LOI DETERMINATION LETTER

DDTBMQ000097

June 1, 2020

Transplant Therapeutics Consortium
Critical Path Institute
1730 E. River Rd.
Tucson, AZ 85718

Dear Dr. O'Doherty,

We are issuing this Letter of Intent (LOI) Determination Letter regarding 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 deemed reviewable on February 14, 2020 and have concluded to **Accept** it into the CDER BQP.[1] We support and encourage the study of a composite biomarker panel to support kidney transplant therapeutic development.

You have proposed qualification of a reasonably likely surrogate endpoint biomarker to predict five-year risk of allograft loss in kidney transplant recipients. Based on our review of the LOI, we agree there is an unmet need, and the development of this composite scoring system to predict patient's long-term outcomes in clinical trials will facilitate the development of novel immunosuppressive therapies (ISTs).

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 comments below may be the most applicable to your qualification effort.

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 biomarker measurement method and clinical validation plan with detailed summaries of existing data that will support the biomarker and its context of use (COU). It also includes descriptions of knowledge gaps and how you propose they will be addressed. 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 have provided initial comments based on your LOI and hope these comments may be useful as you proceed with the preparation of your QP submission.

[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.

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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. 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 Inish O'Doherty (iodoherty@c-path.org), the primary point of contact for this project.

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 QP.

Biomarker Considerations

Requestor's Biomarker Description:

The Integrative Box (iBox) Scoring System includes the following component biomarkers, taken together in the first year after transplantation:

Estimated Glomerular Filtration Rate ('eGFR') [Serum Creatinine]: calculated with serum creatinine (a molecular biomarker) and certain patient characteristics using established equations (most commonly the Chronic Kidney Disease Epidemiology Collaboration, CKD-Epi equation);

Measurement of protein excretion into the urine ('proteinuria'): assessed as either total urinary protein or as a ratio of urinary protein to urinary creatinine (UPCR) (Molecular biomarker, dependent on data available for analysis. Final determination of which specific marker will be used will be made in future submission documents once data sets are procured.

Pathophysiological assessment of percutaneous renal allograft biopsy, based on Banff scoring criteria ('biopsy histology'): Histologic biomarker

Presence or absence of de novo anti-human leukocyte antigen donor-specific antibodies. Additionally, the presence of the dnDSA will be refined into categories based on MFI values. The specific categorical cut-points in the MFI scale will be determined in future submissions once the appropriate patient-level data has been curated. It is envisaged these categorical cut-points for subjects with dnDSA will be based on those described

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in Loupy et al 2019 (Loupy et al. 2019) (Appendix 2): Molecular biomarker

FDA recommended Biomarker Description for continued development:
A composite biomarker panel score to predict five-year risk of kidney allograft loss, taken together in the first year after transplantation, including the following component biomarkers: estimated glomerular filtration rate, proteinuria, biopsy histology and presence or absence of de novo anti-human leukocyte antigen donor-specific antibodies.

1. Instead of referring to the biomarker as the "The Integrative Box (iBox) Scoring System" for qualification purposes the general term "composite biomarker panel" should be used.

2. In your QP please outline the biological rationale for the use of each component of the composite biomarker panel. Outline how each of the components are related to the causal pathway of kidney allograft loss and how their measurement may serve as a surrogate endpoint biomarker to predict a decrease in long term risk of allograft loss in kidney transplant patients in IST clinical trials.

Context of Use (COU) Considerations

Requestor's COU: *The Integrative Box (iBox) Scoring System of eGFR calculated with serum creatinine, proteinuria, kidney biopsy histology assessment using the Banff scoring criteria, and presence or absence of de novo anti-HLA donor specific antibodies, taken together in the first year after transplantation is a reasonably likely surrogate endpoint for the five-year risk of allograft loss in kidney transplant patients for use in clinical trial studies evaluating the safety and efficacy of novel immunosuppressive therapies for Accelerated Approval Program submissions.*

FDA Suggested COU for continued biomarker development: *Composite biomarker panel used in the first year after transplantation is a reasonably likely surrogate endpoint for the five-year risk of allograft loss in kidney transplant patients for use in clinical trials to support evaluation of immunosuppressive therapy applications submitted via the Accelerated Approval Program.*

1. The biomarker description was removed since there is no need to repeat it as part of the COU.

2. In the LOI you say "analysis and discussion of the target population for the composite biomarker panel will thus be discussed in more detail in the QP submission." Please describe the patient population especially considering sex and race differences with some of the assays you plan on using.

3. In your LOI you interchange between the use of immunosuppressive drugs (ISD) and immunosuppressive therapies (IST) as descriptors for the therapies that will be the focus of the clinical trials. Since other immunosuppressive products such as biologics are already indicated to prevent or treat kidney rejection and will likely also be the subject of future clinical trials, we

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recommend that you stick to the IST descriptor.

Analytical Considerations

1. You propose to categorize the presence of dnDSA based on MFI values. However, the thresholds reported for clinically significant MFI values vary widely between studies. How will you overcome the assay reproducibility challenges that have been reported especially for the MFI values between reagent lots, laboratories, instruments and assay kits?

