LOI DECISION LETTER

DDTBMQ000075

September 6, 2018

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

Dear Dr. Sauer:

We are issuing this Letter of Intent (LOI) Decision Letter to the Critical Path Institute's Predictive Safety Testing Consortium Nephrotoxicity Working Group (CPATH PSTC-NWG), and Foundation for the National Institutes of Health's Biomarker Consortium Kidney Safety Biomarker Project Team (FNIH BC-KSP), 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 April 10, 2018, and have concluded to **Accept** it into the CDER BQP[1]. We support and encourage your ongoing study and expanding the use of this promising safety biomarker panel to identify renal tubular injury in healthy individuals and patients with normal renal function in early clinical drug development trials.

You have proposed qualification of a panel of eight urinary proteins as safety biomarkers to be used together with three conventional kidney biomarker monitoring parameters [serum creatinine (sCr), Blood Urea Nitrogen (BUN), and serum cystatin C (sCysC)] in early clinical drug development trials to support conclusions as to whether a drug may be associated with injury to renal tubules in healthy individuals and patients with normal renal tubule function. As this biomarker development effort is refined in subsequent submissions, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below are most applicable.

Based on our review of the LOI, we agree there is an unmet need and agree that development of the proposed panel of safety biomarkers would potentially enable detection of an acute mild injury in the renal tubules before elevation of current standards (sCr, BUN, and sCysC) mentioned above.

[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.

For 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 validation of the 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.

In addition to the qualification effort, we encourage further study of your biomarker including collection of specified exploratory information from 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. 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. John-Michael Sauer, PhD (jsauer@c-path.org) the point of contact for this project, or view the Critical Path Institute website.

Biomarker Considerations

Requestor's Description: *A panel of 8 biomarkers including:*

Acronym	Name (Unique ID (Uniprot))
CLU	Urinary Clusterin (P10909)
CysC	Urinary Cystatin-C (P01034)
KIM-1	Kidney Injury Molecule -1 (Q96D42)
NAG	N-Acetyl-beta-D-Glucosaminidase (O60502)
NGAL	Neutrophil Gelatinase-associated Lipocalin (P80188)
OPN	Osteopontin (P10451)
ALB	Albumin (P02768)
Total Protein	No ID#

FDA's questions for continued development of the biomarker description:
We agree with your description of the above biomarkers.

Context of Use (COU) Considerations

Requestor's COU: *Eight novel renal safety biomarkers are to be used together with conventional kidney biomarker monitoring, serum creatinine (sCr), in early clinical drug development trials to support conclusions as to whether a drug has caused a mild injury response in the renal tubules in healthy volunteers and patients with normal renal function.*

FDA's suggested COU for continued biomarker development: Safety biomarker panel to be used in conjunction with three conventional kidney biomarkers (sCr, BUN, and sCysC) to indicate potential drug-induced injury to the renal tubule in individuals with normal renal function enrolled in early phase drug development clinical trials

To better understand the benefits of the identified panel of renal biomarkers as a Drug Development Tool, and to continue to refine the COU, please provide the following information;

1. After discussions with you surrounding the expanded context of use of the proposed novel kidney safety biomarkers, you have provided a decision tree to guide the use of the novel biomarkers. You have also clarified that the novel biomarkers will be used in conjunction with other clinical and traditional biomarker data to identify the high likelihood of kidney tubule injury and for making treatment decisions on an individual subject basis in early phase clinical trials enrolling normal healthy volunteers (NHVs) or patients with normal renal function in the setting of suspicion of nonclinical evidence of nephrotoxicity when injury and recovery has been demonstrated to be monitorable with these same biomarkers. Please rewrite your context of use to incorporate these concepts.

Analytical Considerations

2. In your previous analysis, you submitted validation data to support a COU for a cohort of healthy volunteers. In this submission, you are proposing that the assays can evaluate these biomarkers for individual patient analysis. Please explain how the analytical validation of the novel urinary biomarkers, excluding urinary albumin and protein (CLU, Cys C, KIM-1, NAG, NGAL, and OPN) is sufficient for decision making on an individual study subject basis and provide limitations regarding length of time that samples can be stored and whether a single batch of assays would be required for following an individual or cohort of subjects.

