



LOI DECISION LETTER

DDTBMQ000071

DATE March 14, 2018

Critical Path Institute
1730 E. River Rd.
Tucson, AZ 85718

Dear Dr. O'Doherty:

We are issuing this LOI Decision Letter to the Critical Path Institute's Type1 Diabetes Consortium to notify you of our decision 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) submission of August 31, 2017, and have concluded to **Accept** it into the CDER BQP. We encourage your further study of this promising susceptibility/risk biomarker that has potential to identify individuals who may be more likely to develop type 1 diabetes (T1D) to study interventions intended to prevent or delay its onset. 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.

You have proposed qualification of islet autoantibodies (AA) as prognostic biomarkers for conversion from pre-symptomatic T1D to symptomatic T1D. The islet autoantibodies (AA) proposed include: insulin autoantibodies (IAA), glutamic acid decarboxylase 65 (GAD-65), insulinoma antigen-2 (IA-2), and zinc transporter 8 (ZnT8) autoantibodies. As your biomarker development effort is further refined, the specifics of your context of use (including the target patient population), and the design of study(ies) proposed for clinical validation of the biomarker will ultimately determine which of the recommendations made below are most applicable.

We support the C-Path Type 1 Diabetes Consortium's proposed plan to study the islet autoantibodies IAA, GAD-65, IA-2 and ZnT8 as susceptibility/risk biomarkers. Based on our review of the LOI, we agree there is an unmet need and agree that development of the islet AA as a susceptibility/risk biomarker of T1D would enable proper patient selection for clinical investigations of earlier interventions for T1D.

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. Inish O'Doherty (iodoherty@c-path.org), the T1D point of contact for this project, or view the Critical Path Institute website.

Biomarker Considerations

Requestor's Description: *The islet AA represents a panel of biomarkers.*

- *Insulin autoantibody (IAA)*
- *Glutamic acid decarboxylase 65 (GAD-65)*
- *Insulinoma antigen-2 (IA-2)*
- *Zinc transporter 8 (ZnT8)*

The biomarker to be qualified is defined as any two of the four islet AAs determined (and confirmed) as positive in a patient.

Islet autoantibodies with sufficient and supportive data will be proposed in the final qualification.

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

Your biomarker description can be refined by addressing the following questions:

1. Is the biomarker a fixed or changeable pair of two islet AAs? Is a pair of islet AAs at one time point sufficient to indicate risk? Would the clinical performance be much improved if the biomarker is a combination of one specific islet AA with any one of the remaining three islet AAs or a combination of at least two additional islet AAs, totaling three or more? What are biologic rationales for the refined biomarker(s) in your final selection?
2. Description of the individual behavior of each individual AA (i.e. duration, peak, persistence, disappearing/tapering).
3. It is unclear whether the proposed islet AA are independent parameters or if there may be correlation or potential confounding between islet AA. Are there data or studies which indicate how these parameters may relate to one another or are independent from each other, and how each relates to the pre-T1D or the early stages of disease? If not, what

studies do you propose to establish independence of the parameters or the basis for their individual relationships to T1D?

4. As relates to a positive signal determined at a single point in time, does it represent risk or does testing at several points in time better represent the subject population of interest (i.e., positive for a specific set of islet AA)? How will you address this in your plan (i.e. requiring at least two positive tests over a pre-defined period of time)?

Context of Use (COU) Considerations

The COU should be defined carefully, clearly and be consistent with and fill the described drug development need. When multiple uses are proposed for a biomarker, the order of uncertainties of its utility increases exponentially and defining its use as a DDT may become very difficult. Providing a precise case for how the biomarker can be used in a clinical trial protocol (i.e. population, time to positive signal) may be very useful when defining the COU.

***Requestor's COU:** Islet autoantibodies (AAs) are prognostic biomarkers for conversion from pre-symptomatic type 1 diabetes (T1D) to symptomatic T1D that may be used for enrichment in early and late-stage clinical trials. Islet autoantibodies of interest include insulin autoantibodies (IAA), glutamic acid decarboxylase 65 (GAD), insulinoma antigen-2 (IA-2), and zinc transporter 8 (ZnT8) autoantibodies and will be evaluated per data availability.*

FDA's suggested COU for continued biomarker development: A susceptibility/risk biomarker that indicates the potential for individuals to develop symptomatic T1D to study interventions intended to prevent the onset T1D.

To better understand the benefits of islet AA as a DDT, and continue to refine the COU, please provide the following information;

5. Please specify the characteristics (i.e. pediatric versus adult population, status as first- and second-degree relatives of individuals with T1D) of the target population in the proposed COU.
6. What additional factors will be used to identify individuals for islet AA screening to identify subjects positive for islet AA biomarkers to enrich/enroll in T1D studies? Discuss the anticipated impact of HLA haplotypes and non-HLA genotype variants associated with increased risk for T1D (e.g. INS, PTPN22) on the prognostic ability power of the proposed islet AA biomarkers.

Analytical Considerations

General analytical considerations regarding the supportive data to be provided in the next steps for the qualification of the biomarker include the following:

7. Some of the assays listed in the LOI have a 510(k) clearance. It is unclear if these cleared assays are the only assays used in the studies. You have listed 4 references to support assay validation. In the references (4-7) listed in the LOI, different assays and laboratories were used to demonstrate performance of the assays in measuring specific islet AA. It appears that the references compare laboratory results, but do not provide

results for the individual assays used. Based on the information provided, the analytical performance of the individual assays that do not have 510(k) clearance is not clear. Please provide a list of assays that will be used in the analysis of AA to support the COU and identify what is measured, how it is measured and list the threshold/cutpoint for a positive and limit of detection analytical performance and data that validate the tests for the expected range of values in the target population.

