LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000086

December 20, 2019

Tufts Medical Center
800 Washington Street,
Boston, MA 02111 USA

Dear Dr. Timothy McAlindon:

We are issuing this Letter of Intent (LOI) Determination Letter to Tufts Medical Center regarding 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 LOI submission that was deemed reviewable on September 5, 2019, and have concluded to **Accept** it into the CDER BQP[1].

You have proposed the qualification of End-stage KOA (esKOA) score as a pharmacodynamic/response biomarker for assessing treatments for knee osteoarthritis. Your proposal is to develop the esKOA as a composite score made up of both novel biomarkers and currently accepted clinical outcome assessment (COA) elements. Since only the biomarker element is novel, we are able to consider your project as part of the biomarker qualification program. Based upon our review, we recommend that you consider developing the proposed biomarker for a **prognostic** context of use. 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.

Based on our review of the LOI, we agree there is an unmet need and think that development of the proposed score as a prognostic biomarker may fill an existing scientific knowledge gap and would potentially enable identifying patients who are experiencing end stage knee osteoarthritis and who are more likely to undergo knee replacement surgery. Please see the comments below related to further development of the esKOA score and FDA's recommendations including a prognostic context of use.

For 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 validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and 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.

[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.

We encourage further study of your biomarker including collection of specified exploratory information from prospective 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 this biomarker in support of an Investigational New Drug (IND) or New Drug Application (NDA) development program they should prospectively discuss this approach with the appropriate CDER review 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 Dr. Timothy E. McAlindon, MD (tmcalindon@tuftsmedicalcenter.org), the point of contact for this project.

Biomarker Considerations

Requestor's Description: *End-stage KOA (esKOA): The composite incorporates WOMAC pain and function, Kellgren-Lawrence (KL) grade, number of compartments affected by osteoarthritis, knee instability, and range of motion. In brief, esKOA is defined by 1) a knee with KL grade = 4 with moderate-intense pain (Likert WOMAC pain + function > 11) or 2) a KL grade < 4 with intense or severe pain (WOMAC pain + function > 22) and limited mobility or instability.*

FDA's questions for continued development of the biomarker description: You described an esKOA score that combined biomarkers, number of compartments affected by osteoarthritis, knee instability, and range of motion, Kellgren-Lawrence (KL) grade, and included the clinical assessments WOMAC pain and function. The esKOA score you propose to qualify is a means to interpret and combine multiple biomarkers and clinical assessments. Please describe each feature, measurement or assessment that contributes to this overall score, how they are measured, how they relate to disease progression towards esKOA, and how they may contribute to identification of patients who will progress or will not progress to knee replacement.

Please note that a composite made of both biomarker and COA components may be unnecessarily complicated. For a prognostic COU (see below), you could simply focus on the biomarker components as a stand-alone drug development tool.

Context of Use (COU) Considerations

Requestor's COU: *"Pharmacodynamic/response biomarker for assessing treatments for knee osteoarthritis."*

FDA's suggested COU for continued biomarker development: "*Prognostic biomarker panel for use in clinical trials with subjects with a diagnosis of knee osteoarthritis to identify patients who are likely to experience long-term disease progression to end stage knee osteoarthritis (esKOA) defined as requiring knee replacement surgery."*

1. In our telecon with you on 9/5/2019, we discussed potential COUs for the esKOA score. In your submission, you identified a potential PD/response COU for esKOA. A PD/response biomarker is used to show that a biological response has occurred in an individual who has been exposed to treatment. To establish a PD/response biomarker, you must show a strong link between response to

treatment and changes in the biomarker. This task will be challenging as you are proposing to combine multiple components for this tool beyond biological measures, including patient-reported outcomes, into a single score. The issue is further complicated by the fact that many of these components alone, such as range of motion, are not well understood making it difficult to establish their connection with response to treatment. We suggest that a more practical COU for the esKOA score at this time would involve prognostic use to identify likelihood of progression to the point of needing knee replacement. You stated that the esKOA score strongly correlates with the risk of future knee replacement. Thus, for the esKOA score, a prognostic COU to identify patients, cohorts, or subsets that are likely to progress to a disease stage where a knee replacement would be necessary to retain same activity level for the patients could be appropriate.

Analytical Considerations

2. In your future QP submission, please include the following information for each of the features that will be a part of the final algorithm:
    a. How each imaging feature or other measurement contributing to the individual grades or scores included in esKOA is measured, derived, and/or scored in detail. Please describe the process for measurement or method of scoring in detail including any reader instructions, number of readers, assumptions, sources of error, specifications of the measurement device.
    b. Please provide the relevant performance characteristics including analytical and clinical validation information for each of the features that will be included in the scores.

3. Please provide an assessment of bias, statistical linearity, uncertainty, repeatability, reproducibility, and sensitivity of your quantitative measurements, an assessment of intra- and inter-rater reliability for any individual qualitative scores, and an analytical sensitivity analysis of your overall esKOA score that addresses the uncertainty associated with each contributing feature.

Clinical Considerations

4. Please include information on the clinical relevance, sensitivity and specificity of each of the components of the proposed biomarker for assessing esKOA.

5. In our suggestion for the COU, we included the requirement for a knee replacement surgery as a potential definition of esKOA. Please state if you agree with our suggestion. If you disagree, please explain what the appropriate criteria would be to decide whether a patient is experiencing esKOA, and how the esKOA score you proposed correlates with this set of criteria.

Statistical Considerations

6. Please submit a detailed statistical analysis plan in your qualification plan. We may have additional comments at that time on your proposed statistical analyses. As discussed above, it will be important to establish that each of these components and their proposed thresholds have truly important effects on clinical outcomes (i.e., long-term disability or need for surgical intervention in OA). Furthermore, you should consider how an effect on a single component, e.g., slight differences

in biomarkers, may affect the overall score and whether this is appropriate.

Sincerely,

Christopher L. Leptak -S

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Christopher Leptak, M.D., Ph.D.
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Office of New Drugs/CDER

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