U.S. FOOD & DRUG ADMINISTRATION

LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000087

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 to notify you of our determination 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 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 Cumulative Damage score and Disease Activity score as Pharmacodynamic/response biomarker for assessing treatments for knee osteoarthritis (KOA). Based upon our review, we recommend that you consider initially developing these two scores for a **prognostic** context of use for enrichment of studies with the population of interest. 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 for treatment of KOA and agree that development of the proposed as a prognostic enrichment biomarker may fill an existing scientific knowledge gap and would potentially enable identifying patients who are more likely to experience disease progression of KOA. Please see the comments below related to further development of these two scores and FDA's suggestions including a prognostic enrichment 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.

We encourage further study of these two scores including collection of specified exploratory information

[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.

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 these scores to support regulatory determination making for an Investigational New Drug (IND) or New Drug Application (NDA) 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 Dr. Timothy E. McAlindon, MD (tmcalindon@tuftsmedicalcenter.org) the point of contact for this project.

Biomarker Considerations

Requestor's Description: *Cumulative damage score: A MR-based composite score calculated from measures of articular cartilage damage at pre-specified informative locations distributed across medial and lateral distal femur, proximal tibia, and patella and localized using a 3-dimensional cartilage mapping application.*
Disease activity score: A MR-based composite score calculated from standardized measures of bone marrow lesion volumes and effusion-synovitis volume.

FDA's questions for continued development of the biomarker description: You described cumulative damage and disease activity scores as biomarkers for KOA. However, biomarkers are characteristics (such as a physiologic, pathologic, or anatomic characteristic or measurement) that are objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention. The two scores you propose to qualify are means to interpret multiple biomarkers in a clinically useful manner. Please describe each feature or measurement that contributes to these scores, including how they are measured and how they are related to the natural disease progression of KOA.

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 enrichment imaging biomarker panels 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 based on Kellgren-Lawrence (KL) grade, the WOMAC pain subscale,* and/or *radiographic lateral joint space narrowing (JSN)."*

1. In our telecon with you on 9/5/2019, we discussed potential COUs for these two scores which are based on structural imaging biomarkers. It is plausible that the changes in these biomarkers may be indicative of altering the underlying disease by a treatment. However, a strong link between changes in these biomarkers and the immediate response to a treatment with a disease altering claim may be difficult to demonstrate, as the effects of the drug on structural changes that is visible in images may be further downstream of immediate response to the drug. Thus, we suggest that you pursue prognostic enrichment for the COU. Our suggestion is based on the fact that currently used

inclusion/exclusion criteria for clinical trials, such as diagnosis of KOA, could be improved by identifying a subset of patients that are likely to have a poorer prognosis based on clinical assessments, and would be good candidates for any disease altering treatment.

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 scores:
    a. How each imaging feature contributing to both cumulative scores is measured, derived, and/or scored in detail. Please describe the process for measurement or method of scoring in detail including any reader instructions, assumptions, sources of error, specifications of the measurement device, or standardization methods.
    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 both the damage and the lesion scores that addresses the uncertainty associated with each contributing feature.

Clinical Considerations

4. Based on your LOI and our discussion with you, we suggest evaluating the possibility of combining multiple sets of structural biomarkers into a single decision algorithm, consisting of a single score or multiple scores used adjunctively, that is strongly associated with progression of knee OA. As such, a biomarker can be useful to objectively assess the change in progression as a response to a disease altering drug in a clinical trial.

5. Please describe the current standard for KOA stages or define a standard measure you may use for comparison to the CD and DA scores.

Statistical Considerations

6. Please provide a Statistical Analysis Plan of your Qualification Plan describing the calculation of any statistics and use of any models with sufficient details to support replication of your results by a reviewer. We may have additional comments on your proposed statistical analyses when reviewing these documents.

7. AUC of a ROC curve is a performance measurement for classification at various threshold settings and provides information on how well a model is capable of distinguishing between two meaningful classes of subjects (e.g., subjects who will have knee surgery and subjects who will not have knee surgery). We note that the thresholds used in the AUC analysis to dichotomize subjects into two

classes (KL progression, medial JSW progression, and WOMAC Pain worsening) have not been justified. For example, it is not clear that medial JSW progression greater than the median change in the development set (-0.23) is a meaningful dichotomization of patients to represent progressors vs. non-progressors. In this light, it is difficult to interpret these statistics.

8. At this time, you have not proposed a cut-off point for your biomarkers. If this is how you intend for this measure to be operationalized (to differentiate potential progressors from non-progressors), we recommend you include an appropriate statistical approach to demonstrate the prognostic utility of your proposed biomarker in the qualification plan.

9. Your analyses are based on 300 subjects from the Osteoarthritis Initiative (OAI) (100 for development, 200 for validation). You indicate in your included manuscript that these subjects were selected using stratified random sampling. Clarify how this sampling was done (e.g., the strata used) and how your sample sizes were chosen.

Sincerely,

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

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