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Submission of comments on 'Islet Autoantibodies (AAs)' (EMA/580542/2021)

Comments from:

Name of organisation or individual
American Diabetes Association (ADA)
JDRF
Karolinska Institutet

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
(To be completed by the Agency)		*(To be completed by the Agency)*
ADA	The ADA has reviewed and welcomes the EMA's Draft qualification opinion for the described context of use. We believe qualification of Islet Autoantibodies together with other patient features (sex, baseline age, OGTT test and HbA1c) will constitute a major step forward for the design and execution of prevention trials in Type 1 Diabetes. We would also like to take this opportunity to note that, as with all qualified biomarkers, it is essential that autoantibody assays be fully validated to ensure performance equivalent to the 'gold standard' assays described in the document. To ensure the accuracy of results we also strongly encourage verification steps such as confirmation of autoantibody presence or absence on two separate occasions.	In the Qualification Opinion statement, the following is mentioned: *"It should be noted that the results and the conclusions of the modeling analysis as assessed during this qualification procedure are considered only applicable when the islet autoantibodies are measured using these methods or methods proved to have at least equivalent analytical performances."* The three studies utilized in the current Qualification Opinion assessed islet autoantibody status from at least two separate timepoints. However, the islet AAs need not be persistent as the T1D Consortium aims to determine the relationship between occurrence of islet AAs at baseline with T1D diagnosis, in combination with other covariates/patient features. This approach reflects the reality of drug development, where single time point screening of potential subjects is likely to occur. Past work has shown a small rate of reversion in multiple islet AA positive individuals (4.1%). Risk of progression to clinical T1D is reduced in these patients. However, given that individuals who have ≥ 2 islet AAs who subsequently revert to fewer than 2 islet AAs would be included in the defined derived baseline, the modeling analysis represents a more conservative overall estimate of disease progress. Thus, we recommend no changes to lines 615 through 624, and that repeat testing of islet autoantibody status not be included as a requirement in the Qualification Opinion. 1. So M, O'Rourke C, Bahnson H, et al. Autoantibody Reversion: Changing Risk Categories in Mulitple-Autoantibody-Positive Individuals.

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		Diabetes Care 2020;43:913-917. https://doi.org/10.2337/dc19-1731 This comment is therefore adequately covered.
JDRF	In 2015, JDRF along with the Endocrine Society, and the American Diabetes Association published a consensus that classified the early stages of T1D to help accelerate the development of disease modifying therapies. The importance of regulatory qualification of these islet autoantibodies was identified as a critical unmet need and JDRF is a member of C-Path Institute's T1D Consortium. To better understand T1D, validated biomarkers are needed at every stage of the disease to accelerate therapeutic development, improve clinical trials by partitioning subjects and results by a factor other than the treatment given, and serve as potential intermediate trial endpoints. Overall, JDRF is pleased with the proposed qualification plan and validation of the selected set of biomarkers as they can aid in the delay or prevention of the clinical diagnosis of T1D. Due to the insufficient predictive power of individual risk factors and the limitations on the current available treatment we understand that this is a critical unmet need that must be addressed. We recommend the EMA grant qualification and urge industry to adopt and utilize these biomarkers in their development of medical products for T1D.	Acknowledged with thanks.

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Christoph Nowak, MD, PhD Assistant Professor, Karolinska Institutet, Stockholm, Sweden Christoph.nowak@ki.se	The analysis does not take into account which of the two or more antibodies occurred first and no distinction is made between which type of antibodies are present. Since the purpose is to use the presence of two or more antibodies alongside personal features as enrichment biomarkers to optimize selection of individuals for clinical trials, I believe that the current analysis potentially omits an important risk stratification captured by HLA haplotype (presence/absence of DR3-DQ2 and/or DR4-DQ8) and the associated primary antibody seroconversion (IAA first or GADA first). Whilst the current analysis assesses high-risk HLA (present/absent) and the presence of two or more antibodies as covariates, it does not distinguish between the kinds of antibodies or HLA DR3/DR4. It might be worthwhile to point out that the risk of developing T1D within 5 years for an 8-year-old child with two or more islet antibodies is expected to differ depending on the type of antibodies and which antibody occurred first. For instance, the presence of ZnT8A is associated with older age at diagnosis (Salonen et al. 2013). Moreover, the peak age for antibody conversion to IAA as the first antibody is around the second year of life, whilst seroconversion to GADA as first antibody peaks between 3-5 years of age. Whilst both seroconversions are associated with the same 10-year risk of T1D (ca.	The derived baseline utilized in the modeling analysis by definition includes subjects positive for any two or more islet autoantibodies at the time of risk assessment. Given the context of use, it is not critical to characterize the time history of seroconversion. The subtypes included in the modeling analysis were limited to those available in the underpinning datasets. As such, during the baseline covariate analysis, HLA status was included as binary presence or absence of the included HLA types. High risk HLA subtype did not show a significant effect on overall survival and was subsequently dropped for further analyses.

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	60%), the different seroconversion ages mean that an average 8-year-old high-risk child with IAA (1st) -> GADA (2nd) will have a slightly higher probability of developing T1D in the near future than an 8-year-old child with GADA (1st) -> IAA (2nd) (Ilonen et al. 2013). The small group of individuals with IA-2A as first antibody were in the same study in the DIPP cohort found to have a more rapid progression to clinical T1D than either IAA-first or GADA-first children (Ilonen et al. 2013). The two most common islet antibody seroconversions are closely associated with HLA haplotype: HLA DR3-DQ2 is associated with GADA (1st) -> IAA (2nd), whilst HLA DR4-DQ8 is associated with IAA (1st) -> GADA (2nd). Given the sample size in the current analysis, statistical power might be limited for tests involving antibody occurrence permutations as covariates (i.e., one covariate each for GADA -> IAA, IAA -> GADA, IA-2A -> IAA etc.). Therefore, using HLA DR3-DQ2 (present/absent) and HLA DR4-DQ8 (present/absent) as covariates might offer a reasonable compromise to capture the two most common antibody conversion sequences (GADA -> IAA and IAA -> GADA) and their associated age of first antibody seroconversion. In conclusion: I believe that HLA haplotype (DR3-DQ2,	

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	which is associated with GADA as first antibody; and DR4-DQ8, which is associated with IAA as first antibody) should be included in the analysis as they might contribute risk stratification information that is not captured by the covariates assessed in the current models. References: Salonen KM, Ryhänen S, Härkönen T, Ilonen J, Knip M; Finnish Pediatric Diabetes Register. Autoantibodies against zinc transporter 8 are related to age, metabolic state and HLA DR genotype in children with newly diagnosed type 1 diabetes. Diabetes Metab Res Rev. 2013;29(8):646-54. PMID: 23861236. Ilonen J, Hammais A, Laine AP, Lempainen J, Vaarala O, Veijola R, Simell O, Knip M. Patterns of β-cell autoantibody appearance and genetic associations during the first years of life. Diabetes. 2013;62(10):3636-40. PMID: 23835325.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.