507 SUMMARY RESPONSE LETTER

DDTBMQ000037

April 12th, 2019

TransBioLine
One Health Plaza, East Hanover, New Jersey

Dear Dr. Mostovy,

We are issuing this 507 Summary Response Letter to TransBioLine 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 507 status update submission of Jan 14, 2019. We encourage your ongoing study of drug-induced vascular injury (DIVI) biomarkers.

You have proposed qualification of this biomarker panel to monitor acute vascular injury. As this biomarker development effort is refined in subsequent submissions, the submitted data, the specifics of your context of use (COU; including the target patient population and the application of the biomarker in what phase of trials), 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 status update submission we encourage TransBioLine to submit a new Letter of Intent (LOI) under section 507 for the following reasons:

- The biomarker panel is not the same one proposed under the initial LOI,
- The biomarker category and COU do not appear to be congruent with a drug development use,
- There is inadequate information on measurement of the biomarker or how you plan to evaluate a panel composed of multiple components, and
- This submission is made by a new requestor, and because there have been several significant changes and new areas that need to be addressed, the requestor must follow the process outlined in section 507.

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 the development of DIVI biomarkers or have information or data that may be useful can contact Dr. Lidia Mostovy, (lidia.mostovy@novartis.com) the point of contact for this project.

Biomarker Considerations

- ***Requestor biomarker description:*** *Drug-induced vascular injury biomarker panel*

  Type of Biomarker: molecular
  Short Name: DIVI biomarkers

  FDA's suggested biomarker description for continued biomarker development: The biomarker description depends on the COU for the new LOI (see COU considerations section).

- This project is still exploratory as highlighted by the fact that quite a few of the biomarkers changed from the LOI submitted by SAFE-T to the status update submitted by TransBioLine. You have outlined that the plan is to do a phase I "learning" stage to test and select the potential biomarkers in patients with vasculotides. You have not outlined what the criteria are to accept or reject a biomarker for the panel. In your LOI please describe what the decision process will be. How do you plan to interpret the panel if conflicting results for individual components are observed?

- You state that the biomarker panel should be able to determine DIVI irrespective of the drug mechanism and have focused on biomarkers that are proteins derived from endothelial cells or smooth muscle and other proteins such as non-specific indicators of inflammation. When you submit your LOI, clearly state the current understanding in the field of which drug mechanisms most often contribute to DIVI and the basis in models and studies for those beliefs.

- Please clarify if your primary interest is establishing biomarkers that detect DIVI risk with high sensitivity, high specificity or response indicative of recovery from injury.

Context of Use (COU) Considerations

- ***Requestor's COU statement:*** *The individual or panel of biomarkers of VI, for use in conjunction with the totality of preclinical and/or clinical information, can sensitively and specifically monitor acute VI (vascular endothelial and smooth muscle damage, and inflammation).*

The COU is still not finalized since you describe the COU as either a safety or monitoring biomarker in different parts of the document. One COU and one biomarker category are permitted per submission to aid us in providing you with relevant, focused recommendations and requests for supporting data in a timely fashion. According to BEST (https://www.ncbi.nlm.nih.gov/books/NBK338448/):

Safety biomarker- a biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

Monitoring biomarker-a biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

FDA's suggested COU for continued biomarker development:
Submit a new LOI for the suggested COU: A safety biomarker panel to aid in the detection of drug-induced vascular injury (DIVI) in phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause DIVI in humans.

Please use this as a guide to construct a COU that describes a drug development use for the specific population and describe the actions taken for the phase of drug development. For more information on construction of a COU please see the Biomarker Qualification Web site at; https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535395.htm. Elements of a COU include: Biomarker category, the population of interest, the DDT-based action (enrichment, dose adjustment, stop exposure, etc.) and phase of drug development.

Analytical Considerations

- You have not described the readout for the IP-LC-MS/MS and sandwich ELISA. How is it derived from the raw data, and what will be the cut-off for a biomarker detecting VI to make it to the confirmatory phase II?

- Next generation sequencing (NGS) for discovery of VI detecting microRNAs is still very exploratory. The same questions raised above for the other analytical methods are relevant to NGS. We recommend that you do not focus on NGS for qualification. Consider using a microRNA gene chip with appropriate candidate sequences for identification of potential target biomarkers. Use of available microarrays may be complementary to your efforts to identify appropriate candidate microRNAs.

- How will you interpret the biomarker panel? We recommend that you submit a decision tree or weighting criteria that will outline the selection process for the final biomarker panel and once selected describe how they will indicate VI. The decision tree should inform the response expected based on biomarker panel findings.

- You should characterize the analytical performance of the biomarkers and the panel (if the individual biomarkers are being somehow combined to generate a result). Therefore, for each biomarker and for the combined result (as needed), you should evaluate: accuracy,

precision/reproducibility, analytical specificity (relevant to the technology, the biomarker and the patient population), detection limits, and linearity (as needed). These studies should be done using relevant clinical samples depending on the matrix type that will be routinely measured for each biomarker (e.g. whole blood, plasma, and urine – including relevant anticoagulants, as needed). 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.

Clinical Considerations

- You have not outlined the action that will be taken once DIVI is detected, which is fundamental for a drug development tool (DDT). What phase of drug development do you plan to use this DDT? Will the drug treatment stop, or will the dose be reduced? What will be the defined threshold at which these decisions will be made and how will it be determined?

- The reference ranges for various components of the panel may be different in healthy subjects and in subjects with a target disease. How will your decision-making process adjust for this?

Statistical Considerations

- What is the variability within each group and the magnitude of difference between groups (healthy population, patients with vascular inflammatory conditions and DIVI patients)? What is the standard error for the observed population values?

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

Christopher L. Leptak -S

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

Norman L. Stockbridge -S

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Date: 2019.04.15 13:21:50 -04'00'

Norman L Stockbridge, M.D., Ph.D.
Director, Division of Cardiovascular and Renal Products (DCaRP)
Office of Drug Evaluation I
Office ofNew Drugs/CDER

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