3. Please provide 510(k) numbers for the additional 2 biomarker tests (urinary Albumin and urinary Total Protein) or provide the analytical validation of the two biomarker tests used in your evaluation.

4. It is apparent from the design of your clinical trial and your statistical analysis plan that, depending on the results of the proposed analyses, it may be determined that the entire panel, a select smaller panel or individual biomarkers may be sufficient for individual subject decision making in early clinical trials. Please explain how these analyses will provide insight into the best combination of biomarkers to use for the proposed context of use and your thoughts regarding the pros and cons of qualifying a limited panel when you have only tested nephrotoxicity with two types of nephrotoxic compounds in your prospective clinical trials.

5. You provided long term stability studies for NGAL, clusterin, osteopontin, cystatin C and KIM-1 in centrifuged urine samples. You claimed that for a given analyte, stability at a time point was met if >67% of the samples met the stability acceptance criteria and an individual sample was considered unstable if it did not meet the acceptance criteria for

two consecutive time points. Stability acceptance criteria was 25% difference from baseline for NGAL and osteopontin and 30% difference from baseline for clusterin, cystatin C and KIM-1. However, different lots, operators, etc. were used at each time point, therefore if the % change in results of the quality controls in the testing exceeded the acceptable between-run precision of the assay, then a correction factor was applied based on the linear regression analysis of the QC results at the time point in question vs. baseline. It's unclear whether you know if instability of the analyte in the quality control would be a contributing factor to the % change of the results at each time point. The acceptable assay between-run precision criteria for this study was very high and it's unclear why these criteria were selected when the highest between-run precision seen in your studies (14.5% for clusterin, without desalting, 12.5% for osteopontin, 11.3% for cystatin C) were not as high as what you deem acceptable for this study. It's also unclear how much of a % change in analyte stability was eliminated in instances when a correction factor was applied. Also, the we do not concur that instability is only to be concluded to have occurred if a sample is unstable for 2 consecutive time points, given the broad acceptance criteria and that instability at the early time point is not being considered. We are concerned that significant analyte instability that would be acceptable per this protocol and the broad acceptance criteria could impact the clinical use of these biomarkers for your proposed context of use. If you think the allowable instability under this protocol and acceptance criteria would not impact the clinical use for this context of use (i.e., would it impact samples and how they would be interpreted per your proposed thresholds), you should provide a justification of why the instability allowable per this protocol would not impact the thresholds you have proposed for the 2 new clinical studies and the ones already performed. If the instability could impact the clinical use for this or future context(s) of use, you should consider: (1) tightening the acceptance criteria to levels that would not impact the clinical use for your proposed context(s) of use and provide your new long term stability claim, (2) assessing shorter long term stability time points or (3) not making claims that samples can be stored long term for testing with these biomarkers for this or any future proposed context(s) of use.

6. For NAG, you informed us that you previously submitted literature supporting long term stability of NAG; however, it is unclear if this was in urine and what the results were and how they would support long-term stability of NAG in urine for these proposed context(s) of use. You should assess the information you previously provided and inform us if the data are sufficient to support that the long-term stability would not impact the clinical use for this context of use (i.e., if would it impact stored samples and how they would be interpreted per your proposed thresholds). As stated above, if it would impact the clinical use for your proposed context of use, you should consider: (1) tightening the acceptance criteria to levels that would not impact the clinical use for your proposed context(s) of use and provide your new long-term stability claim, (2) assessing shorter long-term stability time points, or (3) not making claims that samples can be stored long-term for testing with these biomarkers for this or any future proposed context(s) of use.

