Biomarker Qualification Letter of Intent (LOI)

Administrative Information

1. **Submission Title**:
   - Osteoarthritis prognostic biomarkers assessed from radiographs
2. **Requesting Organization:**
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3. **Submission Dates:**
   August 30, 2019

Drug Development Need Statement

As recently acknowledged by the FDA[1], Osteoarthritis (OA) is a serious disease associated with increased risk of morbidity, disability and even mortality[2,3]. OA (knee and hip) ranks fifth among all forms of disability worldwide[4], and knee OA affects an estimated 250 million people worldwide[5]. Together, knee and hip OA are estimated to affect 10% of men and 18% of women in the world's population over age 60[6]. The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to knee OA alone is greater than that attributable to any other medical condition in people aged 65 years and older[7,8]. The only approved therapeutics for OA are analgesics. The absence of approved therapies to reduce the risk of OA progression[9] is due, at least in part, to the lack of qualified biomarkers to intelligently guide OA drug development and OA trial design and conduct. The current practice of attempting to identify individuals at high risk of progression based on parameters such as age, knee pain, body mass index, and baseline severity of knee OA is poorly prognostic of OA progression[10-12]. Qualified biomarkers are needed to establish a prognostic enrichment strategy (as defined in FDA guidance[13]) to select patients for trial inclusion with a high likelihood of substantial worsening of OA during the trial period (see Attachment 1). The FNIH Biomarkers Consortium PROGRESS OA project aims to address that need by qualifying biomarkers of OA progression, thereby improving the conduct and eventual success of OA clinical trials.

Biomarker Information and Interpretation

***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.

Biomarker type: Radiographic

Primary biomarker category: Prognostic

***Analytical methods*:** Raw measurements are six TBT biomarkers derived from complex FSA data based on a global curve shape analysis. In brief, the analysis involves three steps. **1)** Digital or digitized plain radiographs (the image type primarily used for fractal signature analysis) are first analyzed using the KneeTool software (Optasia Medical, Cheadle, UK). The software requires manual placement of six initialization points on the knee radiographs at the lateral femur, the medial femur, the lateral tibia, the medial tibia, the lateral tibial spine, and the medial tibial spine. Once the initialization points are selected, the software determines the joint space boundary profiles for both the lateral and medial compartments and automatically places a rectangular region of interest for extraction of fractal dimension and radius for FSA. The FSA region of interest (ROI) spans three-fourths of the width of the tibial compartment and has a height of 6 mm (determined using Synaflexer calibration) and a left boundary aligned with the tip of the medial tibial spine. This ROI is standardized based on methods described by Messent et al., who used this area in order to avoid periarticular osteopenia adjacent to marginal osteophytes[14]. **2)** KneeTool utilizes computer-aided detection–based modeling to provide highly reproducible quantitative measurements for FSA of the medial compartment of the subchondral bone of the knee, yielding fractal dimensions (FDs) over a range of scales termed radii and by both a vertical filter (VF) and horizontal filter (HF); a plot of FD versus radius is referred to as a fractal signature. Of note, the VF biomarkers inform on the state of horizontal subchondral bone trabeculae; similarly, the HF biomarkers inform on the state of vertical subchondral bone trabeculae. **3)** Although trabecular structure is not truly fractal in nature, trabeculae possess fractal-like properties at the resolution of the plain radiograph. For this reason, fractal analysis is a valuable analytic tool for characterizing the complicated histomorphometry of bone. One of the major challenges posed by FSA studies is how to analyze the complex fractal signature data. This third step involves statistical shape analysis of the FSA curves to provide a set of six TBT biomarkers for statistical analysis, such as evaluation of the biomarkers as predictors of OA progression in a statistical generalized estimating equation model or as predictors in a statistical linear mixed model.

