507 SUMMARY RESPONSE LETTER

DDTBMQ000038

May 6, 2019

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

Dear Dr. Menetski:

We are issuing this 507 Summary Response Letter to the Foundation for the National Institutes of Health Biomarkers Consortium 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 transition summary submission of November 20, 2018. We support and encourage your ongoing study for development of this panel of imaging biomarkers for prognostic enrichment of clinical trials for treatment of knee osteoarthritis.

You have proposed qualification of a panel of imaging biomarkers for prognostic enrichment to identify subjects with knee osteoarthritis in phase 2 and 3 clinical trials who are likely to experience long-term (up to 36 months) disease progression in the absence of treatment. 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 transition summary, we agree there is an unmet drug development need and agree that development of the proposed biomarker may potentially lead to prognostic enrichment of clinical trials for treatment of knee osteoarthritis.

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.

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 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 decision making for a specific Investigational New Drug (IND) 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. Joseph Menetski, Ph.D. (jmenetski@fnih.org) the point of contact for this project or view the Foundation for the National Institutes of Health website.

Biomarker Considerations

Requestor's Description: *11 knee joint magnetic resonance imaging (MRI) markers under five major MRI feature groups be approved by FDA as* ***prognostic biomarkers*** *for the enrichment/identification of subjects with knee osteoarthritis who are likely to experience long-term (up to 36 months) disease progression in the absence of treatment.*

Type of Biomarker: Imaging
Short Name: *FNIH-BC OA Biomarkers*

FDA's questions/comments for continued development of the biomarker description:

1. We recommend that the biomarker description be changed from "approved" to "qualified."

2. In your transition summary, you identified 11 specific features relevant to the functional integrity of the knee which are proposed to be measured and scored using the MOAKS method. You also stated that in phase 2, each of the 11 features will be evaluated individually and in combination for their potential to identify progression of OA, and a determination will be made on their inclusion in the final biomarker panel. In your biomarker description section in your future qualification plan (QP), please provide a detailed description of each biomarker including the underlying physiological feature(s) and how they are measured or assessed.

Context of Use (COU) Considerations

Requestor's COU: *Prognostic baseline MRI markers to enrich enrollment/identification of osteoarthritis patients that are likely to experience long-term disease progression in the absence of treatment in order to test disease-modifying drugs for knee osteoarthritis in phase 2 and phase 3 clinical trials.*

FDA's suggested COU for continued biomarker development: "*Prognostic enrichment imaging biomarker panel for use in phase 2 and 3 clinical trials with subjects with a diagnosis of knee osteoarthritis who are likely to experience long-term (up to 36 months) disease progression based on the WOMAC pain subscale* and/or *radiographic lateral joint space narrowing (JSN).*"

To better understand the benefits of the identified biomarker as a DDT, and to continue to refine the COU, please provide the following information;

Analytical Considerations

3. 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 the chosen feature 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, and 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 final algorithm individually and for the final algorithm itself (please see the clinical and analytical validation sections).

4. Please provide an assessment of bias, statistical linearity, uncertainty, repeatability, reproducibility, and sensitivity of your quantitative measurements (such as cartilage morphometry), an assessment of intra- and inter-rater reliability for any qualitative scores based on MR, and an analytical sensitivity analysis of your biomarker panel that addresses the uncertainty associated with each contributing feature.

Clinical Considerations

5. We note that there is no uniform definition of disease progression in OA. However, joint failure and the need for joint replacement are evidence of clinically relevant disease progression. Thus, to further support your QP, we recommend that you consider including joint replacement surgery in the definition of disease progression along with the currently proposed WOMAC pain subscale and/or radiographic lateral joint space narrowing. We also encourage you to explore a statistical model describing the prognostic utility of the proposed biomarker.

6. In the definition of radiographic progression, you propose to use JSN $\geq$ 0.7 mm over the follow-up period. We note that the clinical relevance of this threshold is uncertain and will need further justification, which could be informed from the OA Initiative, for example.

7. Related to the previous two comments for clinical consideration, we recommend that you also explore the prognostic characteristics of the proposed biomarkers with respect to a definition of disease progression based only on true clinical endpoints, such as joint replacement surgery and high threshold symptomatic/functional impairment that could be considered as a need for joint replacement surgery (without having the procedure done). Similarly, the definition of such thresholds could be informed by data from the OA Initiative as well.

Statistical Considerations

8. You state that 11 MRI baseline markers, on the basis that they performed well in phase 1 multivariable models, will be assessed to predict longer-term WOMAC pain scale and or clinical outcome of clinically relevant (pain and radiographic worsening) knee OA progression. Please provide details and a rationale to support the selection of the 11 MRI biomarkers.

9. In your draft Phase 1 results report, you state that medial meniscal volume is one of three baseline biomarkers that consistently predicted subsequent radiographic and pain progression. Explain your rationale for not including medial meniscal volume as one of the 11 MRI baseline biomarkers for further study of your proposed COU.

10. You proposed to validate the biomarker panel based on the progressive knee OA data from 6 completed trials. However, insufficient details for each trial are given. Please provide a detailed description of each trial including patient population, primary efficacy endpoint and originally planned sample size.

11. We acknowledge that you stated that you will initiate analyses under the phase 2 project to examine both the discrete cutpoint approach and continuous variables, and you could not advocate for specific cutpoints at this time. Please include the protocol and Statistical Analysis Plan (SAP) of the phase 2 project as part of your QP submission.

12. Please describe how the 11 discrete features will be applied to an individual patient as you stated in your summary. Please provide a very detailed decision algorithm and explain how each of these features will contribute to a decision to identify an individual as likely to experience long-term (up to 36 months) disease progression in the absence of treatment.

If you have questions, please contact the CDER Biomarker Qualification Program (CDER-biomarkerqualificationprogram@fda.hhs.gov) through email. We look forward to working with you on this beneficial project.

Sincerely,

Christopher L. Leptak -S

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