U.S. FOOD & DRUG ADMINISTRATION

LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000082

April 12, 2019

Perspectum Diagnostics Ltd
23-38 Hythe Bridge Street
Oxford, OX1 2ET
United Kingdom

Dear Dr. Jaco Jacobs:

We are issuing this Letter of Intent (LOI) Determination Letter to Perspectum Diagnostics 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 of November 2, 2018, and have concluded to **Accept** it into the CDER BQP[1]. We support and encourage your ongoing study and the use of this promising diagnostic enrichment biomarker.

You have proposed qualification of Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue as a diagnostic enrichment biomarker to be used in in conjunction with clinical risk factors, to identify patients who are more likely to have liver histopathologic findings appropriate for inclusion in non-alcoholic steatohepatitis (NASH) clinical 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.

Based on our review of the LOI, we agree there is an unmet need and agree that development of the proposed biomarker would potentially enable identifying patients who are more likely to have liver histopathologic findings appropriate for inclusion in non-alcoholic steatohepatitis (NASH) clinical trials as mentioned above.

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

[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.

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. 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. Jaco Jacobs, PhD (jaco.jacobs@perspectum-diagnostics.com) the point of contact for this project.

Biomarker Considerations

Requestor's Description: Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue is derived from the fat and water component images acquired during an MR examination, and computed as the ratio: MRI-PDFF $= \frac{FAT}{FAT+WATER} x\ 100\ \%$.

Type of Biomarker: Imaging
Short Name: *MRI-PDFF*

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

Context of Use (COU) Considerations

Requestor's COU: "*Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue is a diagnostic enrichment biomarker that can be used, in conjunction with clinical risk factors, to identify patients who are more likely to have liver histopathologic findings appropriate for inclusion in non-alcoholic steatohepatitis (NASH) clinical trials."*

FDA's suggested COU for continued biomarker development: "*Diagnostic enrichment biomarker for selecting subjects who are more likely to have liver biopsy histopathologic findings of non-alcoholic steatohepatitis (NASH), appropriate for inclusion in NASH clinical trials; such patients will undergo liver biopsy to confirm eligibility for NASH clinical trial enrollment."*

Analytical Considerations

1. Please clarify how region-of-interest and/or segmentation was used to determine a single MRI-PDFF for each patient. Please provide a detailed analysis procedure including the number of MR slices, the regions analyzed, and any other image processing steps utilized in your data.
2. In your future qualification plan (QP), please provide an assessment of repeatability and reproducibility of MRI-PDFF. Regarding repeatability, we mean the same measurement under the same set of conditions within a short period of time (e.g., same patient, same scanner, data acquired back-to-back). Regarding reproducibility, we mean the same measurement acquired under different measurement conditions (e.g., same patient/phantom, different scanners, different days, etc.). Please

ensure that you provide reproducibility data that accounts for different sites and different scanners as well as different MR acquisition techniques. A combination of phantom and clinical data may be useful in these assessments.

3. In your future QP, please provide an assessment of agreement (including bias) of MRI-PDFF compared to histopathology assessment. In this assessment, please include the steatosis grade based on the NASH CRN scoring system (Brunt-Kleiner staging and grading system) and a quantitative assessment of fat in the histopathology sample. Please characterize the uncertainty in the biopsy-based quantitative assessment method (such as a stereology-based approach). If applicable, validation data should be provided for any automated algorithm used for independently assessing digital slides.

4. For any comparison of MR data and histology data, please describe how concurrence between the MR image and the biopsy location was established. We are aware that heterogeneity of tissue in the liver as seen on imaging may present a challenge when comparing to histology data. Please confirm that all of MR data were acquired prior to biopsy and note the time between imaging and biopsy for any data presented.

5. In your comparisons of MRI-PDFF with histopathological assessments of steatosis, please account for potential interactions with NASH activity score and fibrosis stage.

Clinical Considerations

6. You will need to address the following comments:
    a. Clarify which clinical risk factors you will use to identify subjects at-risk for NASH (e.g., BMI ≥30, T2DM, metabolic syndrome, elevated ALT, etc.).
    b. You need to exclude subjects with evidence of cirrhosis, given that steatosis starts to decline as the disease progresses, and in cryptogenic cirrhosis there is no steatosis.
    c. Exclude patients with prior histopathologic diagnosis of NASH.
    d. Currently, the FDA recommends including NASH subjects with NAS ≥4 with at least one point from each component (i.e., steatosis, inflammation and ballooning) and fibrosis stage 2 and 3 as diagnostic histopathologic criteria for enrollment in NASH clinical trials. Clarify for the "NAS ≥4 criterion" whether subjects in your training and validation cohorts met both of these criteria prior and/or post MRI-PDFF assessment. In addition, provide your rationale for use of Brunt steatosis score ≥2 as part of the selection criteria.
    e. MRI-PDFF may be suboptimal in identifying subjects with "NAS > 4" due to decreased accuracy with increasing inflammation and fibrosis.[2] Please address how these concerns may relate to results obtained from your trial.
    f. Your validation cohort study consisted of military subjects (as stated in your "The Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Adults" protocol), that included "all-comers" for detecting the prevalence of NASH. However, for the purposes of

[2] Wildman-Tobriner B, Middleton MM, Moylan CA, Rossi S, Flores O, Chang ZA, Abdelmalek MF, Sirlin CB, Bashir MR. Association Between Magnetic Resonance Imaging-Proton Density Fat Fraction and Liver Histology Features in Patients With Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis. Gastroenterology. 2018 Nov;155(5):1428-1435.e2.

validating the use of MRI-PDFF, the inclusion criterion for the validation study should be "subjects with clinical and/or laboratory risk factors" who undergo MRI-PDFF and liver biopsy to confirm the MRI-PDFF findings and to determine the sensitivity, specificity, and predictive value of the selected MRI-PDFF threshold. If there are no available data from your previous studies to address these concerns, you will need to prospectively address these issues by conducting an additional study(ies).

Statistical Considerations

7. Submit the statistical analysis plan for the clinical validation study that prospectively addresses issues raised in clinical considerations section.

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

Sincerely,

Christopher L. Leptak -S

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Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
Office of New Drugs/CDER

Bindi M. Nikhar -S

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