LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ000108
August 20, 2020

Innovative Medicines Initiative (IMI) TransBioLine
Drug-Induced Kidney Injury (DIKI) Work Package
Attention: Dr. Lidia D. Mostovy
One Health Plaza
East Hanover, New Jersey, 07936

Dear Dr. Lidia D. Mostovy:

We are issuing this letter to Innovative Medicines Initiative (IMI) TransBioLine Drug-Induced Kidney Injury (DIKI) Work Package, to notify you of our determination 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 Letter of Intent (LOI) deemed reviewable on May 15, 2020 and have concluded to **Accept** it into the CDER BQP[1].

Based on our review of the LOI, we agree there is an unmet need and support development of the proposed panel of safety biomarkers that may potentially enable detection of acute drug-induced glomerular injury risk in phase 1 clinical trials.

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.

Your next stage of submission, a Qualification Plan (QP), contains details of the analytical validation plan for the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and includes 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. Below, we provide you with specific considerations and recommendations to help improve your preparation for, and submission of the QP. For more information about your next submission and a QP Content Element outline, please see the BQP Resources for Biomarker Requestors web page.[2]

[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.
[2] https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors

Biomarker Description:

Requestor's Description: *A panel of molecular biomarkers that includes all or a subset of biomarkers listed below:*

Biomarker Protein	Gene	Uniprot ID
Nephrin	NPHS1	O60500
Podocin	NPHS2	Q9NP85
Synaptopodin	SYNPO	Q8N3V7
Angiopoietin 2	ANGP2	O15123
Matrix metalloproteinase 3	MMP3	P08254
Neutrophil gelatinase associated lipocalin	NGAL	P80188
Vascular adhesion protein 1	VCAM1	P19320
Caldesmon 1	CALD1	Q05682
Calponin	CNN1	P51911
Smoothelin isoform b variant	SMTNb	P53814
P-selectin	SELP	P16109
Thrombomodulin	THBD	P07204

FDA's questions for continued development of the biomarker description:

1. In your proposed list of biomarkers to be qualified, you have included multiple biomarkers shown to be directly related to glomerular injury (nephrin, podocin, and synaptopodin). You also included multiple biomarkers mostly related to angiogenesis and/or vascular damage (angiopoietin 2, matrix metalloproteinase 3, NGAL, vascular adhesion protein, p-selectin, and thrombomodulin). In addition, you listed multiple biomarkers known to be related to muscle function and injury (caldesmon 1, calponin, and smoothelin). In our search of scientific literature and regulatory submission databases, we have found that it is plausible for each of these biomarkers to be related to glomerular injury.

   However, since these biomarkers may be expressed for reasons other than glomerular injury, correlating that a change in a given biomarker is the result of glomerular injury may be difficult. When finalizing the list, we strongly suggest eliminating this possibility by carefully considering the reason for any correlation of injury and the biomarker and potentially confirming the results with multiple studies and different patient populations and healthy volunteers that are not likely to have similar sources for expression of these biomarkers.

Context of Use (COU) Considerations

Requestor's COU: *Novel Glomerular Biomarkers or a composite biomarker panel to be used as safety biomarkers in conjunction with traditional measures to aid in the detection of glomerular injury in early clinical trials in subjects with normal kidney function, when there is an a priori concern that the drugs may cause glomerular injury in humans.*

FDA's suggested COU for continued biomarker development:

2. We agree with your preliminary COU. However, the COU you propose is broad and includes possible drug-induced glomerular injuries in healthy volunteers. You may need to restrict the COU to the populations and/or injury mechanisms studied or include additional patient populations and mechanisms of toxicity. Please see comment 10 in the clinical considerations section.

Analytical Considerations

3. You provided analytical considerations in paragraph 4.2, 4.3 and 6 of your submission and you propose to study the following: (1) accuracy, precision, and recovery; (3) the calibration curve; (4) sensitivity; (5) reproducibility; (6) short-term stability (2h and 24h at RT) of analyte in spiked and non-spiked samples (7) and long-term stability (1, 3 and 6 months). However, since the device is still early in development, it is too early to specifically comment on the analytical validation needed to support the proposed COU. The analytical studies needed to demonstrate that the biomarker(s) can be used as stated in the COU will depend on the type of biomarker (e.g., CM or individual biomarkers), how the result will be interpreted (e.g., looking for a change from baseline, using medical decision points), the sample types, the methods, the patient population, the measuring range, etc. However, we noticed that some important analytical parameters were not included in the list or proposed studies including the evaluation of linearity and analytical specificity. Parameters that may be important to the relevant technology used to measure the biomarker(s) should also be considered such as drift and carryover. We recommend that, in your future Qualification Plan (QP) submission, you provide a description of the finalized biomarker measurement methods (including a description of the traceability of the measurement, how the biomarker will be used (and any medical decision points), the matrix type(s) and whether the test is qualitative or quantitative. You should provide detailed protocols used for your studies including a description of the purpose of each study. The protocols should include the following: the method(s) and instrument(s) used, the specimen (e.g., urine, plasma, native, contrived, quality control material), the specific concentrations of each target biomarker, the number of samples tested, the number of replicates tested for each sample, the number of days, the number of operators, the number of reagent lots used, and any reference materials used. All studies should be conducted using stable samples (i.e., stored and handle using validated conditions). The sample type and matrix type should reflect the clinical samples that will ultimate be used

and native patient samples should be used whenever possible (and especially around important medical decision levels). In general, we recommend that you refer to the following Clinical and Laboratory Standards Institute (CLSI) guidelines when designing your validation studies: C62 “Liquid Chromatography-Mass Spectrometry Methods”-First Edition and other applicable guidelines such as EP05-A3 “Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline-Third Edition”; EP06-A “Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline”; EP07 “Interference Testing in Clinical Chemistry”, EP37 “Supplemental Tables for Interference Testing in Clinical Chemistry” and EP17-A2 “Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition”.

