



LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000084

February 10, 2020

Tania Kamphaus, Ph.D.
Foundation for the National Institutes of Health (FNIH) Biomarkers
Consortium 11400 Rockville Pike
Suite 600
North Bethesda, MD 20852

Dear Dr. Tania Kamphaus,

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 October 29, 2019 and have concluded to **Accept** it into the CDER Biomarker Qualification Program¹. We support and encourage your ongoing study and the use of this promising biomarker.

You have proposed qualification of a diagnostic enrichment biomarker to identify patients likely to have liver histopathologic findings of nonalcoholic steatohepatitis (NASH) as assessed by four circulating biomarker panels (to be used alone or in combination). As this biomarker development effort is refined in subsequent submissions, the submitted data 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 your Letter of Intent, we agree there is an unmet drug development need and agree that development of the proposed biomarker would potentially identify patients more likely to meet the histopathologic entry criteria for inclusion in investigational NASH drug clinical trials.

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.

¹In 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.

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 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 Proposed COU: *The selected biomarker “panel” (e.g., NIS-4, OWLiver®, ProC3/C6, ELF, or combination thereof) is a diagnostic enrichment biomarker intended for use, in conjunction with clinical factors, 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.*

FDA comments: We are generally supportive of the proposed COU, but wish to make the following editorial suggestions:

Suggested revised COU: *A diagnostic enrichment biomarker intended for use, in conjunction with clinical factors, 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.*

Biomarker Considerations

Requestor's Proposed Biomarker: *Four circulating biomarker panels (NIS-4, which quantifies microRNA34a-5p, alpha2-macroglobulin, hemoglobinA1c, and chitinase-3-like protein 1; OWLiver®, which combines 25 different molecular triglyceride markers; ProC3/C6, which quantified type III collage; ELF, which provides a quantitative measurement of hyaluronic acid, amino-terminal pro-peptide type III collage and tissue inhibitor or metalloproteinase 1), to be used alone or in combination*

FDA's questions for continued development of the biomarker description: The biomarker, independent of the measurement method, will ultimately be qualified. It appears that you intend to qualify biomarkers of liver inflammation and/or fibrosis; this description is preferable to providing the specific measurement tests in the biomarker description.

Prior to submitting your Qualification Plan, please provide more clarity on which biomarker(s) you intend to qualify, and if you intend to qualify multiple biomarkers, guidelines for use and interpretation of your proposed biomarkers. Our expectation is that your selection of biomarker(s) will be finalized prior to beginning your validation study(ies).

Analytical Considerations

1. The biomarker will ultimately be qualified independent of the measurement method used to assess the biomarker. Please be aware that qualification of the biomarker requires generalization and public dissemination of the performance specifications necessary to ensure that the biomarker can be measured with any test meeting those performance specifications.
2. Your LOI submission considers up to four circulating biomarker panels that you state will be considered as stand-alone panels or used in some combination in your final qualification package. Our comments regarding the analytical validation necessary to support qualification of your final biomarker will depend on which markers or panels you select as your final biomarker; therefore, our ability to provide detailed analytical validation considerations is limited until your final biomarker(s) are selected.

Clinical Considerations

3. Our understanding is that you intend to develop a biomarker to identify patients who are likely to be biopsy screen failures, and thus, should not undergo liver biopsy based on the result of your biomarker. In designing the clinical study to support such a use for your biomarker, we believe it is important that all patients meeting clinical enrollment criteria are biopsied (that is, patients are biopsied regardless of biomarker value); please confirm that this is your intent in the design of your clinical study.

Statistical Considerations

4. As part of your Qualification Plan, please include a Statistical Analysis Plan that describes the statistics and models you intend to use in your analysis in sufficient detail to support replication of your results by an FDA reviewer. Note that we are likely to have additional comments on your proposed statistical analyses after your specific biomarker(s) are finalized.
5. We remind you that your final biomarker will need to be validated using a dataset independent from that used in the development of your biomarker.

Please contact the CDER BQP at CDER-BiomarkerQualificationProgram@fda.hhs.gov should you have any questions regarding the content of this letter (refer to DDTBQP000089).

Sincerely,

**Christopher L.
Leptak -S**

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