

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

COMMENTS: The following information will be made publicly available as per the 21st Century Cures Act

Biomarker Project Information

Biomarker: Islet auto-antibodies (AAs).

Therapeutic area: Endocrine disease, specifically Type 1 diabetes (T1D).

Patient Population: Patients pre-symptomatic for T1D.

Administrative Information

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Submission Date: 8/31/17 with no concurrent EMA biomarker submissions.

Other regulatory agency submissions: No prior regulatory interactions. This qualification project intends to seek feedback from the FDA and EMA. Accordingly, if accepted into the FDA's Qualification Program, we intend to potentially explore a joint qualification review process with the FDA and EMA.

Context of Use

Proposed Context of Use (COU) Statement:

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.

Drug Development Need

The incidence of T1D is on the rise in the US and globally. In the US, the SEARCH study forecasts that the number of youth with T1D will increase by 23% from 2010 to 2050 (1). There are currently no approved therapies to either delay the onset of insulin dependence or prevent the disease entirely. Decades of research into the natural history of T1D has demonstrated a disease continuum that begins prior to the onset of symptoms. The risk of developing the disorder and disease progression can be quantified and characterized into defined stages (2).

The presence of islet AAs allows the definition of different stages of the disease, with symptomatic T1D as the end stage. The 2017 American Diabetes Association (ADA) Standards of Medical Care (3) incorporates the T1D

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

staging criteria and states that “persistence of two or more autoantibodies predicts clinical diabetes”, while recommending AA screening only in the setting of a research trial.

Qualifying the islet AAs as biomarkers of T1D prior to symptomatic disease would enable early intervention in order to delay and ultimately prevent the onset of clinical symptoms. This approach will aid the development of therapies and the design of clinical trials to prevent symptomatic disease and provide a framework to help inform benefit/risk evaluations.

Biomarker Information

- **Biomarker name (for molecular biomarkers, please provide a unique ID) and description:** The islet AAs represent a panel of biomarkers. The presence of two or more of the islet AAs results in an increased risk of progression to symptomatic T1D, Stage 3:
 - Insulin autoantibody (IAA)
 - Glutamic acid decarboxylase 65 (GAD)
 - Insulinoma antigen-2 (IA-2)
 - Zinc transporter 8 (ZnT8)Islet autoantibodies with sufficient and supportive data will be proposed in the final qualification.
- **Biomarker Type & Scheme:** Molecular, UniProt (<http://uniprot.org/>)
- **Biomarker source material:** Blood
- **Biomarker Category:** Prognostic
- **The mechanistic rationale or biologic plausibility supporting the biomarker and associated context of use (COU):** T1D is a chronic, immune-mediated disease that has genetic risk factors and environmental etiologies. T1D is associated with destruction of the insulin-producing beta cells of the islets of the pancreas. Based on insights from multiple natural history studies conducted over the last two decades, distinct stages of T1D have been defined that reflect the T1D disease continuum and pathogenesis (in accompanying attachments). While the T1D-associated islet AAs themselves likely do not mediate beta cell dysfunction or destruction, they are recognized widely as the first evidence of onset of beta cell autoimmunity. This effort is focused on the predictive linkage between individuals whom are seroconverted (stage 1 or 2) and symptomatic T1D (stage 3).
 - Stage 1: Pancreatic Beta Cell Autoimmunity+/Normoglycemia/Presymptomatic T1D: Beta cell autoimmunity is marked by the presentation of two or more islet AAs. The 5-yr risk of progression to symptomatic disease is ~44%, while the lifetime risk of symptomatic disease approaches 100%.
 - Stage 2: Autoimmunity+/Dysglycemia/Presymptomatic T1D: In those with two or more islet AAs plus glucose intolerance, or dysglycemia, the 5-yr risk of progression to symptomatic disease is ~75%, and lifetime risk approaches 100%.
 - Stage 3: Symptomatic T1D: Stage 3 includes clinical symptoms and signs of T1D diabetes or is diagnosed in the presence of metabolic laboratory parameters established by the ADA for a diagnosis of type 2 diabetes.

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

- **Description of the biomarker index/scoring system and its derivation. The biologic rationale for inclusion of each component and weighting of the elements and interpretation of the index/score.** The presence of two or more AAs is associated with a lifetime risk approaching 100% for progression to Stage 3 T1D. Each AA is measured independently and determined as “positive” according to pre-specified thresholds (see next section below). A positive determination must be confirmed within a specific time period. Several AAs have been associated with initiation of the autoimmune response in T1D (Stage 1), but it is anticipated that this project will draw from clinical studies providing data to assess four AAs (IAA, GAD, IA-2, ZnT8). The biomarker to be qualified is defined as any two of those four AAs determined (and confirmed) as positive in a patient.

Biomarker Measurement (Analytical)

- **General description of what aspect of the biomarker is being measured and by what methodology:** The islet AAs are measured in blood using standardized radioimmunoassays and methods; a sample is determined as “positive” or “negative” according to pre-specified thresholds (4-7). Thresholds for defining AA positivity are usually set at an antibody prevalence in a reference population of healthy individuals (8). Ideally, the reference population should have similar characteristics to the at-risk population and be large enough to achieve tight confidence intervals. The cut-off is commonly set at the 99th percentile of the reference population, i.e. a level exceeded by only 1% of these healthy individuals.

The specific approach to define seroconversion in each study will be thoroughly identified for each dataset. This will include a judicious identification of all ancillary variables and data processing rules needed to derive the binary definition for seroconversion. Once the individual study approaches to define seroconversion have been properly characterized, any potential inter-study variation will be identified. Based on the nature of such potential variations, further data management needs will be defined, consulted with the FDA, and then applied for a consistent derivation of seroconversion across all datasets.

