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# Letter of support for "Islet autoantibodies as enrichment biomarkers for type 1 diabetes prevention studies, through a quantitative disease progression model"

On September 4, 2019, the applicant, Critical Path Institute's (C-Path's) Type 1 Diabetes Consortium (T1DC), requested qualification advice for islet autoantibodies (AAs) including anti-insulin AA (IAA), anti-glutamic acid decarboxylase 65 AA (GAD65), and anti-insulinoma antigen-2 AA (IA-2) as enrichment biomarkers for patient selection in clinical trials investigating therapies that are intended to prevent or delay the Type 1 Diabetes Mellitus (T1D). The islet autoantibodies, in addition to other patient features, are intended to be used in a model to predict the time-varying probability of T1D diagnosis. On October 17, 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted the qualification advice provided to the applicant. This letter of support is issued based on the review of the qualification advice.

Drug development need:

T1D is a chronic autoimmune disease that results from the destruction of insulin-producing beta cells (β-cells) in the islets of Langerhans of the pancreas. The ability of T1D patients to make insulin is impaired, and consequently patients are unable to regulate their blood glucose levels. The incidence of T1D is on the rise globally (writing group for the DCCT/EDIC Research Group et al. 2015; Patterson et al. 2019). Insulin replacement therapy remains the cornerstone of treatment for T1D and is used to manage blood glucose levels. However, this approach does not target the underlying destructive autoimmune processes that drive disease pathogenesis. Currently, there are no approved therapies to prevent or delay the onset of T1D, and there is a lack of biomarkers and quantitative tools to optimise patient selection for clinical trials and to quantify risk of conversion to a diagnosis of T1D.

The high degree of variability that exists in the latency phase of this disease, from presentation of multiple islet AAs to ultimate diagnosis of T1D, provides significant challenges in patient selection and the overall design of clinical trials. Biomarkers and tools that are capable of quantitatively describing this variability will enable developers to design informative clinical trials of appropriate and reasonable size and duration that will be capable of adequately evaluating potentially transformational therapies.

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Background and rationale for the proposed novel methodology in drug development:

Model-informed drug development (MIDD) can improve research and development (R&D) decision-making. Examples of the application of MIDD to R&D include: (a) understanding of disease-related targets; (b) selection of dose, schedule and regimens; (c) stage-gate (go/no-go) decisions; (d) optimisation of study design; (e) patient selection; and (f) bridging studies in special populations.

The purpose of this project is to develop a predictive model that describes the time varying probability of T1D diagnosis in at-risk subjects. The model is intended to account for several predictors of T1D diagnosis within the defined subject population (individuals that are first-degree relatives (FDRs) of a T1D patient, or who have a human leukocyte antigen (HLA) haplotype of risk, defined as HLA-DR3/3, DR4/4, DR3/4, DR3/X [X≠3], DR4/X [X≠4]). This model aims to provide the necessary evidence to support the use of islet AAs to enrich clinical trials for T1D prevention of reasonable duration with subjects who have a higher likelihood of reaching T1D onset over time based on population patient features.

The proposed Context-of-Use (COU):

In individuals at risk of developing T1D, the islet AAs can be used together with other patient features, as enrichment biomarkers to optimise the selection of patients for clinical trials of therapies intended to prevent or delay T1D. The islet AAs proposed include IAA, GAD65, and IA-2.

- ***General area:*** Enrichment biomarkers for clinical trials aiming to demonstrate the ability of interventions to delay or prevent T1D.
- ***Target population for use of the biomarkers:*** Individuals at risk of T1D, defined as being a FDR of a T1D patient, or having a specific HLA subtype of risk (HLA-DR3/3, DR4/4, DR3/4, DR3/X [X≠3], DR4/X [X≠4]). It is intended that positivity for the islet AAs be determined in this population, as enrichment biomarkers for clinical trials aiming to demonstrate the ability of interventions to delay or prevent T1D.
- ***Stage of drug development for use:*** All clinical efficacy evaluation stages of therapeutic interventions focused on the prevention or delay of T1D, including early signs of efficacy, proof-of-concept, dose-ranging, and registration studies.
- ***Intended application:*** To utilise the islet AAs as enrichment biomarkers as a means of patient selection in clinical trials investigating therapies that are intended to prevent or delay T1D. These biomarkers, along with additional patient features, may be used as predictors to identify subpopulations at highest risk for a diagnosis of T1D during T1D prevention clinical trials.

The observation that islet AAs are prognostic of T1D is not new. The T1DC has initially demonstrated that the data gathered in support of its ongoing qualification advice effort is in accordance with previous research in the field. These patient-level data from The Environmental Determinants of Diabetes in the Young (TEDDY), and the TrialNet Natural History Study (TN01) indicate that the presence of 2 or more islet AAs at baseline significantly increases the likelihood of T1D onset.

The T1DC's work will quantify the contribution of the islet AAs and other relevant patient features to the prediction of T1D onset in order to enrich patients for clinical trials aiming to delay or prevent T1D. Along with the complete modeling analysis report with R code, a graphical user interface (i.e. a web-based R shiny application) will also be developed and maintained at C-Path and shared with the drug development community to aid clinical trial enrichment. The modeling analysis thus far confirms that islet AAs (GAD65, IAA, and IA-2) are statistically independent predictors of T1D onset, further

supporting their intended application as enrichment biomarkers to optimise the selection of patients for clinical trials of therapies intended to prevent or delay T1D. With respect to the presence of GAD65 & IAA combination, the hazard ratios for the presence of the combinations GAD65 & IA-2, IAA & IA-2, as well as all three islet AAs are 1.87 (p=4.03E-10), 2.8 (p=6E-14), and 2.5 (p<2E-16), respectively. Implementation of the complete modeling analysis plan is currently underway. The modeling analysis plan will include both parametric and semi-parametric multivariate analyses, considering potential covariates such as number and type of islet AAs, demographics, and other clinically relevant features of the disease.

Summary:

The EMA supports the primary objectives of the applicant to address the need for optimised designs of T1D prevention trials. The Agency supports the applicant's proposed COU and issues this letter of support to C-Path's T1D Consortium. The EMA supports the collection of relevant data and encourages collaboration with third parties in order to permit timely and robust development and validation of such a model, including active and control arm data from relevant studies in the intended target population as defined in the COU statement. This will facilitate the development and validation of the proposed quantitative novel methodology. Any groups that would like to join in this effort or have information or data that may be useful can contact T1DC (T1DCAdmin@c-path.org).

Therapies that preserve endogenous β-cell function and can prevent, halt or slow T1D disease progression in a clinically meaningful way would constitute a significant advancement in T1D care. If successful, the quantitative tools proposed by this Consortium have the potential to facilitate the streamlined design, execution, and review of clinical trials targeting this goal.

Yours sincerely,

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Executive Director

References:

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