Biomarker Qualification Letter of Intent (LOI) Template

Administrative Information

Requesting Organization

Name: Tufts Medical Center

Address: 800 Washington Street, Boston, MA 02111 USA

Phone: 617-636-5000

Website: www.tuftsmedicalcenter.org

Primary Contact

Name: Timothy E. McAlindon

Address: 800 Washington Street, Box 406, Boston, MA 02111 USA

Phone: 617-636-5645

Email: tmcalindon@tuftsmedicalcenter.org

Alternate Contact

Name: Jeffrey B. Driban

Address: 800 Washington Street, Box 406, Boston, MA 02111 USA

Phone: 617-636-7449

Email: jeffrey.driban@tufts.edu

Submission Date (MM/DD/YYYY): 05/13/2019

If there is a prior, current, or planned submission to other regulatory agencies, list the agencies and dates as appropriate.

No prior, current, or planned submission to other regulatory agencies.

Context of Use

Proposed Context of Use (COU) (limited to 500 characters)

Pharmacodynamic/response biomarker for assessing treatments for knee osteoarthritis.

Drug Development Need

Describe the drug development need that the biomarker is intended to address, including (if applicable) the proposed benefit over currently used biomarkers for similar COUs (limited to 1,500 characters).

Osteoarthritis of the knee (KOA) is a serious disease and a leading cause of pain, disability, and arthroplasty. KOA has few effective treatments and none accepted to reduce its structural progression. An ultimate goal of disease-modifying treatments is to avoid or significantly delay the need for joint replacement. Unfortunately, joint replacements may be influenced by the patients' expectation, the availability of the procedure in medical centers, the financial situation of the surgeons and the interaction between medical doctors and their patients. Thus, knee replacement in clinical research does not represent a validated endpoint, because the indication for knee replacement may vary by patient groups, countries, and even regions within a country. Furthermore, based on the data published by Ried et al (2015), the low occurrence of knee replacements (cumulative incidences: 0.9% to 12.9%) demands sample sizes that are impractical in clinical trials.

To overcome these barriers, we introduced a definition of "end-stage knee osteoarthritis" (esKOA) as a potential outcome measure. The definition was adapted from an appropriateness algorithm for knee arthroplasty (Escobar et al., 2003) and relies on a person's radiographic disease severity, knee pain, knee function, knee mobility, and

Biomarker Information

Biomarker name and description. If composite, please list the biomarker components.

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.

Type of Biomarker

- Molecular
- Histologic
- ✔ Other (please describe)
  Composite: radiologic, patient-reported outcomes, & clinician assessed range of motion and instability
- Radiologic
- Physiologic characteristic

Biomarker Information

For molecular biomarkers, please provide a unique ID.

Scheme: Please Select One

ID:

Matrix (e.g., blood) or modality (e.g., MRI): PROs

Primary biomarker category (see BEST Glossary): Pharmacodynamic/Response

Describe the mechanistic rationale or biologic plausibility to support the biomarker and its associated COU (limited to 1,500 characters).

End-stage KOA is an optimal biomarker for pharmacodynamic/response because it uniquely and comprehensively assesses KOA as a disorder that leads to structural changes, altered function, knee pain, limited mobility, and ligamentous instability. This overcomes the limitations of other biomarkers for KOA that focus on one aspect of KOA and neglects other relevant constructs. Besides delaying the need for joint replacement, other goals for KOA treatments are to reduce the deterioration of function and worsening of pain and prolong the time to end-stage disease. This biomarker provides a definition for end-stage disease that incorporates function and pain.

If biomarker is an index/scoring system, please provide information on how the index is derived (e.g., algorithm), the biologic rationale for inclusion of each of the components, the rationale for any differential weighting of the elements, and the meaning/interpretation of the index/score (limited to 1,500 characters).

Rationale: The components for esKOA were selected based on a consensus statement on the appropriateness for knee replacements (Escobar et al., 2003) that was adapted by Riddle D et al., 2014. Of particular note, pain and function are patient-centered outcomes that are commonly referenced as therapeutic targets for KOA. Furthermore, measures of radiographic disease severity are the current standard for assessing disease-modification for KOA.

Algorithms: The algorithm for esKOA is a decision tree (Driban JB et al., 2016; see list of publications)

Interpretation: Dichotomous outcome (esKOA or no esKOA)

Biomarker Measurement Information

Provide a general description of what aspect of the biomarker is being measured and by what methodology (e.g., radiologic findings such as lesion number, specific measure of organ size, serum level of an analyte, change in the biomarker level relative to a reference such as baseline) (limited to 1,500 characters).