4. As you develop and validate your biomarker, we recommend that you consider what performance is needed to support the COU of the test and determine acceptance criteria for validation studies based on the performance you determine necessary for this use. We recommend that you define acceptance criteria for each analytical validation study in the context of the cumulative effect that different sources of error, including bias or systematic differences as well as imprecision, have on test performance. You should define acceptance criteria for each parameter such that your total analytical error does not preclude the determination of clinically meaningful differences in the biomarker(s).

5. You also propose to measure the NGBs in urine and plasma in a second study that include 120 normal healthy volunteers to establish the variability in urine and plasma levels of those biomarkers and to assess impact of gender and age on that variability. We recommend that you clearly describe the purpose of this study (e.g., reference range study, cut-off determination study) in future submissions. For determining reference intervals, we recommend the CLSI guideline EP28-A3c “Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, 3rd Edition.

6. As structural components of the podocyte slit diaphragm, nephrin, podocin, and synaptopodin seem reasonable candidates for renal biomarkers. The detection of the other candidate biomarkers is not specific for renal injury as noted above. Depending upon the size of the fragments chosen for detection, the presence of angiopoietin 2, matrix metalloproteinase 3, NGAL, vascular adhesion protein, p-selectin, and thrombomodulin in some combination in the urine may be indicative of renal injury in general but unlikely to show specific glomerular injury.

7. Does the strategy of enzymatic fragmentation address polymorphisms and variability that may affect the fragmentation patterns? Does the strategy also take into consideration combinations of structural proteins that may occur in injury and be released as combined fragments of several different proteins?

8. The rationale for use of doxorubicin for determination of sensitivity is not clear. Doxorubicin

is recognized as producing multiple organ toxicity, including renal. Both tubular and glomerular effects have been noted in the kidney. Similarly, gentamicin, listed for another study, is recognized as producing renal tubular damage.

9. Consider conditions that are not primarily renal that may affect the baseline or variability of results, e.g. hydration status, heart rate, blood pressure, serum osmolality.

Clinical Considerations

10. After completing the learning phase of your development program, you propose to conduct two confirmatory phase clinical studies: one in patients with pre-eclampsia, and the other in patients with cancer who are treated with anti-VEGF antibodies. Drug-induced glomerular injury can be caused by different mechanisms and it is not obvious that the performance of the biomarker panel in patients with pre-eclampsia and patients treated with anti-VEGF antibodies can be extrapolated to other forms of drug-induced glomerular injury, such as those caused by podocyte injury. We encourage you to assess the performance of the biomarker panel in patients with a broader range of glomerular injuries and/or diseases or narrow your proposed context of use to settings in which the findings are most likely to be applicable.

11. We encourage you to assess biomarker variability in patients with stable chronic kidney disease (as defined by a reduced eGFR).

12. In your Work Package, you state that “Using the data sets developed from normal healthy volunteers (NHV) and glomerular injury patient populations proposed in our clinical plan, we will be able to define thresholds or cut-offs which would indicate an increased risk of glomerular injury.” Instead of attempting to define set thresholds/cut-offs, we encourage you to consider using the biomarker data, in conjunction with other clinical data, to develop a risk-prediction model.

13. As we also stated in the biomarker description section, please consider all the other possible sources for the chosen biomarkers. Please confirm that any change in the biomarkers is related to possible glomerular injury. Please choose subjects that are not likely to express the chosen biomarkers due to reasons unrelated to glomerular injury.

Statistical Considerations

14. The composite measure of each biomarker in the learning phase seems to be reasonable. But it is not clear how the threshold was determined in the learning phase so that 5% of normal participants and 30% of the patients with glomerular damage with FCB in CM ≥ the threshold. Will the percentages proposed above differ by age, by gender in normal participants?

15. Given that the threshold was determined as it was in the learning phase, the study design in the confirmation phase does not seem to provide the confirmation needed. You intended to test null hypothesis P_1=0.05 vs. P_2 = 0.30, while the study design and the Z-statistic used can only test P_1= P_2.

16. In the adaptive study design, please clarify the number of subjects to be added in case the interim analysis gives a non-inclusive conclusion. In the meantime, we suggest increasing the sample size at the second interim analysis, not at the first.

Please address each of the specific considerations and recommendations and any data requests cross-referencing the numbered list above in a separate addendum to your QP submission.

When evaluating biomarkers prospectively in clinical trials, requesters 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 plan to use the biomarker prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

The BQP encourages collaboration and consolidation of resources to aid biomarker qualification efforts. 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. Lidia D. Mostovy (lidia.mostovy@novartis.com), the point of contact for this project.

Should you have any questions or if you would like a teleconference to clarify the content of this letter, please contact the CDER Biomarker Qualification Program via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov with reference to DDTBMQ000108 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[3]

Sincerely,

Christopher L. Leptak -S

Digitally signed by Christopher L. Leptak -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300421152, cn=Christopher L. Leptak -S
Date: 2020.08.20 18:32:16 -04'00'

Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
Division of Biomedical Informatics, Research and Biomarker Development
Office of Drug Evaluation Science/Office of New Drugs
Center for Drug Evaluation and Research

[3] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program

Norman L. Stockbridge -S

Digitally signed by Norman L. Stockbridge -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300068764, cn=Norman L. Stockbridge -S
Date: 2020.08.21 05:44:05 -04'00'

Norman Stockbridge, M.D., Ph.D.
Director, Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

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