2. It has been reported that the presence of antibodies to denatured HLA was not associated with decreased graft survival. One possible problem is the denaturation of the HLA antigens during purification and attachment to solid surface such as Luminex bead, exposing cryptic epitopes. In your future submissions please consider this limitation along with the four other limitations discussed in the current submission.

3. Published studies indicated that not all DSAs detected by the Luminex-based assays appear to be equally and clinically relevant in solid organ transplantation. Many groups employ a combination of Luminex-based and cross match (cell-based) methods when assigning immunological risk. Please explain whether you will consider results from other methods (if available) in your analysis.

4. As you mention in your LOI, the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) Laboratory Working Group in collaboration with the European Federation of Clinical Chemistry and Laboratory Medicine initiated an effort aimed to reduce interlaboratory variation in creatinine assay calibration and to enable more accurate estimates of glomerular filtration rate [Clinical Chemistry, 52(1):5-18]. As a result, currently, a reasonable number of creatinine tests legally marketed in the US are traceable to the isotope dilution mass spectrometry reference measurement procedure (IDMS). However, not all laboratories in the US or outside the US (OUS) use methods that are traceable to IDMS and/or comply with the recommendations set forth by the working group. Therefore, you should consider and account for the sources of variability from different assays used to measure serum creatinine when building the composite biomarker panel and analyzing the data from the different specific data sources. You should also plan to account for those sources of variability and performance differences between assays used to validate the composite biomarker panel to show that it is reliable and fit for the context of use. In addition, you should consider using the validated IDMS-traceable equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating GFR for adults using creatinine results from methods traceable to IDMS are part of the recommendations set forth by the NIDDK working group. Also, for methods that produce results that have acceptable bias when compared to an IDMS-traceable method, you should consider the recommendation to use the IDMS-traceable MDRD Study equation.

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5. Measurements of total protein in the urine are widely used in clinical settings and there are many FDA-cleared quantitative and semi-quantitative assays available for use. However, assays that measure total protein in the urine are heterogenous and there is no standardization underway to overcome this heterogeneity. In addition, as you state in your LOI, dipstick tests for urinary protein provide semi-quantitative results whereas other methods used to measure urinary proteins provide quantitative results. It is unclear, at this time, which assays you will include to support the development of the proposed biomarker as you state that the determination of which measure of urinary protein and subsequent assay considerations will depend on the data available and will be discussed in future submission documents. In general, you should consider sources of variability (e.g., different methods to collect urine) and performance differences of the assays that you will use to derive your biomarker. You should plan to account for those sources of variability and performance differences between assays used to validate the biomarker to show that it is reliable and fit for the context of use.

6. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical assays and software may be publicly posted if the biomarker is successfully qualified by the Agency. Please confirm technical parameters 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.

Clinical Considerations

1. In your QP please outline all the biological evidence, with pertinent references, showing that this proposed reasonably likely surrogate endpoint biomarker will be able predict the clinical benefit of decreased kidney allograft failure with IST treatment**.**

2. Like in the Loupy et al. paper,[2] will a separate analysis be done to show the potential effects of treatments on the composite score in IST vs. control arms when such information is available in the datasets?

3. Please lay out your plan for validating the composite biomarker panel and include details of the validation data set.

4. The use of calcineurin inhibitor immunosuppression (cyclosporine or tacrolimus) can decrease the eGFR due to a hemodynamic effect, vasoconstriction of the afferent glomerular arteriole, without any consequence on glomerular mass or renal allograft survival. Please clarify how this potential artefact is addressed in the composite score, since the eGFR appears to be an important variable in calculating the score.

[2] Loupy A et al., 2019, BMJ 2019;366:l4923

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5. In kidney and other organ transplantation studies, Class II dnDSA (particularly DQ-dnDSA) have been reported as more frequent in patients with adverse outcomes and have been associated with late graft failure. How will you account for the differences in antibody class and specificities in your analysis**?**

Statistical Considerations

Please include the Statistical Analysis Plan (SAP) as part of your Qualification Plan submission. This should include a detailed description of your planned methodology to develop and subsequently validate the composite biomarker panel. Some key points are given below for your consideration:

1. You should first identify what datasets you plan to use in this biomarker qualification and provide the details of the corresponding studies in your Qualification Plan. In addition, specify which datasets will be used for the development of the composite biomarker panel as well as which datasets will be used for validating the proposed composite biomarker panel.

2. In addition to the baseline covariates, clearly identify the endpoints available in each dataset, including the availability of data at relevant timepoints (i.e., 12-month data for the potential composite biomarker panel components and 5-year data for the long-term clinical endpoint of allograft loss).

3. In addition, steps to be used for validation of the composite biomarker panel should be specified with details on how model prediction performance will be assessed for the intended context of use.

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].

If you have questions, please contact the CDER Biomarker Qualification Program (CDER-BiomarkerQualificationProgram@fda.hhs.gov) via email. We look forward to working with you on this beneficial project.

Sincerely,

Christopher L. Leptak -S

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Christopher Leptak, M.D., Ph.D.
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[3] https://www.fda.gov/drugs/cder-biomarker-qualification-program/biomarker-qualification-submissions

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