TRANSITION SUMMARY RESPONSE LETTER

DDTBMQ000051

January 19, 2019

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

Dear Dr. Jacobs:

We are issuing this Transition Summary Response Letter to Perspectum Diagnostics Ltd, to notify you of our feedback 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 of September 16, 2018. We support and encourage your ongoing study to use iron corrected T1 (cT1) liver MR images to identify patients who are more likely to have liver histopathologic findings appropriate for inclusion in non-alcoholic steatohepatitis (NASH) clinic trials.

You have proposed qualification of a diagnostic enrichment imaging biomarker to identify patients more likely to have histopathologic findings for inclusion in NASH new drug 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 transition summary, we agree there is an unmet need and agree that development of the proposed biomarker would potentially demonstrate inclusion criteria for investigational NASH drug clinical trials.

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. Jaco Jacobs (jaco.jacobs@perspectum-diagnostics.com) the point of contact for this project, or view the Perspectum Diagnostics Ltd website.

Biomarker Considerations

Requestor's Description: Iron Corrected T1 MR image of liver tissue

Type of Biomarker: Imaging
Acronym: Iron cT1 MRI

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: *Iron corrected T1 (cT1) relaxation time 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 Recommended COU:
Iron corrected T1 (cT1) relaxation time 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 of nonalcoholic steatohepatitis (NASH). Ideally, this biomarker should identify patients with a nonalcoholic fatty liver disease activity score (NAS) $\geq$ 4 and liver fibrosis (NASH/CRN Brunt/Kleiner scale) $\geq$ stage 2 on histopathologic assessment.

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

Analytical Considerations

1. 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. Please provide a full description of the technical performance of your device/software. Please ensure that this information includes:
    a. measurement reproducibility
    b. measurement performance across MRI system vender, model, and software version
    c. analysis of how liver iron concentration affects the performance characteristics
    d. sensitivity and specificity related to decision points defined in the Context of Use

3. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical method may be publicly posted if the biomarker is successfully qualified by the Agency. Please provide a description of your biomarker sufficient to ensure that the biomarker can be used as a drug development tool by any interested party and confirm that you are willing to make this information publicly-available. In addition, please confirm that you are willing to make the technical performance and other pertinent information publicly-available. The biomarker qualification process does not endorse or qualify a specific device/software for use with the biomarker.

4. Different types of biopsy (percutaneous, trans-jugular, intra-operative wedge liver biopsy) may be used to determine the reference standard for NASH or steatosis. Please clarify the details about any assessments used for evaluation of the histology (e.g., local or centralized reader) including the type of system used for assessment of activity (NAS or FAS scoring) and fibrosis (NAS/CRN vs, Ishak, etc.).

Clinical Considerations

5. You should clearly define the intended use (or "at risk") population. We recommend that you identify risk factors or previous medical history that would appropriately identify such patients (e.g., a specific BMI threshold, type 2 diabetes, hyperlipidemia (define level), etc.) and clearly define exclusion criteria for patients not appropriate for biomarker testing (e.g., clinical evidence of cirrhosis). You should also specify what, if any, additional testing should be performed prior to or after iron cT1 MRI (e.g., screening for viral hepatitis, ruling out other liver diseases). In addition, you should describe the potential for false negatives (i.e., patients who would have ordinarily met the histopathological enrollment criteria); clarify how you plan to address this issue. An algorithm may be useful to detail the sequence of events and intended use population for consistency across any interested party.

Statistical Considerations

1. In the Conditions for Qualified Use, there are seven general considerations. Using the second and the third bullets as examples, the data needed to show that cT1 relaxation time is to be used in conjunction with clinical risk factors and/or other diagnostics would be different from data needed to show that cT1 relaxation time is to be used as a pre-screening strategy to select patients more

likely to have histopathologic findings. In your next round of submission, please provide this level of detail for each of the general considerations you aim cT1 relaxation time to achieve.

2. The training cohort (UK) appears to be quite different from the validation cohort (US). Given the proposed COU is to identify patients who are more likely to have liver histopathologic findings of NASH, the estimated performance characteristics of the validation dataset for its diagnostic ability of using a cT1 cut-off of 80ms to discriminate between simple steatosis and NASH only 29% is concerning. Please perform another validation by matching baseline characteristics of the validation cohort with the training cohort and provide the estimated performance of this matched validation dataset, like those presented in Tables 2, 3 and 4.

3. In assessing clinical performance characteristics, please also provide their 95% interval estimates of those measures presented in Tables 2, 3 and 4 based on the defined Context of Use.

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

Digitally signed by Christopher L. Leptak -S
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Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
Office of New Drugs/CDER

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