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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Lauren K. Wood Heckman, MD
BLA 761183
Tzield/Teplizumab (PRV-031)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761183
Priority or Standard	Class 2 resubmission of priority review
Submit Date(s)	February 17, 2022
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PDUFA Goal Date	November 17, 2022
Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO)/Office of New Drugs (OND)
Reviewer Name(s)	Lauren K. Wood Heckman, MD
Review Completion Date	Electronic stamp
Established/Proper Name	PRV-031/teplizumab-mzww
(Proposed) Trade Name	Tzield
Applicant	Provention Bio, Inc.
Dosage Form(s)	2 mg/ 2mL single- (b) (4) vial
Applicant Proposed Dosing Regimen(s)	Intravenous infusion given daily for a 14 consecutive day course. The specific dosing regimen is pending finalization of the Office of Clinical Pharmacology review.
Applicant Proposed Indication(s)/Population(s)	Teplizumab is an anti-CD3 humanized monoclonal antibody indicated for the delay of type 1 diabetes in at-risk individuals
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	TZIELD is indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D

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Glossary

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate aminotransferase
AUC	area under the curve
BLA	biologics license application
BSA	body surface area
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGM	continuous glucose monitor
CLIA	Clinical Laboratory Improvement Amendment
CMV	cytomegalovirus
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DDLO	Division of Diabetes, Lipid Disorders and Obesity
DKA	diabetic ketoacidosis
DLP	data lock point
DRM	Division of Risk Management
DMC	data monitoring committee
EBV	Epstein-Barr virus
GADA	glutamic acid decarboxylase 65 antibody
FDA	Food and Drug Administration

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FDAAA	Food and Drug Administration Amendments Act
IAA	insulin antibody
IA-2A	insulinoma-associated-2-antibody
ICA	islet cell antibody
IND	investigational new drug
INR	international normalized ratio
IV	intravenous
LPD	lymphoproliferative disorder
MedDRA	Medical Dictionary for Regulatory Activities
OCP	Office of Clinical Pharmacology
OGTT	oral glucose tolerance test
OPQ	Office of Pharmaceutical Quality
PCR	polymerase chain reaction
PD	pharmacodynamic
PDUFA	Prescription Drug User Fee Act
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population pharmacokinetic
PREA	Pediatric Research Equity Act
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event
T1D	type 1 diabetes
ULN	upper limit of normal
ZnT8A	zinc transporter 8 antibody

1. Executive Summary

Teplizumab-mzwv (called teplizumab in this review; proposed proprietary name Tzielid) is a first-in-class humanized anti-CD3 monoclonal antibody proposed delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes.

Please see Summary Memo in DARRTS, dated July 2, 2021, for the original clinical review of this BLA (biologics licensing application). This clinical review contains only new information submitted with the resubmission.

The initial BLA was submitted October 31, 2020 and received a Complete Response action on July 2, 2021. The Office of Clinical Pharmacology (OCP) recommended withholding approval because of deficiencies related to the lack of demonstration of bioequivalence between the to-be-marketed drug product (AGC Biologics product) and the drug product used in clinical studies (Eli Lilly product). In addition, the Office of Pharmaceutical Quality (OPQ) recommended withholding approval because of deficiencies related to the (b) (4) manufacturing site and an unacceptable charge variation measured in PRV-031 drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions. Reviewers from all other review disciplines did not find deficiencies precluding approval.

This Complete Response submission includes new and updated safety information on all reports of death, treatment-emergent adverse events (AEs), serious adverse events (SAEs), AEs leading to study drug discontinuation reported with the Data Lock Point (DLP) date of November 24, 2021, from 550 subjects with recent-onset stage 3 T1D from two ongoing trials (PROTECT and TN-10 extension) and the completed Protégé extension trial. The largest study included in the safety update, the PROTECT study, is an ongoing randomized placebo control trial in which 327 subjects were randomized to teplizumab or placebo in a 2:1 ratio and is currently blinded. The blinded data from the PROTECT study were useful for interpreting laboratory related adverse events and adverse events of low baseline frequency in the population being studied: specifically serious infections, cytokine release syndrome, and hypersensitivity analyses. The TN-10 extension study is an open-label extension study to the TN-10 trial reviewed in the original BLA and contained safety data for 4 subjects who were dosed with teplizumab open-label. Protégé Extension was a noninterventional follow-up study to the Protégé study, a study that was included in the original BLA submission. The safety update

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included long-term safety data for 181 participants given teplizumab during the original Protégé study, and safety update analyses were limited to long-term adverse events.

Cytokine release syndrome, infection, laboratory-related adverse events (mainly lymphopenia and liver enzyme elevations), and rash, are all adverse events noted in the original teplizumab safety studies and were observed in similar rates and severity in patients in the safety population as previously reported in the original BLA submission. Less stringent laboratory-based discontinuation criteria were used for the PROTECT study, with notably decreased frequency of premature treatment discontinuations, with approximately half the rate observed in the original BLA submission. On review of the individual narratives for each laboratory adverse-event related discontinuation event there were no serious adverse events related to continued treatment among patients who would have met the prior safety database premature treatment discontinuation criteria. This reviewer therefore concludes that more serious or permanent harms are not expected if less restrictive discontinuation criteria (from the PROTECT study) are reflected in teplizumab's labeling. Additionally, the PROTECT study provided reassuring support that laboratory related adverse events were reversible.

In addition to adverse event reporting, the safety update provided information on ADA formation in the to-be-marketed drug product (AGC Biologics) in comparison to the clinical trial (Lilly) drug product through the unblinded analysis of a pharmacokinetic (PK) / pharmacodynamic (PD) substudy of the PROTECT safety update study as well as information on adverse events experienced in patients given the AGC vs. Lilly products through blinded adverse event analyses of the PROTECT study. This analysis demonstrated that the AGC product was associated with earlier appearance of anti-drug antibodies (ADA) and higher ADA titers than the Lilly product.

After review of this safety update, teplizumab continues to have an acceptable safety profile for its intended use in adults and children aged 8 years or older with stage 2 type 1 diabetes. Additionally, the AGC drug product, which is intended to be used as the drug product in the post market setting was demonstrated to have a similar safety profile to the Lilly AGC product.

1.1. Conclusions on the Substantial Evidence of Effectiveness

See Summary Basis for Approval memo in DARRTS, dated July 2, 2021.

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1.2. Benefit-Risk Assessment

[Benefit-Risk Integrated Assessment](#)

See Summary Basis for Approval in DARRTS, dated July 2, 2021. The B-R-A is unchanged from the original conclusions.

2. Regulatory Background

2.1. Summary of Presubmission/Submission Regulatory Activity

The original teplizumab BLA 761183 was submitted on October 31, 2020 and received a Complete Response on November 2, 2020. For a detailed account of regulatory activity prior to resubmission, please see the primary clinical review dated July 2, 2021. The Complete Response (CR) Letter was issued to the Applicant on July 2, 2021, stating that the FDA could not approve the application in its present state due to the lack of biocomparability between the PRV-031 product used in the clinical safety studies submitted in the original BLA, manufactured by Eli Lilly, and the planned commercial product, manufactured by AGC Biologics. In particular, the PK bridging study, PRV-031-004, failed to show PK comparability between the teplizumab product used in the TN-10 study and the planned commercial product. Additionally, a lack of an acceptable facility inspection at the (b) (4) manufacturing facility, an unacceptable charge variation measured in teplizumab drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions were cited as additional reasons for CR. Other comments were provided by clinical, clinical pharmacology and product quality teams that were not considered approvability issues, including the recommendation to characterize the immunogenicity potential of the proposed commercial product (AGC Biologics) to the clinical trial product (Lilly) and provide justification for any differences noted.

During the weeks after the CR, the sponsor and the Agency exchanged communications regarding the initial Content and Format Package proposal for the safety update. The Agency provided acceptance of the plan for the proposed content of the safety update on July 15, 2021, by general advice letter with the additional recommendation to include an updated analysis of adverse events of special interest (AESI).

On July 27, 2021, the Sponsor submitted an amendment to IND 100262 containing the statistical analysis plan (SAP) for a planned PK/PD substudy for the ongoing PRV-031-001 (PROTECT) study in order to address the concerns related to bioequivalence noted in the complete response letter, as both the clinical trial (Eli Lilly) product and the to-be-marketed (AGC Biologics) product were used as investigational products in the PROTECT study allowing for PK, PD, and immunogenicity comparisons between the products. The Agency replied with an Advice/IR letter on August 6, 2021, in which we strongly recommended the population pharmacokinetic (popPK) model and analysis plan be pre-specified and discussed with the Agency before unblinding of the PROTECT PK/PD and immunogenicity data and that all data

from the PRV-031-004 (single-dose healthy patient bioequivalence study), Protégé study, TN-10 study, and PROTECT study be built in a single (joint) popPK model.

On August 17, 2021, the Sponsor submitted a proposed BLA PK/PD data package and anticipated timelines to support comparability in response to our August 6, 2021, Advice/IR letter. The Sponsor sent a follow up email on August 25, 2021, seeking agreement with the proposed statistical analysis plan (SAP) in order to proceed with data transfer of unblinded PK data to the (b) (4) teams. A subsequent Advice/IR letter was issued on September 1, 2021, stating review expectations and providing comments and recommendations on the SAP and modeling and simulation analysis plan. The Sponsor then requested an informal teleconference for clarification purposes, which was held on September 3, 2021. On September 9, 2021, the Agency confirmed agreement with the Sponsor's proposed approach for the amended two stage PK/PD model design via email.

Concurrent with the clinical pharmacology Sponsor meetings and discussions, a Type A CMC Meeting was held on August 31, 2021, via teleconference with discussion on the planned content to address CMC issues contained in the complete response letter. Meeting minutes are available in DARRTs, checked in on September 22, 2021.

A Type A meeting was held on November 18, 2021 (refer to meeting minutes in DARRTS dated December 8, 2021). The Agency provided feedback on the Sponsor's proposed single joint population PK (popPK) model from the Protégé study, TN-10 study, study PRV-031-004 and the PROTECT study. The goal of this model was to characterize the differences in PK between the teplizumab (PRV-031) products from Lilly and AGC Biologics. The Agency provided recommendations in order to ensure the popPK model captures the difference in PK between products in a consistent manner and avoid study specific effects as much as possible.

A Type B meeting was held for IND 100262 (at-risk population, the IND associated with pre-BLA 761183) on January 25, 2022. The purpose of this meeting was to discuss and obtain agreement on the Sponsor's proposed clinical pharmacology data package as well as the clinical contents for the BLA 761183 resubmission. The preliminary safety update was submitted to the Agency at this meeting, and the Agency agreed that the submitted update was adequate for review with the addition of analyses that use the same definition of hypoglycemia as used in the original BLA submission to assess the safety population in the update, in addition to analyses using revised definitions as well as the inclusion of updated exposure information for the clinical trials in person-time. Additionally, at this meeting the Agency recommended that the Sponsor propose an alternative full 14-day dosing regimen to match the AUC_{inf} and/or C_{trough} exposures between the Lilly and AGC products, using PK simulations from the PROTECT study and individual PK parameters of the Agency-recommended model. It was also recommended

that they provide safety justifications for the modified full 14-day dosing based on previously studied higher dose regimens, as applicable.

On February 17, 2022, the Sponsor submitted the BLA resubmission under review, which included a 13-month safety update, a proposal for 4 alternative dosing regimens (Regimens A-D) with safety justification for the proposed regimens as well as requested pharmacokinetic (PK) comparability data from the PROTECT PK/PD substudy along with requested analyses of concentration-CD3 occupancy analyses, anti-drug antibody (ADA) comparisons between clinical trial and manufactured products.

On June 10, 2022, the Agency sent a Mid-cycle Communication and IR in order to propose an alternative 14-day dosing regimen for the manufactured (AGC) product which met bioequivalence criteria for the pharmacokinetic (PK) model-predicted AUC_{inf} , C_{trough} and C_{max} exposures of clinical trial (Lilly) product derived from both individual (conditional) PK simulations as well as typical (population or average) PK simulations. In this Mid-cycle communication, the Agency confirmed that the Sponsor's proposed regimens did not pass bioequivalence criteria, requesting that the Sponsor also re-run their analyses to confirm this approach. The subsequent submission by the Sponsor including the revised analyses constituted a major amendment, communicated to the Sponsor on June 29, 2022, with a change in Prescription Drug User Fee Act (PDUFA) date from August 18, 2022, to November 17, 2022.

2.2. Devices and Companion Diagnostic Issues

During the initial BLA review cycle, the potential requirement for the development of pancreatic islet autoantibody assays as a companion diagnostic was discussed with the Center for Devices and Radiological Health (CDRH) since T1D autoantibody testing is required for the identification of stage 2 type 1 diabetes. The sponsor has not codeveloped companion diagnostics for the islet autoantibody assays used to identify the intended patient population. In the TN-10 study, patients were selected using islet autoantibody assays developed by the

(b) (4)

The assays used in the TN-10 study were Clinical Laboratory Improvement Amendment (CLIA)-certified but not FDA-authorized and the Applicant has not specified FDA-authorized assays in their proposed the product labeling. A discussion of the autoantibody assays used in the TN-10 study and their performance characteristics is included in Section 6.1.1.3 of the original BLA review.

Following the BLA resubmission, the need for a companion diagnostic(s) was revisited. Dr. Jessica Chu completed the CDRH consult review, dated June 10, 2022. Her assessment is summarized below:

- Autoantibody testing is necessary to identify patients. Because autoantibody testing is necessary but not sufficient to determine patient eligibility for teplizumab, it is a key determinant in the staging of T1D. Thus, these tests would meet the definition of companion diagnostic devices. They would be essential for the safe and effective use of teplizumab because they would identify patients in whom teplizumab has been studied for safety and effectiveness (i.e., patients with two or more autoantibodies and dysglycemia, but not meeting criteria for the diagnosis of T1D). These are the patients most likely to benefit from teplizumab treatment, and there is insufficient information about the safety and effectiveness of teplizumab in any other population.
- Autoantibody testing is not standard of care. It is not clear that practicing clinicians would correctly identify the population in whom teplizumab has been studied for safety and effectiveness because autoantibody testing for T1D staging is not considered standard of care and these tests are not routinely recommended in clinical practice.
- The autoantibody assays are not standardized, and their performance has not been validated by FDA in the intended population of Stage 2 T1D. There is a lack of assay standardization and their performance in the teplizumab intended use population is uncertain. The laboratory developed tests (i.e., CLIA-certified) have not been reviewed by FDA and the performance of the FDA-authorized tests have been established in a different patient population: to “aid in the diagnosis of Type 1 diabetes mellitus”, which is different from a test used to screen for individuals with Stage 2 T1D eligible for teplizumab treatment.
 - Clinical sensitivity for the FDA-authorized tests was determined by assessing true positive test results for samples from diagnosed T1D patients and clinical specificity was determined by assessing true negative test results for samples from patients with non-target diseases (e.g., type 2 diabetes, metabolic syndrome, autoimmune diseases, infection, renal disease, testicular cancer, kidney disease).
 - It is not clear that the sensitivity of the FDA-authorized tests would be the same for diagnosed T1D patients vs. stage 2 T1D patients and that the specificity of the authorized tests would be the same in the non-target disease groups vs. patients suspected of Stage 2 T1DM but determined to be ineligible for the drug.

Dr. Chu concluded by stating, “Without information to understand the performance of the cleared tests in the teplizumab intended use population, we are unable to conclude that cleared tests have high specificity (low false positive rate) in the teplizumab intended use population.”

DDLO extensively discussed and considered the advice of CDRH. We agree that autoantibody testing is required to identify the indicated population for teplizumab. However, we disagree with their conclusion that autoantibody testing is not standard of care and that the performance of the FDA-cleared autoantibody assays is unknown.

The limited available precedent for the development of a companion diagnostic outside of the oncology space, wherein companion diagnostics are typically used to select a subgroup of patients where the safety and efficacy of a drug has been adequately demonstrated, was discussed. An example of such testing includes the first companion diagnostic, a test which identified a subgroup of patients with breast cancer which overexpress the HER-2 protein in order to qualify for treatment with Herceptin (trastuzumab). Companion diagnostics have not typically been codeveloped for autoimmune biomarkers utilized to diagnose a variety of autoimmune diseases (e.g., Hashimoto's thyroiditis and celiac disease), where testing is readily available and commonly used in clinical practice. In addition, it was discussed how the use of autoantibody assays are routinely used in clinical practice to identify type 1 diabetes, i.e., a disease state and not a subgroup of patients with a disease state. It was noted that HbA1c, is commonly used in the diagnosis of type 2 diabetes, but not considered a companion diagnostic for drugs intended for the treatment of type 2 diabetes.

The identification of stage 2 T1D relies on the measurement of islet autoantibodies and glycemia. In the case of islet autoantibodies, there are two standard screening approaches. One consists of global assessment of Islet Cell Cytoplasmic Autoantibodies, also known as Islet Cell Antibodies (ICA), typically used as a non-specific screening test to prompt more specific testing as to which antigens are targeted in case of a positive ICA. The second approach, more commonly used today, is to directly test for the four specific antigens targeted by the islet cell antibodies. Currently, if there is suspicion that an individual is at risk of developing T1D, they are tested for the four islet cell autoantibodies directed at specific islet antigens: insulin antibody (IAA), glutamic acid decarboxylase 65 antibody (GADA), Insulinoma-Associated-2-antibody (IA-2A), islet cell antibody (ICA), and zinc transporter 8 antibody (ZnT8A). If positive for two, they are diagnosed with T1D. However, definitive staging depends not on the results of the autoantibody tests, but on whether they have dysglycemia on oral glucose tolerance testing (Stage 2) or overt hyperglycemia and/or symptoms (Stage 3). There are FDA-authorized versions of the 4 specific T1D autoantibody tests available (IAA, GADA, IA-2A and ZnT8A), indicated "as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune mediated diabetes)".

The following regulatory, scientific, and clinical issues were considered when making the determination as to whether a companion diagnostic would be required:

1. Is the assessment of pancreatic islet cell autoantibodies considered standard of care to aid in the diagnosis of type 1 diabetes?

This reviewer considers T1D autoantibody testing to be standard of care to aid in the diagnosis of patients with type 1 diabetes. Pancreatic islet autoantibodies are commonly used in the identification of patients with type 1 diabetes in two main settings: in clinical research investigating therapeutics intended to delay progression in individuals who meet clinical criteria for early diagnosis of T1D (stage 2 T1D with dysglycemia), and at the time of stage 3 T1D diagnosis (with overt hyperglycemia) to aid in the differentiation of type 1 autoimmune diabetes from type 2 diabetes when the clinical diagnosis is unclear. Stage 2 T1D is also a diagnosis recognized by professional societies responsible for the care for T1D patients (Juvenile Diabetes Research Foundation, Endocrine Society, and American Diabetes Association)¹ and diagnostic requirements have been clearly delineated in the American Diabetes Association Position Statement for the Classification and Diagnosis of Diabetes annual reports since 2017. The criteria for Stage 2 T1D diagnosis are also currently available in the 2022 diagnostic guidelines,¹ with two or more “islet autoantibodies” specified in the diagnostic criteria as well as dysglycemia on oral glucose tolerance testing.

2. Do the clearances for the FDA-authorized islet autoantibody tests, which were validated in patients with new-onset T1D, apply to the population of teplizumab’s intended use: stage 2 T1D?

This reviewer considers stage 2 and stage 3 T1D to be stages of the same disease pathophysiology, although representing different time points along the same disease continuum. Stage 3 T1D only differs from stage 2 T1D by the severity and degree of progression, namely the severity of dysglycemia, which determines the presence of clinical symptoms. The 6-month, 2-year, and 4-year risk of progression to stage 3 T1D once patients have dysglycemia and stage 2 T1D, is approximately 25%, 60%, and 75%, and the lifetime risk approaches 100%.² Therefore, this reviewer considers pancreatic islet autoantibody testing to be used as part of standard of care to aid in the diagnosis of type 1 diabetes, a disease state which includes both stage 2 and stage 3 T1D.

¹ American Diabetes Association Professional Practice Committee; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care 1 January 2022; 45 (Supplement_1): S17–S38. <https://doi.org/10.2337/dc22-S002>

² Krischer, JP, 2013, The use of intermediate endpoints in the design of type 1 diabetes prevention trials, Diabetologia, 56(9):1919-1924

3. For the FDA-authorized versions of the islet autoantibodies, is there sufficient evidence to support the appropriate detection of teplizumab's intended use population?

As mentioned above, there are FDA-authorized versions of the islet autoantibody tests needed to identify stage 2 T1D (GADA, IAA, IA-2A, and ZnT8A) intended "as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune mediated diabetes)". Cleared and validated tests which "aid in the diagnosis" of a disease rely on validation studies where the assay has been tested in a population who also have signs and symptoms of the disease. As stage 2 T1D diagnostic criteria include dysglycemia, an important sign of diabetes indicating beta cell dysfunction and dysregulation of insulin secretion, DDLO considers islet autoantibody testing to appropriately be considered a test which aids in the diagnosis of type 1 diabetes mellitus.

A fifth islet autoantibody biomarker, Islet cell antibodies (ICA) were also used in the TN-10 trial to identify patients with Stage 2 T1D. For this test, ICA, there are no currently available FDA-authorized assays available for provider use. This test was requisite in the identification of 9 subjects in TN-10 (5 teplizumab-treated and 4 placebo-treated). When islet cell cytoplasmic autoantibody results were disregarded, 39/44 (89%) teplizumab-treated and 28/32 (88%) placebo treated patients would have met criteria for TN-10 enrollment by use of FDA-authorized T1D autoantibody tests alone. As there is no FDA-authorized version of ICA available, in the postmarketing period, if ICA is intended to be used as a screening methodology to identify patients who qualify for teplizumab use, we recommend ICA be developed as a FDA-authorized companion diagnostic in order to ensure it adequately meets FDA requirements.

4. Is a companion diagnostic required for safe and effective use of teplizumab?

As FDA-authorized versions are available for 4 of the 5 T1D autoantibody tests, we have determined that the currently available islet autoantibody tests are appropriate for the safe and effective use of teplizumab and therefore, we find it unnecessary to require the Applicant to develop these tests as companion diagnostics. Additionally, if we were to recommend companion diagnostics be developed for each one of these tests, we would greatly limit access to patients, as the FDA-authorized tests are commonly available. Moreover, DDLO strongly concludes that the currently available testing and methodology for the identification of stage 2 T1D is appropriately rigorous that the risk of inappropriate diagnoses and use of teplizumab would be very low. This is related to the need for not only multiple positive autoantibodies which is exceedingly rare in the general population, but the additional need for dysglycemia on the oral glucose tolerance test. For example, each individual islet autoantibody assay is calibrated to be highly specific for type 1 diabetes, with specificities of 98.0-98.6% for each of the FDA-authorized tests and when used as a panel, the specificity has been demonstrated to

be as high as 100%.³ In addition to this reassuring level of specificity, there is evidence from longitudinal studies in patients followed for the development of T1D, that autoantibody titers slightly decrease, or persist at the same level over time.⁴ Therefore, the titers of islet autoantibodies (used to generate the diagnostic cutoff) are generally lower once patients are diagnosed with stage 3 T1D. Although FDA-authorized islet autoantibodies were validated in patients with stage 3 T1D, applying this testing to stage 2 T1D would, in theory, result in slightly less sensitive test, but with greater specificity for T1D in the stage 2 population. Moreover, a patient without dysglycemia would not be eligible to get treatment with teplizumab regardless of the laboratory used for islet autoantibody screening. In patients with dysglycemia, the risk of false positives is extremely low given that disease has progressed to the point of beta cell dysfunction, a crucial component of the diagnosis of stage 2 T1D. The presence of dysglycemia both improves the specificity and reliability of the clinical diagnosis of stage 2 T1D.

Conclusion on whether a companion diagnostic will be required:

Based on the regulatory, scientific, and clinical considerations listed above, this reviewer believes that the currently available FDA-authorized tests are appropriate for the diagnosis of stage 2 T1D and identification of patients who may qualify for teplizumab. Recommending a companion diagnostic be developed in this case would create undue burden on patients who qualify for teplizumab use by limiting access to tests which have been demonstrated to appropriately identify patients for teplizumab's intended use.

For ICA, the only islet autoantibody without an FDA-authorized version, we recommend this test require development as a companion diagnostic in the post-marketing period. Additionally, the sponsor will need to bridge the performance of the ICA autoantibody assays used in clinical trials to the companion diagnostic device in the post-marketing period.

³ Verge CF, Stenger D, Bonifacio E, Colman PG, Pilcher C, Bingley PJ, Eisenbarth GS. Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. *Diabetes*. 1998 Dec;47(12):1857-66. doi: 10.2337/diabetes.47.12.1857. PMID: 9836516.

⁴ Köhler M, Beyerlein A, Vehik K, Greven S, Umlauf N, Lernmark Å, Hagopian WA, Rewers M, She JX, Toppari J, Akolkar B, Krischer JP, Bonifacio E, Ziegler AG; TEDDY study group. Joint modeling of longitudinal autoantibody patterns and progression to type 1 diabetes: results from the TEDDY study. *Acta Diabetol*. 2017 Nov;54(11):1009-1017. doi: 10.1007/s00592-017-1033-7. Epub 2017 Aug 30. PMID: 28856522; PMCID: PMC5645259.

3. Sources of Clinical Data and Review Strategy

For this resubmission, I reviewed the sponsor's submitted analyses for the safety update studies: the ongoing PROTECT and TN-10 extension studies and the completed Protégé Extension study. A summary of each study and its role in the safety update review is outlined in Table 1. I also reviewed individual patient narratives for all SAE, discontinuation events, and adverse events of special interest (AESI) in order to determine whether the additional safety data submitted in this resubmission altered the overall safety profile for teplizumab beyond the original review.

Table 1. Trials Included in the Safety Update & Role in Review

Trial	Study Description & Population	Role in the Review
PRV-031-001 (PROTECT)	Ongoing, randomized, double-blind, placebo-controlled, multicenter and multinational trial evaluating the safety and efficacy of teplizumab Patients aged 8-17 years newly diagnosed with T1D (within 6 weeks of diagnosis) treated with teplizumab (Lilly or AGC Biologics) or placebo	As this study is still blinded, I evaluated SAE, TEAE and AESI for: - unexpected safety signals - expected events with teplizumab use that are considered to be rare in the general population (i.e., cytokine release syndrome, lymphopenia, infection) Analysis of immunogenicity between Lilly and AGC Biologics products
PRV-031-002 (TN-10 Extension)	Open-Label Extension of TN-10 study Teplizumab and placebo-treated subjects who participated in the TN-10 trial (at-risk with stage 2 pre-symptomatic T1D) who were diagnosed with stage 3 T1D participated in this open-label study	Limited evaluation for SAE, TEAE, and AESI based on small sample size (N=4)
CP-MGA031-02 (Protégé Extension)	Non-interventional extension, long-term follow-up study for the open-label (segment 1) and double-blind, placebo controlled (segment 2) Protégé study (CP-MGA031-01). Teplizumab and placebo-treated subjects were invited to participate if they completed the Protégé study through Day 728	Evaluation of long-latency events (ex: malignancy) as this was a non-interventional long-term follow up study

My approach to each study in the safety update differed depending on the type of study, and thus studies were reviewed individually in section 5. For instance, blinded results of the ongoing clinical study (PROTECT) were primarily evaluated for unexpected safety signals or for events that are considered to be rare in the general population (laboratory related adverse events, cytopenias, severe infections and cytokine release syndrome) as well as a review of the comparative immunogenicity between Lilly and AGC Biologics products.

There was minimal data from the open-label TN-10 extension study (4 subjects) included in this safety update, and therefore review of TN-10 extension was limited in scope and conclusions. My review for the completed clinical study (Protégé Extension) was limited to assessment of safety signals associated with long-latency events like malignancy, as this study was limited to long-term safety data.

I did not address efficacy other than summarizing findings from the original BLA review (submitted July 2, 2021) and a discussion in Section 4.1.1 when I review how efficacy conclusions have been incorporated into the labeling strategy for this resubmission review.

4. Integrated Review of Effectiveness

4.1. Additional Efficacy Considerations

4.1.1. Considerations on Benefit in the Postmarket Setting

Discussions of benefit in the postmarket setting were deferred in the original clinical review because of the planned Complete Response action. It was noted that the to-be-marketed product should be demonstrated comparable (PK or other method) to the clinical trial product in order to conclude that efficacy in the postmarket setting will be similar to the treatment effect observed in the clinical development program.