***Measurement units and limit(s) of detection*:** FSA evaluates the complexity of detail of a 2-dimensional image (a projection of the 3-dimensional bone architecture) at a variety of scales (trabecular sizes defined by radii of different sizes) spanning the typical size range of trabeculae (100–300 µm) and trabecular spaces (200–2,000 µm)[15]. The units of measurement are a ratio of fractal dimension/radius. Attachment 2 lists mean (SD) of TBT biomarkers (raw values and z-scores) for comparators and OA progressors from PROGRESS OA Phase I analyses as summarized in Attachment 3[16]).

Biomarker interpretation and utility:

a. Post-analytical application/conversion of biomarker raw measure to the applied measure. Statistical shape analysis of the FSA curve is performed to provide TBT biomarkers for statistical analyses. This analysis involves modeling the shape of each FSA curve. Various statistical methods may be used including, but not limited to, spline, Fourier series, wavelet, polynomial, and the like. The method we have used for all of our work involves a global curve fitting approach with a second-order polynomial regression[11,16,17]. In brief, sets of TBT measurements are generated from fractal dimensions at a range of scales of trabeculae oriented in the vertical and horizontal directions. The fractal signature curves (FD vs. radius) are modeled with second-order (quadratic) multiple regression models using a non-centered polynomial[11,17] and/or a centered polynomial[16]. Thus, the multidimensional correlations between FD measures at these different scales are summarized by two or three

polynomial terms, which describe the functional "shape" of the fractal signature curves yielding TBT biomarkers. TBT biomarkers will be analyzed individually and as a composite using the subset of TBT biomarkers of the six that have the greatest discriminatory power for OA progression. In the Phase I PROGRESS OA study, a composite of three TBT biomarkers (VF linear slope and VF quadratic slope reverse coded and summed with the HF intercept) yielded the strongest predictor of knee OA progression[16]. This composite will be further analyzed in Phase II of the project. The TBT biomarkers are typically converted to z-scores for purposes of statistical analyses and comparison to other biomarkers.

b. Describe rationale for post-analytical elements used as inputs in application or conversion of the raw biomarker measurement. The TBT biomarkers will be used independently and in combination with the biochemical and other imaging (MRI) biomarkers in future to identify the most predictive algorithm for knee OA progression. For these analyses, and to compare the TBT biomarkers head to head with other domains or types of biomarkers, the biomarkers are converted to z-scores.

c. Clinical interpretive criteria. OA is a disorder of the whole joint organ involving cartilage, synovium, meniscus, and subchondral bone. Subchondral bone is one of the earliest tissues to demonstrate changes in OA[18]. TBT analysis is a method of determining the state of the vertical and horizontal trabeculae of a standardized ROI of bone. TBT reflects the state of subchondral bone in OA and therefore provides a promising set of prognostic biomarkers for heralding OA progression based on a plain (traditional) radiograph. TBT determines the complexity (reflecting thickness and thinness) of the vertical and horizontal trabeculae of a standardized ROI of subchondral bone from a radiograph, as described in greater detail below. Baseline TBT of the subchondral tibial bone in cohorts with knee OA has been shown to predict OA structural progression, as defined by radiography and/or MRI, over the ensuing 12–48 months[11,16,17], as well as knee joint replacement[19] and incident OA[20]. TBT also changes concurrently with loss of JSW, joint space area, and cartilage volume on MRI in knee OA progression[11,17]. Notably, TBT has not previously been evaluated for its ability to predict pain progression or the combination of pain progression and structural progression. Cut points have not yet been determined, but establishing cut points is a goal of the Phase II project. Preliminary indications of appropriate cut-points will be generated by analysis of existing FNIH Phase I data.

FSA produces FD values that are related to the roughness and complexity of the image. As described by Messent et al., the complexity of detail quantified by FD is determined principally by the number, spacing, and cross-connectivity of trabeculae[14]. High FD values are associated with high complexity of the image, reflecting thinning, loss, and/or undermineralization of trabeculae. Low FD values are associated with low complexity, reflecting trabecular thickening or a reduction in trabecular number and bony sclerosis[21]. Using nuclear magnetic resonance, it has been determined that the apparent FD is an index of bone marrow space pore size; pore size, in turn, is related to and increases with perforation and disappearance of trabeculae[22]. Buckland-Wright, the first to apply TBT methodology to the study of OA, considered increased horizontal trabecular thickness to be representative of early OA and an alteration that preceded changes in vertical trabeculae representative of later OA[23].

