U.S. FOOD & DRUG ADMINISTRATION

LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000089

February 25, 2020

Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium
11400 Rockville Pike
Suite 600
North Bethesda, MD 20852

Dear Dr. Stephanie Cush,

We are issuing this Letter of Intent (LOI) Determination Letter to FNIH 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 deemed reviewable on September 19, 2019 and have concluded to **Accept** it into the CDER BQP[1]. We support and encourage your ongoing study and the use of this promising biomarker.

You have proposed qualification of Osteoarthritis (OA) prognostic biomarkers as assessed by trabecular bone texture analysis. 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 agree that development of the proposed biomarker would potentially enable identification of individuals at high risk of (OA) progression.

For the 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.

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

[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.

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 determination making for a specific Investigational New Drug (IND) development program, they should prospectively discuss the approach with the appropriate CDER division.

Context of Use (COU) Considerations

Requestor's Proposed COU: *Prognostic enrichment imaging biomarker panel for use in phase 2 and 3 clinical trials to identify individuals with a diagnosis of knee osteoarthritis who are likely to experience disease progression within the subsequent 48 months based on the WOMAC pain subscale and/or radiographic joint space width loss and/or joint replacement.*

FDA's suggestion for continued development of the biomarker: We are supportive of your proposed COU.

At this time, we note that there are residual uncertainties of whether a definition of disease progression based on radiographic joint space width loss represents a clinically meaningful disease progression. Therefore, we encourage the development of a prognostic enrichment biomarker based on accepted measures of disease progression and recommend that you consider removing this metric from your COU.

Biomarker Considerations

Requestor's Biomarker Name: Trabecular bone texture (TBT) biomarkers (n=six) from fractal signature analysis (FSA) curves generated from the tibial subchondral region of plain knee radiographs; the six biomarkers are the vertical filter (VF) intercept, VF linear slope, VF quadratic slope, horizontal filter (HF) intercept, HF linear slope, and HF quadratic slope.

FDA's suggestions for continued biomarker development:

1. When submitting your QP, please provide more clarity on which biomarker(s) will be used, and if you intend to use multiple markers, guidelines for use and interpretation. If in your qualification package you intend to convert the proposed biomarker(s) to z-scores, please provide additional information on the reference population.

2. You state that your trabecular bone texture biomarkers are not yet incorporated into a finalized index/scoring system, but that you intend to explore and finalize an index and scoring system in the Phase II project. In your QP, please provide clarity on any index or scoring system you intend to employ, keeping in mind that development and validation of the scoring system should be conducted independently.

Analytical Considerations

3. You state your intention to use only the Optasia KneeTool software for FSA analysis and to generate the proposed biomarkers of trabecular bone texture. While such an approach may help in minimizing the variability in your analysis, we caution that biomarker qualification does not endorse or qualify a specific device/software. That is, the biomarker, not the measurement method, will ultimately be qualified. In your QP, please provide a description of your proposed analysis method sufficient to ensure that the biomarker can be used as a drug development tool by any interested party and confirm that you are willing to make this technical performance and other pertinent information publicly-available.
4. In your LOI, you provide a preliminary study of inter-observer variability (in which six radiographs were evaluated by three radiologists using the Optasia KneeTool software to generate TBT biomarkers) in which you conclude that the impact of individual analysts on FSA analysis was small and insignificant. We agree that this is an encouraging study of inter-observer variability of the Optasia KneeTool Software. However, as stated above, the biomarker, not the measurement tool, will ultimately be qualified. Therefore, please also plan to include inter-observer variability using different methods of FSA analysis within your Qualification Plan.
5. In addition to the variability introduced by different operators and different methods of performing FSA analysis, the performance of your analysis methods and the biomarker results may depend upon characteristics of the radiograph image quality (e.g., spatial resolution, contrast) and patient positioning (e.g., magnification, joint orientation). Please provide data evaluating the robustness of your biomarker for variation in radiograph image quality, including validation across different x-ray imaging equipment and imaging protocols typical of the clinical setting in which such patient radiographs are acquired according to standard of care for measurement of JSW and Kellgren-Lawrence grades of knee OA severity. You have stated that the image sample sources for Phase II will be radiographs from the placebo arms of seven completed randomized placebo-controlled clinical trials; while this is generally acceptable, the papers you provided as attachments describing these trials do not include sufficient details of the radiographic imaging methods for us to understand whether this data set is robust with respect to the variables mentioned above. Please summarize the x-ray devices used to acquire radiographs in these studies and the protocols used, and please consider stratifying your results by these variables. This data can then be used to objectively define a minimum image quality for which FSA analysis may be performed to obtain your biomarkers.

Clinical Considerations

6. In the absence of a universally accepted definition of disease progression for OA, we are generally supportive of your proposal to evaluate disease progression based on both WOMAC pain subscale and/or radiographic joint space width loss and/or joint replacement. However, we note that there are residual uncertainties of whether a definition of disease progression based on radiographic joint space width loss represents clinically meaningful disease progression.

Statistical Considerations

7. Please ensure that your QP includes a Statistical Analysis Plan (SAP). The SAP should describe how a biomarker will be measured and what statistical analysis methods will be employed to demonstrate statistical evidence regarding your proposed context of use as a prognostic biomarker for clinical trial enrichment. The SAP should also provide details of the statistical methods and statistical models if used, and statistical criteria on what would constitute statistical evidence of a prognostic biomarker. Additional statistical comments may follow upon our review of your SAP.

Please contact the CDER BQP at CDER-BiomarkerQualificationProgram@fda.hhs.gov should you have any questions regarding the content of this letter (refer to DDTBQP000089). We look forward to working with you on this project.

Sincerely,

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

Christopher L. Leptak -S

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Sally Seymour, M.D.
Acting Director, Division of Pulmonary, Allergy, and Rheumatology Products
Office of New Drugs/CDER

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