LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ000112
April 16, 2021

Foundation for the National Institutes of Health Biomarkers Consortium
Non-Invasive Biomarkers of MetaBolic Liver DiseasE (NIMBLE)
Attention: Tania Kamphaus, PhD
11400 Rockville Pike Suite 600
North Bethesda, MD 20852

Dear Dr. Tania Kamphaus:

We are issuing this letter to Foundation for the National Institutes of Health Biomarkers Consortium Non-Invasive Biomarkers of MetaBolic Liver DiseasE (NIMBLE), 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 Letter of Intent (LOI) deemed reviewable on January 14, 2021 and have concluded to **Accept** it into the CDER BQP[1].

Based on our review of the LOI, we agree there is an unmet need and support the development of this composite biomarker for diagnostic screening of NAFLD patients before liver biopsy, may be helpful to reduce the number of patients requiring liver biopsy as part of enrollment in NASH clinical drug development trials.

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.

Your next stage of submission, a Qualification Plan (QP), contains details of the analytical validation plan for the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and includes 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. Below, we provide you with specific considerations and recommendations to help improve your preparation for, and submission of the QP. For more information about your next submission and a QP Content Element outline, please see the BQP Resources for Biomarker

[1] 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.

Requestors web page.[2]

Biomarker Description:

Requestor's Description: *Individual or composite imaging biomarkers that includes all or a subset of biomarkers listed below:*

- Ultrasound biomarkers
  - Shear Wave Elastography (SWE) based Shear wave speed (SWS)
  - Vibration controlled transient elastography (VCTE) based liver stiffness
  - Vibration controlled transient elastography (VCTE) based controlled attenuation parameter (CAP)
- MRI Biomarkers
  - MRI based PDFF
  - MRI based cT1
  - 2D MRE Based liver stiffness
  - 3D MRE based liver stiffness

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

1. It is unclear how the cT1 liver imaging biomarker will be used and with what aspect of liver injury (fibrosis, inflammation, scarring) it is associated. Please provide a description of the impact of this biomarker individually and in the composite biomarker. Please provide a full description of your biomarker, including a clear description of how your device takes input data (such as MR images) and generates the output biomarker value (e.g. cT1 relaxation time).

2. As you state the final composite biomarker is not yet determined. It is unclear from your submission if the final biomarker will be a score of the composite measure, a panel in which each biomarker is independent of each other, or some other type of algorithm. Please provide information for each biomarker and its proposed impact to support the COU before providing analysis of the final composite marker.

3. In your QP submission please provide sufficient detail on the development and derivation of your composite marker. For example, if each biomarker is weighted, please provide information on the weighted value for each component in your final equation. If an algorithm is used to generate a composite score, please include the algorithm as part of your QP submission. If applicable, please include information about feature selection (e.g., if some candidate markers are excluded from the final composite).

[2] https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors

4. You listed seven different imaging biomarkers under considerations in this LOI submission. For the next submission, we suggest selecting the biomarkers or combination of biomarkers that are most promising and provide additional information on these biomarkers for the biomarker development. You may request a pre-qualification plan submission meeting to discuss biomarker selection and any subject specific questions you may have for the qualification plan submission. By selecting a subset of the most promising biomarkers, it may require less analysis and data. We are concerned a more substantial amount of evidence may be requested for all independent biomarkers and any composite, including analytical data for each measurement method, clinical analysis for the seven individual biomarkers, and potentially data to support a composite biomarker as well.

Context of Use (COU) Considerations

Requestor's COU: *A noninvasive imaging-based diagnostic enrichment biomarker intended for use, in conjunction with clinical factors and/or circulating biomarkers, to identify patients likely to have liver histopathologic findings of nonalcoholic steatohepatitis (NASH) and with a nonalcoholic fatty liver disease activity score (NAS) ≥ 4 and liver fibrosis stages 2 or 3 (by Brunt/Kleiner scale); and thus appropriate for inclusion in liver biopsy-based NASH drug development clinical trials focused on pre-cirrhotic stages of NASH.*

Analytical Considerations

5. Please provide a full description of the technical performance of your device and/or software used to measure each biomarker. Please ensure that this information includes:
    a. measurement reproducibility
    b. measurement performance across acquisition system (e.g., MRI, ultrasound) vendor, model, and software version
    c. analysis of how liver iron concentration affects the performance characteristics of cT1
    d. sensitivity and specificity related to decision points defined in the Context of Use

6. For all the imaging methods, please provide the algorithms used to produce the measurement values for the biomarker. This information is needed to understand the inputs and calculations used to derive the biomarker.