Consistent with all prior analyses, in the Phase I PROGRESS OA study, progressor cases were characterized by trabecular remodeling of both horizontal (thicker) and vertical (thinner and more complex) trabeculae of the medial tibial subchondral bone compartment of the affected knee[16]. In the Phase I study, relative to comparators, cases were characterized by higher HF and lower VF FDs, reflecting thinner (more complex) vertical trabeculae and thicker (less complex) horizontal trabeculae, respectively[16]. The summed composite of three TBT biomarkers (as z-scores with reverse coding of the two slope components) at baseline predicted case status with an odds ratio (OR) or 1.24 and C-statistic of 0.64; it must be noted that these data were generated comparing radiographic *and* pain progressors (n=184) to all others (neither radiographic nor pain [n=196], radiographic-only progression [n=98], and pain-only progression [n=100]). It is anticipated that ORs in extant clinical trials may be higher given the primary outcome of radiographic progression versus no radiographic progression and the proximity of the baseline measure in these trials to the outcome—24 months in the Phase II study vs. up to 48 months in the Phase II study).

Context of Use Statement (500 characters)

Primary 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.

Analytical Considerations

Please provide the following information (if applicable or available):

- *General description of what aspect of the biomarker is being measured and by what method*. The TBT biomarkers to be qualified herein are derived from plain knee radiographs. Data for TBT (subchondral bone trabecular texture [or index] biomarkers from subchondral FSA), will be generated from a plain knee radiograph using a method known as FSA based on prior work by Dr. C. Buckland-Wright (summarized in Kraus et al., 2009[11]). TBT data will be extracted from the same fixed flexion knee radiographs used for joint space width (JSW) and Kellgren-Lawrence grades of knee OA severity. Radiographic analyses will be performed using a validated and commercially available semi-automated software (KneeTool by Optasia Medical, Cheadle, UK). The entire process of data extraction for TBT analysis is automated except for a six-point manual initialization to automatically annotate femoral and tibial margins. In brief, with KneeTool, the analyst calibrates the image by deploying an automated process embedded in the software that is dependent on a ball-bearing target or Synaflexer bead apparent in the radiograph. The analyst is then guided through semi-automated measurement using a six-point manual initialization to automatically annotate femoral and tibial margins. The software then automatically determines FDs at approximately 18 radii of a rectangular ROI automatically placed in the medial subchondral tibial plateau; these data are used to extract six TBT biomarkers as described in several previous publications[11,16,17]. In addition, with high precision and reliability, the software automatically determines the inter-margin distances (IMDs), minimum JSW, and anatomic axis of limb alignment. The IMDs inform on the validity of the JSW measurement. The minimum JSW generated by the KneeTool will be used across all participants from all trials included for analysis in Phase II to provide a uniform (i.e., harmonized measure of radiographic knee OA progression). The anatomic axis of limb alignment will be evaluated on an exploratory basis as a covariate in OA progression models.
- *Index/scoring system*. Currently the TBT biomarkers are not incorporated into a finalized index/scoring system. We plan, however, to explore and finalize such an index in the forthcoming Phase II project. In Phase I of the PROGRESS OA project the best composite TBT score was derived by combining the z-scores of the three TBT prognostic biomarkers in univariable models. Two of the TBT biomarkers that predicted case status (VF linear slope and VF quadratic slope) had negative z-scores; therefore, they were reverse coded (sign changed) before they were summed with the HF intercept (for which positive z-scores predicted case status) to create a composite score. Receiver operating characteristic (ROC) curve (C-statistic) analysis was used to determine the predictive capability of the biomarkers. Biomarkers were evaluated individually or as a composite of three[16]. To predict knee OA progression, we aim to identify cutoffs for optimizing the positive predictive value of biomarkers used singly or in combination, as it is possible that a combination of biomarkers will be more useful for predicting knee OA progression than a single biomarker. In addition, we aim to investigate different definitions of knee OA progression: radiographic only, clinical only (pain progression and/or diminished function), radiographic *and* clinical (pain progression and/or diminished function), and knee joint replacement.
- *Description of sample source*. Radiographs (n=1326) from the placebo arms of seven completed randomized placebo-controlled clinical trials will be used: Calcitonin[24] (NCT00486434 and NCT00704847)