In the postmarket setting, teplizumab is anticipated to have a similar treatment effect as was observed within the context of the clinical development program. This determination is based on several important considerations of how teplizumab's use may differ in the postmarket setting and could potentially affect treatment efficacy:

- Potential differences in islet autoantibodies used in screening to detect Stage 2 T1D in patients selected for teplizumab use
- Potential differences in efficacy in subpopulations not represented in the clinical trials: specifically, non-relatives of patients with T1D and patients not included in clinical trials

due to inclusion or exclusion criteria

Restriction of screening for Stage 2 T1D to include the 4 FDA-authorized islet autoantibodies (without ICA)

As detailed in section 2.2 Devices and Companion Diagnostic Issues, there are currently FDA-authorized versions of four of the available five pancreatic islet autoantibodies which were used for the screening and detection of patients with Stage 2 T1D for the TN-10 study. Our division proposes that the only autoantibody without an FDA-authorized version, islet cell antibody (ICA), be developed as a companion diagnostic device. While labeling has not yet been determined, it is possible that teplizumab's label will specify use of an FDA-authorized version of the 4 islet autoantibody tests available, insulin antibody (IAA), glutamic acid decarboxylase 65 antibody (GADA), Insulinoma-Associated-2- antibody (IA-2A), and zinc transporter 8 antibody (ZnT8A) when making a diagnosis of Stage 2 T1D. In the TN-10 study, the number of subjects from each study arm who would have met criteria for enrollment based on results from a four-islet autoantibody panel (IAA, GADA, IA-2A, ZnT8A) alone – disregarding islet cell antibody (ICA) laboratory results are 39 of 44 (89%) teplizumab and 28 of 32 (88%) placebo patients. While this labeling recommendation may limit the number of patients who qualify for teplizumab use in the postmarket setting by 11-12%, it is not expected to lead to a difference in efficacy, as post hoc analyses did not demonstrate a difference in efficacy after exclusion of the 9 subjects who met criteria by ICA positivity.

Expansion of the treatment indication to include non-relatives

Recruitment and enrollment of patients with stage 2 T1D for the TN-10 study was through the TrialNet Pathway to Prevention (TN-01). This screening mechanism facilitated the enrollment of relatives of patients with T1D through active surveillance of families with T1D. Family history is not part of the Stage 2 T1D definition according to professional guidelines^{3,4} and the efficacy outcome of the development program is considered applicable to both Stage 2 T1D patients with or without family history. The pathogenesis and risk of progression for stage 2 T1D individuals who are not T1D relatives are not considered to be significantly different from the population studied in TN-10⁵, and therefore expansion of the treatment indication to include non-relatives is recommended and was generally supported the Advisory Committee meeting. This change is not expected to have an effect on the benefits of teplizumab treatment in the postmarket setting.

Expansion of Inclusion/Exclusion Criteria

⁵ Ziegler, AG, M Rewers, O Simell, T Simell, J Lempainen, A Steck, C Winkler, J Ilonen, R Veijola, M Knip, E Bonifacio, and GS Eisenbarth, 2013, Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children, *Jama*, 309(23):2473-2479.

As discussed in section 6.1.1.3 of the original BLA review, the Applicant implemented several inclusion and exclusion criteria that are likely unnecessary in the post-market setting such as excluding subjects with a history of asthma or atopic disease. However, the implementation of these criteria is not expected to have an impact on teplizumab's efficacy in the post-marketing setting. Exclusion criteria that have clinically meaningful implications, including excluding those with active infections, or patients with cytopenias or aminotransferase elevations at baseline will be recommended for labeling. For TN-10, the Applicant limited enrollment to subjects weighing ≥ 26 kg, which is approximately 50th percentile for pediatrics 8 years of age. Therefore, teplizumab may be administered to pediatric patients < 26 kg in real-world use. This is not expected to impact the efficacy of teplizumab, as dosing is based on body surface area (BSA).

Defining islet autoantibody positivity and dysglycemia in the postmarket setting

Another consideration for applicability of efficacy benefit in the post-market setting relates to the definition of islet autoantibody positivity and dysglycemia applied in the TN-10 study. TN-10 required confirmatory positivity of two or more pancreatic islet autoantibodies on two separate tests, as well as two dysglycemic oral glucose tolerance tests (OGTT), i.e., a secondary "confirmatory" dysglycemic OGTT in patients who are > 18 years prior to enrollment in TN-10. This methodology was considered useful to ensure appropriate subject selection for the interpretation of efficacy in the original BLA efficacy review. Recommending a second screening for islet autoantibodies in the postmarket setting would be a burdensome requirement to enact, given that there is evidence that once two or more islet autoantibodies are detected, the development of dysglycemia on OGTT confirms that the degree of islet cell destruction has reached a threshold that is associated with disease progression.³ The inclusion of a secondary test for dysglycemia is considered to be much less burdensome to patients and there is evidence from the literature that a second confirmatory OGTT improves the specificity of the Stage 2 T1D diagnosis in older patients (age > 18 years). In general, the persistence of dysglycemia on OGTT has been observed to be variable, among patients with 2 or more pancreatic islet autoantibodies. However, among patients younger than age 13 years with a single dysglycemic OGTT, the risk of subsequent development of Stage 3 T1D is extremely high, with an estimated 5-year risk of progression of 94% once a single dysglycemic OGTT is obtained (even if subsequent OGTTs are normoglycemic).⁶ It is important to note that for ages 13-18 years in TN-10 the efficacy of teplizumab was not significantly different than in other age subsets and a second confirmatory OGTT was not required in this age group. Therefore, we recommend a second confirmatory dysglycemic OGTT for patients > 18 years of age in order to ensure the efficacy of teplizumab in the postmarket setting is consistent with the efficacy

⁶ Sosenko JM, Palmer JP, Rafkin-Mervis L, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. *Diabetes Care*. 2009;32(9):1603-1607. doi:10.2337/dc08-2140

observed in the TN-10 trial.

5. Review of Safety

The safety update includes new and updated safety information for two ongoing trials (PROTECT and TN-10 extension) and the completed observational Protégé Extension trial (Table 2).

The data lock point (DLP) date used for the safety update in the Resubmission is November 24, 2021. See Table 2 below for details.

Table 2. Trials Included in the Safety Update

Trial	Study Design & Population	Subjects	Treatment & Follow-up	Data Included
PRV-031-001 (PROTECT) (US, Canada, Belgium, Czech Republic, France, Germany, UK, Poland)	Ongoing, Randomized, Placebo-controlled, Double-blind multinational, multicenter trial Children (age 8-17 years) with newly diagnosed T1D, within 6 weeks of diagnosis	N=327 Currently Blinded, Randomized 2:1 Teplizumab: Placebo	Teplizumab or placebo in two 12-day IV courses, second course at week 26 or 52 Day 1: 106 µg/m ² Day 2: 425 µg/m ² Days 3-12: 850 µg/m ² Total per course: 9.0 mg/m ² Follow up: 18 months	From trial start to current data cut-off (11/24/2021) as this trial is ongoing
PRV-031-002 (TN-10 Extension) (5 sites in the US)	Open-Label Extension of TN-10 study Teplizumab and placebo-treated subjects (age 8 and older) who participated in the TN-10 trial (at-risk with stage 2 pre-symptomatic T1D) who have been diagnosed with stage 3 T1D	N=4 Open-label Teplizumab	Teplizumab administered open-label in single 12-day IV course: Day 1: 106 µg/m ² Day 2: 425 µg/m ² Days 3-12: 850 µg/m ² Total per course: 9.0 mg/m ² Follow up: 18 months	From trial start to current data cut-off (11/24/2021) as this trial is ongoing
CP-MGA031-02 (Protégé Extension) (US, Czech Republic, Estonia, India, Israel, Latvia, Poland,	Non-interventional extension/follow-up study for the Protégé study (CP-MGA031-01). Teplizumab and placebo-treated subjects who	N=181 Teplizumab N=32 Placebo	No intervention was administered Follow up: median 6 months for teplizumab-treated subjects and median 4.5 months for placebo subjects	All data: from extension trial start to trial end (June 2011) This study was terminated prematurely

Romania, Spain, Sweden, Ukraine)	completed the Protégé study through Day 728			
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Source: Clinical Reviewer
UK=United Kingdom; US=United States

In the safety update submission, the Sponsor included all reports and narratives for deaths, serious adverse events (SAEs), adverse events leading to study drug discontinuation, and Adverse Events of Special Interest (AESI) for each trial.

Composite frequencies of Treatment-Emergent Adverse Events (TEAEs) were summarized by treatment arm and reported separately for each of the 3 studies in the safety update. As with the original BLA safety analyses submitted by the sponsor, treatment-emergence was defined as occurring any time after the first treatment day, and therefore any adverse event reported during the follow up period was defined as a TEAE. In the primary review for the original BLA, TEAEs were limited to either the 14-day treatment period, or to within 2 weeks of the last dose of study drug. Therefore, TEAE analyses provided by the sponsor could not be directly compared to the TEAE analyses conducted in the original BLA review. Instead, where indicated, TEAE frequencies were compared to the sponsor's original TEAE analyses, which used the same definition of TEAE.

Exposure in Trials Included in the Safety Update

Total exposure and the number of teplizumab courses administered in each study are summarized in Table 3 for the safety update population.

Table 3. Summary of Exposure and Teplizumab Courses Administrated (Safety Update Population)

		PROTECT N=327 (Teplizumab or placebo with 2:1 randomization)	TN-10 Extension Open-Label Teplizumab N=4	PROTÉGÉ Extension Teplizumab Group N=181	PROTÉGÉ Extension Placebo Group N=38
Number of courses administered					
1	n (%)	327 (100)	4 (100)	N/A	N/A
Completed all 12 infusions		292 (89.3)	3 (75)		
2	n (%)	217 (66.4)	N/A		
Completed all 12 infusions		190 (58.1)			
Exposure (person-years)		261.7	3.3	106.2	16.1

The follow-up time in person-year is calculated as the sum of the duration of study follow-up across all the subjects in the Safety Population. For PROTECT and TN-10 Extension, exposure began the day of the first study drug. For Protégé Extension, exposure was calculated based on date of informed consent as no intervention was administered.

For the ongoing, blinded PROTECT trial, 327 subjects received at least one dose of study drug (teplizumab or placebo) with 261.65 person-years of follow up data for the combined teplizumab and placebo treatment arms. Additionally, 217 subjects received two treatment courses of either teplizumab or placebo (separated by 6 or 12 months).

For the ongoing, open-label TN-10 Extension study, 4 subjects received 1 course each of teplizumab with 3.26 person-years of follow-up data.

In the Protégé Extension study, 181 (82.6%) subjects had received teplizumab and 38 (17.4%) had received placebo during the Protégé study. For the Protégé Extension, teplizumab-treated patients had 106.2 person-years of follow-up data whereas placebo-treated patients had only 16.1 years of follow up data from the date of signed informed consent. Therefore, this reviewer primarily inspected the data for potential drug related AESIs rather than performing incidence rate comparisons.

5.1.1. PROTECT

The PROTECT study is an ongoing, randomized, double-blind, placebo-controlled, multicenter, and multinational trial evaluating the safety and efficacy of teplizumab given to subjects aged 8-17 years old newly diagnosed with T1D (within 6 weeks of diagnosis) as a 12-day course of daily IV teplizumab administered twice, with the second course 6 months or 12 months after the first course.

A total of 327 subjects have been enrolled in the PROTECT study and randomly assigned at a ratio of 2:1 to receive teplizumab or placebo. All subjects are scheduled to be followed through Week 78. While the original protocol stipulated a 2-course dosing regimen administered at randomization and Week 26, the protocol was amended to allow subjects to receive the second course at Week 52 to accommodate infusions that could not be administered due to the COVID pandemic. Per Sponsor communications, only 30 subjects (10% of those enrolled) have been administered the “modified dosing regimen” for teplizumab.

Additionally, in March 2021, subjects randomized to teplizumab started to receive teplizumab manufactured by AGC Biologics (the intended commercial product) while subjects prior to March 2021 received teplizumab manufactured by Lilly (a product from previous clinical trials including TN-10). The sponsor submitted a blinded safety analyses comparing safety data between subjects enrolled prior to March 2021 (N=223) either randomized to Lilly teplizumab or placebo, and subjects enrolled after March 2021 (N=104) either randomized to AGC Biologics

teplizumab or placebo. Review of this analysis can be found in immunogenicity section 5.2.6.

As of this safety update, the treatment arms for the PROTECT study remain blinded. The PROTECT study's last subject was randomized on November 4, 2021, and the last subject, last visit is projected to occur on May 4, 2023.

Per FDA's request, updates from the Data Monitoring Committee (DMC) review of PROTECT (open meeting minutes and the most recent recommendation letter) were submitted on 6/14/2022 (SDN 63) and show there were no new safety concerns with respect to the observed frequency, grade or relationships of adverse events, treatment interruptions or study discontinuations in the PROTECT study.

Since the PROTECT study is currently blinded, for analysis of events that are of low frequency in the general population (i.e., cytokine release syndrome, serious infection and cytopenias), "worst case" safety analyses were completed assuming that all of the detected adverse events occurred in the study occurred in patients randomized to teplizumab. As the blinded study contains 327 subjects, randomized to either teplizumab or placebo in a 2:1 ratio, I adjusted rates of important adverse events to occur out of an estimated 218 subjects randomized to teplizumab, compared with the blinded safety population of 327 subjects treated with either teplizumab or placebo.

5.1.2. TN-10 Extension

TN-10 was a randomized, placebo-controlled, double-blind, parallel-arm efficacy and safety study designed to evaluate the treatment effect of teplizumab compared with placebo in the delay of T1D in individuals with stage 2 T1D, at high risk for developing stage 3 T1D.

The TN-10 Extension study is an ongoing, open-label, multicenter (5 sites in the US) extension trial in subjects who completed the TN-10 trial who were subsequently diagnosed with stage 3 T1D. In the TN-10 extension trial, patients were to initiate open-label treatment with teplizumab within 1 year of diagnosis of stage 3 T1D.

The open-label teplizumab treatment course administered in the TN-10 extension study was the same cumulative dose (9.0 mg/m^2) as the originally studied regimen for TN-10, but administered over a shorter time period, of 12 days. After completing the treatment course, subjects are followed for 78 weeks (18 months) from the first dose of open-label treatment. In addition, subjects had to fulfill all inclusion and exclusion criteria for the TN-10 extension study and sign an informed consent form.

For the original submission, the Applicant included all available safety data for TN-10 up to a median follow up time of 50.6 months of the trial, at the time of trial end, when 43 patients were diagnosed with stage 3 T1D. In this Safety Update, the Applicant provides new safety data for the 4 subjects in the TN-10 Extension study following open-label dosing of teplizumab. Of note, the 4 subjects from the TN-10 Extension study were all randomized to the teplizumab treatment arm in the original TN-10 study, so the open-label teplizumab infusion at the start of the TN-10 Extension study is each subject's second course of teplizumab (per sponsor communication, dated 6/30/2022, SDN 68). As noted in Table 3, 3.3 person-years of follow up were included in the safety update for the N=4 patients enrolled in the ongoing TN-10 extension study.

5.1.3. Protégé Extension

The Protégé Extension study was a 3-year follow-up of the double-blind, placebo controlled Protégé study (CP-MGA031-01). Subjects were invited to participate in the Protégé Extension study if they completed the Protégé study through Day 728 and met all entry criteria. No study treatment was administered in this long-term safety follow-up study.

The original Protégé study was conducted in two parts, segment 1, and segment 2.

- Segment 1
Segment 1 was an open-label safety study in which 38 subjects with recently diagnosed T1D were given intravenous (IV) teplizumab for 14 days, as two identical courses 6 months apart
- Segment 2
Segment 2 was a randomized, double-blind, placebo-controlled, double-blind, dose-ranging efficacy and safety study designed to evaluate the treatment effect of teplizumab compared with placebo on the c-peptide area under the curve (AUC) in individuals who had recently been diagnosed with T1D. Protégé segment 2 was designed to assess three teplizumab dosing regimens (a full 14-day course, a one-third dose 14-day course, and a 6-day course) of daily IV infusions compared with placebo (IV) given as two identical courses, 6 months apart.

Both segments 1 and 2 enrolled patients with recently diagnosed stage 3 T1D, within 12 weeks of diagnosis.

The Protégé Extension study was terminated early by MacroGenics when the Protégé study failed to meet its primary endpoint. This is reflected in the average follow-up time in person-

years for teplizumab-treated subjects (of 6 months) and placebo-treated subjects (of 4.5 months) beyond study day 728.

Thirty-two (14.6%) subjects who completed Protégé Study Segment 1 (open-label) and 187 (85.4%) subjects who completed Protégé Study Segment 2 (double-blind) were included in the safety update population.

As for the role of the Protégé Extension trial in the safety update analysis, it is important to note the limitations of the data for this long-term follow up study. As shown in Table 3, for teplizumab-treated subjects (N=181), there were 106.2 person-years of follow-up, with a median follow-up time of 178 (2-661) days (approximately 0.6 years per person), and for placebo-treated subjects (N=38) there were 16.1 person-years of follow-up, with a median follow up time of 127.5 (22-411) days (approximately 0.4 years per person). This difference in follow-up time in person-years of exposure is due to a combination of a much higher, by approximately 4.7-fold, number of teplizumab-treated subjects (N=181) enrolled in the extension study compared to the number of placebo subjects (N=38) coupled with a 1.4-fold longer median follow-up time, by 50.5 days in the teplizumab group. Therefore, the teplizumab-treated group could be expected to have approximately 5 times the rate of adverse events as the placebo arm when corrected for by study follow-up exposure and enrollment differences.

Overall, limited conclusions can be drawn from the data from the completed Protégé Extension study as there was such a stark a difference in subject follow up between the study arms.

5.1.4. Categorization of Adverse Events

As in the original BLA, the Applicant used the standard medical dictionary for regulatory activities (MedDRA). Adverse events in the PROTECT were coded using version 24.0 of MedDRA, TN-10 Extension using version 24.0 of MedDRA and Protégé Extension using version 23.0 of MedDRA. For the resubmission, the grading scale used to assess severity of events was the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for PROTECT and TN-10 Extension, and version 3.0 for Protégé Extension. In the original submission, grading for studies were unified based on CTCAE version 3.0, the version used for TN-10 and Protégé as well as the Protégé Extension study in the safety update.

For the safety update, the same definition of adverse events of special interest (AESI) were used as were used in the original BLA. Table 4 lists the AESI definitions for the safety update. Grading criteria for AESIs for the studies included in the safety update were specified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for the PROTECT and TN-10 Extension studies and version 3.0 for the Protégé Extension. AESI analyses were

addressed in section 5.2.4 Treatment Emergent Adverse Events, and section 5.2.5 Laboratory Findings.

Table 4. Adverse Events of Special Interest (AESI) for the Safety Update

AESI	Search Criteria	Grading Defined As:
Infections	SOC – ‘Infections and infestations’; ≥Grade 3	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as infection where invasive intervention or IV antibiotic, antifungal, or antiviral intervention is indicated
Acute mononucleosis-like illness	‘Mononucleosis syndrome’, ‘Epstein-Barr virus antibody positive’, ‘Epstein-Barr virus test positive’, ‘Epstein-Barr viremia’, ‘Cytomegalovirus antibody positive’, ‘Cytomegalovirus test positive’, ‘Infectious mononucleosis’, ‘Lymphadenopathy’, ‘EBV IgM antibody positive’	
Lymphomas or other malignancies	SOC – ‘Neoplasms benign, malignant and unspecified (incl cysts and polyps)’ and HLT – includes ‘malignant’ or ‘lymphomas’	
Major Hypoglycemia	PT – ‘Hypoglycemia’, ‘Hypoglycemic seizure’, ‘Hypoglycemic coma’; ‘Hypoglycemic unconsciousness’	
Liver function abnormalities	(HLT – ‘Liver function analyses’; ≥Grade 3	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as ALT or AST >5x ULN or total bilirubin >3x ULN
Thrombocytopenia	PT – ‘Thrombocytopenia’; ≥Grade 3,	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as <50,000 platelets/mm ³
Allergic/Hypersensitivity reaction	PT – ‘Dermatitis allergic’, ‘Drug hypersensitivity’, ‘Anaphylactic reaction’, ‘Immune reaction’, ‘Anaphylaxis’, ‘Hypersensitivity’, ‘Infusion related reaction’, ‘Serum sickness’; ≥Grade 4	≥Grade 4 (CTCAE version 5.0), defined as life-threatening consequences, with urgent intervention indicated ≥Grade 4 (CTCAE version 3.0), defined as anaphylaxis
Rash	SOC – ‘Skin and subcutaneous tissue disorders’; ≥Grade 3	≥Grade 3 (CTCAE version 5.0) defined as lesions covering >30% body surface area with moderate or severe symptoms ≥Grade 3 (CTCAE version 3.0) Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA
Cytokine Release Syndrome	PT – ‘Cytokine release syndrome’	≥Grade 4 (CTCAE version 5.0) defined as Life-threatening consequences or urgent intervention indicated ≥Grade 4 (CTCAE version 3.0) defined as Life-threatening; pressor or ventilatory support indicated

Lymphocyte count <500 mm ³ for 7 days or longer	PT– ‘Lymphopenia’; ≥Grade 3	≥Grade 3 (CTCAE versions 5.0 and 3.0) defined as <500 mm ³ for duration of at least 7 days
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Note: Grading criteria for the studies included in the update were specified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for the PROTECT and TN-10 Extension studies and version 3.0 for the Protégé Extension.

5.2. Safety Results

5.2.1. Deaths

There was one death reported in a study included in the safety update, Protégé Extension. However, this death was submitted and reviewed as a part of the original BLA and therefore there is no new information to discuss regarding this case. Refer to the original BLA review, dated July 2, 2021, for further discussion on deaths in the teplizumab development program.

5.2.2. Serious Adverse Events

All serious adverse events (SAEs) in the safety update were reviewed individually with review of patient narratives and in some cases, individual case report forms, patient profiles and laboratories.

In the original BLA, the most commonly reported SAEs for the TN-10 study were in the Infections and Infestations SOC (0% in placebo and 9.1% in teplizumab). However, all infection SAEs in TN-10 occurred greater than 2 weeks after completion of the teplizumab treatment course and were not considered temporally related to observed lymphopenia or temporary immunosuppression associated with teplizumab. In addition, there was one episode of serum sickness in a teplizumab-treated patient approximately 5 days after completion of the 14-day teplizumab course. The other SAEs were isolated events of dizziness, concussion, ankle fracture, musculoskeletal chest pain and pelvic-ureteric obstruction and considered unlikely related to teplizumab treatment due to the lack of temporal relationship to teplizumab dosing and isolated nature of events. For the 5-study pool safety database submitted with the original BLA, the most commonly reported SAEs were diabetic ketoacidosis (0.8% controls vs. 2.5% teplizumab) followed by Infections (2.0% controls vs. 3.4% teplizumab), hypoglycemia (1.2% controls vs. 1.7% teplizumab) and cytokine release syndrome (0% controls vs. 0.6% teplizumab).

For the safety update population, 27/550 (4.9%) of all subjects reported SAEs. Of these 27 subjects, about half, 51.8% (14/27) were from the ongoing blinded PROTECT study, and thus, the treatment arm for about half of the reported SAEs for the safety update remain blinded.

PROTECT

Table 5 presents a summary of all SAEs in the PROTECT study by preferred term.

Table 5. Serious Adverse Events (Teplizumab and Placebo) in the PROTECT study

	PROTECT (N=327)		Study Day
Preferred Term	Count [n]	%	
Cytokine release syndrome	3 [3]	0.9%	2-3
Hypoglycemia	3 [2]	0.6%	149, 172, 219
Infection*	2 [2]	0.6%	
Device-related bacteremia			3
Palpitations (related to viral myocarditis)			77
Anxiety	1 [1]	0.3%	22
Colitis ulcerative	1 [1]	0.3%	323
Concussion	1 [1]	0.3%	498
Dermatitis atopic	1 [1]	0.3%	82
Nephrolithiasis	1 [1]	0.3%	220
Suicidal ideation	1 [1]	0.3%	328
Syncope	1 [1]	0.3%	63
Vomiting	1 [1]	0.3%	3

Reporting period: Trial start to November 21, 2021, data is sorted by the number of events

*Starred category contains terms grouped by reviewer, recategorized on review of narratives

Source: Reviewer created from text from resubmission 13-month safety update

Of the 16 SAEs reported by 14 subjects from the ongoing PROTECT study, 3 SAEs were reported to be cytokine release syndrome (CRS), an expected adverse event with teplizumab, in a similar rate (0.9%) to that observed in teplizumab-treated patients in the original BLA safety population (0.6%). For a detailed review of the CRS SAEs, see section 5.2.8, Cytokine Release Syndrome.

Two of the SAEs (device-related bacteremia, and palpitations (related to viral myocarditis)) were determined by this reviewer to be related to infections and while the study is still blinded, a causal relationship with treatment is possible due to the timing of each event and associated symptoms. See section 5.2.12.1 for a detailed review of these infection events.

Action taken with respect to study drug for these SAEs included permanent withdrawal of study drug in 3 subjects with CRS SAEs, study drug interrupted in 1 subject, and no action taken in 10 subjects.

Reviewer Comment: The SAEs noted from the blinded analysis of the PROTECT study were either expected with teplizumab use (CRS or infection) or observed in similar, or lower rate than previously demonstrated in the prior teplizumab safety studies. This analysis did not modify the safety profile for teplizumab.

TN-10 Extension

There were no SAEs reported in the TN-10 extension study.

Protégé Extension

For the Protégé extension study, thirteen (13/181, 7.2%) subjects treated with teplizumab in the original Protégé study reported a total of 20 SAEs, shown in Table 5.

Table 5. Serious Adverse Events in the Protégé Extension Study

Preferred Term	Protégé Extension Teplizumab (N=181)		Protégé Extension Placebo (N=38)		Study Day (for isolated events)
	Count [n]	%	Count	%	
Diabetic ketoacidosis	6 [4]	2.2%	0	0	811-1008
Angina pectoris	1 [1]	0.3%	0	0	761
Appendicitis perforated	1 [1]	0.3%	0	0	915
Coronary artery disease	1 [1]	0.3%	0	0	761
Death	1 [1]	0.3%	0	0	980
Diabetes mellitus inadequate control	1 [1]	0.3%	0	0	987
Appendicitis perforated	1 [1]	0.3%	0	0	915
Gastritis	1 [1]	0.3%	0	0	801
Gastroenteritis	1 [1]	0.3%	0	0	729
Hypoglycemic seizure	1 [1]	0.3%	0	0	868
Iritis	1 [1]	0.3%	0	0	793
Peritonitis	1 [1]	0.3%	0	0	915
Spinal compression fracture	1 [1]	0.3%	0	0	868
Spontaneous abortion	1 [1]	0.3%	0	0	814
Varicella	1 [1]	0.3%	0	0	746

Reporting period: Trial start to November 21, 2021, data is sorted by the number of events

Source: Reviewer created from text from resubmission 13-month safety update

All SAEs for the long-term noninterventional Protégé Extension follow-up study were reported, at the earliest, approximately 2 years after enrollment. Additionally, limited conclusions can be drawn from the unblinded SAEs from the completed Protégé Extension as there was a stark difference in subject follow up between the study arms as outlined in section 5, Table 3. Based

on differential follow-up and enrollment, the teplizumab-treated group for the Protégé Extension could be expected to have approximately 5 times the rate of adverse events as the placebo arm when corrected for by study follow-up exposure. It is important to note that DKA events occurred only in patients with stage 3 T1D. In the original BLA, there were no at-risk (stage 2 T1D) patients with adverse event of DKA.

In conclusion, no unexpected pattern or clustering of preferred terms (PTs) was observed, and no new safety concerns were identified based on the reported SAEs from the 2 ongoing clinical trials and the 1 completed trial in the safety update.

5.2.3. Dropouts and/or Discontinuations Due to Adverse Effects

This section first discusses AEs that led to discontinuation of teplizumab treatment for the original BLA safety population followed by each study included in the safety update, focusing on any relevant findings from the safety update that impact labeling.

According to the teplizumab study protocols, teplizumab dosing was to be fully withdrawn if certain clinical laboratory criteria were met (Table 6). This table was included in the original BLA review and updated to include the PROTECT study laboratory and adverse-event related discontinuation criteria for this resubmission review. The two other studies included in the safety update, TN-10 extension and Protégé extension, had the same discontinuation criteria as their primary studies, TN-10 and Protégé, respectively.

Table 6. Prespecified Discontinuation Criteria for Studies in Original Submission + Safety Update

Parameter	TN-10	AbATE	Protégé	Encore	PROTECT
Bilirubin	>1.3 mg/dL on Day 1; ≥2.0 mg/dL on other days	>1.3 mg/dL on Day 1; ≥2.0 mg/dL on other days	>2 times ULN	>2 times ULN	>3 times ULN
AST/ ALT/ LDH	AST level >2 times ULN on Day 1 AST, ALT or LDH ≥3.0 times ULN on other days.	AST level >2 times ULN on Day 1 AST, ALT or LDH ≥3.0 times ULN on other days.	AST or ALT >3 times ULN	AST or ALT >3 times ULN	AST or ALT >5 times ULN Or AST and/or ALT >3 times ULN AND total bilirubin >2 times ULN (Hy's Law)
Platelet count	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<50,000
Neutrophils	<1000 cells/mm ³	<1,000 cells/mm ³	<1,000 cells/mm ³ on 2 consecutive evaluations performed on different days	<1,000 cells/mm ³ on 2 consecutive evaluations performed on different days	<500 cells/mm ³

Hemoglobin	≤8.5 g/dL or a drop in ≥2 g/dL compared with prior to infusion to a value <10.0 g/dL	≤8.5 g/dL or a drop ≥2 g/dL to <10 g/dL	<8.5 g/dL or a reduction of >2 g/dL from pre-treatment level	<8.5 g/dL or a reduction of >2 g/dL from pre-treatment level	<8.5 g/dL
Coagulation	INR >0.1 above ULN	INR >1.3	N/A	N/A	NA

Source: Reviewer. The protocol for Delay was not available.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio; ISS, integrated summary of safety; LDH, lactate dehydrogenase; ULN, upper limit of normal

Original Safety Population

In the original BLA, 12.5% of teplizumab-treated patients in the safety database did not complete the first cycle of treatment, with the majority of discontinuations related to the laboratory withholding criteria, as detailed in Error! Reference source not found. above. The most common adverse events leading to treatment discontinuation in the original safety population were related to transaminase elevations, for which 5.6% of teplizumab-treated patients and 0.9% of controls discontinued the first course of treatment, followed by decreased hemoglobin (1.8% teplizumab-treated and 0 controls), leukopenia, lymphopenia, and anemia (1.5% of teplizumab-treated and 0.5% controls) and cytokine release syndrome (1% of teplizumab-treated and 0.5% controls).

