BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

COMMENTS: The following information will be made publicly available as per the 21st Century Cures Act

Biomarker Project Information

Biomarker: Lipoarabinomannan (LAM) concentration with other microbiological measurements.

Therapeutic area: Pulmonary disease, specifically Tuberculosis (TB).

Patient Population: Adult patients with TB infection.

Administrative Information

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Submission Date: June 23, 2017 with no concurrent EMA biomarker submissions.

Drug Development Need

Current measurements of efficacy in TB drug development are based on culture, using either solid or liquid media. The first evidence of efficacy is usually obtained in early bactericidal activity (EBA) trials, which require quantitative culture (changes of colony forming unit counts on solid media). However, 4-6 weeks are needed to obtain quantitative culture on solid media, and the process is extremely labor and resource intensive. EBA trials are currently only performed in a very limited number of laboratories. Later phase 2 trial designs, which may range from 8 to 24 weeks in duration, focus on the proportion of sputum culture conversion (SCC) or the time to SCC on solid and/or liquid media (MGIT culture). The determination of SCC requires 6-8 weeks, therefore, causing a significant delay in obtaining efficacy results. The lack of a real-time assessment of efficacy prohibits accelerated and novel approaches to TB drug development.

A biomarker that can quantitate bacterial load during treatment in real time is likely to greatly improve TB drug development. If the real-time determination of LAM dynamic changes in sputum is shown to be equivalent to bacterial load dynamic changes measured by quantitative sputum culture, the sputum LAM could be used as a real-time decision-making tool in adaptive clinical designs of new TB treatment regimens.

- **Additional improvement by the proposed biomarker upon currently used standards**: Sputum LAM is a promising pharmacodynamic/response biomarker: LAM concentrations measured by the LAM ELISA correlate well with quantitative culture results, and results from the LAM-ELISA can be obtained in 5 hours.

- **Description of limitations for use of the proposed biomarker:** One limitation of the LAM ELISA is its lower

sensitivity, compared to that of MGIT culture. However, the LAM ELISA has a sensitivity similar to that of solid media based culture, with solid media cited in regulatory guidance as suitable for assessing sputum culture conversion as an endpoint in clinical trials. Additionally, specimens with LAM below the detection limit but still MGIT culture positive likely have very low bacterial load. Therefore, when considered with LAM prior to the start of the treatment, LAM dynamic changes can provide an estimate of treatment response. An additional limitation is that the LAM antibodies may not be MTB specific, and the LAM ELISA may detect non-tuberculosis mycobacteria (NTM). However, sensitivity of detecting NTM is much lower than for MTB. In a TB drug development clinical trial setting, subjects infected with NTMs (determined by other available tests) can be excluded from data analysis.

- **Is there potential use of the biomarker across multiple drug development programs?** Yes.

- **The biomarker is a composite biomarker (made up of several individual biomarkers combined in a stated algorithm to reach a single interpretive readout):** No

- **Therapeutic area:** Infectious disease

Biomarker Information

- **Biomarker name (for molecular biomarkers, please provide a unique ID) and type** (Molecular/Image/Anatomic, etc.): Lipoarabinomannan (LAM) in sputum is a molecular biomarker.

- **Biomarker description:** LAM is a major component of mycobacterium cell wall comprising up to 1.5% of total bacterial weight and thus is a major antigen of Mycobacterium tuberculosis (MTB) bacilli.

- **Biomarker Category:** Pharmacodynamic/Response

- **Biological rationale (underlying biological process):** The LAM ELISA measures the concentration of LAM in sputum. LAM is a major component of mycobacterium cell wall comprising up to 1.5% of total bacterial weight and thus is a major antigen of Mycobacterium tuberculosis (MTB) bacilli. Sputum coughed up from the lungs of pulmonary TB patients is used as the specimen for this test. The change in the concentration of LAM in sputum likely reflects the change of bacterial number in the lung lesion(s), as LAM concentration correlates with quantitative sputum culture.

- **Is this a composite biomarker?** No.

Context of Use

- **Proposed Context of Use (COU) Statement:**
  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.

- **Conditions for Qualified Use Include:**

1) An analytically validated LAM ELISA immunoassay should be used for the measurement of LAM in sputum,
2) Patient population is adult patients in clinical trials of drugs/regimens for treatment of pulmonary tuberculosis,
3) A sputum specimen is required to ensure the accurate measurement of bacterial load in the lung. Contamination of sputum with other bacteria should not impact the measurement of LAM,
4) It is proposed that this biomarker will be used in all phases of clinical testing to provide real time measurement of treatment response and facilitate adaptive clinical trial designs for testing new TB treatment regimens.

- **Drug Development Space for Biomarker Use:**
  - Early-phase clinical trials (e.g., Phase I or II)
  - Late-phase clinical trials (Phase III or post-marketing)

Biomarker Measurement (Analytical)

- **General description of what aspect of the biomarker is being measured and by what methodology**: The biomarker is LAM concentration in sputum. It is measured by an immunoassay using monoclonal antibodies against LAM. The available test, the LAM ELISA, uses the format of an enzyme-linked immunosorbent assay (ELISA). Second generation immunoassays with faster turn-around-time and larger dynamic range using the same antibodies are being developed. Sputum specimens are used for this test.

- **The biomarker test/assay is available for public use?** Yes.

- **The biomarker assay/test is cleared/approved or under review within the FDA Center for Devices and Radiological Health?** No.

- **The biomarker assay/test will be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory?** No.

- **A standard operating procedure (SOP) exists for sample collection, storage *and* test/assay methodology:** Yes.

- **A laboratory SOP exists for the assay/methodology:** Yes.

- **Performance characteristics are available for the biomarker assay/tests (sensitivity, specificity, accuracy and precision):** Yes.

- **Information about the specific technical platform:** Not applicable.

- **An analytical validation plan or data exist (e.g., sensitivity, specificity, accuracy, and/or precision of the assay or method)**: Yes.

Biomarker Measurement (Clinical)

Biomarker study and data considerations;

- **Clinical study data supporting the biomarker:** Yes.
- **Non-clinical study data supporting the biomarker:** Yes.
- **Type(s) of data available to support the proposed COU of the biomarker:** Retrospective data, prospective data, randomized controlled trials data, and non-clinical data.
- **Planned future studies:** Yes.
- **Statistician participating in biomarker qualification effort:** Yes.
- **Previous Qualification/Scientific advice received:** Critical Path Innovation Meeting on March 3, 2017, and informal discussions with EMA have occurred.

References:

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