Pain: Knee-Specific WOMAC Pain Subscale (PRO)
Function: Knee-Specific WOMAC Function Subscale (PRO)
Radiographic severity: Kellgren-Lawrence (KL) grade and number of compartments with joint space narrowing on a posterior-anterior weight-bearing semi-flexed radiograph
Knee stability: Clinician assessed varus-valgus laxity based on a varus and valgus stress test with the knee flexed 20°
Range of motion: Clinician assessed flexion contracture (≥5°) based on goniometric assessment

Is the biomarker test/assay currently available for public use? ○ Yes ◉ No

Indicate whether the biomarker test/assay is one or more of the following:

- Laboratory Developed Test (LDT)
- ✔ Research Use Only (RUO)
- FDA Cleared/Approved. Provide 510(k)/PMA Number:

If the biomarker is qualified, will the test/assay be performed in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory? ○ Yes ◉ No

Is the biomarker test currently under review by the Center for Devices and Radiological Health or the Center for Biologics Evaluation and Research?
○ Yes
◉ No
○ Don't Know

Is there a standard operating procedure (SOP) for sample collection and storage? ○ Yes ◉ No

Is there a laboratory SOP for the test/assay methodology? ◉ Yes ○ No

Biomarker Measurement Information

Describe the extent of analytical validation that has been performed (e.g., sensitivity, specificity, accuracy, and/or precision of the assay or method) (limited to 1,500 characters).

The definition of esKOA underwent a validation process:

We identified two groups of individuals: (1) never esKOA, neither knee met the criteria for esKOA at any visits in the Osteoarthritis Initiative, and (2) incident esKOA, neither knee met the criteria for esKOA at baseline, but at follow-up, ≥1 knee met the esKOA criteria. We calculated baseline and longitudinal descriptive statistics of individuals that never had esKOA or had incident esKOA. Longitudinal change was calculated based on value from the last available visit minus baseline values. We conducted independent sample t tests and chi-squared tests to determine differences between groups. To account for multiple comparisons, we used a Bonferroni-adjusted criteria to determine statistical significance ($p \leq 0.05$ divided by nine comparisons, $p \leq 0.0056$).

To evaluate if incident esKOA (outcome) was associated with osteoarthritis risk factors, we conducted unadjusted logistic regression analyses and then adjusted logistic regression analyses that included variables that were statistically significantly associated with esKOA in unadjusted analyses. Prior to conducting the

Additional Considerations for Radiographic Biomarkers

How has the method for image acquisition, analysis, and integration of the data been optimized? (Limited to 1,000 characters.)

Data Acquisition: The Osteoarthritis Initiative has an extensive protocol on how to acquire knee radiographs and assess knee range of motion and instability. The WOMAC questionnaire also has a detailed manual.

Analysis: SAS code is available to ensure consistent calculations of esKOA.

Does data currently exist to support the proposed cut point(s), if imaging results are not reported as a continuous variable?

○ Yes
◉ No

Provide the name and version of the software package to be used for image acquisition and analysis (limited to 500 characters).

N/A

Supporting Information

Please summarize existing preclinical or clinical data to support the biomarker in its COU (e.g., summaries of literature findings, previously conducted studies) (limited to 2,000 characters).

Among participants in the Osteoarthritis Initiative (OAI), 9.7% developed incident esKOA over a 48-month observation period. Only 82 (2.1 %) of participants received a total knee replacement within the same period. Those with incident esKOA had poorer health outcomes at baseline and greater declines in health outcomes, with the exception of SF-12 mental health score. Five out of nine tested risk factors were associated with incident esKOA in unadjusted analyses, with older age (≥65 years; odds ratio= 1.44, 95 % confidence interval=1.19 to 1.83) and quadriceps weakness (odds ratio = 0.78, 95 % confidence interval= 0.71 to 0.86) remaining significant in adjusted models.

Within the Osteoarthritis Initiative, a knee with prevalent esKOA at baseline (28.6%) or incident esKOA (19.4%) was more likely to receive a knee replacement than those who never had esKOA (1.1%).

Both the incidence of esKOA and knee replacements over the first four years of the OAI increase with rising age, severity of OA, and being female. The sample sizes to detect disease-modifying efficacy are considerably smaller if reduction of the incidence of esKOA is chosen as an endpoint instead of reduction of the incidence of knee replacement. Specifically, among adults with KL grades 2 and 3 and older than 50 years, the four-year cumulative incidence of knee replacement would be 6.99% (5.1 – 8.8) and the sample size for a hypothetical trial to demonstrate a 50% reduction of the incidence of knee replacement would be 671 per arm. In the same study group, the four-year cumulative incidence for esKOA would correspond to 23.36% (20.1 – 26.3) and the sample size to show a 50% reduction of the incidence of esKOA would be 199 per study arm, which in the real setting of

Please summarize any planned studies to support the biomarker and COU. How will these studies address any current knowledge gaps? (Limited to 2,000 characters.)

We are well aware that the proposed biomarker needs to be validated in future prospective controlled trials. Therefore, we recommend that the outcome “reduction of the occurrence of esKOA from baseline” should be included as secondary endpoint in future DMOAD trials.

Previous Regulatory Interactions

✔ None

Letter of Support (LOS) issued for this biomarker on date: _____

Discussed in a Critical Path Innovation Meeting (CPIM) on date:

Previous FDA Qualification given to this biomarker with DDT Tracking Record Number:

_____

Attachments

Please provide a list of publications relevant to this biomarker development proposal.

Optional* – If this biomarker development effort is part of a longer-term goal, please summarize your long-term objectives.*

Optional* – If you have other supporting information you would like to provide, please submit as attachment(s).

*Optional information will not be posted publicly.

Please refer to the Biomarker Qualification Contacts and Submitting Procedures for the mailing address and other important submission-related instructions. If you have any questions about submission procedures, please contact CDERBiomarkerQualificationProgram@fda.hhs.gov.