APPEARS THIS WAY ON ORIGINAL

PROTECT

My analysis of treatment discontinuations for the safety update was primarily limited to the ongoing, blinded PROTECT study.

In general, the laboratory-related discontinuation criteria for PROTECT had higher thresholds (i.e., AST or ALT >5x ULN) compared to the original safety studies in the BLA (i.e., AST or ALT >3x ULN) and as expected, there were fewer study discontinuations observed in this study.

In the PROTECT study, there were 18/327 (5.5%) study discontinuations and 13/327 (4.0%) course 1 treatment discontinuations (i.e., patients who didn't complete the first course of either teplizumab or placebo). 77% of the premature course 1 treatment discontinuations occurred on days 2-3 of treatment. Since PROTECT is still blinded, if all discontinuations were attributed to teplizumab-treated patients (approximately 218 of the 327 randomized), then 5.9% (13/218) of teplizumab-treated patients likely were unable to complete the full course of teplizumab, approximately half the rate of discontinuations observed in the original BLA population (12.5%).

On review of the patient narratives for the 13 patients who didn't complete treatment course

1, three subjects discontinued treatment due to adverse events of cytokine release syndrome (CRS), one due to cellulitis and device-related bacteremia, one due to pregnancy, one where an adverse event was not specified, one due to diarrhea in the context of fever, four discontinued related to elevated liver transaminases meeting discontinuation criteria (with concomitant CRS in 3/4), 1 discontinued due to elevated alanine aminotransferase (ALT), but did not meet protocol-directed laboratory discontinuation criteria as ALT was 2x ULN on study day 6, and 1 discontinued due to elevated bilirubin which was also present 7 days prior to dosing and elevated at baseline. For the discontinuations related to cytokine release syndrome, all were noted on study days 2-3, required hospitalization and were considered resolved within 1-9 days. These are all reasonably likely to be associated with teplizumab except for pregnancy.

In contrast to the original BLA population, where 5.6% of teplizumab-treated patients discontinued treatment due to liver function test abnormalities, for the PROTECT study, only 1.2% (4/327), and in “worst case scenario”, 1.8% (4/218) discontinued treatment prematurely due to liver transaminase abnormalities meeting protocol-specified laboratory thresholds for discontinuation. There were no noted premature treatment discontinuations related to thrombocytopenia, lymphopenia, neutropenia, or anemia. The rate of discontinuations related solely to CRS was approximately 0.9% (3/327) or 1.3% (3/218) using “worst case scenario” analysis and is very similar to the rate of discontinuations related to CRS in the original safety database (1%). Given the reduction in discontinuations related to both transaminase elevations and cytopenias, it is likely that more relaxed discontinuation criteria for laboratory-related adverse events of the PROTECT study led to the overall lower rate of discontinuations (up to 5.9%) compared to the original BLA safety population (12.5%).

There is no evidence that the less conservative discontinuation criteria led to prolonged or unresolved laboratory abnormalities.

Reviewer comment: The use of less conservative laboratory criteria for discontinuation (specifically for liver enzyme elevations, lymphopenia, neutropenia, thrombocytopenia, and decreased hemoglobin) resulted in fewer treatment discontinuations in the PROTECT study without noted adverse sequelae (see analysis in section 5.2.5, Laboratory Findings). Therefore, the PROTECT study demonstrated that higher laboratory thresholds for discontinuation could be enacted safely in patients receiving teplizumab. For labeling, I recommend providers be informed of the permanent discontinuation criteria used in the PROTECT study, with details regarding the timing and extent of expected laboratory abnormalities, and the timeline for laboratory normalization, without specific recommendations for treatment discontinuation.

TN-10 Extension

The TN-10 extension had a patient who prematurely discontinued treatment, with 1 of 4 patients completing 11 of 12 infusions due to adverse events of fever and pharyngitis. For the TN-10 extension the sponsor reported no study discontinuations as that patient continued on study following treatment.

Protégé Extension

The Protégé extension study was terminated early by the sponsor, and therefore, all of the subjects included in the safety update discontinued this study prematurely. Given Protégé Extension was a non-interventional follow up study, an analysis of discontinuation events was not performed for this resubmission review.

5.2.4. Treatment Emergent Adverse Events and Adverse Reactions

PROTECT

Similar to the original BLA, lymphocyte abnormalities were commonly reported in the PROTECT study, but were coded under two different system organ classes (SOCs) with preferred terms (PTs) of lymphocyte count decreased (22.3%) and lymphopenia (12.8%).

Reviewer comment: In the original BLA, leukopenia and lymphopenia were the most frequently reported AEs. Therefore, despite being blinded, the PROTECT study also reflects a similar adverse event profile for teplizumab treatment.

The most commonly reported TEAEs in the PROTECT study included hypoglycemia (59.3%), headache (30.6%), nausea (29.7%), rash (24.8%), and vomiting (21.7%). While nausea, rash and vomiting were all expected TEAEs frequently observed in the original BLA safety population, hypoglycemia was not observed as a frequent adverse event, and was reported in 6.8% of subjects in the original BLA safety population (combined treatment arms).

Due to this discrepancy in reported events of hypoglycemia, the sponsor was asked to provide a detailed analysis of hypoglycemia events for the PROTECT study, which were reported in 38.9% of subjects (127/327) within the first 30 days of treatment (either teplizumab or placebo) and 59.3% (194/327) during the entire follow-up period. The sponsor reported that the high rate of hypoglycemia noted in the PROTECT study was largely due to different hypoglycemia reporting criteria from the original BLA studies and the addition of blood glucose recording and reporting by continuous glucose monitoring (CGM) and the inclusion of non-symptomatic hypoglycemia events in adverse event reporting for the PROTECT study.

As the PROTECT study is ongoing and treatment arms are blinded, it is unknown whether the high number of hypoglycemia adverse events are related to teplizumab treatment, or simply a higher reporting rate in a population with stage 3 T1D when CGM monitoring is used. When the analyses of the safety update population from the PROTECT study were limited to clinically significant hypoglycemia events, specifically those requiring treatment with glucagon or associated with seizure, coma or unconsciousness, the risk appeared to be lower in the safety update population than the original BLA population, as shown in Table 7 below.

Table 7. Hypoglycemic Adverse Events Requiring Treatment or Associated with Clinical Events in PROTECT study compared to original BLA safety database

Adverse Event	Original BLA	PROTECT
	N=1018 n (%) (Tep/Placebo combined)	N=327 n (%) (Tep/Placebo combined)
Hypoglycemia requiring treatment (glucagon)	7 (0.7%)	3 (0.9%)
Hypoglycemic seizure	6 (0.6%)	0
Hypoglycemic coma	2 (0.2%)	0
Hypoglycemic unconsciousness	4 (0.4%)	0

In order to further characterize and compare hypoglycemia between the PROTECT study and the original BLA safety population, the Sponsor performed an analysis to equilibrate the hypoglycemia analyses from the original BLA dataset with the safety update population (which used CGM and had a different definition of hypoglycemia) via assessing local and central laboratory reports for blood glucose levels in the original safety database. Based on this analysis, detailed in Table 8 below, a similar proportion of subjects experienced laboratory hypoglycemia at each level. Further, it should be noted that more severe low blood glucose levels <54 mg/dL were reported in a lower proportion of subjects in the Safety Update Population.

Table 8. Summary of Sponsor's evaluation of laboratory reports (local and central laboratories) for blood glucose levels in the original safety population compared to the PROTECT study

	Original Safety Population		PROTECT
	Teplizumab	Placebo	
	N=791	N=245	N=327
Glucose Level	n (%)	n (%)	(Tep/Placebo)
55-69 mg/dL	261 (33)	67 (27.3)	62 (19)

40-54 mg/dL	115 (14.5)	27 (11.0)	56 (17.1)
30-39 mg/dL	20 (2.5)	8 (3.3)	1 (0.3)
<30 mg/dL	8 (1.0)	2 (0.8)	3 (0.9)
54 mg/dL and below	132 (16.7)	34 (13.9)	13 (4)
30 mg/dL and below	27 (3.4)	10 (4.1)	4 (1.2)

Reviewer comment: Overall, when we look at TEAE other than hypoglycemia, the analysis for TEAEs in PROTECT are consistent with the original safety review. Upon further investigation of the hypoglycemia signal, I agree with the Sponsor's conclusion that this signal is largely driven by the reporting of non-symptomatic hypoglycemia events by continuous glucose monitoring, as focused analysis clearly demonstrated no increase in rates of symptomatic hypoglycemia events from the original safety population.

Diabetes-specific AEs related to insulin use like hypoglycemia are not unexpected in a trial population of patients with recent-onset stage 3 T1D. Similar to the original review, we do not expect common AEs observed in the T1D patient population in the safety update like hypoglycemia to be applicable to the intended population.

TN-10 Extension

In the TN-10 Extension study, two subjects reported treatment-emergent adverse events of nausea and headache. Otherwise, the following TEAEs were reported by one subject each: cellulitis, COVID-19, pharyngitis, pruritus, rash, bradycardia, pyrexia, cytokine release syndrome (CRS), eosinophil count increased, lymphocyte count decreased, white blood cell count decreased, pharyngeal erythema, and hypertension. On review of the severity grading, the majority of these TEAEs, 69%, were mild in severity. The adverse events with severity greater than mild were headaches (moderate) and expected laboratory-related adverse events of lymphocyte count decreased in levels expected based on teplizumab's known pharmacodynamic profile.

Reviewer comment: The individual TEAEs reported in the 4 patients from the TN-10 Extension study who received open-label teplizumab are consistent with AEs observed in the prior teplizumab safety program, including cytokine release syndrome, laboratory abnormalities, and infection.

Protégé Extension

Comparative TEAE analyses were not performed for the Protégé Extension given the study is a long-term non-interventional follow-up study with lack of adequate comparator follow up time.

5.2.5. Laboratory Findings

Laboratory data included in this resubmission

As part of this safety update, the Applicant included blinded by-subject data for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) viral loads by quantitative polymerase chain reaction (PCR) and EBV and CMV serologies (IgG and IgM) for all PROTECT subjects with available data. In the PROTECT study, EBV and CMV quantitative PCR (copies/mL) were collected at baseline, day 28, 84, 210, 273, 364 and 546 and serologies were collected at baseline.

Other than viral titers and serologies for the blinded PROTECT study, no other raw laboratory data or laboratory data analyses were submitted as a part of this resubmission. As the PROTECT study remains blinded, the viral titers and serologies were not analyzed as a part of this safety update review.

Laboratory-related adverse event analysis

Laboratory-related adverse events were common in the original BLA review, especially cytopenias (lymphopenia, leukopenia, neutropenia, thrombocytopenia), decreased hemoglobin, and liver function test abnormalities. In the resubmission safety update, the sponsor included an analysis of specific laboratory-related adverse events that were defined as adverse events of special interest (AESI) in the PROTECT study. As presented in Table 6, and discussed in Section 5.2.3, the PROTECT study had less conservative laboratory-related adverse event withdrawal criteria, resulting in fewer discontinuations (approximately 5.5% versus the original BLA safety pool of 12.5%) and fewer discontinuations attributed to laboratory-related adverse events (approximately 2.7% versus the original BLA safety pool of 9.9%). Therefore, analyses were performed by the FDA to assess rates of lymphopenia, neutropenia and liver function test abnormalities reaching a specific threshold in the PROTECT study in order to evaluate if the more relaxed discontinuation criteria resulted in any additional safety concerns not observed in the original safety population. It was thought that the rates of certain laboratory abnormalities (lymphopenia, neutropenia, thrombocytopenia, anemia, and liver function abnormalities) meeting the AESI thresholds are low enough in the general population to assume that all AESI were due to teplizumab and therefore, “worst case scenario” analyses were used to further evaluate the safety profile of teplizumab for the currently blinded

PROTECT study.

Lymphopenia meeting AESI threshold, a lymphocyte count <500 cells/ m^3 for 7 days or longer, was reported in 3/327 (0.9%) of subjects in the PROTECT study, and in “worst case scenario” 1.3% (3/218) of teplizumab-treated subjects. On review of the individual patient profiles, one patient was noted to have lymphopenia (200 to <500 cells/ m^3) on study day 4, with resolution by study day 55. Study treatment was paused for 1 day with resumption and completion of the entire course of study treatment. The other two cases of lymphopenia were noted starting within 2-3 days of study drug infusion initiation and resolved within 1 week of noting the AE without modification of study drug treatment.

Neutropenia meeting threshold, <1000 polymorphonuclear leukocytes/uL on two consecutive evaluations, was reported in 5/327 (1.5%) of subjects in the PROTECT study, and in “worst case scenario” 2.2% (5/218) of teplizumab treated subjects. In all cases, this AESI was noted within 2-4 days of initiating the study drug, with resolution within 1-6 days despite continued treatment in 3 subjects, or temporary (1 day) dose withholding in 2 subjects.

In terms of liver function test abnormalities, there were 6/327 (1.8%) of subjects who met criteria, and in “worst case scenario” 2.7% (6/218) of teplizumab treated subjects. Four subjects had alanine aminotransferase (ALT) increased ($>5x$ ULN to $20x$ ULN), three with aspartate aminotransferase (AST) increased ($>5x$ ULN to $20x$ ULN) and one with blood bilirubin increased ($>3x$ to $10x$ ULN). Of the subjects with increased ALT, the events were reported study days 4-9 and study drug was discontinued in all cases, with normalization of ALT within 5-22 days of drug discontinuation. Of the subjects with increased AST, this AE was first noted on study days 2-9 with resolution following 1 day of dose interruption in one subject and resolution within 8-20 days of study drug discontinuation in two subjects. For the subject with blood bilirubin increased, this was noted day 4 of study drug and resolved within 8 days of study drug discontinuation. In summary, all subjects noted to have abnormal liver function tests meeting threshold were discontinued from drug with documented recovery of the adverse event within 22 days of discontinuation.

Reviewer comment: I conducted a review of individual patient reports for laboratory-related adverse events reported as adverse events of special interest (AESI) for the PROTECT study. While the study remains blinded, the reports of recovery despite continued treatment for cases of lymphopenia and neutropenia were overall reassuring and lead to the conclusion that drug pausing criteria could be safely included in the labeling (as opposed to drug discontinuation criteria) for lymphopenia and neutropenia. For cases of liver function test abnormalities, the current discontinuation criteria proposed in the labeling (ALT

or AST (b) (4) ULN and total bilirubin (b) (4) ULN) appear to be appropriately protective, with the resolution of all cases of ALT/AST/bilirubin elevations following discontinuation at this threshold.

5.2.6. Immunogenicity

Please refer to the original BLA review (section 8.4.10).

The resubmission and safety update included new unblinded immunogenicity (ADA) data from the PROTECT study.

The PROTECT study collected information on Anti-drug antibodies (ADA) at baseline (pre-treatment), day 12, 28 and 56 and subjects were considered to have overall positive ADA status if there was at least one confirmed post-baseline positive result on day 12, 28 or 56. Overall, ADA were identified in 93.3% (126/135) of teplizumab-exposed subjects with available data in the PROTECT study compared to the original BLA safety population, where ADA were observed in 50 to 92% of teplizumab-exposed patients in Protégé, Encore and TN-10, during the first course of teplizumab across the various treatment regimens, and the incidence of ADA was as high as 90% when a second course was administered.

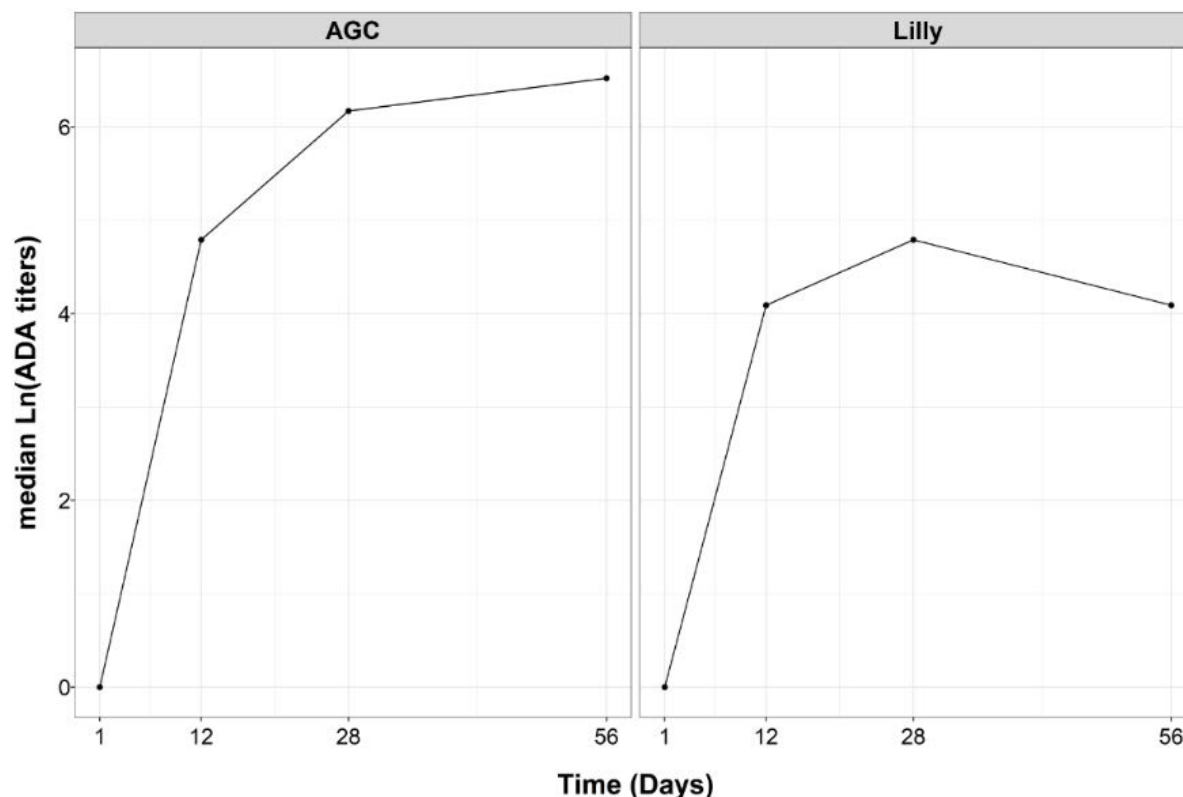
Unblinded immunogenicity results for 32 subjects treated with AGC biologics and 137 subjects treated with Lilly were available for review. There were comparable rates of immunogenicity observed in the subjects randomized to the AGC biologics product (31/33, 93.9%) compared to the subjects randomized to the Lilly product (95/102, 93.1%) at 52 weeks. However, patients treated with the AGC biologics product compared to the Lilly product, tended to have earlier ADA appearance, as illustrated in an analysis provided by the FDA Pharmacometrics reviewer, Table 9 below, with higher ADA titers, as illustrated in Figure 1 below.

Table 9. Proportion of subjects with appearance of ADA (grouped by titer) at each study day grouped by product (AGC vs. Lilly) for the PROTECT substudy

	AGC product (N=32)	Lilly product (N=137)	PROTECT sub-study (N=169)
maximum Ln(ADA Titer) levels			
Missing	0 (0%)	28 (20.4%)	28 (16.6%)
Null	2 (6.3%)	37 (27.0%)	39 (23.1%)
0 < value < Ln(30)	2 (6.3%)	0 (0%)	2 (1.2%)
value ≥ Ln(30)	28 (87.5%)	72 (52.6%)	100 (59.2%)
Ln(ADA Titer) levels on Day 12			
Missing	1 (3.1%)	36 (26.3%)	37 (21.9%)
Null	6 (18.8%)	38 (27.7%)	44 (26.0%)
0 < value < Ln(30)	3 (9.4%)	8 (5.8%)	11 (6.5%)
value ≥ Ln(30)	22 (68.8%)	55 (40.1%)	77 (45.6%)
Ln(ADA Titer) levels on Day 28			
Missing	5 (15.6%)	38 (27.7%)	43 (25.4%)
Null	4 (12.5%)	38 (27.7%)	42 (24.9%)
0 < value < Ln(30)	1 (3.1%)	0 (0%)	1 (0.6%)
value ≥ Ln(30)	22 (68.8%)	61 (44.5%)	83 (49.1%)
Ln(ADA Titer) levels on Day 56			
Missing	4 (12.5%)	41 (29.9%)	45 (26.6%)
Null	3 (9.4%)	43 (31.4%)	46 (27.2%)
0 < value < Ln(30)	1 (3.1%)	4 (2.9%)	5 (3.0%)
value ≥ Ln(30)	24 (75.0%)	49 (35.8%)	73 (43.2%)

Source: Generated by FDA Pharmacometrics Reviewer from nonmemdata4studs14jun22.xpt (SD 65, 6/17/2022)

Figure 1. Median titer level (in log titer) for subjects randomized to AGC vs. Lilly by study day



Source: Generated by FDA Pharmacometrics Reviewer from nonmemdata4studs14jun22.xpt (SD 65, 6/17/2022)

Because PROTECT is ongoing, at this time it is not possible to examine the relationship between ADA and efficacy and safety outcomes.

5.2.7. Blinded AEs for AGC vs. Lilly

This reviewer evaluated blinded AE reports by product (AGC vs. Lilly). In total, the adverse event analysis includes data from 223 patients who either received Lilly teplizumab or placebo and 104 patients who either received AGC teplizumab or placebo. No meaningful differences were apparent.

5.2.8. Cytokine Release Syndrome

CRS is considered an important safety signal in the teplizumab development program. Among the original BLA safety population, CRS events were identified in up to 5% of teplizumab-treated patients using the Applicant's analysis based on Common Terminology Criteria for

Adverse Events (CTCAE) version 3.0 criteria, and there were 7 patients (0.9% of the teplizumab treatment group) who required hospitalization for CRS.

For the safety update population, 3/327 (0.9%) subjects in the PROTECT study had SAEs of CRS which all occurred within the first three days of study drug administration requiring hospitalization. If it is assumed that all cases occurred in teplizumab-exposed patients, the incidence rate is 1.5%. Importantly, the reviewed CRS cases resemble the previously reported CRS cases in the original BLA with respect to severity, onset, and symptoms. In all three cases, the study treatment was discontinued, and each subject was discharged from the hospital within 48 hours of admission. One of the subjects, a 9 year-old male, required intravenous fluid and a single dose of epinephrine for hypotension.

The sponsor evaluated the data for possible differences in adverse event frequency between the AGC and Lilly products. 16/223 (7.2%) of the subjects treated with either Lilly or placebo reported AE of CRS, compared to 1/104 (1%) of the AGC or placebo-treated subjects.

None of subjects (N=4) in the TN-10 Extension study experienced SAEs of CRS, with one reported TEAE of CRS. The non-interventional Protégé Extension was not considered relevant for the analysis of CRS.

Reviewer comment: The safety update information does not change the original safety conclusions with respect to CRS.

5.2.9. Hypersensitivity/ Rash

In the safety update, AEs with the PT of 'hypersensitivity' were reported in 1/327 (0.3%) of PROTECT subjects and no patients in the TN-10 Extension study. The sponsor performed an additional analysis at the request of the Agency (received 6/14/2022, SDN 63) which revealed 2/327 (0.6%) of PROTECT subjects reporting the PT of 'infusion related reaction'. These 3 AEs were mild to moderate in severity, considered by the investigators to be related to study drug and recovered despite continued treatment with study drug. There were no reported adverse events with the following PTs: 'anaphylaxis', 'drug hypersensitivity', 'immune reaction' or 'serum sickness' reported in either the PROTECT or TN-10 Extension studies. The noninterventional Protégé Extension study was not considered relevant for this analysis due to the inclusion of only safety data at least 2 years after teplizumab dosing.

There were no SAEs of rash in the safety update. Rash was noted as one of the common AEs for the PROTECT study 81/327 (24.8%), consistent with previous observations in the clinical program. One rash was reported in the TN-10 extension study, 1/4 (25%). The

noninterventional Protégé Extension study was not considered relevant for this analysis due to the inclusion of only safety data at least 2 years after teplizumab dosing.

Reviewer comment: The safety update information does not change the original safety conclusions with respect to hypersensitivity/rash.

5.2.10. Lymphopenia

Lymphocyte abnormalities and white blood cell (WBC) abnormalities occurred in up to 22% of teplizumab-treated subjects in the PROTECT study, consistent with the original BLA safety data where a consistent association between lymphopenia was observed though placebo-controlled phase 3 data.

5.2.11. Evaluation of Potential Drug Induced Liver Injury

No laboratory analyses were included for the studies included in the safety update; however, no cases of potential drug induced liver injury were reported.

5.2.12. Infections

5.2.12.1 General Infections

In the safety update population, there were 2 infection SAEs, both in the PROTECT study. The first SAE was reported to be “IV-related bacteremia” and “cellulitis” starting after the 3rd infusion of study drug treatment. During the hospitalization, this subject was found to have staphylococcal bacteremia and started on oral antibiotics with resolution of symptoms and the AE following treatment. A temporal relationship with lymphopenia was observed in this subject, and although the lymphopenia in this case was mild, it is plausible that temporary immunosuppression from teplizumab may have contributed to the development of cellulitis and bacteremia despite the baseline risk of this AE from an indwelling catheter. It should be noted that this subject has not yet been unblinded so the treatment is currently unknown, and no safety conclusions can be made based on this case.

Another subject (blinded to treatment assignment) had experienced a viral infection requiring hospitalization during the PROTECT study. This subject, a 15 year-old female, initially presented with a SAE of palpitation to the emergency room and was found to have abnormally elevated troponin 125 ng/L (normal range <16.47 ng/L) and was diagnosed with myocarditis and mild pericardial effusion on thoracic echocardiography, requiring hospitalization. This SAE occurred from study days 76-82, approximately 2 months after completion of the first course of either teplizumab or placebo. Following outpatient cardiology consultation after hospital discharge it

was determined that the myocarditis and pericarditis were due to Coxsackie B4 virus infection based upon the viral serology of 1:640. This subject also had experienced recent infectious mononucleosis reactivation from study day 29-43 with complete resolution of EBV viral titers by study day 137 when EBV viral titers were <200 copies/mL. It is possible that temporary immunosuppression contributed to this patient's development of viral myocarditis, although the case report did not contain enough information to conclude that the subject was experiencing immunosuppression (lymphopenia or neutropenia) at the time of this infection event. On evaluation of these two events in a currently blinded study there are barriers and limitations in the assessment of causality. However, even in the setting of a blinded study, the possibility for infection with teplizumab use remains biologically plausible and continues to be recommended as a Warning & Precaution in labeling.

Reviewer comment: As noted in the original BLA review, infection secondary to immunosuppression is an important safety issues of interest for teplizumab. While the safety update does not contribute additional information beyond two cases of infection in PROTECT study patients currently blinded to treatment arm, the individual case narratives continue to reflect that infection remains a potential issue with teplizumab use. Therefore, it remains prudent to continue to recommend a Warning and Precaution for a potential risk of serious infection as a risk mitigation measure.

5.2.12.2 Epstein-Barr Virus (EBV) Infection

In the safety update, the Sponsor repeated an analysis for "acute mononucleosis-like illness" using the PROTECT study and the most common events reported by this analysis were "lymphadenopathy" reported in 8/327 (2.4%) of the subjects, who remain blinded to treatment assignment. According to the sponsor's analysis, none of the cases were associated with clinical symptoms or a diagnosis of mononucleosis or mononucleosis-like syndrome, or positive EBV or cytomegalovirus (CMV) viral titer elevation on review of the case reports. There was 1 subject (0.3%) each reporting Epstein-barr viraemia and Epstein-barr virus infection and 5 subjects with "EBV test positive" listed as an adverse event in PROTECT (1.5%, 5/327). There was little additional information from the safety update regarding this signal, but the sponsor submitted detailed reports representing the current (blinded) safety data they have collected on each subject (including EBV and CMV quantitative PCR (copies/mL) collected at baseline, day 28, 84, 210, 273, 364 and 546 and serologies at baseline). Therefore, the safety update included reassuring safety data that the sponsor will continue to collect adequate safety data related to EBV/CMV infections for the PROTECT study to further understand this risk upon future analysis of the unblinded data.

5.2.13. Diabetic Ketoacidosis

For the safety update, there were no DKA events reported in the PROTECT study (which remains blinded) or the TN-10 extension study.

