LOI DECISION LETTER

DDTBMQ #000070

October 31, 2017

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

Dear Dr. Hanna:

We have completed our review of your updated Letter of Intent (LOI) submission of June 23, 2017 and have concluded to Accept it into the CDER Biomarker Qualification Program. Please note that the 21st Century Cures Act was signed into law and adds new section 507 to the Food, Drug, Cosmetic Act (FD&C Act) concerning the qualification of drug development tools (DDTs). For this project, we will be following the 507 process for DDT qualification.

For your project, you have proposed qualification of LAM (lipoarabinomannan) as a pharmacodynamic/ response biomarker to assess treatment response in clinical trials of patients with pulmonary tuberculosis (TB).

Based on our review of the LOI, we agree there is an unmet need in TB clinical trials for real-time assessment of treatment response during drug development. Currently, in TB clinical trials determination of efficacy is based on results of liquid or solid culture which may take up to 8 weeks. In contrast, LAM ELISA results can be available within 5 hours, enabling a much earlier determination of treatment response for an individual patient and thereby fostering potential for novel or adaptive clinical trial designs. In addition, LAM ELISA technology could broaden the opportunity for participation of more clinical trial sites in contrast with the limited number of laboratories capable of quantitative culture assessments. Initial studies appear to support the potential use of LAM for this context, but additional information is needed to confirm the acceptability of its use for the proposed context of use (COU).

The comments and questions contained in this document represent CDER's biomarker development recommendations for your proposed COU. For the 507 DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the recommendations outlined below and contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its COU, and descriptions of knowledge gaps and how they will be mitigated. If future studies are planned, please include the study protocols as part of your QP submission.

Biomarker Considerations

Requestor's Description: *Lipoarabinomannan (LAM) in sputum*

- We agree with your biomarker description.
- Please describe the specificity of LAM to *Mycobacterium tuberculosis*.

Context of Use (COU) Considerations

Requestor's COU: The LAM (lipoarabinomannan) biomarker will be used for quantitative measurement of bacterial load in sputum. A decrease of LAM in sputum reflects the reduction of bacterial load in the lung. This biomarker should be considered with other microbiological measurements, such as culture, as a real-time evaluation of treatment response in clinical trials of patients with pulmonary tuberculosis.

FDA's suggested COU for continued biomarker development: LAM assessment by ELISA is qualified as a monitoring biomarker for the real-time assessment of infection and drug treatment response, used in conjunction with other microbiological measurements (e.g., liquid or solid culture results), in clinical trials enrolling adult patients with pulmonary tuberculosis.

- Please note that culture results plus relapse-free survival one year after treatment completion would still be used as the primary endpoint in clinical trials that will be the basis for approval of a new drug.

- Are there patient populations for which the LAM ELISA would not be appropriate? Based on the information provided, the sensitivity decreases to 50-70% when the smear is negative and MGIT culture is positive. Should the use of LAM be limited in this patient subpopulation?

Analytical Considerations

- Based on your description, the LAM-ELISA kit is commercially available for purchase. Please provide information regarding the kit TB LAM ELISA by Otsuka Pharmaceutical Co., Ltd.

- Please provide details regarding the sensitivity and specificity of the ELISA kit antibodies including epitope mapping. An analysis of the sensitivity of the assay using samples obtained from patients with active pulmonary TB who are HIV positive and negative should also be provided.

- Based on the provided information, the LAM ELISA assay has a lower sensitivity than a MGIT culture. You have also stated that newer immunoassays with higher sensitivity are being developed. Do you plan to optimize the assay further to improve its sensitivity?

- A prototype version of the assay was used for studies 1 and 3 and a newer version for studies 2 and the FIND Panel Study. Before submission of your Qualification Plan, the expectation is that the analytical validation of the LAM assessment has been demonstrated for the version of the assay you plan to use for the future planned studies, and the cut-off value determined for the version of the assay selected, before conducting the clinical validation of the biomarker.

- Please clarify how you plan to address the potential for lot-to-lot variability of the antibody.

Once your LAM ELISA has been established and analytically validated, please provide the following information in the QP submission to determine if the LAM ELISA test would result in collection of useful data to support biomarker qualification:

- Measuring range of the test system including:
  a. Limit of Quantitation
  b. Limit of Detection
  c. Linearity and recovery evaluation of the measuring range

- Intra-assay precision. If multiple labs will provide data to support qualification, please also provide inter-assay precision. Please include your plan to address a potential issue of inter-assay consistency for the biomarker if the biomarker would be measured by different assay systems from the assays used in the biomarker qualification submission.

- If any interferents are known or suspected for the selected method, please provide a list, and the measures that will be taken to assure that interference is accounted for in the testing.

- Information about how any biomarker cutoffs and/or algorithm were developed. We recommend that this dataset be independent from the validation dataset since it is our experience that using the same dataset to develop and validate a biomarker can overestimate the performance of the biomarker.

- Information about the quality control material. We recommend that the control material should be of the same matrix (sample type) as the unknown samples being analyzed (if possible), be specific for the analyte, and sensitive enough to signal whether a component of the test system is malfunctioning. If biomarker cutoff levels are used, at least one QC material should be at, or near the cutoff, for each biomarker.

- A description of sample collection and storage conditions. We recommend that the sample collection and storage conditions be compatible with the testing method to ensure that the test result is reliable.

- If multiple sample preparation methods (e.g., with preservative) are used in testing, please provide evidence that the test results are equivalent across sample preparation methods.

- Description and traceability of any standards (i.e., controls and calibrators) used for the assays.

- Additional information should be provided on factors that impact LAM assay results, cross-reactivity, LAM measurements using sputum samples from patients with pulmonary disease other than TB, and data on the correlation of LAM concentrations to colony forming units (CFU) using solid and liquid culture.

Clinical Considerations

- Please provide any available additional data to support the interpretation that a LAM measurement of bacterial load below the lower limit of detection (LLoD) is equivalent to a negative sputum culture.

- Please describe how the slope of the bacterial load decline [similar to the 14-day early bactericidal activity (EBA) trials] will be used to select drug regimens and/or be used in adaptive clinical trials. A decision tree of how the biomarker information will impact clinical trial decisions would be useful.

- Please note that LAM is not intended to replace culture-based endpoints in clinical trials to support marketing approval.

Statistical Considerations

- If future studies are planned for qualification consideration, please include the statistical analysis plan for each study as part of your QP submission.

If you have any questions, please contact the Biomarker Qualification Program at CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Sincerely,

Christopher Leptak, MD/PhD
Director, CDER Biomarker Qualification Program
CDER/Office of New Drugs, Immediate Office

Sumathi Nambiar, MD
Director, Division of Anti-Infective Products
CDER/Office of New Drugs