols and the statistical analysis plan for each study as part of your QP submission.

We encourage further study of your biomarker including the proposed clinical trials. When evaluating biomarkers prospectively in clinical trials, sponsors are encouraged to submit study data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Please note that the Kidney Transplant Therapeutic Area User Guide v1.0 is available on the CDISC.org website.[2] Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization.

If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a specific Investigational New Drug (IND) development program, they should prospectively discuss the approach with the appropriate CDER division. Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Peter Nickerson (peter.nickerson@umanitoba.ca), the primary point of contact for this project.

Biomarker Considerations

Requestor's Biomarker Description: A computational measurement of the degree of gene loci HLA-DRB1/3/4/5 and HLA-DQA1/DQB1 molecular sequence differences between a kidney donor and the transplant recipient. The donor and recipient DNA must be HLA typed at the allele level (i.e., 4-digit) for all the HLA-DR and HLA-DQ gene loci. Publicly available computational software (e.g., HLA-DR/DQ/DP Matching, version 2.0; http://www.epitopes.net) inputs the donor and recipient 4-digit HLA typing to generate individual HLA-DR and HLA-DQ Molecular Mismatch Scores.

Specifically, this program identifies patches (3 angstrom radius) of polymorphic amino acids on the HLA molecule surface (referred to as "eplets" by the software developers) and reflects the central part of the entire epitope that an antibody would bind. The number of donor-recipient eplet mismatches at the HLA-DR and DQ loci are then calculated to generate individual HLA- DR and HLA-DQ Molecular Eplet Mismatch Scores.

To move the individual HLA-DR and HLA-DQ Molecular Eplet Mismatch Scores into a prognostic biomarker, a combined (or composite) HLA-DR/DQ Molecular Eplet Mismatch Score is developed based on the composite highest risk category associated with the patient's HLA-DR and HLA-DQ Mismatch Scores. Patients are broadly categorized as; Low, Intermediate or High risk groups, based upon studies using individual level patient data.

[2] CDISC website: https://www.cdisc.org/standards/therapeutic-areas/kidney-transplant, accessed on 11/8/2018

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Pre-determined risk thresholds assign the transplant recipient into one of three prognostic marker risk categories (low, intermediate or high) for post-transplant de novo HLA-DR/DQ DSA development, graft rejection and graft failure.

To better understand the benefits of the identified biomarker as a DDT, and to continue to refine the COU, please provide the information requested below. We acknowledge that some of the responses to questions and comments below may already be included in your publications or other publicly available resources, (such as the Epitope Registry or at www.epitopes.net). However, for completeness, we recommend that they be adequately summarized in the Qualification Plan.

FDA's questions/comments for continued development of the biomarker description:
We agree with your description of the above biomarker taking into consideration the comments below;

1. Please provide a list of the specific target eplets that are used in the scoring paradigm. Please provide the reference library(ies) used to identify the eplets (i.e., http://www.epregistry.com.br/, or other), including version, the paradigm used in eplet identification and the basis for eplet selection, if relevant. Please include information about the relative immunogenicity of target eplets, if known and describe whether relative immunogenicity factors into mismatch scoring.

2. Please explain whether all potential eplets, or only antibody-verified eplets, will be used to determine the mismatch score.

3. We propose to add the words "eplet" to the proposed biomarker name to indicate the mismatch score is eplet-based. If you further refine your approach to HLA molecule eplet mismatch scoring, please name the biomarker so it reflects a description of the biomarker (e.g., HLA-DR/DQ single allele Molecular Eplet Mismatch Score).

Context of Use (COU) Considerations

Requestor's COU: *Prognostic biomarkers (i.e. determined at the time of transplant in conjunction with baseline testing to rule-out preformed alloimmunity) categorizing kidney transplant patients as high, intermediate, or low risk for de novo DSA, graft rejection and graft failure, with categories to be used independently, in pairs or triplet risk categories to enrich phase 2 and 3 clinical trials with patients based upon risk category in studies evaluating novel drugs.*

FDA's suggested COU for continued biomarker development: *Prognostic biomarkers (i.e. determined at the time of transplant in conjunction with baseline testing to rule-out preformed alloimmunity) categorizing kidney transplant patients as high, intermediate, or low risk categories for de novo DSA formation, graft rejection and graft failure, with categories to be used independently or in pairs for enrichment, or use all categories to stratify risk in phase 2 and 3 clinical trials*.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Analytical Considerations

Pre-Analytical Sample Collection, Handling, Stability and Supporting Standard Operating Procedures

4. Please provide standard operating procedures used in collection and handling of samples for HLA genotyping.

Validation: Calibration, Controls, and Verification of Repeat Measures (Variability) and Demonstration of Capability for Full Parameter Range (Performance)

5. We acknowledge you plan to use FDA-cleared HLA genotyping kits to determine HLA-DR/DQ genotypes at high resolution. If you choose to use other assays that are not FDA-cleared, please adequately validate these assays before using the genotyping results to generate the mismatch scores.

Confirmation of Transparency of Analytics Technical Parameters

6. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical assay and software may be publicly posted if the biomarker is successfully qualified by the Agency. Please confirm technical parameter and other pertinent information about the assay and software that may be made public to ensure the biomarker can be used as a drug development tool by any interested party. The biomarker qualification process does not endorse the use of any specific device, assay or software with a qualified biomarker.