For the Protégé Extension study, 1.7% (3/181) teplizumab-treated subjects experienced DKA SAEs. By comparison, DKA SAEs occurred in 1.9% of the teplizumab-treated original BLA safety population. All DKA events were reported as SAEs, and no patients treated with placebo reported DKA events. One subject reporting two events of DKA in the Protégé Extension population also experienced two DKA events during the original Protégé study (reported as a part of the original BLA safety analyses). There are some limitations to interpreting adverse events reported during the Protégé Extension study as there was a difference in safety exposure information between the study arms in the Protégé Extension study, which may lead to a 5-fold higher rate of adverse events among the teplizumab arm, which had higher enrollment and follow-up time than the placebo arm. Overall, similar rates of DKA were observed among the Protégé Extension study as the original BLA safety population with stage 3 T1D.

Reviewer comment: While a higher proportion of teplizumab-treated patients (1.7%) versus control patients (0%) experienced DKA events in the long-term follow up period of the Protégé Extension study, the rate of DKA is similar to the rates observed in the teplizumab-treated patients in the original BLA safety analyses. Additionally, there are limitations to interpreting this data given the follow up period was greater for teplizumab-treated patients.

5.3. Safety Analyses by Demographic Subgroups

In the original application, our analyses demonstrated that there were no important safety differences significant treatment-emergent adverse events (cytokine release syndrome, infections, cytopenias, hepatic enzyme elevations) among subgroups by age, sex, and race. The safety update did not contain enough unblinded demographic and safety information to perform these analyses in the update population which contained data from two blinded, ongoing studies and one unblinded long-term follow-up study.

5.4. Additional Safety Explorations

5.4.1. Human Carcinogenicity or Tumor Development

The number and types of cancers reported from the updated data were reviewed. There were no events from TN-10 Extension or Protégé Extension studies which met criteria for lymphoma

or malignancy.

For the PROTECT study, there were two reported events for the SOC “lymphoma or other malignancies”, one for AE term “papilloma” with verbatim term “verrucae planae juveniles” for an 8 year old female starting 52 days after the first dose of study treatment (teplizumab or placebo), and the second “papilloma” AE term with verbatim term “warts right foot” for an 11 year old male which was noted 35 days after the first dose of study treatment (teplizumab or placebo).

As verrucae or warts are common in children, and the treatment group remains blinded, it is possible that these events are unrelated to study treatment dosing in both cases. Similar to the original BLA, we did not detect a safety signal related to cancer for the safety update.

For details regarding the original BLA human carcinogenicity assessment please refer to the original review (July 2, 2021). It is important to note that the clinical safety data submitted in the original BLA was not sufficient to evaluate the potential risk of malignancy or lymphoproliferative disease because of the short duration of follow-up as well as the relatively young age of the safety population. The longest trial duration available in publication is the 7-year follow-up of the AbATE trial (n=43), and this trial reported no malignancy among the 43 patients treated with two courses of teplizumab (given 1 year apart). Following this safety update, there were no notable signals for malignancy, but uncertainty remains regarding rare or long-latency risks which could be addressed through the creation of a postmarketing patient registry for approximately 10 years in order to assess further the risk of malignancy.

5.4.2. Human Reproduction and Pregnancy

Since the original submission, one pregnancy was reported during PROTECT. This participant discontinued course 1 treatment and the treatment group remains blinded at the time of this safety update. Per the Data Monitoring Committee (DMC) open minutes, the pregnancy resulted in a healthy baby.

5.5. Safety in the Postmarket Setting

5.5.1. Expectations on Safety in the Postmarket Setting

The teplizumab clinical trials in the original BLA submission had broadly similar discontinuation criteria that provided a standardized approach to discontinuing drug treatment, with provisions to stop treatment for laboratory abnormalities including bilirubin and aminotransferase

elevations, or abnormal platelet, neutrophil, hemoglobin, or coagulation parameters, and the occurrence of certain adverse events. If this approach to treatment discontinuation is applied in the postmarket setting, it is estimated that approximately 10% of patients will not be able to complete the full course of teplizumab therapy. This rate of treatment discontinuation is expected in the post-market setting if similar drug discontinuation criteria are put in place in labeling.

Less stringent laboratory and adverse event-based discontinuation criteria were used for the PROTECT study, with an observed lower rate of discontinuations related to adverse events, at 3.7%. While the PROTECT study remains blinded, if these discontinuations are attributed to patients only treated with teplizumab in worst-case scenario analyses, the discontinuation rate would be 5.5%, approximately half the discontinuations observed in the original safety database.

On review of the individual narratives for each laboratory adverse-event related discontinuation, including discontinuations related to aminotransferase elevations, neutropenia and lymphopenia, each adverse event resolved following either the discontinuation of product, withholding dosing for 1-2 days, and in the majority of cases of neutropenia and lymphopenia, despite continued treatment with study drug. Notably, there were no serious adverse events related to continued treatment among patients who would have met premature treatment discontinuation criteria. This reviewer therefore concludes that more serious or permanent harms are not expected if less restrictive discontinuation criteria (from the PROTECT study) are reflected in teplizumab's approved labeling. Additionally, the PROTECT study provided reassuring support that laboratory related adverse events were reversible, even after application of less stringent discontinuation criteria, and therefore the PROTECT study discontinuation criteria adequately mitigate risk of severe adverse events and can be safely adopted in the postmarketing period. A discussion on the discontinuation criteria and findings from this analysis are discussed extensively in section 5.2.5, Laboratory Findings.

Otherwise, there are no other modifications to the expectations of safety in the postmarket setting based on the safety data included in this resubmission. Please refer to the original review, dated 7/2/2022 for details regarding safety expectations and section 6 for proposed labeling and section 8 for Postmarketing Requirements and Commitments.

5.6. Integrated Assessment of Safety

The integrated assessment of safety is not meaningfully changed with the safety update.

6. Labeling Recommendations

6.1. Prescription Drug Labeling

Labeling recommendations are contained within this review as appropriate.

The labeling issues discussed during this submission included the following:

1. Update to proposed language for the Established Pharmacologic Class
2. Update to proposed language for the indication statement
3. Updated with revised dosing regimen based on recommendations of the clinical pharmacology review team
4. Inclusion of laboratory safety data for the PROTECT study in section 6.1, Clinical Trial Experience, Laboratory Abnormalities
5. Additional information regarding serious infection signal observed in the clinical trial populations in warnings and precautions
6. Inclusion of additional information related to immunogenicity in Section 12.6, and
7. Revision of information in Clinical Trials limiting Table 1 to adverse event data from the only study in the indicated population (TN-10) with descriptive trial data for studies conducted in the unapproved population (stage 3 type 1 diabetes) where appropriate.

7. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was recommended for the original BLA and this recommendation continues upon this resubmission based on no new significant safety signals noted in this resubmission.

During the original BLA primary review, the Division of Risk Management (DRM) and DDLO discussed potential FDA-driven communications close to the time of approval to highlight the novel treatment for patients with stage 2 T1D and to convey safety information regarding cytokine release syndrome (CRS). Given the extension to the PDUFA timeline for this application, this FDA-driven communication will be composed after the completion of this primary review.

8. Postmarketing Requirements and Commitments

The Pediatric Research Equity Act (PREA) requirement is discussed in the original BLA review, dated July 2, 2021. This section discusses potential (Food and Drug Administration Amendments Act of 2007) FDAAA-related postmarketing requirements (PMRs) and postmarketing commitments (PMCs). The final decision about PMRs/PMCs is deferred to the CDTL memo.

During the original review we identified the following safety issues, for which we considered a PMR safety study: CRS, infection, and longer latency events like LPD or other malignancy. The Applicant was notified of these potential PMR issues during the mid-cycle communication meeting for the original submission.

At the time of the initial review, we determined that malignancy is a safety issue that cannot reasonably be resolved in a premarket development program for teplizumab, and therefore considered a 10-year registry study with long-term follow-up for documentation and evaluation of any events of malignancy as a conservative approach to address any uncertainty about the potential safety issue.

Regarding the safety risks of cytokine release syndrome (CRS), and lymphoproliferative disease, we are not currently recommending any postmarketing requirements (PMRs) or postmarketing commitments (PMCs) for further characterization of these events; these events should be reported in routine Periodic Safety Update Reports.

Following advice from DPMH, we initially recommended a pregnancy study for women and their offspring who are exposed to teplizumab during pregnancy in order to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. However, it is anticipated that pregnancy with use of teplizumab (a 14-day course) would be exceedingly rare as the treatment is transient. Given the recommended screening for pregnancy prior to treatment and that the population of intended use consisting primarily of youth and adolescents being treated for a very limited time period (14 days) we anticipate that there will be minimal numbers of pregnancies and that any study performed in this way would be of limited value.

9. Appendix

9.1. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators (submitted on 6/14/2022, SDN 63). Due to the PROTECT PK/PD substudy being an important source of PK data for the Population PK modeling, this study was included in the evaluation of financial disclosures for the resubmission.

Covered Clinical Study (Name and/or Number): PROTECT PK/PD Substudy (PRV-031-001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>46</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAUREN K WOOD HEICKMAN
07/14/2022 03:24:30 PM

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07/14/2022 04:53:21 PM

Clinical Review
Lauren K. Wood Heickman, MD
BLA 761183
Tzield/Teplizumab (PRV-031)

CLINICAL REVIEW and SUMMARY BASIS FOR REGULATORY ACTION

Application Type	BLA
Application Number(s)	761183
Priority or Standard	Priority
Submit Date(s)	October 31, 2020
Received Date(s)	November 2, 2020
PDUFA Goal Date	July 2, 2021
Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO)/Office of New Drugs (OND)
Reviewer Name(s)	Lauren K. Wood Heickman, MD
Review Completion Date	Electronic stamp
Established/Proper Name	PRV-031/teplizumab-mzwv
(Proposed) Trade Name	Tzield
Applicant	Provention Bio, Inc.
Dosage Form(s)	2 mg/ 2mL single-use vial
Applicant Proposed Dosing Regimen(s)	Intravenous infusion given daily for a gradually escalating, 14 consecutive day course. The dose is calculated based on body surface area (BSA), with a total cumulative dose of 9 mg/m² administered over 14 consecutive days according to the following regimen: • (b) (4) 1: 51 µg/m² • (b) (4) 2: 103 µg/m² • (b) (4) 3: 207 µg/m² • (b) (4) 4: 413 µg/m² • (b) (4) 5-14: 826 µg/m²
Applicant Proposed Indication(s)/Population(s)	Teplizumab is an anti-CD3 humanized monoclonal antibody indicated for the delay of type 1 diabetes in at-risk individuals
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	At-risk individuals who are ≥8 years of age who have two or more T1D-related autoantibodies (anti-GAD [glutamic acid decarboxylase], micro insulin, anti-IA-2, islet cell antibody [ICA], anti-ZnT8) and abnormal glucose tolerance on a 2-hour oral glucose tolerance test

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Glossary

ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
AWC	adequate and well-controlled
BLA	biologics license application
BMI	body mass index
BSA	body surface area
CE	confirmatory evidence
CEX-HPLC	cation-exchange high performance liquid chromatography
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CRS	cytokine-release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DHM1	Division of Hematologic Malignancies 1
DKA	diabetic ketoacidosis
DP	drug product
DPTCHEN	Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology
DRM	Division of Risk Management
DS	drug substance
DSMB	data safety monitoring board
EBV	Epstein-Barr virus
ECG	electrocardiogram
EOSI	adverse events of special interest
FDA	Food and Drug Administration
HLA	human leukocyte antigen
IASP	Islet Autoantibody Standardization Program
ICA	islet cell antibody
ICH	International Council for Harmonization
IND	investigational new drug
INR	international normalized ratio
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intention-to-treat

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IV	intravenous
LPD	lymphoproliferative disorder
MedDRA	Medical Dictionary for Regulatory Activities
mISS	modified integrated summary of safety
MMTT	mixed-meal tolerance test
NFAT	nuclear factor of activated T-cells
NHLBI	National Heart Lung and Blood Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NOAEL	no-observed-adverse-effect level
OCP	Office of Clinical Pharmacology
OGTT	oral glucose tolerance test
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PDUFA	Prescription Drug User Fee Act
PK	pharmacokinetics
PMR	postmarketing requirement
PT/INR	Prothrombin Time/International Normalized Ratio
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEE	substantial evidence of effectiveness
T1D	type 1 diabetes
ULN	upper limit of normal
VZV	varicella zoster virus

1. Executive Summary

Materials reviewed for this memo include the following:

Table 1. Summary of Review Materials

Office of New Drugs (OND) Action Package Material Reviewed/Consulted	Names of Discipline Reviewer(s); Dates of Review in DARRTS or Panorama
Biostatistics review	Yu Wang; 6/29/21
Pharmacology Toxicology	Dan Minck; 5/5/21
Office of Pharmaceutical Quality (OPQ)	Jennifer Swisher; 5/14/21
Clinical Pharmacology and Pharmacometrics	Harisudhan Thanukrishnan and Elyes Dahmane; 4/30/21
Interdisciplinary Review Team for Cardiac Safety Studies	Email from QT-IRT; 6/25/21
Clinical Consult Division of Hematologic Malignancies 1 (DHM1)	Emily Jen; 4/29/21
Office of Scientific Investigations (OSI)	Cynthia Kleppinger; 4/28/21
Division of Medication Error Prevention and Analysis-human labeling and proprietary name review	1/14/21; 3/12/21; 2/26/21; 3/24/21
Division of Risk Management (DRM)/Office of Surveillance and Epidemiology (OSE)	Till Olickal; 6/4/21; 7/1/21
Division of Pediatrics and Maternal Health	Catherine Roca; 3/29/21
Office of Prescription Drug Promotion	Deferral memo pending action
Division of Medical Policy Programs-patient labeling review	Deferral memo 4/30/21

1.1. Product Introduction

Teplizumab-mzwv (called teplizumab in this review; proposed proprietary name Tzielid) is a first-in-class humanized anti-CD3 monoclonal antibody proposed to delay the onset of type 1 diabetes mellitus (T1D) in high-risk individuals.

The Applicant has proposed a 14-day intravenous (IV) dosing regimen, involving a 4-day ramp up of the following doses (51 $\mu\text{g}/\text{m}^2$ on Day 1, 103 $\mu\text{g}/\text{m}^2$ on Day 2, 207 $\mu\text{g}/\text{m}^2$ on Day 3, and 413 $\mu\text{g}/\text{m}^2$ on Day 4) followed by repeated doses of 826 $\mu\text{g}/\text{m}^2$ on Days 5 to 14. The proposed dose form for teplizumab is a 2 mg/ 2 mL solution in a vial. Teplizumab is a new biologic product and has not been previously marketed.

If approved, teplizumab would be the first treatment for patients at risk of developing T1D. (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness (SEE) for the delay of T1D in at-risk¹ individuals to support approval. The SEE consisted of one adequate and well-controlled (AWC) trial plus confirmatory evidence (CE).

The single AWC trial, TN-10, was a randomized placebo-controlled trial that investigated the effect of teplizumab to prevent the onset of T1D (also called 'stage 3' T1D). TN-10 successfully demonstrated the treatment effect of teplizumab in delaying T1D diagnosis in at-risk patients. The results were robust to sensitivity analyses under a range of conservative assumptions for missing data and baseline imbalances in patient demographics and disease characteristics. The estimated magnitude of the treatment effect was clinically meaningful.

The Food and Drug Administration (FDA) has issued guidance documents on demonstrating SEE: the 1998 Guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" and the 2019 Draft Guidance for Industry "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biologic Products." One of the scenarios described for meeting the substantial evidence standard is one adequate and well-controlled (AWC) trial plus CE, as noted in section 115(a) of the Food and Drug Administration Modernization Act (FDAMA), which amended the 21 U.S.C. § 355(d), to state: "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." As CE of effectiveness, the Applicant provided results of a meta-analysis of C-peptide changes from baseline from five previously conducted studies of teplizumab in patients with new- or recent-onset T1D. FDA's independent analyses confirmed that teplizumab demonstrated superiority to control at 1 year of follow-up with respect to C-peptide preservation. In the meta-analysis, teplizumab's statistically significant impact on the rate of decline of C-peptide at a later stage of T1D is considered evidence of a similar treatment effect on C-peptide decline and delay in T1D diagnosis at an earlier stage of disease, in at-risk patients.

C-peptide is a 31-amino-acid polypeptide that connects insulin's A-chain to its B-chain in the proinsulin molecule, and after processing, equimolar amounts of C-peptide and insulin are released into circulation. Therefore, measurement of C-peptide is a method to establish the endogenous insulin secretion of a patient; in a patient with T1D, a lower C-peptide measurement denotes greater dependence on exogenous insulin. C-peptide is typically measured through the oral glucose tolerance test (OGTT) prior to a diagnosis of T1D, and through a mixed-meal tolerance test (MMTT) after clinical T1D diagnosis. Teplizumab is considered a 'disease modifying' therapy. In contrast to insulin, teplizumab targets the underlying autoimmune disease process. Therefore, teplizumab is expected to either prevent

¹ Discussion of the term 'at-risk' is included in Section 7 of this review.

further beta-cell loss or restore beta-cell function which would be manifest by either stabilization or improvement in C-peptide concentrations.

The relevance of the change in C-peptide in new-onset T1D as CE with respect to the proposed indication for teplizumab (delay of T1D) is supported by the continuous nature of the T1D disease process, i.e., stage 2 T1D is a phase in the continuum of this irreversible and progressive autoimmune disease. Natural history studies following children and adults from stage 2 T1D to stage 3 T1D have shown that an impaired C-peptide response to an OGTT may arise more than 5 years before the diagnosis of T1D (Evans-Molina et al. 2018). Once a critical mass of insulin-producing beta cells is destroyed, T1D (i.e., stage 3) begins with subsequent need for exogenous insulin replacement. The progressive nature of the disease is well-accepted with a predictable rate of beta-cell decline and ultimate diagnosis of T1D.

This biologics license application (BLA) was brought to the Endocrine and Metabolic Advisory Committee (EMDAC) on May 27, 2021 to discuss the question of whether SEE had been met for the proposed indication. We carefully considered the committee's discussion, and we do not agree with the committee's view that the C-peptide meta-analysis does not constitute CE for this BLA. The lack of support for the use of C-peptide as CE appeared to be largely based on a statement in the FDA background document that C-peptide is not a validated surrogate endpoint for traditional regulatory approval. Although FDA's evidentiary standard for effectiveness has not changed since 1998, FDA's December 2019 draft guidance provides clarity that compelling mechanistic evidence, in the setting of well-understood disease pathophysiology, may be sufficient to provide SEE of a new drug or a new indication. In this case, the mechanistic evidence would "be obtained from clinical testing using a relevant and well understood pharmacodynamic endpoint not accepted by itself as an endpoint to establish evidence of effectiveness." In our view, the use of the C-peptide meta-analysis to support a conclusion of SEE conforms well to this standard.

Importantly, the Division considers C-peptide to be a reasonably likely surrogate endpoint (RLSE) for clinical trials in new-onset T1D to demonstrate preservation of beta-cell function and to support a regulatory submission through the Accelerated Approval pathway, although it has not yet been used as the basis of approval for any application. C-peptide is not a validated surrogate endpoint because the relationship between C-peptide and clinical outcomes is understood through correlational studies (e.g., diabetes control and complications trial [DCCT]) as no intervention trials establish that therapeutics that increase C-peptide result in predictable and quantifiable clinical outcomes regardless of mechanism of action. We also note that C-peptide is consistently recommended as a primary outcome measure for new- or recent-onset T1D trials (Palmer et al. 2004). At a June 2021 workshop sponsored by the Critical Path Institute, "Design of Clinical Trials in New-Onset Type 1 Diabetes: Regulatory Considerations for Drug Development," stakeholders including FDA, the European Medicines Agency (EMA), the Juvenile Diabetes Research Foundation (JDRF), and several industry representatives, discussed

the important role of C-peptide endpoints in clinical trials intended to support regulatory decision-making in the T1D therapeutic area.

The remaining question is to consider whether this regulatory pathway, a single AWC trial with CE, is appropriate for establishment of SEE. When considering the feasibility of establishing SEE based on a single AWC trial plus CE, the 2019 draft guidance cites the persuasiveness of the trial, the robustness of the CE, the seriousness of the disease, the size of the patient population, and the presence of unmet need as factors for consideration. As will be discussed in this review, TN-10 is a persuasive trial, and the CE is robust. T1D is a serious disease, with no spontaneous remission. Although T1D is not a rare disease, the population of at-risk individuals who are available for enrollment in trials meant to delay T1D is very small. The low prevalence of stage 2 T1D makes it challenging to identify 'at-risk' patients for clinical studies, and studies of relatively long duration are needed to observe outcomes and quantify treatment benefits. Furthermore, there is an unmet need in this population, as there are no approved therapies to delay the onset of T1D. And given the lack of available therapies, an additional trial, if conducted, would necessarily compare teplizumab to a placebo. The community may lack the equipoise necessary to support another placebo-controlled trial; we have questions about the ethics of dosing children at risk of T1D with placebo. In summary, in light of the severity and rarity of the disease, the lack of treatments to delay its onset, and the impracticality of conducting a second long-term clinical trial, it is appropriate to consider the single AWC trial (TN-10) plus CE as meeting the standard for SEE.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Teplizumab is a first-in-class humanized anti-CD3 monoclonal antibody intended to delay the onset of type 1 diabetes mellitus (T1D) in high-risk individuals, who have two or more T1D-related autoantibodies and dysglycemia and consequently have a 75% risk of disease progression within approximately 4 to 5 years, and a lifetime risk of nearly 100%. Teplizumab's proposed indication is novel, and teplizumab would be the first disease-modifying therapy for T1D.

T1D is a serious, life-long autoimmune disease that presents most commonly in childhood. The autoimmune process destroys insulin-producing beta cells, and over time, declining production of insulin results in dysregulation of glucose homeostasis and hyperglycemia with a requirement for exogenous insulin for survival. Despite exogenous insulin use, many patients are not able to fully control their hyperglycemia, especially without adverse sequelae such as life-threatening severe hypoglycemia. Additionally, constant vigilance is required with respect to glucose management, causing significant stress on patients and their families. Even with treatment, life-threatening complications can occur. Chronic hyperglycemia can lead to macrovascular (heart disease and stroke) and microvascular disease (kidney, eye, and dental disease; nerve damage). Kidney failure can occur, necessitating dialysis or a kidney-pancreas transplant, and diabetes is a leading cause of blindness and lower extremity amputation in the US. Evidence suggests the risk of these complications is highest in those who develop T1D in early childhood. Thus, there is a significant unmet need for therapies that delay or modify the disease pathogenesis of T1D.

The benefit of teplizumab in delaying the onset of T1D was demonstrated in the TN-10 trial, a randomized, placebo-controlled, event driven trial in 76 patients at risk of T1D, with 44 given teplizumab and 32 given placebo intravenously in a single 14-day course. After approximately five years of follow-up, 18 patients in the teplizumab group (41%) and 22 in the placebo group (69%) had been diagnosed with T1D, meeting the primary endpoint. Teplizumab significantly delayed the onset of T1D by a median of 2 years. The observed delay is clinically meaningful (see Benefit Risk Framework), as it is expected to result in improved quality of life, and potentially lower cumulative risk of complications of chronic hyperglycemia, as well as acute risks of insulin therapy, e.g., hypoglycemia.

Cytokine release syndrome (CRS) and serious infections were the most important identified risks and were not unexpected given teplizumab's action to engage T-cells and cause lymphopenia. Importantly, the majority of CRS cases identified in the teplizumab program were mild to moderate without requirement for intervention other than antipyretics. Serious infections were more frequent within 1 to 3 months of teplizumab dosing, but there were no permanent sequelae related to infection in the teplizumab-treated patients. A single case of serum sickness and several hypersensitivity reactions occurred; the majority of patients developed anti-drug antibodies (ADA) which may be, in part, contributory. As association of ADAs and rash was also noted; rash occurred at a 13-fold higher rate in the teplizumab group compared with the placebo group, again likely related to CRS or drug hypersensitivity. With the exception of two serious adverse events (SAEs) related to rash, however, the rashes were generally non-serious and did not require additional intervention.

Laboratory abnormalities including cytopenias and transaminase elevations were predictable and self-limited. Approximately 10% of patients were unable to complete their treatment course with the majority of events related to protocol-driven laboratory drug discontinuation criteria. Laboratory abnormalities leading to drug discontinuation included transaminase elevations, hematologic parameters (lymphopenia, neutropenia, anemia, and thrombocytopenia) and cytokine release syndrome. It is important to note, however, that the safety profile must be interpreted in light of the conservative drug discontinuation criteria employed in the clinical protocols. If similar discontinuation criteria are used in the real-world setting, over 10% of patients will not be able to receive the full course of teplizumab, but a similar safety profile to that observed in the clinical trials can reasonably be assured.

Overall, we did not identify irreparable harms, and conclude that the nature and level of severity of these risks are acceptable in light of the expected benefit, with the understanding that heretofore unrecognized risks may be observed post-marketing. Our belief is that the risks can be adequately managed with standard product labeling without need for a REMS.

Uncertainties that remain include potential longer-term risks including lymphoproliferative disorders caused by Epstein-Barr virus reactivation or other malignancy due to immunosuppression. Although, these safety issues were taken under consideration within the context of the benefit risk assessment, these risks are only theoretical at this time as they are more likely to be associated with chronic immunosuppression. An exposure registry may help elucidate if there are any longer-term risks that may have an impact on the benefit risk assessment. Also, the safety and effectiveness in children under 8 years of age have not been

established, and a PREA PMR will be issued to study teplizumab in this age group.

Based on literature, the Advisory Committee meeting, and other expert opinion and patient testimonial, there is no question that a 2-year delay is highly meaningful, and it is likely that patients would accept the risks of teplizumab for even less of a delay than 2 years. For this reason, the uncertainty around the estimated treatment effect is not a concern with respect to determination of a favorable benefit-risk assessment. As noted above, the development of T1D is virtually inevitable once two autoantibodies and dysglycemia are present.

Although the patient population selected for TN-10 was limited to relatives of patients with T1D, a large majority of individuals with T1D (85%) have no family history of disease. Furthermore, the risk of progression to T1D for stage 2 T1D individuals who are not relatives appears to be similar. As was generally supported at the advisory committee meeting, expansion of the treatment indication to include non-relatives is recommended, while keeping the intended population otherwise narrow, to the population that was studied in TN-10 (age ≥ 8 years with presence of stage 2 T1D).