7. There are significant differences between your proposed use of the Fibroscan® device and what it has received in the 510K clearances. In your QP, please provide your analytical validation data for the device based on your proposed COU. Some of the analytical validation available 510k submissions may be applicable, but please provide an explanation on how this data supports your context of use. Additional analytical validation testing may be needed based on your proposed context of use and/or needed performance to support your context of use.

8. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Analytical information about the assays, device, and software may be publicly posted if the biomarker is successfully qualified by the Agency. To ensure the biomarker can be used as a drug development tool by any interested party, please confirm technical parameters and other pertinent information about the assays, device, and software that may be made public. The biomarker qualification process does not endorse the use of any specific device, assay or software with a qualified biomarker.

Clinical Considerations

9. You state histopathology will be used to provide a more comprehensive assessment of these biomarkers. Please provide the timeframe when the biopsy was taken and the imaging data was collected.

10. We recommend that you prespecify an algorithm or strategy to "deselect" several imaging biomarkers from the original seven that are identified. Ideally, one biomarker or perhaps two biomarkers would emerge as the optimal choice to submit for formal biomarker qualification.

11. Please provide comparison data from each imaging method. Ideally it would be helpful to analyze the different imaging modalities on the same patient to assess if the imaging biomarkers have similar trends in the patient. This comparison data from the different imaging methods will help assess the abilities of each imaging method and the individual contributions of each imaging method if a composite biomarker is proposed.

Statistical Considerations

In your Qualification Plan, please include a Statistical Analysis Plan (SAP) that describes the statistical methods you intend to use in your analysis with sufficient details to support validation of your proposed thresholds. Our preliminary statistical comments can be found below. We may have additional comments on your planned approach after review of the submitted Qualification Plan.

12. Your Qualification Plan should prospectively pre-specify what studies will be used to validate your biomarker performance. We recommend that you provide descriptions of design elements including study population, reference standards, sample size, and how the individual subject data will be collected and available by study.

13. You proposed different biomarkers methods and thresholds for your context of use. Please provide your rationales and ensure that you have sufficient numbers of patients in each of the categories of steatosis and fibrosis stage (i.e., <F2, F2, F3, and F4) and present diagnostic accuracy (i.e., specificity and sensitivity) for each category separately. Having sufficient number of subjects for each fibrosis stage is crucial to reliably estimate the diagnostic performance for enrichment in the NASH patient population.

14. The cutoff value (in kPa) shown in Table 5.3 of the LOI document "VCTE-based cutoff values (Young's modulus) by histologic fibrosis stage" is the same for any fibrosis, significant fibrosis and advanced fibrosis. Although the interest in classification may be to distinguish between stage 4 and the lower stages inclusive of stages 1, 2, 3 (or stages 0, 1,2, 3), as indicated in bullet #15 above, you will need to identify a unique cutoff value a priori for classifying patients into each of the stages.

Please address each of the specific considerations and recommendations and any data requests cross-referencing the numbered list above in a separate addendum to your QP submission.

When evaluating biomarkers prospectively in clinical trials, requesters 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 plan to use the biomarker prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

The BQP encourages collaboration and consolidation of resources to aid biomarker qualification efforts. 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 (tkamphaus@fnih.org), the point of contact for this project.

Should you have any questions or if you would like a teleconference to clarify the content of this letter, please contact the CDER Biomarker Qualification Program via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov with reference to DDTBMQ000108 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[3]

Sincerely,

Jeffrey N. Siegel -S

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Jeffrey Siegel, M.D.,
Director, Office of Drug Evaluation Science
Office of New Drugs
Center for Drug Evaluation and Research

[3] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program

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