LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000090

February 25, 2020

Foundation for the National Institute 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, in part[1], into the CDER BQP[2]. We support and encourage your ongoing study and the use of this promising **prognostic** biomarker.

You have proposed qualification of Osteoarthritis (OA) prognostic biomarkers as assessed by immunoassays. 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

[1] See "Context of Use (COU) Considerations" section, below
[2] 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.

collection of specified exploratory information from 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 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 Primary COU: *"Prognostic enrichment molecular biomarkers 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."*

Requestor's Secondary COU: *"Prognostic biomarkers based on time-integrated concentrations (TICs) from baseline to 12 months, to provide a method for early identification of osteoarthritis patients to define 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 suggested COU for continued biomarker development:
We are supportive of your Primary proposed COU.

The Biomarker Qualification Letter of Intent (LOI) Content Elements (https://www.fda.gov/media/120058/download) specify that "only a single COU should be initially articulated for a given biomarker qualification submission." As the bulk of the supporting information in the application relates to the Primary COU provided, only it will be considered for this LOI. If you would like to continue development of the Secondary COU, please submit a separate LOI with its own supporting materials.

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: *"Osteoarthritis prognostic biomarkers as assessed by immunoassays: [urinary=u, serum=s] uCTXII, sPIIANP, and uC2C-HUSA (derived from COL2A1); sNTXI, uNTXI, sCTXI, uCTXIalpha, and uCTXIbeta (derived from COL1A1); and sHyaluronan (PDB name: 3HYA)"*

FDA's suggestions for continued biomarker development:

1. Please propose a single biomarker – either a single analyte or a fixed combinatorial model of multiple analytes whose performance in the proposed context of use can be evaluated and qualified.

Analytical Considerations

1. You plan to test serum and urine samples that have been stored either at -20°C for 8-10 years or at -80°C for 12 years. However, the analytical validation reports that you provided did not include evidence supporting long term stability of the biomarkers under each of the storage conditions where the specimens have been kept. We also note that in the freezing and thawing stability studies the "baseline samples" used underwent 1 cycle of freezing and thawing prior to testing. The purpose of an analyte stability study is to validate the specimen conditions that will yield results that reflect as accurately as possible the analyte levels of the patient when the specimen was collected. Therefore, the baseline sample should be a specimen that is analyzed soon after collection and prior to any storage condition, such that the difference in assay performance due to sample storage can be adequately evaluated. Please provide evidence sufficient to support that the long-term storage at -20°C and -80°C does not impact the stability of CTXI, HA, NTXI, and PIIANP in serum and C2C-HUSA, CTXIalpha, CTXIbeta, CTXII and NTXI in urine when results are compared to a valid baseline result.
2. The sCTXI, sPIIANP, uCTXIalpha, uCTXIbeta and uCTXII assays use biotin-streptavidin conjugation technologies, however, the analytical validation reports that you provided did not assess biotin interference for these assays. You should conduct a new interference study to characterize the susceptibility of sCTXI, sPIIANP, uCTXIalpha, uCTXIbeta and uCTXII assays to biotin interference. In addition, interference testing for endogenous and exogenous compounds (e.g. specific gravity and pH for assays intended to measure analytes in urine, the drugs that would be reasonably expected to be present in the intended use population) should be tested. We recommend that you reference CLSI EP07 guideline "Interference Testing in Clinical Chemistry; Third Edition", 2018, and CLSI supplement EP37 "Supplemental Tables for Interference Testing in Clinical Chemistry; First edition" 2018 when designing your interference testing studies.
3. Please evaluate the susceptibility of all the immunoassays to high dose hook (prozone) effect.
4. The reference range for PIIANP in serum from non- osteoarthritis (OA) 'super controls' was determined to be 1690 - 4431 ng/mL. However, the reportable range of the sPIIANP assay appears to be from 33 ng/mL (LLOQ) to 2100 ng/mL (highest calibrator concentration) and the report does not include evidence that samples above 2100 ng/mL can be accurately measured. Please provide evidence to support that the sPIIANP assay can be used to analyze samples with concentrations above 2100 ng/mL.

Clinical Considerations

1. 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 the 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 a clinically meaningful disease progression.

Statistical Considerations

1. 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 DDTBQP000090). 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.
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