In summary, the lack of available disease-modifying therapies, significant unmet medical need, severity of T1D, and the clinical meaningfulness of a median 2-year delay of onset of T1D on a patient's quality of life outweigh the observed and potential risks of teplizumab which were self-limited and expected based on the drug's mechanism of action.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Type 1 diabetes mellitus (T1D) is a serious, life-long autoimmune disease that presents most commonly in childhood. It has been estimated that T1D affects 4.5% of the world's population under the age of 14 years (Karvonen et al. 2000). - Over time, declining production of insulin from autoimmune beta cell injury results in dysregulation of glucose homeostasis and hyperglycemia. The long-term effect of prolonged hyperglycemia is vascular damage, resulting in a high rate of cardiovascular and renal morbidity and mortality, highest in those with longer duration of disease.	Type 1 diabetes mellitus (T1D) is a serious chronic autoimmune disease that results in progressive beta-cell loss and life-long insulin dependence. Inadequate glycemic control is associated with increased risks of micro- and macrovascular disease. The burden of insulin therapy, as well as its acute risks (DKA, severe hypoglycemia)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There is evidence of increased mortality and higher cardiovascular morbidity in patients with younger age of T1D diagnosis, before 10 years of age (Rawshani et al. 2017). • The natural history of T1D development has been defined by longitudinal studies in at-risk populations. Relatives of patients with T1D who have two or more islet autoantibodies have close to a 100% lifetime risk of developing type 1 diabetes, termed “stage 1 T1D”. Once a patient reaches stage 1 T1D, 40% will progress to dysglycemia within 2 years, and once patients develop dysglycemia on oral glucose tolerance testing, e.g., “stage 2 T1D”, the 2-year risk of disease is 60% and 4- to 5-year risk of T1D is 75%. • Longitudinal natural history studies have demonstrated that impaired beta cell function (as measured by C-peptide, a biomarker of endogenous insulin production) may arise in patients at-risk of T1D more than 5 years before diagnosis. Once a critical mass of insulin-producing beta cells is destroyed, symptomatic T1D (i.e., stage 3) begins with subsequent need for exogenous insulin replacement. • Once T1D is diagnosed, maintenance of C-peptide levels has been correlated with important clinical benefits, and treatments that arrest this decline in insulin production, as measured by C-peptide, even after the new-onset period, may have clinical benefit. • Although it is relatively well understood that the progression to T1D in at-risk individuals is predictable, a large majority of individuals with T1D (85%) have no family history and are not identified at earlier stages of T1D prior to need for insulin dependence. Therefore, the pool of patients who are currently identified as at-risk for T1D is extremely small.	contributes to poorer quality of life. Based on natural history studies, the progression to T1D is predictable, and steady loss of beta cell function (as measured by C-peptide) is observed prior to the onset of disease. It is possible to identify patients at high risk of developing T1D based on the presence of diabetes-related autoantibodies and dysglycemia. In these patients there is a high unmet need to modify the disease process and delay the onset of T1D requiring insulin therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Current Treatment Options</u>	- There are no current treatment options for the delay of T1D in at-risk individuals. - Although there are therapies to improve glycemic control in patients with T1D, there are no currently approved disease-modifying therapies.	There are no treatment options to delay T1D available at this time.
<u>Benefit</u>	- In TN-10, a randomized placebo-control trial designed to evaluate teplizumab's efficacy in the delay of T1D onset in at-risk children and adults aged ≥ 8 years, teplizumab successfully delayed T1D diagnosis in at-risk relatives of T1D patients for a median time of approximately 2 years. Among 76 patients enrolled, 44 were given teplizumab and 32, placebo. After approximately five years of follow-up, 18 patients in the teplizumab group (41%) and 22 in the placebo group (69%) had been diagnosed with T1D (met the primary endpoint). - The median time to T1D diagnosis was 49.5 months in the teplizumab group vs. 24.9 months in the placebo group. In the primary analysis of time to T1D diagnosis, the hazard ratio was 0.41 (95% confidence interval (CI): 0.22 to 0.78, $p=0.0066$). The treatment effect was statistically significant and robust to sensitivity analyses under a range of conservative assumptions for missing data. - The magnitude of benefit patients could expect from treatment is best approximated by the median time to diagnosis of 49.5 months in the teplizumab-treated group, where the lower limit of the 95 % CI was 32.1 months, whereas median time to diagnosis in the placebo patients was 24.9 months (95% CI: 9.5, 48.6 months). - In addition, a delay in the onset of T1D can avoid the significant disease burden associated with T1D on both the patient and caregivers, and result in an improved quality of life as later age of onset of diabetes has been associated with improved health-related quality of life, glycemic control, given that HbA1c values are higher in patients with younger age	Teplizumab significantly delayed the onset of T1D by a median of 2 years. The observed delay is clinically meaningful, as it is expected to result in improved quality of life, and potentially lower cumulative risk of complications of chronic hyperglycemia, as well as acute risks of insulin therapy, e.g., hypoglycemia. The magnitude of delay of T1D that is considered clinically meaningful may vary among at-risk individuals, e.g., delay of T1D in a young child may be more meaningful than in an adult. Based on literature, the Open Public Hearing portion of the Endocrine and Metabolic Advisory Committee meeting, and expert opinion there is no question that a 2-year delay is highly meaningful. Should general population screening become more widespread, the availability of a therapeutic meant to delay the onset of this chronic disease would potentially benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	at onset than in those with later onset (Rawshani et al. 2018). Younger age of onset of T1D (<7 years) is also associated with worse cognitive function as compared to older age of onset of T1D (>7 to 17 years) (Ferguson et al. 2005). Finally, a diagnosis of T1D earlier in life is associated with a loss of life expectancy, with a loss of 17.7 years for women and 14.2 years for men (Kalyva et al. 2011). In addition, a delay in the onset of T1D avoids the significant disease burden associated with T1D on both the patient and caregivers, and the strain of having a chronic illness, resulting in an improved quality of life (Ferguson et al. 2005; Kalyva et al. 2011; Rawshani et al. 2018). • A delay in the onset of T1D, with the maintenance of endogenous insulin production, allows patients to avoid diabetic ketoacidosis (DKA), which is associated with worse cognitive function in newly diagnosed pediatric T1D patients, as compared to age-matched T1D without DKA (Jessup et al. 2015). • A delay in the onset of T1D allows the avoidance of insulin therapy and the accompanying risks of insulin therapy, such as iatrogenic hypoglycemia.	more individuals than are currently identified through family screening programs.
Risk and Risk Management	• The safety of teplizumab was evaluated in 791 pediatric and adult patients, 44 at-risk patients (study TN-10) and 747 patients with new- or recent-onset T1D. • The most important safety concerns were related to immunosuppression and cytokine release. Lymphopenia was common, reported in ≥75% of teplizumab-treated patients during the 14-day dosing period, but resolved within 2-4 weeks of dosing, and in the majority of patients, while teplizumab dosing continued. Cytokine release syndrome was also an important safety concern and was identified in up to 5% of teplizumab-treated patients. This event occurred primarily in older	Overall, the safety profile has been reasonably well characterized in the relevant population of at-risk patients and a similar population with new- or recent-onset T1D. The safety issues were not unexpected given the drug's mechanism of action. The safety profile for teplizumab appears qualitatively similar to, but more benign than, that of other T-cell stimulating monoclonal

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(median age 19) male patients, began within 3-5 days of dosing initiation and did not require intensive care or ventilator use. Most cases were mild or moderate. This safety concern was expected given teplizumab's mechanism. CRS rates differed by grading method, and FDA pursued another grading system, which detected a high rate of CRS among placebo/control subjects, without any change in risk difference between the groups. - Rash was a common adverse event (AE) among teplizumab-treated patients (45%) but was self-limited and all cases resolved without sequelae. Drug hypersensitivity was expected given the behavior of other monoclonal antibodies; however, a strong signal was not detected. Other than a single patient with serum sickness, other possible cases of drug hypersensitivity were few. Continued monitoring for events in the post-market setting would help to improve our understanding of the true risk. - Transaminase elevations were also frequently reported AEs and were observed in ~25% of teplizumab-treated patients. Similar to lymphopenia, transaminase elevations are also attributed to cytokine release and were transient with documented recovery, the majority recovering within 2 weeks after treatment. Transaminase elevations leading to drug discontinuation occurred in 5.6% of teplizumab patients and 0.9% of control patients. Half of drug discontinuations in the clinical studies were related to transaminase elevations. Analyses of transaminase elevations, including outlier analyses, did not reveal a signal for drug-induced liver injury. - Approximately 10% of patients were unable to complete their treatment course, the majority related to protocol-driven laboratory drug discontinuation criteria. Laboratory abnormalities leading to drug discontinuation included transaminase elevations (discussed above), hematologic parameters (lymphopenia, neutropenia, anemia, and	antibodies. Safety issues include cytokine release, infection, immunosuppression, lymphopenia, and rash, although many of these adverse events were self-limited, mild, or transient (limited to the 14-day dosing period). There are some uncertainties related to infection, and drug hypersensitivity risks, although the observed risks of these events appear to be low. Assessments of such events in the postmarket setting would aid in further characterization of teplizumab's safety. In addition, there are some theoretical concerns related to the higher frequency of Epstein-Barr virus (EBV) reactivations observed during the teplizumab clinical studies, and the associated risk of lymphoproliferative disease (LPD) when EBV reactivations are observed with more intensive immunosuppression. Because of endocrinologists' lack of experience with CRS, a communication plan REMS was considered, but not recommended by DRM; the risks of CRS were determined to not meet the severity typically needed for initiation of REMS. In the Oncology space, tools like REMS have been used to inform providers of the risks of severe cytokine release syndrome (e.g., with blinatumomab,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	thrombocytopenia) and cytokine release syndrome. It is unknown if adhering to prespecified drug discontinuation criteria prevented more serious adverse events during the clinical trials; therefore, a conservative approach to mitigate risk will be to incorporate a modified version of the discontinuation criteria included in the integrated summary of safety (ISS) studies into teplizumab's labeling. - Other safety findings that were expected for an immunomodulatory biologic agent included increased risk of serious infections (including reactivation of EBV) and cytokine release syndrome. As EBV reactivation is a risk of teplizumab, there is a theoretical risk for later malignancy from lymphoproliferative disease (LPD). Nonclinical findings in chimpanzees also support a potential risk for LPD with teplizumab, as non-neoplastic B-cell lymphoproliferative disease associated with an EBV-like virus and accompanied T-cell immunosuppression was observed at high doses. In the clinical development program, no lymphoproliferative disorders were observed among the pooled safety population with T1D, and an increased risk of general malignancy was not identified, although the safety database was not sufficient in duration to observe long-latency events such as malignancy. Given the increased risk of EBV reactivation, uncertainty remains regarding the potential for lymphoproliferative disease. - In the postmarket setting, providers who are intended to use teplizumab may not have experience with identification and treatment of cytokine release syndrome. - There was a high rate of ADA development in TN-10 patients, observed in 59% of patients at 3-6 months post-randomization; however, there was little impact of ADA status on efficacy or safety . ADA formation was higher after a second treatment course which did affect pharmacokinetics. Very limited data indicate a potential for higher ADA	which has a much higher risk for severe CRS, with associated neurotoxicity). Instead, risk mitigation can be managed through labeling or through non-REMS sponsor-mediated communication with the provider. Further assessment of ADAs is only needed if the Applicant eventually pursues a change to the approved dosing regimen (to add a second treatment cycle) and/or in the context of establishing biocomparability of the commercial and clinical trial product. Off-label use is unlikely because the product will need to be administered by a health care professional in an infusion center and face reimbursement issues. Nevertheless, off-label use is not considered high risk from a safety perspective. No mitigation measures to prevent off-label use are warranted. Uncertainty regarding rare or long-latency risks could be addressed through the creation of a patient registry for approximately 10 years in order to assess further the risk of malignancy. In addition, the long-term safety is uncertain.

Clinical Review
 Lauren K. Wood Heckman, MD
 BLA 761183
 Tziel/Teplizumab (PRV-031)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	formation with the commercial product compared to the clinical trial product. • Teplizumab will be indicated for patients ages 8 years and older with two or more diabetes-related autoantibodies and dysglycemia. Off-label use in the postmarket setting could be attempted in a broader patient population, e.g., individuals with two or more autoantibodies but without dysglycemia (stage 1 T1D), or patients younger than 8 years of age, which may change the benefit/risk considerations. • The development program was not designed to assess rare safety events with long latency such as malignancy or lymphoproliferative disease.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:		Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as	
	☐	Patient reported outcome (PRO)	
	☐	Observer reported outcome (ObsRO)	
	☐	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☒	Patient experience data that were not submitted in the application, but were considered in this review:		
	☒	Input informed from participation in meetings with patient stakeholders	Open Public Hearing at Advisory Committee meeting
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
		Observational survey studies designed to capture patient experience data	
	☒	Other: Network of Experts program	We consulted experts in pediatric endocrinology and T1D through the FDA Network of Experts (NoE) program
☒	Patient experience data was not submitted as part of this application.		

2. Therapeutic Context

2.1. Analysis of Condition

Type 1 diabetes mellitus (T1D) is caused by autoimmune destruction of the pancreatic islet beta cells. Over time, declining production of insulin from the damaged beta cells results in dysregulation of glucose homeostasis and hyperglycemia. Although approximately 25% of patients are diagnosed with T1D as adults (Haller et al. 2005), children are disproportionately affected, and the peak ages of diagnosis are between 5 to 7 years of age and at or near puberty (Maahs et al. 2010).

Autoimmune diseases like T1D are initiated by the loss of immune tolerance to self-antigens, usually maintained through immune system regulatory mechanisms, and it is well-established that T-cells are the primary effector of damage to the pancreatic beta cell in T1D. Although many aspects of the etiology of T1D are still unclear, both genetic and environmental influences appear to play a role. T1D is a polygenic disorder, but class 2 Human Leukocyte Antigen (HLA) genes, responsible for antigen presentation, account for approximately half of the overall genetic risk of T1D. The HLA haplotypes that confer high susceptibility to T1D are DR4—DQ8 (often abbreviated DR4) and DR3—DQ2 (abbreviated DR3). It is estimated that up to 90% of patients with T1D have either DR4 or DR3 haplotypes, and about 30% of patients have a combination of the two (Redondo et al. 2018). These haplotypes are prevalent in White populations (DiMeglio et al. 2018).

The incidence of T1D varies widely depending on the population studied, with age-adjusted incidences ranging from as low as 0.1/100,000 per year in China and India to as high as >60/100,000 per year in Finland (Atkinson et al. 2014). In the US, incidence has been estimated to be from 22 to 24/100,000 per year for youth. From 2001 to 2009, the prevalence of T1D in US youth increased by 21%, and the number of youths with T1D in the US is estimated to triple from 2010 to 2050 (Imperatore et al. 2012; Dabelea et al. 2014). It has been estimated that T1D affects 4.5% of the world's population under 14 years of age (Karvonen et al. 2000). The increase in T1D incidence noted worldwide has largely been attributed to environmental factors, as the trends in new diagnoses are not explained by genetic changes, but no specific environmental factor has been determined to have unequivocal influence on T1D (Atkinson et al. 2014).

Although T1D is diagnosed in females and males in youth at similar rates, T1D is slightly more common in males when diagnosed in adulthood (Maahs et al. 2010). The group with the highest incidence of T1D in the US are non-Hispanic White youths, but with increases in incidence over the last two decades observed in non-Hispanic Black youths, with the largest incidence increases observed among Hispanic youths (Mayer-Davis et al. 2017). Additionally, the growing

prevalence of T1D is thought to be driven by a striking increasing incidence of T1D in young children (age <5 years), a trend that has been observed since the 1990s, and has been confirmed in several populations (Dabelea 2007; Vehik et al. 2007; Patterson et al. 2009).

Insulin therapy, administered via multiple daily injections or insulin pump, is required for survival, but patients are at risk of acute complications related to insulin under- or over-dosing, including diabetic ketoacidosis (DKA) and hypoglycemia. DKA is a substantial risk in children and adolescents and can be fatal. One in 14 US pediatric patients with T1D duration ≥ 1 year are diagnosed with DKA requiring treatment in a health care facility, with the majority of US studies showing a rate of DKA in pediatric patients of 1 to 15% per established patient per year (Maahs et al. 2015). Severe hypoglycemic events occur at rates of 5 to 10% per year for pediatric patients with T1D, with highest rates in the youngest age group, <6 years old (Cengiz et al. 2013). Adult patients with T1D are also affected by severe hypoglycemia at rates as high as ~19% per patient, per year for patients age 40 and older, with higher risk with longer duration of T1D (Weinstock et al. 2013).

Children and adults with T1D have a complex and demanding daily treatment regimen, with the need to administer the correct dose of insulin at the right time. Continual attention to diabetes management pervades nearly all of the patient's daily activities causing strain on patients and families.

Microvascular disease is one of the chronic complications of T1D. It is characterized by nephropathy, retinopathy, and neuropathy. Diabetes is a leading cause of kidney failure and blindness. Nephropathy affects patients with T1D more severely and disproportionately than type 2 diabetes (Zhao et al. 2009) and is implicated in approximately 60% of nontraumatic amputations in the US (Melendez-Ramirez et al. 2010). The presence of early microvascular complications is common, with one in three individuals with T1D showing early signs of complications or comorbidities after just 8 years of average disease duration, at an estimated age of 21 years (Dabelea et al. 2017).

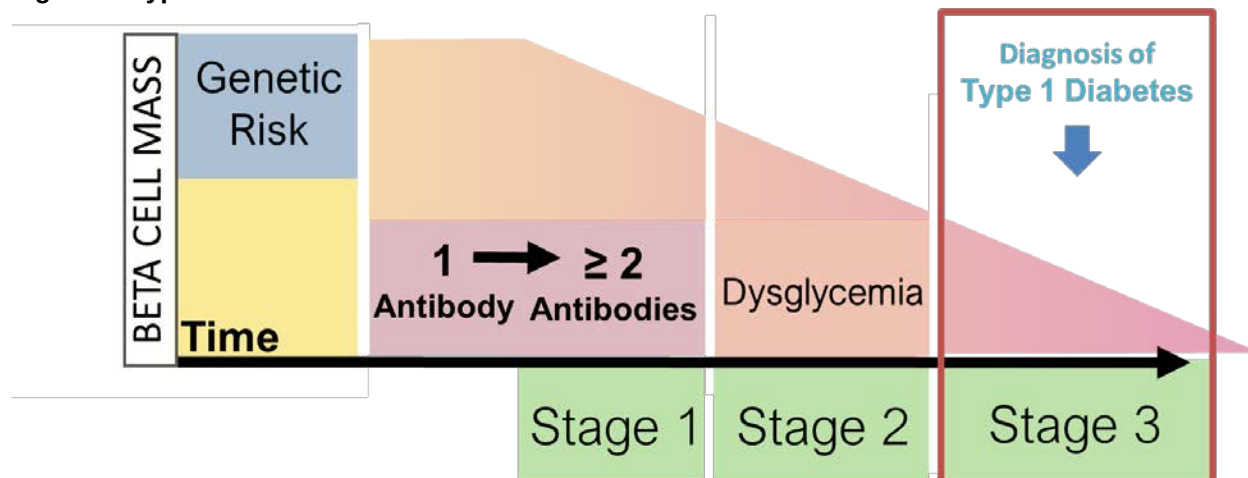
In addition to microvascular disease, patients with T1D have increased morbidity and mortality related to macrovascular disease with higher rates of coronary heart disease, cerebrovascular disease, and peripheral artery disease, with cardiovascular events occurring earlier and more frequently in patients with T1D than age-matched nondiabetic populations. There is also evidence that a younger age of diagnosis is associated with worsened cardiovascular outcomes, with a recent study demonstrating a 30 times higher rate of cardiovascular morbidity in patients diagnosed with T1D before the age of 10 years, compared to patients diagnosed between 26 to 30 years of age. The Pittsburgh Epidemiology of Diabetes Complications study reported that T1D patients younger than 40 years of age with disease onset before age 17, have cardiovascular events at a rate of 1% per year, and an annual mortality rate of 1.5% (Pambianco et al. 2006). Although improvements in insulin management and administration have led to

significant reductions in long-term macro- and micro-vascular complications of the disease, cardiovascular morbidity and mortality remain a significant concern.

Despite advances in diabetes management tools, e.g., continuous glucose monitoring, the mean hemoglobin A1c (HbA1c), a clinically relevant measure of glycemic control, has increased in children and adolescents with T1D (Foster et al. 2019). As a consequence of worsening glycemic control and increasing disease incidence among the youngest age groups, as well as the aging and growth of the population with the longest duration of disease, the overall adverse effect of diabetes on public health is increasing (Ingelfinger and Jarcho 2017).

Based on screening programs, which typically focus on family members of patients with T1D, a greater understanding of the natural history of T1D has been achieved, and a model that classifies T1D into 3 stages has been proposed [Figure 1](#). These programs screen for circulating autoantibodies to pancreatic islet cells; the most commonly tested autoantibodies are insulin antibody (IAA), glutamic acid decarboxylase antibody (GADA), protein tyrosine phosphatase-like antigen antibody (IA-2A or ICA-512), islet cell antibody (ICA), and zinc transporter 8 antibody (ZnT8A). In family members of patients with T1D followed longitudinally, a greater number of positive autoantibodies is associated with a more rapid progression from stage 1 (≥ 2 T1D autoantibodies) to stage 2 T1D (≥ 2 T1D autoantibodies + dysglycemia) (Verge et al. 1996). Data suggest that only a small proportion of children and adults who develop a single T1D-specific autoantibody progress to T1D disease. An individual with two or more autoantibodies is classified as having stage 1 disease. As beta cell mass progressively declines, abnormal glucose metabolism, or dysglycemia, develops. The period between development of dysglycemia, but not yet meeting diagnostic criteria for T1D, is classified as stage 2. The 6-month, 2-year, and 4-year risk of progression to T1D at this stage is approximately 25%, 60%, and 75%, and the lifetime risk approaches 100% (Krischer 2013). Once T1D is diagnosed, the patient is considered to have entered stage 3 T1D (Insel et al. 2015).

Figure 1. Type 1 Diabetes Disease Model

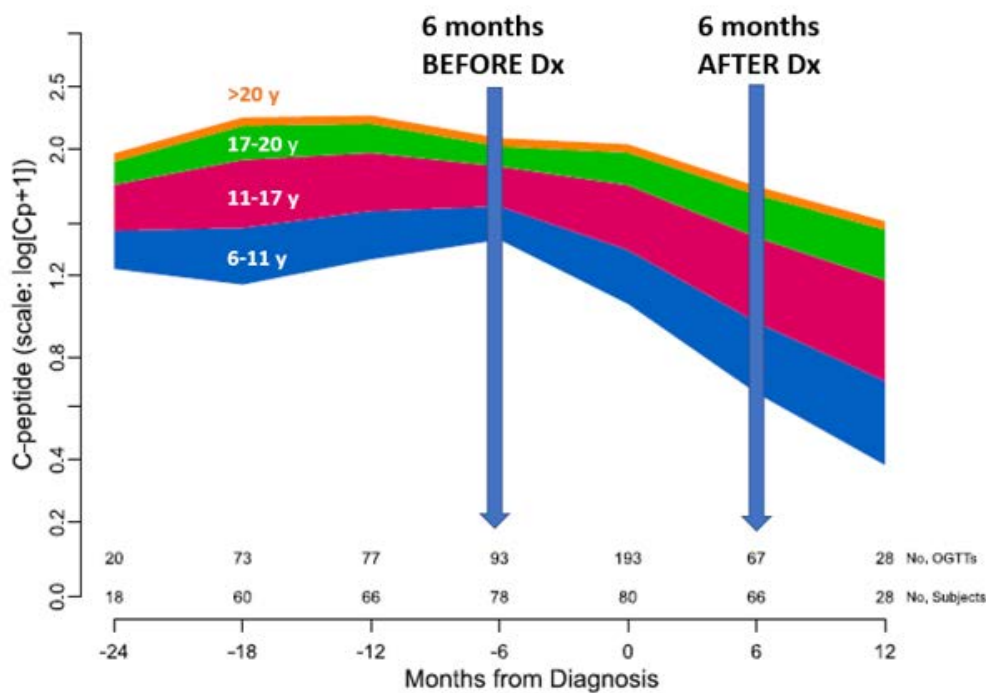


Source: Reviewer generated, adapted from article by (Insel et al. 2015).

Worldwide screening initiatives in multiple populations have repeatedly demonstrated that Although relatives of patients with T1D have a higher risk (15X) compared to the general population, 85% of those newly diagnosed with T1D have no family history of disease (Mahon et al. 2009; Insel et al. 2015).

Longitudinal natural history studies have demonstrated that impaired beta cell function (as measured by C-peptide) may arise more than 5 years before diagnosis (Evans-Molina et al. 2018). [Figure 2](#) shows natural history data in children and adults from the Trial Net TN-01 cohort. Following an initial period of relatively stable gradual stimulated C-peptide decline, there is a rapid decline, beginning 6 months before diagnosis that continues at the same rapid rate for 12 months after diagnosis (Bogun et al. 2020). Once a critical mass of insulin-producing beta cells is destroyed, symptomatic T1D (i.e., stage 3) begins with subsequent need for exogenous insulin replacement.

Figure 2. Rate of C-peptide Decline Before and After T1D in At-Risk TrialNet TN-01 Cohort Followed Longitudinally



Source: Adapted from article by (Bogun et al. 2020).
 Abbreviations: Dx, diagnosis; OGTT, oral glucose tolerance test; T1D, type 1 diabetes

Immediately following diagnosis, the majority of patients with T1D retain the ability to produce endogenous insulin in amounts that reduce their daily exogenous insulin requirement to maintain glycemic control, a time termed the “honeymoon.” Experience with large cohorts of individuals with new-onset T1D suggest that for at least 2 to 4 years after the clinical onset of T1D, many patients still retain detectable levels of endogenous insulin production, as measured by C-peptide (Greenbaum et al. 2012; Hao et al. 2016). Therefore, a disease modifying therapy may be expected to show a favorable effect on C-peptide even after T1D is diagnosed (see also Section 1.2).

Although T1D as a whole is not considered a rare disease, the population of individuals at-risk of disease who are can be identified for enrollment in trials meant to delay or prevent T1D is very small; therefore, conducting trials in this population is challenging. Only a fraction of those followed in family screening programs will develop T1D, with the risk of first-degree relatives developing T1D estimated to be 4 to 7% by 30 years of age. The prevalence of stage 1 and 2 T1D was determined to be 0.48% in a US primary care pediatric cohort (McQueen et al. 2020), and 0.31%, in a similar population in Bavaria, Germany. Remarkably, the German study screened 90,632 children over a period of 4 years and identified 26 children, aged 2 to 5 years with stage 2 T1D, for a prevalence of 0.03%, and a combined prevalence of 0.31% for stage 1 and 2 T1D (Ziegler et al. 2020).

2.2. Analysis of Current Treatment Options

Currently, there are no approved agents that are considered disease-modifying, or that affect the underlying pathophysiology of T1D; thus, there are no current treatment options for patients with 'stage 2' disease (two positive autoantibodies and dysglycemia). Treatment of hyperglycemia begins once T1D is diagnosed, and treatment consists of insulin therapy, typically in a basal bolus regimen or delivery of insulin via an insulin pump. An additional drug approved to improve glycemic control in patients with T1D is the amylin analog Symlin, although this product has not gained widespread use. Insulin is a necessary (life-saving) treatment for patients with T1D as severe insulin insufficiency results in ketoacidosis and death. Although insulin therapy is required, it carries significant risks, most importantly, severe hypoglycemia associated with overdose and use errors. In addition, insulin administration is highly burdensome, requiring constant attention to caloric intake, activity level, and symptoms of hypoglycemia, despite recent advances in insulin delivery systems (e.g., artificial pancreas devices), and many patients still do not achieve glycemic goals.

Finally, pancreas transplant has been used to restore beta-cell function, and although islet-cell transplant is being investigated as a possible treatment for T1D, it has not gained widespread use.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Teplizumab is a new molecular entity (NME) not approved for marketing in the US or elsewhere. Teplizumab is also being developed under IND 100262 for the treatment of recent-onset T1D. (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

The TN-10 study, the single trial in the intended population, was conducted under IND 102629 (delay or prevention of T1D in at-risk relatives of patients with T1D). As noted above, additional clinical studies evaluating teplizumab in the new or recent-onset T1D population were conducted under IND 100262 (treatment of recent-onset T1D).

IND 102629 for PRV-031 (formerly MGA031) was submitted by MacroGenics, Inc., on December 23, 2009, to investigate the delay or prevention of T1D in relatives of type 1 diabetics at risk for developing T1D. On May 21, 2018, the IND sponsor was changed from MacroGenics, Inc., to

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Provention Bio, Inc. (Provention Bio). [Table 2](#) outlines the key meetings and regulatory interactions.

