U.S. FOOD & DRUG ADMINISTRATION

LOI DECISION LETTER

DDTBMQ000094

February 4, 2020

TransBioLine
One Health Plaza
East Hanover, New Jersey 07936

Dear Lidia Mostovy,

We are issuing this 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 Letter of Intent (LOI) submission of September 27, 2019 and have concluded to **Accept** it into the CDER BQP.[1] We support and encourage the study of biomarkers for drug-induced vascular injury (DIVI).

You have proposed qualification of a safety biomarker for drug-induced vascular injury (DIVI) for acute vascular injury. Based on our review of the LOI, we agree there is an unmet need and that the development of a safety biomarker panel may be helpful in early clinical drug development trials to detect DIVI in healthy volunteers when there is an a priori preclinical concern that a drug may cause DIVI in humans.

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 it's 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 initial QP submission.

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[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.

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 Lidia Mostovy (lidia.mostovy@novartis.com), 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: *Drug-induced vascular injury biomarkers. A panel consisting of protein-based biomarkers across three categories: endothelial, smooth muscle and inflammation.*

1. This proposed biomarker composite includes many potential biomarkers. You have also proposed different analytical techniques for the different biomarkers. See clinical and analytical considerations sections for concerns about how you will narrow down this list to determine the final biomarker panel composition.

Context of Use (COU) Considerations

Requestor's COU: *A safety biomarker panel to aid in the detection of acute drug-induced vascular injury (DIVI) in early clinical trials in healthy volunteers when there is an a priori concern that a drug may cause DIVI in humans.*

1. The COU statement is acceptable

Analytical Considerations

1. The preliminary biomarker panel that you have proposed will include IP-LC-MS/MS, turbidimetric assay, ELISA, ECLIA, NGS, and RT-qPCR-based measurements. It is not clear if each assay will be evaluated independently, or if the results will be combined. If the results of the different assays

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are combined, you should consider how the different platforms will be consolidated into a test system. For example, if you combine the assays, the error rate that you are willing to tolerate in each assay will be additive across your test system.

2. Please note that the proposed discovery of the miRNA DIVI signature by next-generation sequencing and analysis of novel imaging methods for glomerular and ocular vascular injury/vasculitis are considered exploratory and won't be reviewed by FDA. There is no need to provide this information to FDA at this time.

3. You plan to use the Roche Cobas hsCRP assay to quantify C-reactive protein in serum (which is an FDA-cleared assay). You should consider for this context of use, if there are any additional risks or additional validation that you should conduct when considering this assay for inclusion in your test system.

4. You plan to conduct analytical validation of each assay included in your test system using contrived samples. It is not clear how contrived samples are representative of specimens that would be obtained from the intended use patient population. You should validate your test system using samples that are reflective of patient samples- both the composition of the specimen (e.g. anticoagulant, matrix) and the range of analyte concentrations that you anticipate may occur. It may be acceptable to supplement your testing with contrived samples if you can demonstrate that the contrived samples are representative of native patient samples.

5. You have not proposed analytical accuracy studies to assess if the assays that will make up your test system can successfully quantify the biomarkers you intend to target. For analytical accuracy, sponsors typically compare their device to an FDA-recognized reference method/standard or an FDA-approved or -cleared device, if available.

6. You have not proposed interference studies to assess the analytical specificity of each assay. Please refer to Clinical and Laboratory Standards Institute guidelines EP07-A3 "Interference Testing in Clinical Chemistry; Approved Guideline—Third Edition", EP37 "Supplemental Tables for Interference Testing in Clinical Chemistry", and EP05-A3 "Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition" when planning your study designs and data analyses. Your study design should consider the intended use population and the endogenous and exogenous interferents that are relevant to that population.

7. You have not described the metrological traceability of your test system; the results reported by your test system should be related to reference material(s) and/or reference method(s), if available, or internal standards through a documented, unbroken chain of calibrations, with each calibration contributing a stated uncertainty to the total uncertainty of your test system.

8. You have not defined the acceptance criteria for each study that you plan to conduct, and for those studies that you did define the acceptance criteria, the acceptance criteria were very broad. You should define acceptance criteria for each study that are reflective of the analytical performance that

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your device should achieve to support the context of use.