provided as Attachment 4; VIDEO[25] (ISRCTN94818153 trial of vitamin D) provided as Attachment 5; Cindunistat[26] (NCT00565812 trial of iNOS inhibitor) provided as Attachment 6; Sprifermin (I and II)[27] (NCT01033994 trial of FGF-18) provided as Attachment 7; and SEKOIA[28] (ISRCTN41323372 trial of strontium ranelate) provided as Attachment 8. The sample size available from the Calcitonin and VIDEO trials is dictated by the available biospecimens; the sample size available from the Cindunistat, Sprifermin I and II, and SEKOIA trial cohorts is dictated by the availability of MRI images at baseline and 12 or 24 months due to the fact that MRI biomarkers are being qualified in parallel with these radiographic TBT biomarkers in these trials.

- *Description of pre-analytical factors and quality assurance/quality control (QA/QC) plans*. Quality control for this study involves two measures: the primary radiographic outcome of change in JSW and the TBT measures. Only archived radiographs will be used for this research. The Optasia KneeTool software will be used to generate medial compartment JSWs for all radiographic images (n=1,326) in Phase II of the project. This will provide a harmonized primary outcome across all studies. The software also provides data on the medial tibial plateau IMD (distance between anterior and posterior rims of the tibial plateau) to determine the quality of the radiograph and thereby the precision of the primary outcome. Of note, although this criterion is important for accurate serial JSW determinations, it is not at all important for TBT biomarkers[11]; in fact, robustness of TBT to different knee positions constitutes one of its major advantages as an imaging biomarker for knee OA. To date, the interrater reliability of TBT has been excellent. As published previously[16], a subset of six radiographs (three from OA patients and three from non-OA controls) were analyzed by three analysts to test whether the FSA evaluation differed among individual analysts. The range and distribution of filter elements and the fractal signature for both the horizontal and vertical FDs were evaluated. The impact of individual analysts on FSA was small and nonsignificant. In order to test the impact of the analysts, linear regression was used to plot the findings of each analyst versus the mean filter element size or the mean fractal signature (horizontal and vertical) of the six knee radiographs. Using horizontal fractal signatures, the intercept and slope (R^2) in the findings of three analysts were determined to be 0.105 and 0.958 (0.93), -0.006 and 1.009 (0.86), and -0.99 and 1.032 (0.81). Using vertical fractal signatures, the intercept and slope (R^2) in the findings of three analysts were determined to be -0.05 and 1.022 (0.97), -0.13 and 0.94 (0.97), and -0.07 and 1.31 (0.97). Using a non-centered polynomial extraction, the intercept was determined to be 0 for all three, and the slope was determined to be 1.002, 1.002, and 0.995 (R^2 >0.99). Since the box used for FSA is not placed manually, we reviewed both the magnification factor of the Synaflexer calibration and the digitally determined location of the box used by the three analysts as a possible source of variation and found it to be small and nonsignificant. In all cases but one, the magnification factors were identical. In the other case, there was a 2.8% variation between one analyst and the other two. The median box size for the group of patients was 157 pixels (range 140–183) by 39 pixels (range 37–47). The differences in the area of the box were <9% among the individual analysts and for all patients.
- *Analytical validation plan*. This Phase II study represents the validation of the Phase I study in which TBT biomarkers at baseline and over 12 and 24 months predicted radiographic and radiographic plus pain progression of knee OA. Development of prognostic models will follow accepted model development strategy[29]. Each biomarker's predictive association to each outcome will be explored individually. Multivariable models with all candidate biomarkers will be constructed, using backward selection to remove variables not meeting nominal inclusion criteria ($\alpha = 0.05$). Final model performance will be assessed based on discriminatory ability and calibration. For identification of a combinatorial model, nomograms will be created based upon final multivariable models to provide a risk generation tool to assist in the identification of high-risk progression. Clinical nomograms are a pictorial representation of a complex mathematical formula and have been used in the OA literature to predict non-response to total knee replacement[30]. Optimal cutoffs will be explored retrospectively using existing Phase I data and validated in Phase II.
- *Once the SOP and analytical validation plan is finalized, describe how you will use this process to validate the final version of the measurement tool*. This Phase II study represents the final validation of the