Table 2. Key Meetings and Regulatory Interactions for BLA 761183/IND 102629

Date Application	Submission Type/Meeting	Comments
8/12/2008 PIND102629	Type B PIND meeting	The sponsor (MacroGenics, NIDDK and TrialNet Investigators) was advised to stagger enrollment of pediatric patients in TN-10 until 6 months of safety data from at least 20 children and adolescents were available from the Protégé Study (Protocol CP-MGA031-01), evaluating patients with new-onset T1D, for Agency review. Enrollment was initially limited to ages 16-45.
12/24/2009	New IND for TN-10 study	TN-10 study allowed to proceed on 2/12/2010
3/29/2011	Protocol Amendment	TrialNet requested to revise the TN-10 protocol to include ages 8-45 based on data from Protégé. FDA requested additional analyses of Protégé data to justify the prospect of benefit in communications dated April 12, 2011 and May 6, 2011, as the Protégé study had failed to meet its primary endpoint.
5/9/2011	FDA Pediatric and Maternal Health Consult	Percutaneously inserted central catheter (PICC) placement for placebo treated subjects was cleared by several institutional review boards (IRBs), but found to not be compliant with Subpart D—Additional Safeguards for Children in Clinical Investigations of the Code of Federal Regulations (CFR) Part 50, as it represented greater than a minor increase over minimal risk to enrolled subjects without any prospect of direct benefit. This was communicated to the sponsor in an advice letter dated 8/17/2011. The sponsor had submitted a clinical amendment dated 3/8/2011 for clinical sites to continue use of midline catheters in children and adolescents randomized to receive placebo. This was approved and communicated to the sponsor in an advice letter dated 6/29/2011.
5/23/2012	Type C meeting with MacroGenics, TrialNet and NIDDK	Based on review of data from the Diabetes Prevention Trial-1 (DPT-1), TrialNet Natural History Pathway to Prevention Study (TN-01), Study 1, Protégé, AbATE, Delay and TN-10 trials, FDA agreed to expand the study population to include patients as young as 8 years. <i>FDA did not agree that transitioning the placebo-treated arm to an observational control arm would maintain TN-10 as a registration quality study.</i>
5/29/2018	Sponsor Transfer for IND	Transfer of IND sponsorship from MacroGenics Inc to Provention Bio, Inc.
4/12/2019	Type C Meeting Package	This meeting request was to discuss the development pathway for Teplizumab in at-risk relatives of individuals with T1D. Written responses were issued on 5/31/2019. The Agency stated that <i>“In principle, we agree that the results from the single trial TN-10/At-Risk</i>

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Date Application	Submission Type/Meeting	Comments
		<i>study in subjects with “stage 2” T1D, along with adequate supportive data from subjects with “stage 3” T1D, may be sufficient for a BLA submission; however, we do not have complete information at this time to determine if the currently available data are sufficiently robust, and further discussion is warranted prior to a BLA submission”.</i> The agency requested additional clarifications from the sponsor regarding the results of the TN-10 study. In addition, OPQ stated that <i>“insufficient information was provided in the meeting package to determine whether your comparability approach is acceptable. We recommend additional communications with the Agency (e.g., CMC Type C meeting) to discuss your strategy to demonstrate comparability to support the use of materials derived from the new drug substance (DS) manufacturing facility in the Phase 3 clinical study and future clinical studies.”</i>
8/2/2019	FDA Correspondence	Breakthrough Therapy Designation granted for the delay or prevention of clinical T1D in at-risk individuals
8/7/2019	FDA Advice letter	The sponsor submitted a protocol amendment dated 5/31/2019 containing a statistical analysis plan (SAP) for TN-10. The Agency indicated that because the data were already unblinded and the analysis had already been performed, further issues associated with the statistical analyses would be considered review issues.
11/7/2019	Type B Meeting	An initial comprehensive multidisciplinary breakthrough therapy meeting was held. The OPQ team raised review issues regarding the commercial manufacturing process and stability testing. In addition, the clinical Pharmacology reviewers stated that <i>“we do not agree that the proposed studies are adequate for filing a BLA. You need to establish a bridge between your final to-be commercialized formulation and the formulation that was used in previous clinical (including PK/PD) studies. We recommend that at minimum, you conduct a PK bridging study in healthy volunteers. In this study, you should also plan to include a comparison of PD data, leveraging prior experience from the PK/PD studies for a feasible PD marker.”</i> FDA stated that any analytical differences caused by the transfer to the new drug substance manufacturing facility (i.e., AGC Biologics) and associated changes to the drug substance manufacturing process may warrant additional clinical or non-clinical studies. FDA reiterated the need for the sponsor to submit a complete comparability data package that included data supporting the bridging of methods and the stability of the current reference standard. The sponsor was advised to submit C-peptide data to support a delay in the decline of C-peptide levels in patients with T1D from their exploratory analysis for Agency review. FDA also requested that the sponsor submit to the IND the draft protocol for their proposed meta-

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Date Application	Submission Type/Meeting	Comments
		analysis. FDA stated that the sponsor should provide data to support the claim of lack of chronic immunosuppression in the stage 2 population, and similar safety profile between stage 2 and stage 3 T1D patients.
1/31/2020	Rolling Review Request	Rolling review designation request granted on 2/12/2020
2/07/2020	Type B meeting package	Written responses by the statistical team were issued on 3/20/2020 for the draft statistical analysis plan for the C-peptide meta-analysis including the model, standard measurement units across studies, primary variable transformation and interpretation, handling of missing data and sensitivity analysis and C-peptide analysis for the TN-10 study.
04/07/2020	Initial Pediatric Study Plan (iPSP)	The iPSP was discussed with the Pediatric Review Committee (PeRC) on 6/26/2020. The sponsor had initially proposed (b) (4). The PeRC did not agree with the sponsor's plan to request (b) (4). The PeRC recommended including pediatrics less than 2 years of age in the deferred studies. The PeRC agreed that only patients with stage 2 T1D should be included in the proposed safety and PK study.
4/17/2020	Type B meeting	A teleconference was held to discuss the content, including format and data sets of clinical Modules 2 and 5 (including format of patient narratives), validation methods and analyses for pharmacokinetics (PK), anti-drug antibodies (ADA), and neutralizing antibodies (NAb) to be included in the BLA. FDA clarified the expectation that the sponsor must ensure that due diligence has been performed with respect to looking for any potential unique safety events that may have occurred in the older trials (Study 1, Abate, Delay). Meeting minutes were issued on 5/8/2020.
4/10/2020 and 6/15/2020	Amendments - final SAP for C-Peptide Meta-analysis	In comments dated 6/8/2020, FDA noted it did not agree with the proposed primary analysis model, MMRM, which implicitly assumes missing data are missing at random, instead recommending the Applicant propose a primary analysis model, such as an ANCOVA model, with a plan to impute missing data appropriately, and resubmit for review. In another advice letter dated 6/17/2020, the sponsor was advised to impute the missing data multiple times in Protégé and Encore due to study modification/termination using information from completers, assuming missing at random.
7/1/2020	Thorough QT Waiver Request	The Agency agreed with the sponsor's request to waive a thorough QT study because teplizumab has a low likelihood of direct ion channel interactions.

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Date Application	Submission Type/Meeting	Comments
8/13/2020	CMC Type B meeting	A type B meeting was held with OPQ to discuss the adequacy of the analytical and functional data to demonstrate comparability between the pre-change and post-change drug substance lots.
8/20/2020	Type B Pre-BLA Meeting	The sponsor clarified that the original bioanalytical method validation reports for both teplizumab concentrations and ADA concentrations from the Protégé study were available. The Protégé bioanalytical data reports (study sample analyses) for both PK and ADA were not available. Therefore, they prepared abbreviated bioanalytical data reports for PK and ADA, for Protégé. FDA stated that although we understood that Provention Bio had made its best efforts to compile the necessary data, the bioanalytical method details submitted must substantiate that the data are scientifically accurate. Specifically, the information must confirm that the study actually used the validated method. Further, if any changes were made from the validated method during the conduct of the study, the information should also confirm if there was appropriate documentation of those changes and that the results were analyzed accurately. FDA stated that we are willing to accept the BLA submission for filing without the original reports, but acceptability of these data will be a review issue.
8/24/2020	Type C Meeting - CMC	The sponsor discussed adequacy of the planned contents of Module 2 and 3 to support filing of the BLA. This included the individual method validation reports for testing of drug substance and drug product, Comparability data package for manufacturing process, analytical comparability between pre-change and post-change drug substance (DS), supportive comparability data-antibody effector functions, DS and drug product (DP) release specifications, comparative stability data, viral clearance studies, stability protocols (e.g., testing time-points) for drug substance and drug product, and extractable/leachable studies.

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Date Application	Submission Type/Meeting	Comments
10/13/2020	Type B meeting Written responses	FDA issued a letter stating that that teplizumab may require companion diagnostic device(s) for its safe and effective use. On 12/7/2020, Provention Bio submitted a meeting request in response to this letter. The Agency indicated that T1D-specific autoantibodies appear to meet the definition of a companion diagnostic should language instructing providers to select patients on the basis of autoantibody status be included in the future labeling for teplizumab. The sponsor was advised that the Agency is continuing to discuss internally the requirement for a companion diagnostic(s) for teplizumab. They were advised that “Given these uncertainties, you should consider seeking additional advice from the Agency on the process of companion diagnostic development, as it remains possible it will be required as a post-marketing commitment. In addition, should a companion diagnostic be required, you may need to bridge the performance of the assays used in the clinical trials to the companion diagnostic devices”.

Source: Created by Clinical Reviewer
Abbreviations: ADA, anti-drug antibodies; ANCOVA, analysis of covariance; CMC, chemistry, manufacturing, and controls; DS, drug substance; MMRM, mixed-effect model for repeated measures; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; OPQ, Office of Pharmaceutical Quality; PD, pharmacodynamics; PIND, pre-investigational new drug application; SAP, statistical analysis plan; T1D, type 1 diabetes; PK, pharmacokinetics

3.3. Foreign Regulatory Actions and Marketing History

Teplizumab is not currently marketed in any country.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For details refer to the OSI review by Dr. Cynthia Kleppinger dated November 10, 2020.

A routine (i.e., not “for-cause”) OSI audit was requested for the TN-10 study because: (1) it provided the sole adequate and well-controlled evidence of efficacy, (2) the study was small, and (3) the study participants were concentrated in a few potentially influential study sites.

Of the 30 total sites participating in TN-10, the Division of Diabetes, Lipid Disorders and Obesity (DDLO) requested inspections for the three domestic sites with the highest enrollment. The inspection also included remote inspections of the contract research organization (CRO) and the Applicant.

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OSI identified regulatory deficiencies in one clinical site (Barbara Davis Center, site 7) with 10 enrolled patients in TN-10. At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for a failure to adhere to protocol whereby a peripherally inserted central catheter (PICC) line was placed prior to gaining proper approval. Per the OSI reviewer, the observed violations are not expected to have an impact on safety or efficacy analyses. There were no objectionable conditions noted in the other clinical sites.

The COVID-19 global pandemic limited the Office of Regulatory Affairs' ability to conduct a foreign onsite good clinical practice (GCP) inspection for the Applicant sites located outside of the United States (Canada and Germany).

Overall, based on the inspections of the three domestic clinical sites and the remote regulatory assessment of the contract research organization (CRO) and Applicant, the inspectional findings support validity of data as reported by the Applicant under this BLA.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommended a Complete Response to this BLA. Dr. Jennifer Swisher was the lead OPQ reviewer; for details refer to her Office of Product Quality (OPQ) summary review in Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) dated May 14, 2021. The pertinent review findings are summarized below.

Overall Conclusion

The data submitted in this application are not sufficient to support a conclusion that the manufacture of Tziel is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. The Cation-Exchange High Performance Liquid Chromatography (CEX-HPLC) acceptance criteria are unacceptably wide, and variability of the CEX-HPLC data under long-term storage conditions for the DP preclude a determination of shelf life and introduce uncertainty regarding interpretation of the CEX-HPLC data to support comparability between proposed commercial and clinical materials (manufactured at AGC Biologics and Eli Lilly, respectively). Although it cannot be confirmed whether this variability arises from product instability or method variability, either cause would preclude a recommendation that teplizumab is approvable at this time. Therefore, from a chemistry, manufacturing, and controls (CMC) standpoint, OBP is recommending a Complete Response.

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The list of deficiencies is included on page 2 of the OPQ summary memo and also can be found in the Complete Response Letter. There are four CMC deficiencies in total. In brief, these are related to:

- Unacceptable charge variation measured in teplizumab drug substance (DS) and drug product (DP) under recommended storage conditions which precluded the ability to assign a shelf-life for either
- Lack of information regarding plans to monitor Master Cell Bank and Working Cell Bank stability
- Deficient protocol for requalification of the primary reference standard
- Insufficient information regarding the levels and types of leachates in teplizumab derived from its container closure and the risk to patients from any leachates that are potentially present in the drug product by the end of the expiry period

Additional chemistry, manufacturing, and controls (CMC) issues that are not approvability issues are also listed in the OPQ summary review and CRL.

Additionally, this application cannot be approved due to facility deficiencies. As of 5/14/2021, there is a potential official action indicated (pOAI) alert for (b) (4) the DP manufacturer. During an ongoing inspection of the manufacturing facility, deficiencies were conveyed to the representatives of the facility by investigators from FDA. Satisfactory resolution of the observations is required before this BLA may be approved. OPQ is recommending a withhold status, which will be communicated in the Complete Response letter.

Review Summary

Environmental assessment

The Applicant claimed a categorical exclusion from the requirement to prepare an environmental assessment, as this biologic product is comprised of substances that occur naturally in the environment. The OPQ review agreed this is acceptable.

Immunogenicity

Pharmacokinetics, anti-drug antibody (ADA) and neutralizing antibody (Nab) data are available only for pivotal trials: Protégé, Encore, and TN-10. Method 1A, Method 1B and Method 3 were developed to assess ADA for each individual clinical trial, respectively. No deficiencies related to the immunogenicity assays were reported in the OBP review.

Drug product

The proposed drug product is a 2 mL sterile solution pre-filled in a single-dose vial. The teplizumab concentration is 1 mg/mL, in phosphate (b) (4) (pH 6.1, (b) (4) NaPO₄,

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(b) (4) NaCl, 0.05 mg/mL polysorbate 80). All excipients are compendial per USP. The teplizumab drug product formulation and filling process has been carried out at (b) (4) and very few changes have been made to the DP manufacturing process throughout development.

Drug product compatibility

Both (b) (4) are compatible with teplizumab. In addition, the material made from (b) (4) should not be used for drug administration.

Drug product facilities

The DP is manufactured at (b) (4). During an ongoing inspection of this manufacturing facility, deficiencies were conveyed to the representatives of the facility by investigators from FDA. Satisfactory resolution of the observations is required before this BLA may be approved.

Drug substance

Teplizumab-mzww is a humanized IgG1_{kappa} monoclonal antibody produced in CHO cells and consists of two heavy chains that are each composed of 449 amino acids and two light chains that are each composed of 213 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 299 (Asn299). It is a humanized version of the mouse monoclonal antibody OKT3 with additional leucine to alanine mutations at positions HC 234 and 235. The Ala-Ala ("LALA") mutations reduce binding to complement and FcγR that can result in T cell activation and cytokine release syndrome. The molecular weight of (b) (4). Teplizumab is an agonist of cluster of differentiation 3 (CD3) on T lymphocytes and engages signaling through CD3ε and (nuclear factor of activated T cells) NFAT-dependent signaling cascades downstream.

The teplizumab drug substance was originally developed by MacroGenics. Eli Lilly partnered with MacroGenics in December 2007 with the intent to manufacture teplizumab DS at the Lilly (b) (4) site. The teplizumab DS used in the clinical studies to support this BLA was manufactured either at the MacroGenics facility in (b) (4) or, later, the Eli Lilly facility in (b) (4). Provention Bio acquired teplizumab from MacroGenics in 2018 and transferred the DS manufacturing technology to AGC Biologics (AGC) where additional improvements were made, and the process was scaled up to a (b) (4). The AGC product is the intended commercial product.

During review of stability testing data, the OPQ team identified unacceptable variability in a control parameter, charge heterogeneity, via CEX-HPLC for the to-be-marketed formulation. CEX-HPLC is used to detect the relative presence of positively and negatively charged amino acids and negatively charged glycans in teplizumab. Changes in the CEX-HPLC signature can

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indicate

(b) (4)

The variability between batches, and over time, was higher when compared to the reference (Lilly) product.

OPQ concludes the variability of the CEX-HPLC data under long-term storage conditions for DP preclude a determination of shelf-life and introduce uncertainty regarding interpretation of the CEX-HPLC data to support comparability between proposed commercial and clinical materials (manufactured at AGC Biologics and Eli Lilly, respectively). Importantly, the results of the CEX-HPLC call into question the validity of the analytical similarity assessment. Therefore, OPQ concluded the data submitted in this application are not sufficient to support a conclusion that the manufacture of teplizumab (Tziel) is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

Drug substance facilities

Teplizumab DS is manufactured at the AGC

(b) (4)

Dating period and storage conditions

The unacceptable charge variation under real-time storage conditions at (b) (4) months precludes setting an expiry for the DS at this time.

Comparability testing of the clinical trial (Lilly) product to the proposed commercial product (AGC)

Analytical comparability testing was carried out in order to demonstrate that the proposed commercial material being manufactured at AGC Biologics is comparable to the material that demonstrated safety and efficacy in the clinical studies. The main differences found between AGC and Lilly material were

(b) (4)

The Applicant was advised in a teleconference held April 23, 2021 regarding this issue that they may wish to investigate whether these differences could have caused the increased clearance

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of the teplizumab manufactured at AGC as compared to the clinical lot manufactured by Eli Lilly.

4.3. Clinical Microbiology

The microbiological controls used in the drug product manufacturing process, including , drug product specifications for sterility, container closure integrity, endotoxin, validation, depyrogenation and component sterilization, media fill studies, hold times, and postapproval stability commitment, were reviewed and determined to be acceptable by OPQ. *For details refer to the Office of Product Quality (OPQ) review by Dr. Jennifer Swisher dated May 14, 2021.*

4.4. Nonclinical Pharmacology/Toxicology

The Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPTCHEN) concluded the nonclinical data package supports approval and does not have any recommendations to convey to the Applicant. Dr. Dan Minck was the primary nonclinical reviewer, *for details refer to the nonclinical pharmacology/toxicology review dated May 5, 2021.* Findings from Dr. Minck's review are summarized here.

Teplizumab cross-reacts only with human, gorilla, chimpanzee, and gibbon CD3+ T cells. As a result, a minimal number of nonclinical studies were conducted with teplizumab. Instead, a (b) (4) surrogate monoclonal antibody (mAb) that binds to CD3 in was developed and used for multiple dose toxicology and reproduction and developmental toxicology studies in mice. Treatment of mice with this surrogate induced analogous effects on T-cell populations, B-cells, and cytokines (where evaluated), which supports the use of the surrogate as a model for teplizumab. The surrogate antibody has an apparent affinity for the mouse CD3ε similar to that shown by teplizumab for human CD3.

4.4.1. General Toxicology

The most relevant in vivo study with the original version of teplizumab was conducted in the chimpanzee in which a single subcutaneous dose of 0, 0.1, 1.0, or 10 mg/kg was administered. At the highest dose, all animals died or were euthanized. The cause of death was attributed to a suspected EBV (Epstein-Barr virus)-like lympho-cryptovirus infection. The T-cell suppression occurring as a result of the pharmacologic activity of the drug was a contributing factor. The no-observed-adverse-effect level (NOAEL) for the study was considered the middle dose of 1 mg/kg, or 34 mg/m² based on body surface area (BSA). This is 3.8-fold higher than the cumulative dose studied in humans (9 mg/m²) in a full 14-day cycle of treatment. Animals treated with a single higher dose (10 mg/kg) died or were euthanized due to infection. Other effects were noted, such as reductions in T-cell populations and increases in cytokines such as TNFα, IL-6, and IL-10. These effects were consistent with the magnitude and time course observed in the clinic.

Two repeat-dose toxicity studies were conducted in mice using the surrogate mAb. This (b) (4) surrogate was used in repeat-dose studies of subcutaneous and intravenous administration in mice. In the murine studies, lymphoid tissue was identified as the target organ, with dose-related reduction in T-cells with a trend toward partial recovery following a 2-week rest period. For a 6-day repeat-dose study, there were no observed off-target effects, the NOAEL for the murine studies was considered to be 20 mg/kg, equivalent to a human dose of 60 mg/m², approximately 7x the total human dose administered in a cycle of treatment based on body surface area (BSA). In a second repeat-dose murine study, where the teplizumab surrogate was administered every 3 days for 1 month, deaths began to occur following the fourth dose administration at all dosages preceded by symptoms of severe hypersensitivity reactions, the NOAEL was determined to be <0.3 mg/kg. These findings were not reproduced in the reproductive and developmental toxicity studies, with similar dosing regimens.

No stand-alone safety pharmacology studies were performed. Cardiovascular and respiratory functioning was evaluated as part of the single dose study in chimpanzees. Central nervous function (CNS) was evaluated as a component in non-dedicated toxicology studies; no observations suggestive of an effect on the CNS were noted.

4.4.2. Genotoxicity and Carcinogenicity

No genetic toxicology or carcinogenicity studies were submitted for review.

4.4.3. Reproductive and Developmental Toxicology

One embryo-fetal development study was performed in mice using the surrogate antibody. Drug or control was administered to pregnant dams on gestational days 6, 10, and 14. There was a numerically small, but statistically persuasive difference in the mean number of viable fetuses per dam in the high dose group (20 mg/kg) compared to lower doses and controls (0, 0.03, 0.3 mg/kg): 11.9-12.1 viable fetuses versus 9.1. Mice that received the high dose exhibited reduced food intake; however, it is not clear if the litter loss was a result of reduced food intake and maternal body weights. The effects at the high dose were considered adverse, leading to identification of 0.3 mg/kg (0.9 mg/m²) as the NOAEL for the study. The NOAEL for the dose level is 1/10th the cumulative clinical dose based on BSA scaling. The NOAEL for the cumulative dose is 3/10th the cumulative clinical dose based on BSA scaling. Importantly, treatment with the surrogate did not affect fetal gross, visceral, or skeletal development. Of note, the next highest dose studied is 60-fold higher, which limits the precision of the NOAEL.

One prenatal and post-natal development study was conducted in mice using the surrogate antibody. Three dose levels of surrogate (b) (4) anti-CD3 or control were administered once every three days starting on gestational day 6 and ending on lactation day 19. Assuming a gestational period of 21 days, up to 12 doses were administered. There were no effects on the

ability of maternal animals to maintain a pregnancy, deliver a litter, and rear the litter. As a result, the F0 maternal NOAEL was considered the highest dose (HD) of 20 mg/kg. At the low dose 0.3 mg/kg (0.9 mg/m²), pup levels ranged from 16% to 37% of maternal levels, but pup levels were not obtained at birth, so it was not possible to determine if the levels in pups reflected placental transfer, transfer from milk, or both. The offspring of dams exposed to the “high dose” had reductions in sperm count and motility and a reduction in the number of resulting pregnancies, but no difference in the ability to maintain a pregnancy and deliver a viable litter. The mid dose (MD) of 3 mg/kg was considered the NOAEL for effects on the offspring. The 3 mg/kg group received cumulatively up to 12 times higher dose than the cumulative clinical dose. The Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPTCHEN) concludes a potential risk exists for effects on the offspring of maternal animals administered high doses of the mAb as an increased incidence of embryofetal loss was observed in an embryofetal development study. Furthermore, treatment of maternal animals through pregnancy and lactation was associated with pharmacologic effects on T and B cell populations, primary and secondary immune responses, and fertility of the F1 animals. DPTCHEN plans to summarize these effects in the proposed label.

4.5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP), Division of Cardioresenal and Endocrine Pharmacology and Pharmacometrics reviewed the information contained in BLA 761183. The OCP review team recommends a complete response (CR) until the sponsor can adequately address the issue related to lack of comparability between the clinical trial and to-be-marketed drug products. Dr. Harisudhan Thanukrishnan and Dr. Elyes Dahmane were the primary clinical pharmacology and pharmacometrics reviewers. *For details of the clinical pharmacology assessment, refer to the review dated May 5, 2021.* Findings from OCP’s review are summarized here.

Teplizumab targets the cluster of differentiation 3 (CD3) antigen, which is co-expressed with the T-cell receptor (TCR) on the surface of T lymphocytes. Though the mechanism of action of teplizumab for the proposed indication has not been confirmed, it appears to involve weak agonistic activity on signaling via the TCR-CD3 complex, which is thought to expand regulatory T-cells and re-establish immune tolerance.

Pharmacokinetic parameters were estimated using population pharmacokinetics. The central and peripheral volume of distribution is 3.4 and 6.9 L, respectively. The mean clearance of teplizumab is 2.3 L/day, and its terminal half-life is ~4 days. Under the proposed clinical dosing regimen, the average accumulation ratio for area under the curve (AUC) between Day 5 and Day 14 (the first and the last day with the full dose administration) is predicted to be 3.4. Steady state is not expected to be achieved at the end of dosing on Day 14. Teplizumab is expected to be catabolized into smaller peptides and is not expected to inhibit or induce major

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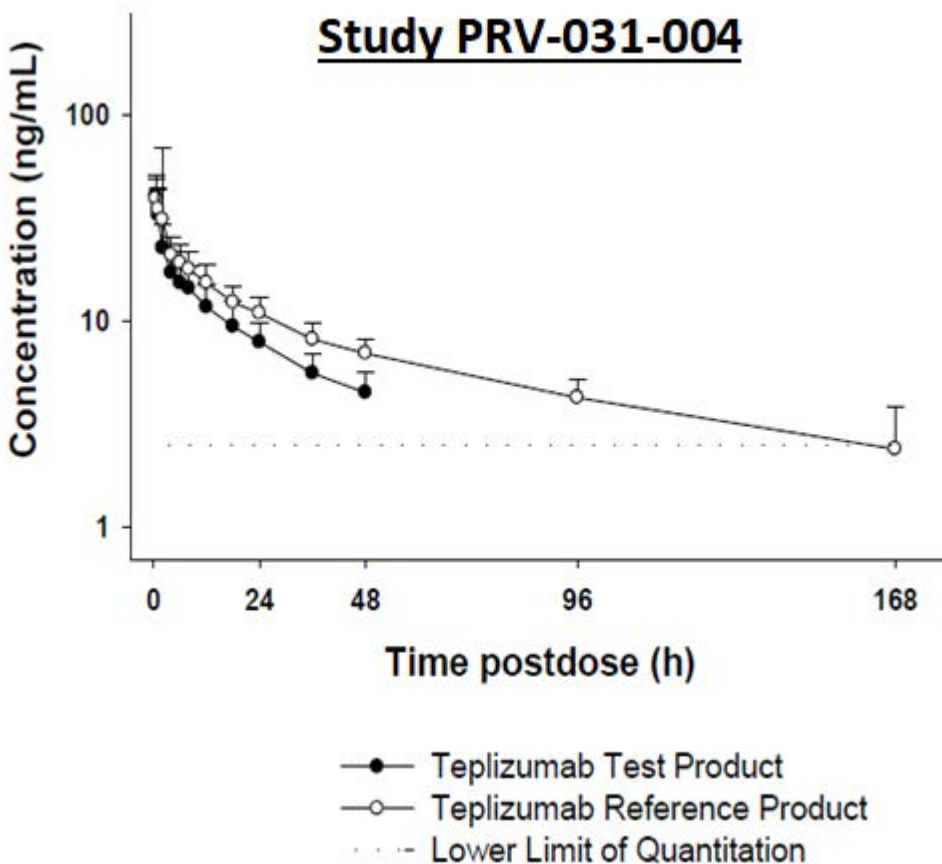
CYPs or transporters. Exposure to teplizumab after BSA-based regimen was found to be independent of age and body weight. Intrinsic/extrinsic factors are not expected to impact the exposure to this monoclonal antibody.

The majority (~60 to 70%) of study subjects developed anti-drug antibodies (ADA) to teplizumab in response to the single 14-day course. Teplizumab PK concentrations after course 1 were similar when compared between the ADA status. Supporting studies revealed that there was a greater impact of ADA on teplizumab exposure (clearance increased by up to 438%) during course 2, when the 14-day regimen was repeated after 6 months, however, this is not directly relevant to the proposed indication, as a single course will be administered, but may be important to understand from a mechanistic perspective because the Applicant may be planning to study a second treatment course for at-risk patients.

The bioanalytical methods for teplizumab PK assessments partially met the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development'. The rationale provided for not meeting the specific criterion on sample storage and method performance during study sample analysis were accepted and their implications are documented in the OCP review. The assays for C-peptide were found adequate to support use as an efficacy biomarker.

In addition, the Applicant had initiated manufacturing of commercial product from a new batch of drug substance at a new facility (AGC Biologics) and submitted results from a bio-comparability study to establish equivalence between the clinical (Eli Lilly and MacroGenics) and the to-be-marketed product (manufactured by AGC Biologics). The results of the pivotal bio-comparability study failed to establish an appropriate bridge between the clinical trial and the to-be-marketed teplizumab products. Although the C_{max} was comparable between products, indicating similar drug quantity was delivered, AUC was substantially lower (approximately (b) (4) %) indicating faster clearance of the to-be-marketed formulation. This finding suggests there is a difference in the to-be-marketed antibody, rather than a difference in potency, leading to faster clearance.

Figure 3. Mean (+/- SD) Teplizumab Concentration-Time Profiles Following Single-Dose Administration of Teplizumab Manufactures Using DS from AGC Biologics (Test Product) and Eli Lilly (Reference Product)



Source: Sponsor, PRV-031-004 CSR
Abbreviations: DS, drug substance; SD, standard deviation

The Applicant provided a comparison of reduction in circulating lymphocyte counts as support for biocomparability. However, the validity of lymphocyte count as a single surrogate marker for the proposed indication is not yet established. Hence, PK parameters, during this review, were considered as the sole criterion for the bio comparability assessment from a regulatory perspective (for comparison of product's quality attributes). As PK comparability was not established, a CR is recommended.

4.6. Devices and Companion Diagnostic Issues

A companion diagnostic was not included in the BLA. Commercially available autoantibody assays were used in the teplizumab clinical trials, and the Applicant did not propose specific FDA cleared assays for the product labeling. Center for Devices and Radiological Health (CDRH) identified a potential requirement for the development of autoantibody assays as a companion diagnostic because T1D autoantibody testing is requisite for the identification of the patient

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population for teplizumab's intended use. A discussion of the autoantibody assays and their performance characteristics is included in Section [6.1.1.3](#).

At this time the Division has not concluded whether a companion diagnostic will be needed for this BLA. The discussion of this issue is being deferred to the next cycle for this application, and the Applicant is aware that should a companion diagnostic be required, they will need to bridge the performance of autoantibody assays used in clinical trials to the companion diagnostic devices in the post-marketing period.

4.7. Consumer Study Reviews

Teplizumab is intended to be administered by health care professionals. No label comprehension or human factors studies were necessary for this application.

5. Sources of Clinical Data and Review Strategy

Teplizumab was evaluated in one trial, TN-10, for the delay of T1D in at-risk individuals and in new- or recent-onset T1D in five clinical trials ([Table 3](#)).