- **The biomarker test/assay is available for public use?** Yes, as a Laboratory Developed Test (LDT), Research Use Only (RUO) and FDA Cleared/approved 510K/PMA Number IAA, k070183; GAD, k05061 and k072135; IA-2, k073590.
- **The biomarker assay/test will be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory?** No.
- **The biomarker test is currently under review in CDRH?** Don't know.
- **A standard operating procedure (SOP) exists for sample collection, storage:** Yes.
- **A laboratory SOP exists for the assay/methodology:** Yes.
- **Performance characteristics for the biomarker assay/tests (sensitivity, specificity, accuracy and precision):** Yes.
- **Description of the level of analytical validation performed (e.g., sensitivity, specificity, accuracy, and/or**

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

precision): The Islet Autoantibody Standardization Program (IASP), formerly the Diabetes Autoantibody Standardization Program (DASP), is an international effort to improve and harmonize measurement of AAs associated with T1D through the use of common standards and conduct of proficiency testing, as well as through providing support, training, and information. The Centers for Disease Control and Prevention (CDC) have participated in this National Institutes of Health (NIH) sponsored standardization effort. Sample sets from T1D patients and control subjects as well as reference standard reagents are made available to participating laboratories, and the results released to laboratories to allow their determination of assay sensitivity and specificity. As a result, these assays are well characterized and analytically validated. Overall concordance for determination of patient samples as positive or negative for each AA can be determined (5, 6).

For this qualification project, data were generated at laboratories actively participating in IASP or DASP at the time of AA measurement. Measurement methodology and in some cases, assay validation results, for assays utilized in the clinical study datasets have been reported (4-7).

For future measurement of the AAs, post-qualification by sponsors of T1D trials, we recommend that laboratories participating in IASP be utilized or that sponsors discuss an appropriate level of AA assay validation or bridging strategy with the FDA review division.

Supporting Information

This qualification project builds upon the T1D staging criteria that have been widely accepted into the diabetes field, including into the ADA's Standards of Medical Care in Diabetes-2017. Birth cohort studies have been of enormous value in shaping this staging model, and data from these studies will be employed as possible in this qualification exercise (Attachment 2). The large birth cohort studies where AAs have been measured longitudinally in children screened for genetic risk of T1D are briefly as follows:

- The Colorado Diabetes Autoimmunity Study in the Young (DAISY)
- The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study
- The German BABYDIAB and BABYDIET studies
- The Swedish Diabetes Prediction in Skåne (DiPiS) study
- The Environmental Determinants of Diabetes in the Young (TEDDY), US and Europe

Large prospective studies designed to develop cohorts for T1D prevention and intervention trials that incorporate cross-sectional evaluation of beta cell AAs with patient follow up also represent support for the proposed COU. These include the TrialNet Natural History Study (TrialNet NHS) and Diabetes Prevention Trials (DPT-1). These cross-sectional studies screened first- and second-degree relatives of individuals with T1D for the existence of Stage 1 or 2 T1D.

The data sets from these clinical trials should provide diverse patient demographics to help inform and characterize specific covariables such as age, sex, HLA haplotype, etc. that influence disease progression along with seroconversion. In a study that combined DAISY, DIPP and BABYDIAB/BABYDIET cohorts, the 10-year progression rate to symptomatic T1D, Stage 3 after initiation of Stage 1 was approximately 70%. Similar data is emerging from the ongoing TEDDY study, whose median follow-up is approximately 7 years. While screening in TrialNet and DPT-1 is cross-sectional in nature, the data also support that the presence of

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

multiple AAs are associated with risk of progression to Stage 3.

- **Planned studies supporting the biomarker, COU and how these will address current knowledge gaps:**
The persistent presence of two or more islet AAs is well-established as a sign of autoimmunity and the first stage of T1D. Because these AAs are detectable for a variable period of time before T1D clinical onset, Stage 3, additional patient features must be used to characterize the rate of progression from pre-symptomatic T1D to symptomatic T1D.

Patient-level data from several clinical trials will be used to characterize the linkage between AA seroconversion (together with other patient features, data permitting) and progression to a clinical diagnosis of T1D, Stage 3. This will constitute a framework for a regulatory-oriented disease progression modeling analysis of the time-varying probability of reaching Stage 3, based on the presence of AAs, together with other patient features. The proposed model will be developed to enable its use in drug development, as well as to support biomarker qualification.

The first part of the analysis will be performed using a ROC curve analysis to investigate the relationship between AA seroconversion and disease onset, Stage 3. The positive AAs that maximize the prediction of Stage 3 will be identified in this step. The second part of the analysis will include the construction of a parametric survival model to assess the relationship between time and disease onset for T1D trial design. Several widely-used survival functions, including exponential, log normal, Weibull, and gamma, will be tested and the most predictive additional patient features (covariates) that maximize the prediction of Stage 3 will be identified, including AA seroconversion. Seroconversion at specific ages of interest will be tested in the model as a covariate to detect the earliest seroconversion that ultimately best predicts Stage 3 (i.e., the survival function). Other covariates of interest (data permitting), may include, but are not limited to gender, ethnicity, HLA and non-HLA susceptibility genes, family history and blood glucose measures.

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

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3. American Diabetes Association. Classification and Diagnosis of Diabetes. *Diabetes Care*. 2017 Jan 1;40(Supplement 1):S11–24.
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6. Schlosser M, Mueller PW, Törn C, Bonifacio E, Bingley PJ, Participating Laboratories. Diabetes Antibody Standardization Program: evaluation of assays for insulin autoantibodies. *Diabetologia*. 2010 Dec;53(12):2611–20.
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Measurement methodology

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BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

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BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

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