9. You have not provided sufficient information to determine if the experiments that you intend to conduct will be adequate to validate the performance of the RT-qPCR or LC-MS/MS assays. For each validation study, you should provide a detailed study protocol that describes (e.g.) the type of specimen used (native, contrived, or quality control), the specific concentrations of each target analyte (if known), the number of samples tested, the status of those participants (healthy vs. affected), the number of replicates tested, the number of days, the number of operators, if masking or randomization of samples was performed, the number of reagent lots used, and any reference materials used. For example, in the proposed limit of detection and limit of quantification studies for your RT-qPCR assay, you indicated "The evaluation of miRNA LLoQ will be performed using a 6-points serial dilution of synthetic oligonucleotides containing the targeted sequences". It is not clear from your brief descriptions that the 6-point serial dilution you intend to prepare will challenge your device, or that the synthetic oligonucleotides are representative of the intended use specimen. Your study protocols should be sufficiently detailed so that the reader could replicate your test and observe comparable results. In general we recommend sponsors refer to the following guidelines: 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", and EP17-A2 "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition" when planning your study design and data analysis.

10. You have not described the studies that you intend to conduct to validate analyte stability in each assay that will be included in your test system. In our experience, sample stability can vary depending on the analyte and the methods used. You should confirm the stability of the analytes you intend to measure under the context of use for this device.

11. You have not described the studies that you intend to conduct to validate the performance of the turbidimetric assay, ELISAs, or ECLIAs that will be included in your test system. For each assay that will make up your test system, you should evaluate accuracy, precision/reproducibility, analytical specificity, detection limit, and linearity (as needed). These studies should be done using relevant clinical samples from your intended use population. All studies should be conducted using samples that have been handled and stored using validated sample collection and storage conditions. We recommend you refer to the following Clinical and Laboratory Standards Institute guidelines: 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", and EP17-A2 "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition" when planning your study design and data analysis.

12. Section 507 of the FD&C Act includes transparency provisions that apply to your submission.

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Certain information about the analytical assay 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. You plan to evaluate the effects of sex, age, and ethnicity to establish reference range for healthy subjects. In your phase 1 study, consider evaluating other factors, e.g., food intake or circadian rhythm that may affect the reference range.

2. Will the drugs analyzed in the trials always be administered acutely or will there also be chronic administration? If chronic administration is also being considered, please describe the temporal regulation of the biomarker levels after exposure of the drugs under consideration in animals for a longer period.

3. You state that the vascular injury (VI) biomarker panel will minimally include ≥ 1 biomarker from each compartment (endothelial, smooth muscle, inflammation) to convey specificity to the vascular system as well as maintain sensitivity. However, since you have so many biomarkers to consider, and they are being measured in 3 different matrices by three different assays, how do you plan to consolidate all this information for the final biomarker panel? We understand that there is a learning and confirmatory phase, however an outline on your plans to determine the final biomarker panel will be necessary to include in the QP.

4. Will all the biomarkers have to change, or just a subset, for a clinical decision to be made. Can different combinations of biomarkers be used to effectively diagnose DIVI?

5. Will the biomarker panel be the same for each drug or will it vary depending on the drug or drug class being administered?

6. Will the results be quantitative (elucidate degrees of DIVI) or qualitative (indicating presence or absence, but not severity)?

7. In your QP please include a table that clearly outlines all the preclinical and clinical studies that show the evidence informing the selection of the proposed biomarkers. Include all the studies that have been done in both animals and humans using the same drugs or drug classes that are known to cause DIVI.

Statistical Considerations

1. In the decision tree (Figure 7-1), you mention “threshold guidance”. Please provide specifics for the determination of this thresholds guidance at which clinical decisions will be made (e.g. weighting,

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composite score)?

2. It appears that the components of the safety biomarker panel in the "confirmatory" phase may still be in progress, though it may reduce to a smaller set of biomarkers to be evaluated or selected from. In your qualification plan, please provide detailed statistical analysis plan (SAP) regarding your final safety biomarker panel. The SAP should describe how each component of the biomarker panel will be measured and what statistical analysis method(s) will be employed to demonstrate statistical evidence regarding your proposed context of use as a safety biomarker to aid in the detection of acute DIVI in early clinical trials in healthy volunteers where there is an a priori concern that a drug may cause DIVI in humans.

3. It was mentioned in the LOI document that "In the confirmatory phase, selected biomarkers from the learn phase will be further qualified using cross-sectional and longitudinal studies with larger patient cohorts with the same disease and conditions. Please ensure that your SAP includes specific studies (cross-sectional and longitudinal) and how each study will be analyzed in reference to the statistical comment #2 above. Additional statistical comments may follow upon our review of your SAP.

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.[2]

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.

Christopher L. Leptak -S

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

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