LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ000117
December 16, 2022

Histoindex Pte Ltd
Attention: Anthony Lie
79 Ayer Rajah Crescent
#04-05/06 JTC LaunchPad
Singapore 139955

Dear Dr. Lie:

We are issuing this letter to Histoindex Pte Ltd, 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) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act. We have completed our review of the Letter of Intent (LOI) deemed reviewable on July 12, 2022 and have determined to **Not Accept** it into the CDER BQP[1]. As stated in section 507(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), an LOI submission may not be accepted based upon several different factors. A not accept determination is not a final determination for a biomarker and its context of use (COU). We encourage you to revise and resubmit an LOI for qualification upon addressing the listed considerations and recommendations.

We have provided you with considerations and recommendations in the appendix to help improve your preparation for re-submission of an amended LOI. Please fully address each of the relevant considerations, recommendations, and any data requests in your resubmission and in a separate addendum to your LOI resubmission, referencing the numbered list.

Biomarker Description:

Biomarker Name and description: *qFibrosis - Histology based quantitation of liver fibrosis using stain-free imaging modality*

Context of Use (COU) Considerations

Requestor's COU: *A diagnostic biomarker that is stain-free and AI-based, intended for use, in conjunction with clinical factors, to identify patients likely to have liver biopsy histopathologic findings of nonalcoholic steatohepatitis (NASH) and with a nonalcoholic fatty liver disease activity*

[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.

score (NAS) ≥4 and liver fibrosis stages 2 or 3 (NASH CRN system); and thus, appropriate for inclusion in liver biopsy-based NASH drug development clinical trials focused on pre-cirrhotic stages of NASH.

Based on our review of your LOI, the COU does not support how you plan to use the qfibrosis biomarker in clinical trials. Your LOI submission states that current histological assessment of liver biopsy sections is prone to inter- and intra-reader variability and error. Patients selected for NASH trial enrollment based on review of histology by a pathologist may no longer meet study eligibility criteria upon re-read which can impact study enrollment and assessment of drug efficacy. Based on the FDA draft guidance *Non-cirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment,* patients with a NASH activity score (NAS) ≥4 with at least one point each in inflammation and ballooning along with a NASH CRN fibrosis greater than stage 1 fibrosis but less than stage 4 fibrosis are eligible for clinical trials investigating non-cirrhotic NASH.[i] It is unclear how using this biomarker will facilitate execution of NASH clinical trial because the NAS score is a necessary component for eligibility and your biomarker only targets evaluation of fibrosis. Finally, it does not appear that your proposed study design will support how the biomarker will be used once qualified. More detailed comments are provided in the appendix.

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. Anthony Lie (Anthony.lie@histoindex.com) 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 DDTBMQ000117 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[2]

Sincerely,

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

Mary T. Thanh Hai -S

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Mary Thanh Hai, M.D.,
Deputy Director for Clinical
Office of New Drugs
Center for Drug Evaluation and Research

Frank A. Anania -S

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Frank Anania M.D.
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APPENDIX

Context of Use (COU) Considerations

1. The proposed COU does not appear to reflect the use of this biomarker in clinical trial use. The patients have been biopsied and this biomarker would not help select patients for biopsy who are more likely to have fibrosis stage F2 or F3. In addition, this biomarker does not evaluate the components of the NAS score and it is unclear how this biomarker would assist in determining patients who are more likely to have an NAS ≥4. The COU can be to help diagnosis patients for NASH clinical trials, but should also describe how it will be used as a diagnostic biomarker. Your COU should be revised to state how this biomarker will be used in drug development trials.

2. It is unclear how this biomarker will be used in clinical trials if it is qualified. Your proposed studies appear to show that this tool will help reduce variability when the histopathology is evaluated by different pathologists. If this biomarker is qualified, will it be used to reduce variability in readings from different histopathologists? Alternatively, will it be used to decrease the need for consensus readings for fibrosis staging? If your proposed study is successful, i.e., demonstrates a high concordance between a single pathologist reading with AI and an expert consensus read, it will still not avoid the need for consensus reading for NAS grading, and will therefore not decrease the need for pathologist consensus readings. Please provide a better explanation of how this biomarker will be incorporated into clinical trials and the benefits of its use.

Analytical Considerations

3. In addition to "The sequential procedure for establishing the algorithm includes (1) detection of collagen parameters …, (2) quantification of the architectural parameters …, (3) selection of the most significant parameters …, and (4) model construction, combination of parameters into a single index for fibrosis", provide further details on how the machine-learning algorithm was developed, what are the input and the output of the algorithm. How was the model constructed that should include specific parameters selected, selection criteria and how these parameters were combined into a single index for fibrosis? Clarify what is meant by stratified randomization when samples were assigned a priori.

Clinical Considerations

4. In your LOI submission, please explain how the qfibrosis score is compared to the current NASH CRN fibrosis scoring system. How is the qfibrosis score converted to the NASH CRN fibrosis score?

5. Given that criteria for enrollment and efficacy endpoints consider both stage of fibrosis and grade of inflammation, we recommend you consider incorporating NAS assessment in your study design (refer to above comment regarding COU considerations).

Statistical Considerations

1. Table 3 shows qFibrosis performance based on a dichotomized grouping. Provide the thresholds of the single index used for each row, e.g., F0 vs F≥1 and the standard of truth used to produce sensitivity, specificity, PPV and NPV. Also provide the details on the sample sizes to produce Table 3 analysis results.

2. Figure 2 provides a flow of how the qFibrosis score would be incorporated into clinical trials. It is unclear how this biomarker could be used as a diagnostic biomarker from the Figure. It is also not clear from the flow chart how qFibrosis will be used to improve agreement between histopathologist readings. Will the qFibrosis score be used before or after the individual histopathologist assessment of the slides. Will the study take into consideration if viewing the qFibrosis score produces any bias in the histopathologist readings?

3. Regarding the decision tree for the implementation of qFibrosis in Figure 2, it appears the cases where the liver biopsy is consistent with NASH, and staged F2, F3, but disagrees with qFibrosis is not taken into consideration. Please clarify.

4. There are three kinds of assessments, local pathologist assessment, qFibrosis read, and central pathologist assessment (panel consensus). There appears to be fundamental deficiencies (contradictions) in Figure 2 of decision tree and Figure 3 of validating qFibrosis:
   a. Based on Figure 2 decision tree of patient screening, whether a patients can be enrolled into pre-cirrhotic NASH clinical trial will first be assessed/screened by local pathologist along with qFibrosis, then assessed/screened by central pathologist for final decision. Thus, local pathologist assessment along with qFibrosis are not to replace central assessment via a sequential screening with the central assessment serving as final decision. However, in Figure 3, validating qFibrosis utility is through the comparison of qFibrosis with central assessment. Thus, there appears to be inconsistency between Figure 2 and Figure 3.
   b. Since there are three kinds of assessments, local, central and qFibrosis, how to refine/modify Figure 2 and Figure 3 to fulfil the COU and evaluate the utility of qFibrosis may be challenging.
   c. Another challenge is that, based on the COU and Figure 2, qFibrosis will be used to assist local pathologist assessment. However, there are inevitable

cases whether the local pathologist assessment and qFibrosis disagree with each other. Moreover, there will be central assessments as final decision. Thus, inclusion of qFibrosis in the Figure 2 decision tree appears to provide no utility.

d. Central assessment should include at least 3 central readers to make panel consensus.

[i] https://www.fda.gov/media/119044/download