generalizability of TBT as a prognostic biomarker (biomarkers used singly or in combination) for OA progression in eight extant clinical trials.

- *Additional considerations for imaging biomarkers*. All radiographs have already been acquired and therefore represent a "real-world" clinical trial scenario for testing TBT. As one of its strengths, radiographic TBT analysis does not require a perfectly positioned knee to provide high-quality data. However, to provide a reliable measure of radiographic progression, a properly positioned knee is important. As mentioned above, the integration of the studies will be accomplished by generating a measure of radiographic progression using the KneeTool software on all knee radiographs included in the Phase II analysis, and quality control will be tested using the KneeTool-generated IMD measure. The extraction of TBT biomarkers has been optimized by software interfacing with fractal data sets to generate TBT biomarkers quickly, efficiently, and reliably. This code was deployed in the Phase I aspects of this qualification effort[16] and will be utilized in Phase II as well. A subset of radiographs from Phase I will be reanalyzed by the radiographic image analysis provider to ensure reliability of code deployment in extracting the TBT biomarkers.

Clinical Considerations

- *Describe how the biomarker measurement is used to inform drug development. Please provide a decision tree to guide how the biomarker information would be used in drug development or a clinical trial*. The potential uses of TBT biomarkers in drug development or a clinical trial are described in Attachment 9.
- *Describe patient population or drug development setting in which the biomarker will be used*. The biomarkers are intended to identify individuals with radiographic knee OA who are at high risk of subsequent progression in order to enrich enrollment of knee OA progressors in OA clinical trials and thereby increase study power to show a treatment effect with disease-modifying OA drugs (DMOADs) once available.
- *Clinical validation: Provide information to support biological and clinical relevance of the biomarker as applied in the COU. Describe how normal or other reference values are established, provide study design(s), analytical plan, etc.* OA is characterized by an active and complex process involving mechanical, inflammatory and metabolic alterations that may affect the multiple joint structures of the joint organ[31], as demonstrated by MRI, including the hyaline articular cartilage, subchondral bone, synovium, and soft tissue structures such as the menisci[32]. Change in all these structures has been shown to be associated with clinically relevant progression of the disease. OA subchondral bone in particular has been likened to the "canary in a coal mine" due to its ability to serve an an early indicator of pathological changes[18]. TBT specifically evaluates subchondral bone. Six TBT biomarkers will be assessed in this Phase II analysis based on statistically significant prognostic capabilities demonstrated in the PROGRESS OA Phase I multivariable models that showed TBT could predict longer term clinical outcomes of clinically relevant (pain and radiographic worsening) knee OA progression[16]. It is still to be determined what will be used as the cut-off values, cut-points/thresholds, or boundaries/limits of the biomarkers to draw an actionable conclusion based on the biomarker result. These cut-off values will be determined by analyzing the existing data from Phase I and the data to be generated from the Phase II study. Qualification of TBT biomarkers will be performed comparing knee OA radiographic progressors—defined by $\geq$0.7mm of joint space width loss over the follow-up (12, 24, or 36 months)—versus non-progressors not meeting this definition.
- *Benefits and risks of applying the biomarker in drug development or a clinical trial*. Current OA trials suffer from low power due to inability to identify a subset of patients likely to undergo OA progression during the course of the trial. The TBT biomarkers are intended to overcome this major challenge to drug development by providing a cost-effective screening strategy (based on analysis of the typical screening knee radiograph obtained nearly universally in all trials to initially establish a radiographic OA diagnosis for potential enrollment) for enriching a trial with individuals likely to progress over the 24 months following enrollment in the trial. A strategy for even modest enrichment of a trial for OA progressors or for reducing screen failure rates (i.e., risedronate trials for OA had screen failure rates of 73%[33]) could have significant beneficial cost implications. The risk of not applying such a strategy will be to perpetuate the high failure rate of OA trials and

delay development of DMOADs.

- *Describe any current knowledge gaps, limitations and assumptions in applying the biomarker in drug development or a clinical trial*. Studies to support these biomarkers and COUs will be performed in Phase II of PROGRESS OA, an FNIH Biomarkers Consortium project. In Phase II, six TBT biomarkers will be qualified using available radiographs from the placebo arms of seven extant completed randomized controlled clinical trials (as described above). Presuming an OA progression rate of 11% (i.e., 148 participants out of 1349 progress), a predicting biomarker would have 83% power to be detected if its true underlying odds of impacting progression was 1.3 (i.e., 30% increase in odds of having clinical OA progression). In Phase I, the composite TBT score (consisting of three biomarkers) at baseline yielded an OR of 1.24 (p=0.02) for predicting clinically relevant (radiographic plus pain) OA progression; ORs were higher for TBT time-integrated values over 12 and 24 months (ORs of 1.32–1.43, p<0.005). Any increase in either progression or underlying odds of clinical progression increases power. Based on available data, we anticipate a 15% rate of progression in the extant trials used for these analyses, so these power estimates are likely conservative. We will generate a uniform measure of radiographic JSW using KneeTool software (Optasia Medical) for standardization and harmonization of the radiographic progression metric across studies. Funding is currently available for baseline quantification of TBT biomarkers. Because the Optasia KneeTool automatically generates FSA data along with JSW and all baseline and 24-month radiographs will be analyzed by the KneeTool, future analyses could evaluate kinetic responses (time-integrated values) for TBT biomarkers from baseline to 24 months.

Supporting Information

- *Underlying biological process or supporting evidence of association of the biological process with the biomarker*. Described above in Clinical Considerations, Clinical Validation subsection.
- *Summary of existing preclinical or clinical data to support the biomarker in its COU: (e.g., summaries of literature findings, previously conducted studies)*. In Phase I of the project, the association and prognostic validity of baseline imaging biomarkers with disease progression over 48 months was assessed both individually and in combination in a multivariable model aimed to determine the biomarkers that best describe the risk of future OA progression. The multivariable model was derived using logistic regression to evaluate the association between cases status and biomarkers. The models were evaluated unadjusted, adjusted for covariates (sex, race, baseline minimum JSW, baseline WOMAC pain score, age, body mass index, Kellgren-Lawrence grade, and use of pain medications), and adjusted with 10-fold cross-validation. Three different stepwise selection methods were used to determine the best subset of predictors, with selection based on Akaike information criterion (AIC), Schwarz-Bayesian information criterion (SBC), and p-value (p=0.2 for entry/p=0.1 for retention). The AIC and SBC differ with respect to model fitting: the AIC tends to favor more complex models that risk overfitting, while the SBC tends to favor less complex models that risk underfitting. Area under the curve (AUC) of the ROC curve (C-statistic), the integrated discrimination improvement (IDI), and the category-less net reclassification (NRI) were assessed for each model. The C-statistic for the composite TBT score was 0.64 for predicting clinically relevant (radiographic plus pain) progression.
- *Summary of any planned studies to support the biomarker and COU*. We will perform a retrospective analysis of Phase I results (generated from Osteoarthritis Initiative [OAI] biospecimens) to identify cut-point thresholds to optimize the positive predictive value. These cut-points will be assessed and tested in the eight new clinical trial validation data sets to determine their positive predictive value for knee OA progression.
- *Please describe alternative comparator, current standard(s), or approaches*. The current approach of identifying progressors relies on patient characteristics such as age, gender, and body mass index; these characteristics have been repeatedly shown to be poor prognostic indicators of risk for knee OA progression (summarized in Kraus et al., 2009 and 2018[11,16]). TBT radiographic biomarkers are attractive as a first-stage screening approach to identifying progressors due to their cost effectiveness and their derivation from a radiograph that has become the standard for all trials. Alternative approaches are being developed in parallel to qualify MRI and biochemical biomarkers as prognostic indicators of knee OA

progression.

Previous Qualification Interactions and Other Approvals (if applicable)

- *Qualification submissions to any other regulatory agencies with submission number:* None
- *Prior or current regulatory submissions to Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH):* DDTBMQ000038 and update submission for DDTBMQ000038 submitted 11.28.2018 related to MRI biomarkers as prognostic biomarkers for knee OA progression. In addition, a companion LOI is submitted concurrently for qualification of biochemical biomarkers in the PROGRESS OA Phase II study.

Attachments

- *Please provide a list of publications most relevant to this biomarker development proposal*. See list of attachments below.

- *Optional: If this biomarker development effort is part of a longer-term goal, please summarize your long-term objectives*. In future we also wish to analyze the treatment arms of these trials to test 1) whether these more sensitive biomarkers identify treatment benefits not recognized with the less sensitive radiographic endpoints and 2) whether a reanalysis of study participants, selected on the basis of a biomarker(s) cutoffs at baseline, yields a sample set showing drug benefit on the basis of the radiographic outcomes. We also plan retrospective analyses of existing Phase I PROGRESS OA data to inform Phase II analyses when the new data are available. For these analyses we will simulate a clinical trial screening process with biochemical and radiographic criteria as a first screen to simulate identification of trial participants for subsequent MRI with modeling of screening costs based on different strategies. Because the Phase I study included biochemical, radiographic (TBT), and MRI biomarkers, we will evaluate scenarios for their use in combination to optimize trial costs and performance; a draft manuscript is provided (Attachment 10) in which all three domains of biomarkers were evaluated using a multivariable regression approach. We expect to complete these analyses over the next 3 years in keeping with the FNIH Phase II PROGRESS OA project plan timeline.

- *Optional: If you have other supporting information you would like to provide, please submit as attachment(s):*
  - **Attachment 1:** Study design summary for TBT biomarker qualification
  - **Attachment 2:** Baseline values for the six TBT parameter values from the FNIH PROGRESS OA Phase I cohort study
  - **Attachment 3:** Phase I study of TBT biomarkers in the OAI cohort reported in Kraus et al. Predictive validity of radiographic trabecular bone texture in knee osteoarthritis: the Osteoarthritis Research Society International/Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. *Arthritis Rheumatol*. 2018;70(1):80-87.
  - **Attachment 4:** Study results of two oral salmon calcitonin trials (NCT00486434 and NCT00704847) reported in Karsdal et al. Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials. *Osteoarthritis Cartilage*. 2015;23(4):532-43.
  - **Attachment 5:** Study results of main VIDEO trial (ISRCTN94818153) reported in Arden et al. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. *Osteoarthritis Cartilage*. 2016;24(11):1858-1866.
  - **Attachment 6:** Study results of Cindunistat trial (NCT00565812) reported in Hellio le Graverand et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. *Ann Rheum Dis*. 2013;72(2):187-95.

- **Attachment 7:** Study results of Sprifermin trial (NCT01033994) reported in Lohmander et al. Intraarticular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2014;66(7):1820-31.
- **Attachment 8:** Study results of SEKOIA trial (ISRCTN41323372) reported in Pelletier et al. Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss. *Ann Rheum Dis*. 2015;74(2):422-9.
- **Attachment 9:** Decision tree describing use of biochemical biomarkers to inform drug development and clinical trials
- **Attachment 10:** Multivariable Phase I Results—DRAFT manuscript
- **Attachment 11:** References list