8. Discuss the reversibility of the islet AA assays: how often does a subject revert from positive to negative?

For the assays listed in your LOI which have 510(k) clearance (IAA, k070183; GAD, k051061 and k072135; IA-2, k073590):

9. Please provide your threshold values for each autoantibody, and explain how the performance characteristics of the assays with 510(k) clearance support your thresholds for your proposed context of use. Address impact of isoforms or other potentially cross-reacting epitopes on measurements using these assays.
10. You state that the islet AA are measured in blood using radio-immunoassays and a sample is determined as positive or negative according to pre-specified thresholds in the references (4-7) provided with the LOI. These thresholds were established to help in the diagnosis of diabetes not to determine if a person is predisposed to diabetes, though some of the references do state that these islet AA may also help assist in the determination of a person being pre-disposed to develop Type I diabetes. Please provide justification in your qualification plan for your threshold values and how these values are applicable in determining that a person is pre-disposed to developing type I diabetes. You propose that a combination of any two of the four islet AA will constitute a positive result. The 510(k) cleared assays have thresholds that are validated for use as a single assay only, not in combination; therefore, you should provide data to validate the sensitivity and specificity of your proposed AA paired combinations.

For the assay(s) that will be used in your qualification plan that are not FDA cleared, in addition to the questions and comment above:

11. Please provide validation information for these assays. You should provide information regarding the analytical performance characteristics of the assay(s) such as: precision, accuracy, detection limits and limits of quantitation, linearity, cross-reactivity of isoforms or related epitopes; interference from endogenous and exogenous substances, and analytical specificity and sensitivity for the proposed thresholds or cutoffs. You may wish to refer to the following CLSI documents for examples of analytical validation protocols.
 - CLSI EP05-A3 – Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.
 - CLSI EP06-A – Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.
 - CLSI EP07-A2 – Interference Testing In Clinical Chemistry; Approved Guideline – Second Edition.
 - CLSI EP09-A3 – Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition
 - CLSI EP17-A2-Evaluation of Detection Capability for Clinical Laboratory Measurement

Clinical Considerations

General clinical considerations regarding the COU and its utility as a DDT. Please be advised that some of the questions and considerations may not apply to the qualification depending upon the specific COU:

12. Is the biomarker intended as a predictor of progression rate to disease in adults?
13. What is the definition of persistently positive? How does the proposed definition of the biomarker classify subjects whose individual assay results are intermittently positive and negative, such that different pairs of islet AA are found simultaneously positive at various times?
14. Discuss whether any one of these islet AAs is more likely to be associated with progression than any other or if they should all be given equal weight.
15. The time to onset of T1D, from observation of positive islet AA to overt T1D disease, is variable and can be as long as 5-10 years or more. How will the long latency and variability in onset impact study design and duration for the intended drug intervention studies? What criteria do you use to identify transition to T1D disease? How will you determine when an individual subject has a delayed or has not transitioned to T1D disease, demonstrating efficacy of investigational preventive therapeutic intervention(s)?
16. What benefits do positive islet AA provide in drug development for T1D?
17. Clearly indicate for any analyses of antibody incidence/prevalence the specific cohort(s) that provided the raw data. Discuss differences in findings among cohorts and whether non-U.S. cohorts are applicable to the U.S population for the purposes of biomarker development.
18. Clarify the relevance of the titer and the established threshold of each antibody vs. simple dichotomization of assay results into “positive” and “negative”.
19. Discuss the anticipated impact of other environmental and lifestyle factors including diet, exercise, and physiologic factors including the microbiome in the progression/pathogenesis toward T1D in the study populations.
20. Is there an understanding of how islet AA relate to development of T1D and describe how they are related to the causal pathway of disease?

Statistical Considerations

Please provide the following information in the qualification plan:

21. You have proposed: “The biomarker to be qualified is defined as any two of the four islet AAs determined (and confirmed) as positive in a patient.” Therefore, the combinations of the assays should be validated using performance characteristics such as sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), in addition to any threshold validation for each individual assay. Please conduct a sensitivity analysis and provide tables showing likelihood ratios or other similar statistical data for 0 of 4, 1 of 4, 2 of 4, 3 of 4, and 4 of 4 AAs determined (and confirmed) as positive.
22. Please address biological variability of the islet AA titers in an individual and population. How reproducible are the findings, over what timeframe? Refer to comment 15, there might be confounding risk factors that are not correlated with islet AA but influence the

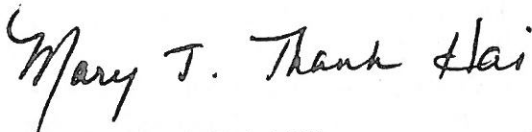
onset of T1D. We recommend that you consider a statistical analysis approach that can account for confounding risk factors in your statistical analysis plan.

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,

A handwritten signature in black ink, appearing to read 'Christopher Leptak', with a long horizontal line extending from the end of the signature.

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

A handwritten signature in black ink, appearing to read 'Mary T. Thanh Hai', written in a cursive style.

Mary T. Thanh Hai, M.D.
Director (Acting),
Division of Metabolic and Endocrine Products
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