Post-Analytic Conversion of Sequencing Data to a Mismatch Score: Eplet Mismatch Scoring Software Considerations

7. Please provide the algorithm used for the Molecular Eplet Mismatch Scoring to include all inputs and outputs. Please explain how the algorithm calculates the identified mismatches; whether all eplets are given equal weighting, how a mismatch is characterized, where error in the scoring of a donor-recipient pair may occur, and provide a reproducibility estimate for independent runs of the same sample or the intra-subject reproducibility of the scoring software.

8. What standard operating procedure(s) or approach(es) do you propose to use to ensure the mismatch scoring software output for individual donor-recipient pairs is accurate and reliable, (e.g., run samples with known control samples)?

9. Validation: Please provide a description of the existing data or study protocol(s) designed to demonstrate that the proposed HLA-DR/DQ analysis using the HLA-DR/DQ Molecular Eplet Mismatch Scoring software can correctly identify the mismatched eplets and the method(s) used to reproducibly and reliably generate mismatch scores. For the QP, please provide summary of the existing data, or if other studies are planned, the protocols and the analysis plan(s) of future studies. The data used for validation of the approach should include a sufficient number of donor-recipient pairs and provide a reasonable coverage of HLA-DR/DQ alleles.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

10. You have indicated in your submission that you plan to use only Version 2.0 of the software. While this may limit potential for uncontrolled changes, there may be necessary changes in the future to ensure continuing compatibility with search engines, operating systems, etc. Please explain who will be responsible for the software and the Web site to ensure consistency of results throughout the software's life cycle and how you will ensure integrity and reliability of the software when software modifications are necessary?

11. Please provide procedures you will use to ensure the security, integrity, reliability and accuracy of the software used in Molecular Eplet Mismatch Scoring that is in the public domain. Please ensure that these procedures address protection from deliberate risks from malware or hackers, and unintentional errors or inadvertent changes to programming.

Clinical Considerations

Background

12. Please provide background or scientific history and evolution of the eplet mismatch concept as relates to transplantation including:
    a. limitations of the current donor/recipient HLA assessment in alloimmune risk prediction,
    b. descriptive information on HLA molecules, triplets, epitopes and eplets; including a comparison and contrast of impacts when used in kidney transplantation, and
    c. the basis for the choice of the HLA-DR/DQ Molecular Eplet Mismatch Scores as opposed to, for example, class I HLA eplet mismatch scores or other biomarkers to predict alloimmunity.

Interpretive Criteria (Cut-offs/Boundaries), Application & Validation in population

13. Please provide a rationale and data for the proposed HLA-DR/DQ Molecular Eplet Mismatch Score cut-offs for the three risk categories (low, intermediate and high). For the Qualification Plan (QP), please explain the basis for the final cut-offs and why other cut-off values have been proposed in the literature and in your submission but were not adopted.

Gaps and Proposed Studies

14. Identify potential limitations, gaps and assumptions in the proposal. It would be helpful to know if the prognostic performance for an HLA-DR/DQ Molecular Eplet Mismatch Score and cut-off differs in patients treated with different immunosuppressive drugs (is influenced by the presence of immunosuppressive agents). Please also address gaps related to the relevance of the eplets to specific sub-populations; for example, potential interracial differences for the eplet mismatch scoring system efficiency as you mention in your LOI.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Statistical Considerations

15. Please provide details on how AUC, sensitivity, and specificity were calculated in your QP submission. It is not clear what criteria were used in the AUC analysis, specificity and sensitivity to determine the HLA-DR eplet mismatch cut-offs. Please provide the details for the cut-offs proposed for the biomarker.

16. In Wiebe et al., (2017), specificity appears to be low based on the cut-off of >11 mismatches, i.e., 0.53 with HLA-DR eplet mismatch in predicting HLA-DR *dn*DSA development and 0.45 with HLA-DQ eplet mismatch in predicting HLA-DQ *dn*DSA development. The analysis performed appears to assume two categories for specificity calculation. We acknowledge that you may be changing the cut-offs and that may ultimately change the specificity. We ask that you please explain the usefulness of prognostic enrichment or stratification of studies in relation to the sensitivity and specificity performance of the selected cut-offs.

17. In slide #18/19 "FDA Sept 2018 Nickerson Final Version.pdf", you stated that "Similar or better than current standard (AUC=0.54-0.58)" under "Statistical Consideration", please provide the reference.

18. The quantification proposal was largely based on a consecutive cohort study of 596 patients. As stated in the reference article, the study represented a relatively low-risk group of patients. Please discuss the generalizability of the results of this patient group to the general transplant population in the U.S.

19. You state that investigator-initiated biomarker-stratified RCTs are being planned to validate the prognostic utility of the HLA-DR/DQ Molecular Eplet Mismatch Score. Please include the protocol and Statistical Analysis Plan (SAP) for each study as part of your QP submission.

Other: Please specify

20. Please provide a glossary of terms and index to acronyms that are used in submissions.

Please note that section 507 of the FD&C Act includes transparency provisions that apply to your submissions. Certain information contained within your submissions may be made publicly available on the Internet, as required by section 507. For examples of transparency and prior submissions see the Biomarker Qualification Submissions webpage.[3]

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

If you have questions, please contact Chris Leptak (christopher.leptak@fda.hhs.gov) via email. We look forward to working with you on this beneficial project.

Sincerely,

Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
Office of New Drugs/CDER

Renata Albrecht, M.D.
Director,
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs/CDER

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov