



## TRANSITION SUMMARY RESPONSE LETTER

DDTBMQ000054

October 16, 2018

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

Dear Dr. Kamphaus:

We are issuing this Transition Summary Response Letter to the Foundation for the National Institutes of Health 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 August 9, 2018. We support and encourage your ongoing study of the use of changes in dual-energy X-ray absorptiometry (DXA) bone mineral density scans in subjects at risk of hip and non-vertebral fractures as a quantitative response biomarker in investigational studies of anti-osteoporosis drug treatments.

You have proposed qualification of this imaging biomarker for subjects at risk of hip and non-vertebral fractures as an objective measure of response to investigational anti-osteoporosis drug treatments. 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 need and agree that development of the proposed biomarker would potentially demonstrate a measurable response to investigational anti-osteoporosis drug treatments.

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. Tania Kamphaus, PhD (tkamphaus@fni.h.org) the point of contact for this project or view the Foundation for the National Institute of Health website.

### **Biomarker Considerations**

***Requestor's Description:*** Bone Mineral Density

Type of Biomarker: Imaging

Acronym: DXA BMD

**FDA's questions for continued development of the biomarker description:** We agree with your description of the above biomarker.

1. You define the biomarker as "percent (%) change in DXA total hip bone mineral density (BMD)." Elsewhere in the proposal you do not include a skeletal site such as hip (e.g. p. 3, last paragraph). Please be consistent and explicit regarding the skeletal site(s) associated with your proposed biomarker.

### **Context of Use (COU) Considerations**

***Requestor's COU:*** Proportional change in dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) can be used to predict outcomes of hip fracture. We propose that results from DXA BMD scans in subjects at risk for hip and non-vertebral fracture can be a quantitative surrogate endpoint for response to investigational anti-osteoporosis drug treatments.

**FDA's suggested COU for continued biomarker development:** As a surrogate endpoint biomarker for traditional approval for patients at risk for osteoporotic (spine, hip and non-vertebral) fracture for assessment of investigational anti-osteoporosis drug treatments.

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

2. In the submission, you state the target population of interest will be postmenopausal women with osteoporosis. Please revise the COU to include the target population. If you decide to evaluate other subgroups of patients, you can revise the COU to include these subgroups.



3. It is important to clearly define the context of use of the biomarker and identify only one BEST<sup>1</sup> biomarker category. For example, although your COU is focused on response, in other parts of the submission you make reference to prognostic enrichment as well. While BMD may already be acceptable for use for other clinical trial purposes (e.g., inclusion criteria), it is helpful to be clear what the new COU goal is for this biomarker development effort.

### **Analytical Considerations**

4. Will the protocol require that the same DXA system be used for both baseline and 24-month measurements for *each subject* in a clinical trial? If so, an individual's percent change in DXA BMD will not be affected by changes in DXA system or normative database. If not, please explain how the protocol will account for differences in quantification due to using different systems at baseline and at 24 months for the same subject.
5. Will the protocol require that the same DXA system be used for *all subjects* in a clinical trial? If not, please explain whether and how the protocol will account for any differences in quantification due to different DXA systems. You suggested the possibility of pursuing "achievement of a specific level of BMD (a target)" instead of "percentage change in BMD." BMD level may be more dependent on manufacturer, model, and QC practices than percentage change. If you pursue BMD level, please explain how you will account for differences in manufacturers, models, and QC practices. You discuss universal standardized equations that you used in your meta-analysis. Would the protocol allow reliance on these equations for BMD-biomarker-based clinical trials?
6. Please state if any other method will be used with this method to assess or to adjust the measure of bone density.
7. To establish a baseline for the biomarker in the target population compared to healthy controls, you state the NHANES III study collected proximal femur BMD by DXA from over 7000 men and women age 20 years and older. Please confirm that the BMD-biomarker protocol will require that T-scores for postmenopausal women be computed using databases of women only.
8. Please describe the method to define a specific BMD cut point which could determine if there is a pharmacodynamic response. If percent change is the most reliable metric, how will a cut point be established for percent change in BMD for patients.
9. You state there are no interfering substances for this method. Metal pins or screws could affect the image. Please consider all sources of image interference or distortion in your analysis.
10. You should provide a list of minimum technical specifications for DXA systems to be used on BMD-biomarker clinical trials.



## **Clinical Considerations**

11. You refer to animal studies and other preclinical studies in your submission. Please provide a summary of the preclinical and animal studies used to support your studies. Please state how these studies support any clinical claims or understanding.
12. Since DXA BMD is used in medical practice, please describe how this qualification process will change how the biomarker is could be used in clinical trials or drug development.
13. BMD measurement in itself may not be adequate to determine the efficacy of a drug. Please consider including other bone mineral analysis or observations of bone such as bone histomorphometry to confirm safety or effectiveness of the drug.
14. In the analysis, total hip, femoral neck, and lumbar spine sites are used to measure the change of BMD. It is unclear why total hip is selected as the only site to assess BMD. Please explain why the total hip site will provide adequate information to assess BMD, and the other sites individual measurement or a combination of measurements is not needed to assess BMD.
15. The submission states that the study population will be post-menopause women who are diagnosed with osteoporosis. If a new drug is developed with a different mechanism of action targeting a different population such as men, the data from this study may not be sufficient to use BMD as a surrogate endpoint. Please consider the population and the drug mechanism of action during analysis and development of your context of use. Please define the population and types of drugs that will be assessed by the BMD biomarker.

## **Statistical Considerations**

16. Please provide more details on the FRAX statistical model. Please explain if this method will be part of the process to quantify DXA BMD data.
17. The following comments were previously conveyed as part of the legacy process and are still relevant:
  - a. Provide detailed documentation on the data structure and standardization of the data for the database that will be used to validate total hip BMD as a surrogate for hip fracture reduction. Include details about individual patient data quality, loss/exclusions (if any), and how missing data will be handled, etc.
  - b. Provide a detailed statistical analysis plan for both the study level and individual level meta-analyses.
  - c. Clearly define the study populations and subgroups of interest. Inclusion and exclusion criteria for analysis and stratified factors should be pre-specified.
  - d. To explore the relationship between total hip BMD and hip fracture, different candidate statistical models can be proposed for our review, e.g. time to fracture analysis or joint



modeling approach. The prediction performance of the chosen model should be evaluated. The duration of drug use and other important risk factors should be taken into account. The same analyses can be conducted with placebo treated subjects only to understand the natural relationship between total hip BMD and hip fracture.

- e. We suggest use of forest plots (study level vs. drug class etc.) to present treatment effects. Discussion of heterogeneity among studies or among drug classes should be part of the analysis plan and the clinical report.
- f. When preparing your statistical analysis plan, descriptions on how the PTE is calculated, e.g., in the non-linear model that you currently propose, should be included in the plan.

If you have questions, please contact Chris Leptak ([christopher.leptak@fda.hhs.gov](mailto:christopher.leptak@fda.hhs.gov)) through email. We look forward to working with you on this beneficial project.

Sincerely,

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