7. We have reviewed the analytical validation provided for clusterin and NGAL in your submission for the PSTC/FNIH Nephrotox limited COU. As clusterin and NGAL are also

included in your current COU, you should address the following in your future analytical validation:

a. For clusterin, we recommend that all analytical and clinical validation should be done with a single sample type, desalted centrifuged urine, since results are significantly different when samples are prepared without desalting and centrifugation, as the data shows. In the PSTC/FNIH Nephrotox limited COU data, precision was not provided for desalted, centrifuged urine samples. Since desalting provided different results than samples that were not desalted, precision should be established for this sample type.
b. For NGAL, we recommend that precision be established for samples between 46 and 100 ng/mL since the precision evaluation provided only covered less than half of the claimed measuring range unless clinical samples will usually be limited to observed NGAL levels < 46 ng/mL.
c. You should describe how endogenous levels of the analytes were established, where applicable (e.g. recovery).
d. Recovery issues: Donor 25 had poor recovery at 2 dilutions (240 and 115 ng/mL (observed)) and no rationale or root cause was provided as to the cause of the poor recovery or in the phone call with you on 2/13/2018. The assay validation document states "It is assumed that an unknown interferent caused the inconsistent results for two out of three levels for Donor 25" but no information to support this assumption was provided. You should provide a root cause when issues with recovery (or significant issues in other analytical studies are detected) in future analytical validation studies for other contexts of use.
e. Interference testing for endogenous and exogenous compounds previously requested by FDA (e.g. specific gravity, pH, the drugs being given in this population) should be tested for clusterin and NGAL.
f. Clusterin stability at 2-8^{o}C, room temperature and -70^{o}C in the desalted sample type should be established and provided. Acceptance criteria like the other biomarkers in this context of use should be used. The criteria should be tight enough to minimize potential clinical impact.

Clinical Considerations

8. In your LOI, you stated that eight urinary biomarkers, or a subset thereof, will be used as a panel in conjunction with clinical information and the other traditional kidney function indices (sCr, BUN, and sCysC) to monitor for renal tubule injury. If only the primary efficacy endpoints are statistically persuasive, how will you describe to users how to make decisions on dosing in an individual subject? The adjudicators had access to but did not need to rely upon the 4 novel renal biomarker guideposts for making decisions, yet how they made their decisions and why they would not rely on the guideposts are not explained. How would the directions for use be written to help clinicians with guidance on how to interpret the novel biomarker results? Further, if some of the first secondary endpoints are met, do you think that a computer algorithm will be a better way to make individual subject decisions? The answer to this question may be based on the results. Please provide your thoughts on these issues and describe a sampling of different scenarios and how decisions might be made.

9. Please explain what action should be taken by the investigators if a single, multiple, or all biomarkers point to a potential renal tubule injury occurrence or if action should be decided upon (and prespecified) on a case-by-case basis depending on the seriousness of the medical condition and/or whether there is an unmet medical need?

10. In studies of the panel of biomarkers, how do you plan to control for other potential exogenous or endogenous sources of elevated urinary biomarkers, i.e., hypertension, sepsis, autoimmune disease, renal thrombosis, diurnal variation in biomarker concentrations, etc.? Will there be a caveat regarding interpretation of the qualified panel of biomarkers in these settings, or in the setting of concomitant injury to another organ, such as liver?

11. Please define the terms "healthy individuals," "normal renal function" and "mild injury response" and include the parameters and cut offs you will use in making these determinations.

12. In your COU, you state that the biomarkers will be used as a safety biomarker to assess for renal tubule injury in healthy individuals in early drug trials. You have provided 4 studies to support the qualification of these biomarkers for the proposed use in identifying renal tubule damage. None of the proposed studies include healthy volunteers under a drug trial who may be susceptible to renal tubule injury. Please explain how the data you have will be applicable for the subject population in your COU. If data from the animal studies completed since the original nonclinical qualification in 2008 will help support qualification of the panel for individual subject decision making in clinical trials enrolling normal healthy volunteers, please provide a synopsis of the data and be prepared to discuss any questions or provide data on those studies if requested.

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

Sincerely,

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