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Table 3. Clinical Studies to Support Efficacy and Safety (Teplizumab Administered IV)

Clinical Study Phase & Dates	Study Population & Sample Size	Study Design/ Type of Control	Dosing Regimen	Treatment & Follow-Up Duration	Primary Efficacy ³ Endpoints
Stage 2 T1D Population					
TN-10 (At-Risk Study) Phase 2 Jul 2011 to Nov 2018	Age ≥8 years Relatives of patients with T1D at high risk for development of clinical T1D based on the presence of at least two positive autoantibodies and abnormal OGTT Enrolled total: 76 (44:32) Follow-up was still ongoing at the clinical cutoff date of TN-10	R, DB, PBO controlled, 2-arm, multicenter study Randomization ratio: 1:1	Full 14-day regimen; total dose ~9034 µg/m ²	Single course Defined by time to protocol-specified number of T1D events observed; with median duration approximately 2 years	Time to T1D Diagnosis
Stage 3 T1D Population					
Study 1 Phase 1/2 May 1999 to Aug 2001	Age 7.5 to 30 years New onset T1D (within 6 weeks of dx) Enrolled total: 42 (21:21)	R, OL, 2-arm, standard of care control Randomization ratio: 1:1	14-day regimen; total dose ~495 µg/kg 12-day regimen; total dose ~19,500 µg/m ²	Single course 2 years	Change from baseline C-peptide AUC during the 4-hour MMTT

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Clinical Study Phase & Dates	Study Population & Sample Size	Study Design/ Type of Control	Dosing Regimen	Treatment & Follow-Up Duration	Primary Efficacy ³ Endpoints
Protégé Phase 2/3 Feb 2007 to Jun 2011	Age 8-35 years New-onset T1D (within 12 weeks of dx) Enrolled total: Segment 1: 38 (38:0) Segment 2: 513 ¹ (207:102:106:98)	Segment 1: OL Segment 2: R, DB, PBO controlled, multicenter, multinational, 4-arm, dose-ranging study Randomization ratio: 2:1:1:1	Segment 1: Full 14-day regimen Segment 2: Arm 1: Full 14-day; total dose ~9034 µg/m ² Arm 2: 1/3 dose 14-day; total dose ~2985 µg/m ² Arm 3: 6-day; total dose ~2426 µg/m ² Arm 4: Placebo 14-day course	Segments 1 & 2: Two identical courses, 26 weeks apart 2 years	Proportion of subjects who had both a total daily insulin dose of less than 0.5 U/kg/day and an HbA1c less than 6.5% at 52 weeks after randomization.
Encore Phase 3 Sep 2009 to Apr 2012	Age 8-35 years New-onset T1D (within 12 weeks of dx) Enrolled total: 254 (63:66:63:62)	R, DB, PBO controlled, multinational, 4-arm, dose-ranging study Randomization ratio: 1:1:1:1	Arms 1-4: Same as Protégé	Two identical courses, 26 weeks apart 89.8% completed 1 year and 29.1% completed 2 years	The proportion of subjects who had both a total daily insulin dose <0.25 U/Kg/day and an HbA1c level <7.0% at Study Day 365.
AbATE Phase 2 Sep 2005 to Apr 2011	Age 8-30 years New-onset T1D (within 8 weeks of dx) Enrolled total: 77 (52:25)	R, OL, 2-arm, multicenter study, standard of care control Randomization ratio: 2:1	Full 14-day regimen; total dose ~9034 µg/m ²	Two courses, 1 year apart 2 years	Change from baseline in the mean C-peptide 4-hour AUC in response to an MMTT at Month 24
Delay ² Phase 2 Sep 2006 to Aug 2011	Age 8-30 years Recent T1D (within 4-12 months of dx) Enrolled total: 60 (32:28)	R, DB, PBO controlled, multicenter study, with OL extension Randomization ratio: 1:1	Full 14-day regimen; total dose ~9034 µg/m ²	Single course 1 year	C-peptide AUC during the MMTT at the 12-month

Source: Reviewer adapted from ISS and ISE

Abbreviations: AUC, area under the curve; DB, double blind; Dx, diagnosis; HbA1c, hemoglobin A1c; ISE, integrated summary of efficacy; ISS, integrated summary of safety; IV, intravenous; MMTT, mixed meal tolerance test; OGTT, oral glucose tolerance test; OL, open-label; R, randomized; PBO, placebo; T1D, type 1 diabetes

¹ Protégé: 516 randomized, 513 received at least one dose of study drug

² 18 Delay subjects initially randomized to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count.

³ Note: Safety endpoints are discussed separately in Section 8.

5.1. Review Strategy

For the efficacy review, the clinical reviewer and the FDA statistician reviewed TN-10 as the single adequate and well-controlled trial submitted to provide substantial evidence of effectiveness for the intended population of patients at risk for T1D. The clinical reviewer and statistician confirmed the Applicant's analyses and conducted additional sensitivity and subgroup analyses that are presented in this review.

The second line of efficacy evidence (confirmatory evidence) was a meta-analysis of five other clinical trials conducted in patients with new- or recent-onset T1D. This group of studies is referred to herein as the 'Integrated Summary of Efficacy,' or 'ISE.' For the efficacy review, the clinical reviewer and FDA statistician did not review the ISE studies in full, but rather focused on the C-peptide change from baseline endpoint, regardless of whether the primary endpoint was C-peptide change from baseline. To explain further, the studies in the ISE were originally designed to evaluate teplizumab's efficacy in preventing further beta-cell decline in patients already diagnosed with T1D, but with residual beta-cell function. The primary endpoint in Protégé was the proportion of subjects who had both a total daily insulin dose of <0.5 units/kg/day and an HbA1c level $<6.5\%$, and in Encore was the proportion of subjects who had both a total daily insulin dose <0.25 U/Kg/day and an HbA1c level $<7.0\%$, whereas the three other studies evaluated the change from baseline in the mean C-peptide 4-hour AUC in response to an MMTT. The FDA statistician used different methodology to perform the meta-analysis (the rationale for which is acceptable and explained in detail in the FDA statistical review). In this review, we present the results of the C-peptide meta-analysis conducted by the FDA statistician. Please note that data from TN-10 were not included in the efficacy meta-analysis. Whereas TN-10 collected stimulated C-peptide data, different endpoints and testing methodologies were used, with 2-hour OGTTs used in the TN-10 study, compared to 4-hour MMTTs in the other supporting studies, making direct comparison difficult. In addition, TN-10 did not collect C-peptide data after T1D diagnosis.

For the safety review, the Applicant's integrated summary of safety (ISS) database included a pool of five studies (AbATE, Delay, Protégé, Encore, and TN-10) and served as the basis for the Applicant's safety analysis. The FDA clinical reviewer used the ISS for independently conducted safety analyses.

There are several important distinctions between patients with new- or recent-onset overt T1D and at-risk patients studied in TN-10 that influence the interpretation of adverse events (AEs). For example, rates of DKA and hypoglycemia would not be comparable between patients with and without overt T1D. Therefore, a secondary pool including the four studies in new or recent-onset patients with T1D was analyzed separately from TN-10, using a dataset referred to as the

modified ISS (mISS). Analyses from the mISS were supplementary to the Applicant's safety analyses.

In the Delay study, 18 patients received placebo in the randomized portion of the study but received teplizumab during the open-label extension. In the Applicant's ISS, safety data from these 18 patients were included in both placebo and teplizumab groups. The FDA reviewers analyzed these 18 patients per their originally assigned treatment group and limited analyses to the course 1 treatment period; this approach resulted in a different total number of patients in the full ISS pool and the modified ISS pool compared to the Applicant's analyses. The FDA analyses are presented in this review.

Study 1 was not included in the ISS because it used different dosing regimens than the other studies. Study 1 and other completed controlled trials evaluating teplizumab for the treatment of conditions (e.g., transplant) other than T1D were surveyed for any AESI (adverse event of special interest) or serious adverse event (SAE) that may be informative to the T1D population.

Three supportive studies (AbATE, Encore, and Protégé) used a second treatment cycle of teplizumab. Therefore, AE incidence rates under these conditions may not be comparable to the proposed indication. Additionally, a higher proportion of patients treated with teplizumab in these three studies (vs. comparator) in the first cycle did not receive treatment in the second cycle. Dropout rates may be influenced by study treatment, and thus the AE data in the second cycle may be biased. For this reason, FDA analyses estimating incidence rates and risk differences in the ISS dataset generally present results limited to the first treatment cycle.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. TN-10

6.1.1. Study Design

6.1.1.1 Overview and Objective

TN-10 was an efficacy and safety study designed to evaluate the treatment effect of teplizumab compared with placebo in the delay of T1D in individuals at high risk for developing T1D.

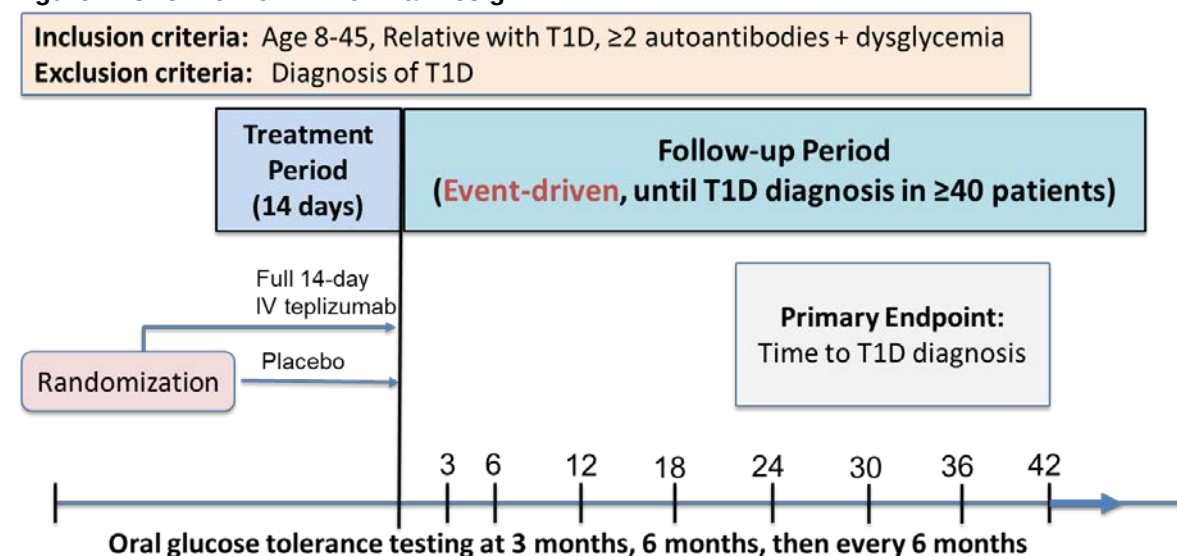
6.1.1.2 Trial Design

TN-10 was a randomized, placebo-controlled, double-blind, parallel-arm study. Patients were randomized 1:1 to receive teplizumab or placebo by daily intravenous infusion (over at least 30 minutes) for a 14-day treatment period.

TN-10 was blinded (blinded to patient and clinical investigator) to reduce potential bias during treatment evaluation. The trial medications were identical in appearance, handling, preparation, and administration.

The TN-10 trial was conducted at 30 sites in the US, Canada, United Kingdom, Australia, and Germany. Randomization was stratified by study site and age (<18 years or ≥18 years) by a central TrialNet coordinating center. TN-10 trial design is summarized in [Figure 4](#).

Figure 4. Overview of TN-10 Trial Design



Source: Reviewer-generated, from TN-10 Study Report
Abbreviations: IV, intravenous; T1D, type 1 diabetes mellitus

Reviewer comment: The TN-10 study design is adequate for the stated objective(s).

6.1.1.3 Subjects

Study subjects were identified through their participation in the TrialNet TN-01 Natural History Study, a longitudinal monitoring program for relatives of patients with T1D sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which was established to improve understanding of the demographic, immunologic, and metabolic characteristics of individuals at risk for developing T1D and to provide a source of subjects for enrollment into prevention trials. Individuals aged 8 years or older with two or more islet autoantibodies and dysglycemia on oral glucose tolerance testing, but not meeting criteria for a diagnosis of T1D, were eligible for enrollment in TN-10.

Inclusion Criteria (summarized):

1. Participated in the TrialNet Natural History Study (TN-01) and thus, a relative of a patient with T1D
2. Positive for two or more diabetes-related autoantibodies (anti-GAD65, anti-ICA512, micro-insulin autoantibody (mIAA), ZnT8 antibody, and/or ICA on 2 occasions, with the more recent within the 6 months prior to study drug administration. Note, the confirmation test did not need to involve the same two autoantibodies as were found on the first occasion. T1D Autoantibodies were counted positive by the following cutoff values: anti-GAD65 >20 units/mL, anti-IA-2 >5 units/mL, mIAA >0.010 JDF (Juvenile Diabetes Foundation) units, ICA ≥10 JDF units, anti-ZnT8 >0.020 JDF units.
3. Between the ages of 1 and 45 years at the time of enrollment in TN-01 and ≥8 years at the time of randomization
4. Met criteria for abnormal glucose tolerance on TrialNet-conducted OGTT:
 - Abnormal glucose tolerance defined as a fasting plasma glucose ≥110 mg/dL and <126 mg/dL, or a 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or a 30, 60, or 90-minute value on OGTT ≥200 mg/dL.
 - If <18 years of age at time of randomization, a single OGTT demonstrating abnormal glucose tolerance within 7 weeks of the baseline visit.
 - If ≥18 years of age at the time of randomization, two consecutive OGTTs demonstrating abnormal glucose tolerance, the most recent of which had been within 7 weeks of the baseline visit.
5. Body weight ≥26 kg
6. Female and male subjects on appropriate contraception
7. Willing and able to postpone live vaccine immunizations for 1 year after treatment

Exclusion Criteria (summarized):

8. A diagnosis of T1D, or
 - If ≥18 years old, having an OGTT in which fasting plasma glucose ≥126 mg/dL, or 2-hour plasma glucose ≥200 mg/dL
 - <18 years old, having a screening random glucose ≥200 mg/dL
9. Lymphopenia (<1000 lymphocytes/μL), neutropenia (<1500 polymorphonuclear neutrophils/μL), thrombocytopenia (<150,000 platelets/μL), abnormal coagulation (international normalized ratio [INR] >0.1 above upper limit of normal [ULN]), or anemia (hemoglobin <10 grams/deciliter) at baseline

10. AST (aspartate aminotransferase) or ALT (alanine transaminase) $>1.5 \times$ ULN, and bilirubin $>1.5 \times$ ULN (with the exception of subjects with the diagnosis of Gilbert's syndrome)
11. Infection: Chronic active infection other than localized skin infections, including a positive tuberculin purified protein derivative (PPD) test, or serological evidence of current or past HIV, hepatitis B or hepatitis C infection.
12. Acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV), or a history of infectious mononucleosis within the 3 months prior to enrollment.
13. Vaccination with a live virus within 8 weeks or with a killed virus within 4 weeks of randomization
14. Pregnant, actively attempting to get pregnant, or lactating
15. Current use of medications that affect glycemic control
16. Chronic use of steroids or other immunosuppressive agents, and/or a history of asthma or atopic disease requiring chronic treatment
17. Untreated hypothyroidism or active Graves' disease at randomization
18. Prior OKT3 or other anti-CD3 treatment, or administration of a monoclonal antibody within the year before randomization
19. Participation in any type of therapeutic drug or vaccine clinical trial within the 12 weeks before randomization
20. Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the subject

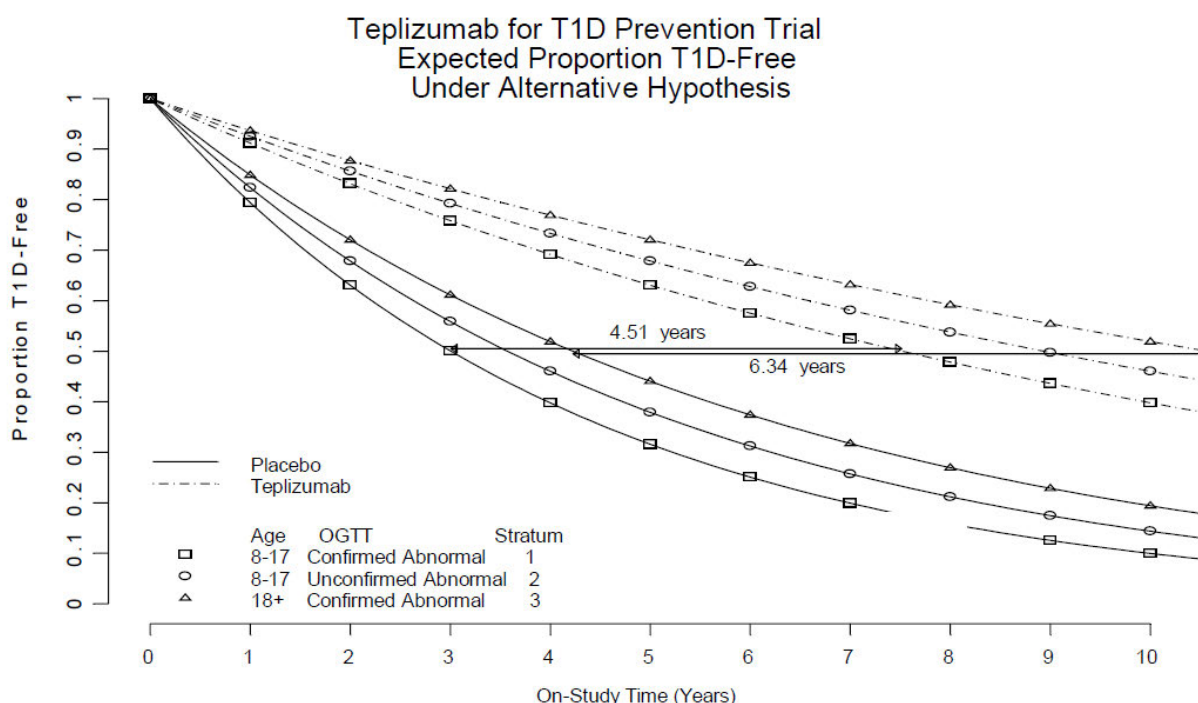
Reviewer comments:

Inclusion criteria

A key inclusion criterion was that the subject was to be "Positive for two or more diabetes-related autoantibodies (anti-GAD65, anti-ICA512, micro-insulin autoantibody (mIAA), ZnT8 antibody, and/or ICA) on two occasions." The other key inclusion criterion was meeting criteria for abnormal glucose tolerance on TrialNet-conducted OGTT. As discussed previously in Section 2.1, the risk of developing T1D in patients with two autoantibodies (AA) with dysglycemia has been estimated in natural history studies to be approximately 40% at 6 months, and 74% at 4 years. Together, these criteria enrich the study population to speed the accrual of events and also represent the appropriate target patient population for treatment with teplizumab. Prior studies in at-risk populations have indicated that among at-risk stage 1 patients who ultimately develop T1D, there are fluctuations between the normal and dysglycemic states before the onset of T1D (Sosenko et al. 2009). In TN-10, adult subjects required a

confirmatory test to diagnose diabetes, although allowed the inclusion of pediatric patients (<18 years old) without a second result confirming dysglycemia on OGTT. Natural history studies in at-risk populations have demonstrated that the estimated hazard rate of developing T1D for ages 8 to 17 years without a confirmed OGTT is 0.194, greater than the hazard rate of developing T1D in age 18 or older with a confirmed OGTT (0.164) (Figure 5). It is also important to note that there was no age by treatment interaction detected in our analysis of TN-10 (see Section 7).

Figure 5. Model for Time to T1D Adjusting for Baseline Age and OGTT Status



Source: TN-10 Protocol, generated by TrialNet investigators using data from the Natural History Study (TN-01) to estimate hazard rates for the control group assuming a constant risk over time. Sample size estimates were determined from this model by applying the eligibility criteria for TN-10 study.

Abbreviations: OGTT, oral glucose tolerance test; T1D, type 1 diabetes

If approved, product labeling should emphasize the importance of a confirmatory test among the age group >18 years old.

With respect to the following inclusion criterion: Participated in the TrialNet Natural History Study (TN-01), it is important to note that all participants in TN-01 were relatives of a patient with T1D, and TN-01 was used to recruit patients for TN-10. Therefore, this was a convenience criterion. The applicability of the TN-10 data to non-relatives is discussed elsewhere in this review.

Patients at least 8 years of age were enrolled in TN-10 because children are disproportionately affected with T1D. In addition, 501 children ages 8 to 17 years old had received teplizumab treatment in other clinical trials lending reassurance with respect to safety in this age group.

Only patients with body weight ≥ 26 kg were eligible for enrollment in this trial, which is approximately 50th percentile for pediatrics 8 years of age. As teplizumab dosing is based on body surface area, overdose is not a concern for real world use, and I do not recommend a labeling restriction based on body weight. See Section [7.2.1](#) for additional discussion on efficacy and safety considerations regarding this inclusion criterion.

Subjects also needed to be willing and able to postpone live vaccine immunizations for 1 year after treatment in order to enroll in TN-10. Therefore, the safety of live vaccine immunizations after a course of teplizumab was not investigated in the clinical study. Following consultation with the Division of Hematologic Malignancies 1 (DHM1) regarding the risk of immunosuppression, the withholding of live vaccination for 1-year post-treatment per the protocol does not appear to be guided by the true risks of immunosuppression with teplizumab. Instead, the DHM1 team recommended consideration of a Warning and Precaution against live viral vaccination within 4 weeks prior to planned use and within at least 3 months after treatment with teplizumab, which would sufficiently mitigate the risk of serious infections.

Exclusion criteria

The TN-10 glycemic-related exclusion criteria prevented patients who were likely to have already progressed to T1D from enrolling so were fully justified.

Excluding patients for lymphopenia or transaminase abnormalities is related to the potential for teplizumab to cause cytokine release syndrome (discussed elsewhere in this review). Similarly, the protocol excluded patients with chronic active infection and active infection with EBV or CMV for subject protection in light of the immunosuppressive effect of teplizumab. Therefore, these criteria are reasonable and may need to be considered for labeling.

TN-10 exclusion criterion 10 prevented patients with untreated hypothyroidism or Graves' hyperthyroidism from enrolling. This was likely an efficacy consideration as untreated thyroid disorders have been shown to worsen the metabolic control of patients with T1D, with the assumption that this too may impact progression to T1D in at-risk patients (Biondi et al. 2019). Patients with genetic risk of T1D are also susceptible to other autoimmune disorders such as autoimmune

hypothyroidism, which is relatively common; therefore, inclusion of patients with treated hypothyroidism, like the TN-10 protocol, would be recommended if approved. Similar to the TN-10 protocol, treatment should be delayed in patients with active Graves' disease or untreated hypothyroidism in order to avoid the risk of adverse events associated with both conditions, e.g., hemodynamic events.

The protocol also excluded patients with asthma or atopic disease requiring chronic treatment for the purpose of improving interpretation of the trial's efficacy, as glucocorticoid use in these conditions may contribute to dysglycemia, and there was concern regarding added immunosuppression with corticosteroid use. I do not recommend disallowing patients with asthma or atopic disease requiring chronic treatment from receiving teplizumab therapy post-approval. Many children use inhaled daily corticosteroids or topical steroids for atopic disease, and systemic side effects (such as adrenal suppression and hyperglycemia) risks are minimal for patients receiving low doses but can be substantial for high doses (National Asthma Education and Prevention Program 2007). Therefore, in real world use, implementation of these broad exclusion criteria may overly restrict the population that could benefit from teplizumab. Instead, I recommend consideration of a Warning and Precaution for immunosuppression with teplizumab if the patient is taking corticosteroid doses with significant risk of immunosuppression.

Although exclusion criteria for TN-10 mentioned any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the subject, there were no patients reported as screen failures meeting this criterion, and therefore, this criterion did not affect the safety or efficacy conclusions for TN-10.

Screening T1D Autoantibody Testing

A focused discussion on T1D autoantibody testing is warranted because these tests are not routinely recommended in clinical practice, and there are assay considerations that must be addressed.

(b) (4) developed autoantibody assays. Screening for T1D autoantibodies to identify at-risk patients for TN-10 was performed entirely through the TrialNet Pathway to Prevention screening study (TN-01) through (b) (4). These autoantibody assays are not FDA cleared, but are widely used in clinical practice and in the research setting.

In general, surveillance of the quality of T1D autoantibody assays has largely been provided by the Islet Autoantibody Standardization Program (IASP) workshop, organized by the NIH NIDDK

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and the Immunology of Diabetes Society. IASP organizes international interlaboratory comparisons and provides participating laboratories with blinded T1D, multiple islet autoantibody-positive at-risk first-degree relatives of T1D patients, and control serum samples to assess and compare interlaboratory sensitivity, specificity, and accuracy. Centralized collection and analysis of results by the IASP provide participants with an unbiased comparison of assay performance. The Applicant provided IASP validation certificates from the (b) (4) demonstrating the consistency of the specificity of these tests at 97-100% during this time period (Table 4). (b) (4) assay is also CLIA²-certified.

Table 4. IASP Workshop Results for the (b) (4)

Year	Insulin		GAD		IA-2		ZnT8	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
2010	56	99	84	99	66	100	64	99
2012	50	100	66	99	70	100	62	98
2013	36	100	70	99	64	100	68	99
2015	52	100	82	99	72	100	70	97
2016	54	98	68	100	72	100	66	100
2018	66	99	82	99	62	100	68	100
2020	62	99	78	99	72	100	74	100

Source: (b) (4)

Source: Applicant's table, from information request communication dated 1/13/2021

Abbreviations: GAD, glutamic acid decarboxylase; IASP, Islet Autoantibody Standardization Program; ZnT8, zinc transporter 8

In addition, at the Agency's request, the Applicant submitted comparisons showing that the (b) (4) are comparable in sensitivity and specificity to the FDA-cleared assay (b) (4) used by large central laboratories in the US, (b) (4), for the detection of islet autoantibodies (Table 5).

² The Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing and require clinical laboratories to be certified by the Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing <https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia>

Table 5. Comparison of Clinical Sensitivity and Specificity of the BASED Assay Compared to the FDA-Cleared (b) (4) Assay

<i>AA assays</i>	(b) (4) (CLIA)	(b) (4) (FDA-cleared assays)
GAD	<u>RBA</u> Sensitivity: 86% Specificity: 98%	<u>ELISA</u> Sensitivity: 84% Specificity: 99.5%
IA-2	<u>RBA</u> Sensitivity: 64% Specificity: 99.5%	<u>ELISA/RIA</u> Sensitivity: 58%/49% Specificity: 97%/98.5%
ZnT8	<u>RBA</u> Sensitivity: 60% Specificity: 99%	<u>ELISA</u> Sensitivity: 68% Specificity: 98%
IAA	<u>RBA</u> Sensitivity: 66% Specificity: 99%	<u>RIA</u> Sensitivity: 50% Specificity: 98.5%

The type of assay methodology is underlined.

Source: Applicant's table, from information request communication dated 1/13/2021

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; ELISA, enzyme-linked immunosorbent assay; GAD, glutamic acid decarboxylase; IAA, insulin autoantibody; IA-2, IA-2 Ab; RBA, radio binding assay; RIA, radio-immunoassay; ZnT8, zinc transporter 8

Reviewer comment: The Applicant provided evidence that screening T1D autoantibodies used in the TN-10 study were highly specific for the identification of the at-risk population (stage 2 T1D) and comparable to the FDA-cleared (b) (4) assay. In TN-10, the presence of ≥ 2 T1D autoantibodies was verified with a second confirmatory antibody panel, which improved the specificity of this testing. Although the antibody type did not need to be consistent between the initial and confirmatory test, the presence of 2 or more T1D autoantibodies, regardless of type, is highly predictive of risk of T1D (Ziegler et al. 2013). Additionally, the requirement for the presence of dysglycemia ensures that all patients enrolled in the trial have stage 2 disease. For these patients, false positives for antibody assessments are unlikely because dysglycemia distinguishes advancement from stage 1 to stage 2 T1D.

6.1.1.4 Study Treatments and Dose Selection

The treatment course consisted of daily doses of 51 $\mu\text{g}/\text{m}^2$, 103 $\mu\text{g}/\text{m}^2$, 207 $\mu\text{g}/\text{m}^2$, 413 $\mu\text{g}/\text{m}^2$ during the first 4 days, respectively, and 10 subsequent daily doses of 826 $\mu\text{g}/\text{m}^2$, with a total cumulative dose of 9034 $\mu\text{g}/\text{m}^2$ ($\sim 9 \text{ mg}/\text{m}^2$). Less than 10% of the total dose is given on the first 4 days of ramp-up as a precaution to avoid adverse reactions mediated by immune cell activation, especially cytokine release syndrome. In addition to avoidance of adverse events, dose selection was made considering evidence from studies conducted in patients with new- or recent-onset T1D. Analysis of secondary and exploratory endpoints of the Protégé study

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demonstrated a significant improvement in AUC mean C-peptide during a 4-hour MMTT in patients with new-onset T1D treated with the same full-dose 14-day course as used in TN-10 ($\sim 9 \mu\text{g}/\text{m}^2$) compared with placebo ($p=0.046$), but not with a 1/3 dose 14-day course ($\sim 3 \mu\text{g}/\text{m}^2$) or a 6-day curtailed regimen ($\sim 2.4 \mu\text{g}/\text{m}^2$) (Sherry et al. 2011).

Teplizumab or saline was to be given as an IV infusion over a minimum of 30 minutes in an outpatient research or hospital setting. The infusion was scheduled at the same time each day $\pm$ 4 hours.

Study drug infusion was to be withheld in the case of laboratory abnormalities or other adverse events (discussed in subsequent sections), but there was no provision for dose reduction in the case of adverse events. In addition to withdrawal of consent and pregnancy for female patients, study drug infusion was withheld for the following laboratory abnormalities:

- Hepatic abnormalities (total bilirubin $>1.3 \text{ mg}/\text{dL}$ on day 1, $\geq 2.0 \text{ mg}/\text{dL}$ on other days. AST level $>2\times$ ULN on Day 1. AST, ALT or (lactate dehydrogenase) LDH $\geq 3\times$ ULN on other days)
- Thrombocytopenia (platelets $<140,000/\mu\text{L}$ on day 1, $<100,000/\mu\text{L}$ on other days)
- Neutropenia ($<1000 \text{ cells}/\text{m}^3$)
- Anemia (hemoglobin $\leq 8.5 \text{ g}/\text{dL}$ or a drop in $\geq 2 \text{ g}/\text{dL}$ compared with prior to infusion to a value $<10.0 \text{ g}/\text{dL}$)
- Coagulopathy (INR >0.1 above ULN)

Study drug infusions were also held for anaphylaxis, fever of grade 3 or higher on Day 0 or Day 1, or any Grade 3 or higher adverse event (except for lymphopenia, hypoglycemia, hyperglycemia, fatigue/malaise, insomnia, cheilitis, dry skin, nail changes, hot flushes/flushes, headache, myalgia, flu-like symptoms) or any medically important event that in the opinion of the investigator, contraindicated continued dosing. Several of these criteria were developed by the data safety monitoring board (DSMB) following a safety review performed in 2006. In patients with new-onset T1D, the DSMB identified a symptom complex consistent with cytokine release syndrome (CRS) during the first 6 days of teplizumab treatment, requiring drug discontinuation in about 10% (6/60) of patients with T1D. The DSMB identified a grade 3 fever (defined as temperature $>40^\circ\text{C}$ [104°F] for 24 hours or more), increase in prothrombin time (PT) and/or partial thromboplastin time (PTT) and an increased D-dimer, and increase in total bilirubin, hypotension and increase in liver enzymes in these cases. Importantly, all cases identified were self-limited, did not progress, and completely resolved without sequelae.

Reviewer comment: The protocol-specified dose withholding instructions for TN-10 seem reasonable. In addition, the Applicant explained in detail how specific drug withdrawal criteria relate to the DSMB's identification of features of CRS; therefore, stringent criteria for withholding drug were developed to improve the safety of teplizumab administration. As we do not know if the protocol-specified

withdrawal criteria may have prevented more serious or permanent harms from continued dosing, the specific drug discontinuation criteria used in TN-10 should also be provided in labeling.

Unblinding—Importantly, given that safety lab assessments were performed on the same day prior to each infusion, there is potential for unintentional unblinding in TN-10, as the investigators were required to perform laboratory assessments including assessment for lymphopenia prior to drug infusions. As constitutional symptoms and lymphopenia were frequently observed in teplizumab-treated patients, it is plausible that investigators were able to distinguish teplizumab from placebo.

6.1.1.5 Study Visits and Procedures

Patients in TN-10 underwent a screening visit, 14 dosing visits, and follow-up safety visits at Day 20, 6 weeks, 3 months, 6 months and then every 6 months thereafter. A table of study visits and procedures is presented in [Table 6](#).

A screening visit with OGTT occurred within 7 weeks of the first dosing visit. The screening visit and follow-up visits could be completed at any TrialNet site, whereas the baseline and infusion visits (Day 1 to 14) were completed at a limited number of designated TrialNet infusion sites.

Safety assessments (physical examination, vitals, chemistry and hematology labs, HbA1c, EBV and CMV viral loads, serologies, etc.) and efficacy assessments (OGTT and assessments for symptoms of T1D) were performed according to the schedule of activities as summarized in [Table 6](#).

1. Screening Visit (Day -1): Because patients were identified through their participation in the Natural History/Pathway to Prevention screening study (TN-01), the ‘screening visit’ was the visit in which the presence of stage 2 disease was either identified (in patients <18 years) or confirmed (in patients 18 years and older). Following this visit, patients were assessed for inclusion/exclusion criteria and completed informed consent. At this visit, patients received HbA1c and random glucose testing (if <18 years of age and not undergoing an OGTT on the same day). Also, HIV and Hepatitis B and C serologies and PPD testing were performed.
2. Dosing Visits (Day 0-13): Vital signs were monitored for 2 hours after each infusion. Laboratory studies were obtained prior to each dose and the results of chemistries including liver function tests, complete blood count (CBC), and coagulation parameters were reviewed each day prior to commencement of the drug infusion. An EKG was performed and reviewed prior to initiation of study drug. Ibuprofen and antihistamine were administered prophylactically prior to teplizumab and placebo infusion on the first 5 days of treatment. Further dosing of Ibuprofen, antihistamines, and/or acetaminophen was used as

needed for fever, malaise, headache, arthralgia, or rash. Mechanistic assessments including samples for RNA, plasma, serum, DNA, and measures of B and T cell number and function were collected at baseline, day 20, months 3, 6, 18, 30, 42, 54, 66, and every 6 months thereafter, to understand the effect of teplizumab on the immune system and risk for infectious disease. The schedule for these assessments could vary as appropriate. At no time would the blood draw volume exceed what was allowable according to the patient's age and body weight.

Reviewer comment: The protocol-guided premedication with prophylactic ibuprofen and antihistamine in TN-10 may have had a role in mitigating infusion-related reactions or masking some symptoms of CRS (like fever). We reviewed the premedication guidance for TN-10 with the FDA Division of Hematologic Malignancies 1 (DHM1) in consultation, who agreed that the premedication in the protocol was appropriate. We recommend that the same premedications should be included in section 2 of the label.

3. Follow-Up Safety & Efficacy Visits: In addition to routine safety monitoring, other important monitoring included EBV and CMV serologies and viral loads. Additional blood samples were drawn in the case of symptoms of EBV/CMV or for drug withholding. Blood was collected for the assessment of anti-drug antibodies (ADAs) at 3 months. An EKG was performed at month 12. A limited physical exam was performed at months 3, 6, 18, 30, 42, 54, 66, and every 6 months thereafter. All patients had interim contact with study personnel for formal inquiry about AEs, presence or absence of blurred vision, polyuria, polydipsia, or unintended weight loss. In addition, random glucose samples were obtained at 3-month intervals, alternating with scheduled OGTTs, and those with symptoms or random glucose >200 mg/dL underwent fasting glucose or OGTT evaluation. Patients who developed diabetes during the follow-up period (and thus reached the study endpoint), were offered annual follow-up, but this was optional.

Reviewer comment: Even though the TN-10 protocol specified continued follow-up for safety assessments after patients met the primary endpoint (diagnosis of T1D), these safety analyses post-diagnosis were not pre-specified and were not included in the BLA as the majority of patients did not attend post-diagnosis follow-up safety visits.

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Table 6. Schedule of Events for TN-10 Study

Visit (Day/Month)	Study Drug ¹	Chemistries ^{2,3}	CBC with Diff ²	Liver Function ^{2,3}	PINR ²	EBV&CMV Viral Loads ⁴	EMV/CMV Serology	OGTT ⁵ , HbA1c	Urine Pregnancy Test
Screening Visit (Day -1)		X	X	X		X	X	X	X
Baseline, Randomization (Day 0)	X	X	X	X	X			X	X
Dosing Visit 1 (Day 1)	X	X	X	X	X				
Dosing Visit 2 (Day 2)	X	X	X	X	X				
Dosing Visit 3 (Day 3)	X	X	X	X	X				
Dosing Visit 4 (Day 4)	X	X	X	X	X				
Dosing Visit 5 (Day 5)	X	X	X	X	X				
Dosing Visit 6 (Day 6)	X	X	X	X					
Dosing Visit 7 (Day 7)	X								
Dosing Visit 8 (Day 8)	X		X						
Dosing Visit 9 (Day 9)	X								
Dosing Visit 10 (Day 10)	X								
Dosing Visit 11 (Day 11)	X	X	X	X	X				
Dosing Visit 12 (Day 12)	X								
Dosing Visit 13 (Day 13)	X	X	X	X	X				
Follow-up Visit 14 (Day 20)			X			X			
Follow-up Visit 15 (Week 6)		X	X			X			
Follow-up Visit 16 (Month 3)			X			X		X	X
Follow-up Visit 17 (Month 6)			X					X	X
Follow-up Visit 18 (Month 12)		X	X	X		X	X	X	X
Follow-up Visit 19 (Month 18)			X					X	X
Even Follow-up Visits 20-24									
Every 12 months (Months 24-48)		X	X	X		X	X	X	X
Odd Follow-up Visits 21-77									
Every 12 months (Months 30-66)								X	X
Follow-up Visits 26 onwards (Month 60+) ⁶		X	X	X				X	X

Source: Modified by Clinical Reviewer from Applicant's TN-10 study protocol

Abbreviations: BUN, blood urea nitrogen; CBC with Diff, complete blood count with differential; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EBNA, Epstein-Barr nuclear antigen; HbA1c, hemoglobin A1c; INR, international normalized ratio; LDH, lactate dehydrogenase; OGTT, oral glucose tolerance test; VCA, viral capsid antigen

¹ Drug dosing: Day 0: 51 µg/m², Day 1: 103 µg/m², Day 2: 207 µg/m², Day 3: 413 µg/m², Days 4 - 13: 826 µg/m².

² These test results had to be reviewed prior to drug administration. INR and CBC with differential were done locally at all specified visits.

³ Liver Function tests (ALT, AST, LDH, alkaline phosphatase, total protein, albumin, total and direct bilirubin) and chemistries (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatine) were done locally at specified visits 0-13. Tests were done centrally at all other specified visits.

⁴ At Screening, EBV viral loads were measured on all subjects except those with positive EBV serology. After screening, EBV/CMV viral loads were collected from all subjects.

⁵ Screening OGTT only applicable for subjects ≥18 years unless abnormal glucose tolerance confirmed by a previous TrialNet OGTT within 7 weeks of randomization. Glucose, insulin, and C-peptide were collected at each OGTT. Subjects <18 years underwent OGTT at or prior to the baseline visit (these results did not determine eligibility for the study)

⁶ The assessments at month 60 were repeated every 6 months.

Administrative Structure

For the purposes of adverse event reporting, an independent physician masked to treatment assignment was designated to serve as the medical monitor for TN-10, and reviewed all adverse event reports, and had the duty to file event reports.

The data safety monitoring board (DSMB) met approximately every 3 months to review indicators of safety. In addition, they met every 6 months to review the interim effectiveness and potential toxicity of the study treatments based on interim analyses of indicators of effectiveness and safety. The DSMB was firewalled from the investigators and sponsor.

A (b) (4) which was masked to treatment assignment, was to review all relevant information for each patient in TN-10 who was diagnosed with T1D by way of symptoms and casual glucose >200 mg/dL. The Committee was to determine whether the diagnosis of diabetes in each of these patients sufficiently sound so as to include that patient among the cases who have reached the primary outcome in the statistical analysis.

Reviewer comment: The majority of patients meeting the primary outcome, 34/43 the T1D diagnoses were derived based on two consecutive OGTTs. Only two patients were brought to the committee via this method for adjudication and these records were reviewed by the FDA and determined to be adequate in demonstrating that these patients met the primary endpoint at the date selected.

6.1.1.6 Study Endpoints

Primary Endpoints

The primary efficacy endpoint for TN-10 was the elapsed time from randomization to diagnosis of T1D or time of last contact. The diagnosis of T1D is a clinical endpoint as it directly assesses how a patient feels or functions. This endpoint was not discussed with FDA prior to conduct of the study but was agreed upon at the pre-BLA meeting between the FDA and Applicant that it was an acceptable endpoint to support the proposed indication. See Section 3, Regulatory Background. There is no regulatory precedent for this endpoint.

T1D was diagnosed by the following criteria: a 2-hour plasma glucose of ≥ 200 mg/dl on oral glucose tolerance testing, a casual plasma glucose >200 mg/dL plus symptoms of diabetes (defined as polyuria, polydipsia, or weight loss), or a fasting plasma glucose ≥ 126 mg/dL. These criteria had to be confirmed on two occasions at least 1 day apart. Diagnosis occurred on the date of the confirmatory test. In addition, the presence of unequivocal hyperglycemia with acute metabolic decompensation, or diabetic ketoacidosis (or DKA) was also considered diagnostic of T1D. Cases diagnosed with these latter criteria were to be adjudicated by the

(b) (4) If diagnosis was confirmed through adjudication, diagnosis occurred on the date the patient was confirmed to have met criteria.

Oral glucose tolerance tests (OGTTs) for ascertainment of the primary endpoint were performed at baseline, month 3, month 6, and every 6 months thereafter until diagnosis of T1D or study termination. In addition, at 3 month intervals in which there was no OGTT scheduled, random post-prandial blood glucose levels were measured, and via intermittent phone contact, patients were asked directed questions about the presence or absence of symptoms associated with diabetes (blurry vision, unintended weight loss >3 kg, polyuria, and polydipsia). If indicated by symptoms or random screening glucose levels, a fasting blood glucose or OGTT screening was performed.

Reviewer comment: The method of event ascertainment is acceptable and is consistent with clinical practice (the method of diagnosis of T1D in TN-10 is the same that is used in clinical practice, with the exception of not including the HbA1c $\geq 6.5\%$ criterion). The frequency of testing (every 3 months) is also acceptable. As discussed earlier, there is a reasonable possibility that unintentional unblinding occurred in the TN-10 study. However, the primary endpoint is based on an objective laboratory-based measure.

Secondary Endpoints

In addition to the analyses supporting the primary endpoint, time to diagnosis of T1D, the Applicant provided assessments of C-peptide, a biomarker that reflects beta cell function.

C-peptide is typically measured through the oral glucose tolerance test (OGTT) prior to a diagnosis of T1D, and through a MMTT after clinical T1D diagnosis. These methods result in a 'stimulated' C-peptide result (i.e., stimulated by oral intake of carbohydrate).

Stimulated C-peptide from a 2-hour OGTT was a secondary endpoint in TN-10. C-peptide data in response to OGTT were collected pre-baseline (up to 1 to 2 years before randomization as part of the TN-01 study), at baseline (randomization), then month 3, month 6 and every 6 months thereafter until the primary endpoint of T1D diagnosis was met. C-peptide was not collected after T1D diagnosis. The C-peptide parameters included area under the curve (AUC), mean AUC, and peak C-peptide. Glucose and insulin measurements were also collected.

In this review, we focused on mean C-peptide AUC as this parameter was also used in the meta-analysis included as confirmatory evidence to support efficacy. In addition, our analyses focused on C-peptide data for the first 12 months of observation only. It is important to note that because patients did not continue to have 2-hour OGTT monitoring after T1D diagnosis, upon diagnosis, there was informative censoring, rendering an analysis of available C-peptide

data uninterpretable after the point when censoring became an issue (approximately 6 to 12 months post-randomization).

Statistical Analysis Plan

The statistical analysis plan (SAP) is reviewed in detail in Dr. Wang's statistical review. Provided here is a brief overview and commentary on aspects or issues of the SAP that have clinical relevance or affect interpretation of the efficacy results.

The SAP was reviewed by the FDA prior to submission, and SAP revisions were made following recommendations from the FDA with regard to handling of missing data and revisions to sample size. The original study protocol planned to enroll 144 subjects over 2 to 3 years. Because of slower than expected accrual rates, the protocol was revised to reduce the sample size to 71 and revised to follow all enrolled subjects until 40 subjects were diagnosed with T1D (event-driven trial). The study was targeted to detect an effect size measured by a hazard ratio of 0.4 for teplizumab vs. placebo, with 80% power at a one-sided alpha level of 0.025. The Agency agreed that 40 events would be sufficient, and revisions were made to the protocol and the SAP. In addition, the FDA reviewed the SAP (March 27, 2018 version) prior to interim efficacy monitoring or unblinding of TN-10 study results.

Defined analysis populations included the intention-to-treat (ITT) population, all patients who were randomized; the full analysis set (FAS), which included patients who received any study treatment; and the safety population, which analyzed patients based on treatment received. Analyses on ITT and FAS sets were conducted by assigned treatment, regardless of treatment adherence.

Per the SAP, at the time of the study cutoff date, patients who had experienced a T1D diagnosis were considered as having "completed study." Study completion was defined as the date the patient was confirmed as meeting criteria for T1D. Study completion status for patients who were still T1D-free and continued to be followed at the study cutoff date was categorized as "ongoing", and patients were to be censored at the last OGTT measurement or physical examination, whichever was later. If patients discontinued the study before the clinical cutoff, they were censored at their last contact date.

The Applicant summarized the primary endpoint using Kaplan-Meier (KM) estimates to demonstrate the proportion of patients free of T1D by time since randomization. A Cox proportional hazards (PH) model was used to analyze the time to T1D diagnosis, stratified by age and OGTT status at randomization. The Cox model was adjusted for age, with the exception of the interaction test for age (<18 years vs. ≥18 years) but was not adjusted for multiple testing.

The Applicant prospectively planned three sensitivity analyses to handle missing data:

- Sensitivity analysis #1 (SA1) set time-to-diagnosis of T1D to 1 year for placebo patients whose time to event was within 1 year. By delaying event time in a portion of patients in the placebo arm, this approach favors placebo to an extent depending on the actual data.
- Sensitivity analysis #2 (SA2) assumed that subjects who were censored before study cutoff had been diagnosed with T1D at their last evaluation. SA2 penalizes missing data without favoring either treatment group at the analysis planning stage. The actual data determine which arm will benefit from this approach.
- Sensitivity analysis #3 (SA3) was a combination of SA1 and SA2.

The three pre-planned sensitivity analyses (SAs) were all considered reasonable by the FDA statistical reviewer in handling missing data.

Reviewer comment: In addition, the FDA statistical reviewer also performed a fourth sensitivity analysis, which was similar to SA2, but only applied the imputation (T1D diagnosis) to teplizumab patients who were censored before study cutoff.

The Applicant also prespecified specific subgroup analyses based on baseline age, sex, body mass index (BMI) at baseline (<median, ≥median), autoantibody type (anti-GAD65, micro insulin, anti-IA-2, ICA, anti-ZnT8), HLA type (HLADR3, HLA-DR4), pretreatment C-peptide (<median, ≥median) and glucose levels (<median, ≥median) during the oral glucose-tolerance tests. These subgroup analyses were planned to be presented as a forest plot, with hazard ratios and 95% confidence intervals to compare teplizumab's effects between each subgroup.

Reviewer comment: In addition to corroborating the Applicant's subgroup analyses per the SAP, FDA performed additional subgroup analyses evaluating important baseline characteristics from the literature with the potential to modulate teplizumab's treatment effect, including patient age (by quartile), BMI, BMI-z, genetic characteristics (HLA type), and autoantibody number.

The initial TN-10 study design (the original protocol, dated June 25, 2014; Statistical Analysis Plan (SAP), dated October 26, 2017) included plans on assessing treatment effect on secondary efficacy endpoints such as C-peptide AUC from a 2-hour OGTT. The original objective was to determine whether treatment with teplizumab was superior to placebo with respect to C-peptide response to oral glucose, as obtained from repeated collections during longitudinal tests.

Reviewer comment: Because of both the varying lengths of patients' participation in this time-to-event study and the discontinuation of C-peptide AUC collection upon T1D diagnosis, the C-peptide variables were determined by FDA to be

insufficient to support an appropriate intent-to-treat analysis, but instead were considered exploratory analyses for descriptive purposes.

There was one planned interim analysis conducted when 18 subjects were diagnosed with T1D. Please refer to the statistical review for further information. We confirmed that results of the interim analysis were firewalled from investigators and from the sponsor of teplizumab at the time (MacroGenics); only the closed-group DSMB had access.

6.1.1.7 Protocol Amendments

The original study protocol for TN-10 was amended four times during the study. Key changes to the protocol are listed below and were incorporated into the final protocol, which was dated June 25, 2014.

The most substantiative protocol changes were related to modifications to the target sample size because of slower than expected enrollment. This prompted changes in the study accrual goals (71 patients vs. the original 140), study cutoff point (at 40 T1D diagnoses vs. the original 69) and study duration (6 to 10 years vs. the original 2 to 3 years). These changes to accrual goals and changes in study design power calculations were acknowledged by FDA, in addition to revisions in the SAP made to address these changes. In addition to changes in study accrual goals, inclusion criteria were modified to bolster enrollment through “expanded eligibility criteria.” These expanded criteria changed the requirement for a second confirmatory dysglycemic OGTT (within 7 weeks of the baseline visit), to allow individuals <18 years to qualify for enrollment based on a single qualifying OGTT meeting criteria for dysglycemia; the confirmatory OGTT remained a requirement for patients ≥18 years. As noted previously, this determination was guided by evidence that the risk of progression to T1D is similar among at-risk patients <18 years of age with a single dysglycemic OGTT compared to at-risk patients ≥18 years of age with two consecutive OGTTs consistent with dysglycemia. Analyses outlined for the primary efficacy endpoint were also adjusted to be stratified by age and OGTT status (confirmed abnormal or not) prior to randomization. In addition, exclusion criteria were modified to exclude at-risk patients <18 years of age with screening random glucose ≥200 mg/dL in order to prevent the enrollment of patients who had already progressed to T1D.

There were minor changes to the laboratory-based exclusion criteria to allow the enrollment of patients with Gilbert’s syndrome, who could enroll despite meeting laboratory based exclusion criteria, e.g., they were allowed to have total bilirubin above 1.5x ULN, provided they had no other causes of hyperbilirubinemia. This amendment was considered in the Agency’s review of safety data for this subgroup of patients with baseline elevations in total bilirubin.

Other than enrollment criteria modifications, there were changes made to the method and timing of monitoring for the primary endpoint, which was changed from monitoring specifying “3-month intervals by phone contact” outside of scheduled visits to monitoring via “routine

contact between visits.” As contact was specified in the schedule of assessments at every 3-month intervals, this amendment allowed for more frequent contact by methods other than phone.

6.1.2. Study Results

Compliance with Good Clinical Practice

The Applicant provided attestation that the TN-10 study was performed in compliance with International Council for Harmonization (ICH) guideline on Good Clinical Practice.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators, and no investigators had disclosable financial interests. See Section 13.2 for details.

6.1.2.1 Patient Disposition

In total, 146 patients were screened, of whom 76 were randomized and included in the full analysis set (Table 7). Of the 76 patients randomly assigned to the two treatment groups: 44 (58%) were assigned to the teplizumab group and 32 (42%) to the placebo group. All patients received at least one dose of the randomized treatment.

Of the 70 screen failures, 37/70 (52.9%) had normal OGTT results, i.e., did not meet criteria for dysglycemia on OGTT, and 20/70 (28.6%) failed screening because of OGTT results meeting criteria for T1D. Six of 70 (8.6%) patients were lost to follow-up, 3/70 (4.3%) withdrew consent prior to randomization, 2/70 (2.9%) failed screening secondary to chronic steroid use, 1/70 (1.4%) had a T1D autoantibody count not meeting criteria, and 1/70 (1.4%) had lymphopenia.

Table 7. TN-10 Analysis Sets (All Screened Patients)

Analysis Set	Teplizumab	Placebo	Total
All screened, N			146
Screen failure, N			70
All randomized patients, N	44	32	76
Intent-to-treat population, n (%)	44 (100)	32 (100)	76 (100)

Source: FDA Statistical Reviewer

Reviewer comment: Despite 1:1 randomization, there was a notable imbalance in the number of patients randomized to each treatment group. The Applicant postulates that with stratified randomization, although near balance was reached within strata, imbalance for the total trial occurred due to chance. This imbalance did not affect the interpretation of the trial integrity or efficacy endpoint.

[Table 8](#) summarizes treatment completion status and study completion status. Three patients discontinued study treatment during the 14-day treatment course: one (2.3%) from the teplizumab group, and two (6.3%) from the placebo group. The reason for treatment discontinuation was *protocol specified drug withholding* for all three patients. To prevent missing data, these patients were followed up in the same fashion as patients who completed treatment.

As prespecified in the SAP, the clinical cutoff of the study occurred when at least 40 patients were diagnosed with T1D. At that time, patients who had experienced T1D diagnoses had “completed study.” Study completion status for the 30 patients who were still T1D-free and continued to be followed-up was categorized as “ongoing.” Six patients discontinued the study before the clinical cutoff: 3 were diagnosed with T1D, and 3 were censored at their last contact date.

Table 8. TN-10 Patient Disposition

Characteristic	Teplizumab N=44 n (%)	Placebo N=32 n (%)	Total N=76 n (%)
<i>Treatment completion status</i>			
Completed	43 (97.7)	30 (93.8)	73 (96.1)
Discontinued	1 (2.3)	2 (6.3)	3 (3.9)
Reason for discontinuation of treatment			
Protocol specified drug withholding	1 (2.3)	2 (6.3)	3 (3.9)
<i>Study completion status</i>			
Completed study	19 (43.2)	21 (65.6)	40 (52.6)
Ongoing: Follow-up still ongoing at cutoff date	22 (50.0)	8 (25.0)	30 (39.5)
Discontinued from the study	3 (6.8)	3 (9.4)	6 (7.9)
Reason for discontinuation from study			
Discontinued and had T1D onset time recorded			
Onset of diabetes	0	2 (6.3)	2 (2.6)
Patient chose to no longer participate	1 (2.3)	0	1 (1.3)
Discontinued with missing T1D onset time censored at last contact date			
Lost to follow-up	0	1 (3.1)	1 (1.3)
Participant's decision	2 (4.5)	0	2 (2.6)

Source: FDA Statistical Reviewer
Abbreviations: T1D, type 1 diabetes

6.1.2.2 Protocol Violations/Deviations

There was a single diagnosis of T1D in the teplizumab treated group in a patient who did not complete the confirmatory OGTT following clinical alert. The patient met criteria for diagnosis of T1D by initial OGTT but upon date of confirmation OGTT, there was failure to obtain IV access. The notes state that the investigator did not want to put the participant through an additional OGTT for the purpose of confirming a new diagnosis of T1D. On review of additional records, this patient was not reported to initiate insulin therapy until approximately 20 months

after the initial critical OGTT date. Because the date of T1D diagnosis was reported as the date of the initial OGTT, this protocol violation may have biased the results in favor of placebo.

6.1.2.3 Demographic Characteristics

The mean age of TN-10 patients was 19 years, more patients were male (55%) and the majority were White (97%) and from the US (95%). Almost 75% of randomized patients were younger than 18 years of age. FDA further grouped the population by age, with results presented below. Treatment groups were balanced for sex, race, and country.

Table 9. Demographic Characteristics for Patients in TN-10

Characteristic	Teplizumab N=44	Placebo N=32	Total N=76
Age, years			
Mean (SD)	19 (12)	18 (11)	19 (12)
Median (min, max)	14 (9, 49)	13 (9, 45)	14 (9, 49)
Age group/strata, n (%)			
≥18	15 (34.1)	6 (18.8)	21 (27.6)
<18	29 (65.9)	26 (81.3)	55 (72.4)
<18 OGTT confirmed	24 (54.5)	23 (71.9)	47 (61.8)
<18 OGTT not confirmed	5 (11.4)	3 (9.4)	8 (10.5)
Age quartiles to support age subgroup analysis, n (%)			
Pediatrics 1: 8.5 to 11.2 years	10 (22.7)	8 (25.0)	18 (23.7)
Pediatrics 2: 11.3 to 13.8 years	10 (22.7)	9 (28.1)	19 (25.0)
Pediatrics 3: 13.9 to 17.4 years	9 (20.5)	9 (28.1)	18 (23.7)
Adults: 19.4 to 49.5 years	15 (34.1)	6 (18.8)	21 (27.6)
Sex, n (%)			
Female	19 (43.2)	15 (46.9)	34 (44.7)
Male	25 (56.8)	17 (53.1)	42 (55.3)
Race, n (%)			
Asian	0	1 (3.1)	1 (1.3)
Multiple	0	1 (3.1)	1 (1.3)
White	44 (100)	30 (93.8)	74 (97.4)
Country, n (%)			
US	41 (93.2)	31 (96.9)	72 (94.7)
Ex-US ¹	3 (6.8)	1 (3.1)	4 (2.6)

Source: FDA Statistical Reviewer

Abbreviations: ITT, intent-to-treat; OGTT, oral glucose tolerance test; SD, standard deviation

¹ Ex-US includes Germany and Canada

Reviewer comment: There is an inverse association between age and onset of T1D, and disease incidence peaks in childhood between 10 to 14 years of age (Maahs et al. 2010). This association has been shown in several cohorts of individuals at risk of T1D (Ziegler et al. 2013; Steck et al. 2015; Gorus et al. 2017), including stage 1 and 2 T1D (Jacobsen et al. 2020). It is unclear whether age impacts the risk of progression to T1D once metabolic disturbances (such as the dysglycemia seen in stage 2 T1D) are present.

The observed baseline age imbalance between teplizumab and placebo groups may bias the results in favor of teplizumab because the expected rate of progression to T1D would be slower in adults than in children; however, the primary analysis model included age as a covariate.

Most of the enrolled patients were from the US and for the most part, the demographic characteristics of the enrolled patients are representative of US patients at risk for T1D. A possible exception is the near 100% White racial distribution. Although T1D occurs predominately in White patients, a non-negligible percentage occur in non-White patients and in patients of Hispanic ethnicity. These demographics are not represented in the trial.

6.1.2.4 Other Important Baseline Characteristics

BMI and T1D-Related Disease Characteristics

The following additional factors have been identified in the literature to have a potentially modulating effect on the risk of progression to T1D in at-risk individuals: BMI z-score, presence or absence of high-risk genes, i.e., the human leukocyte antigen (HLA) genes, and islet autoantibody number and type. There are some baseline imbalances in these factors, likely related to small study size.

Notably, on average, these additional baseline characteristics appear representative of the U.S. population of at-risk T1D patients.

Table 10. TN-10 Additional Baseline Characteristics

Parameter	Teplizumab N=44	Placebo N=32	Total N=76
BMI, kg/m ²			
Mean (SD)	21.9 (6.4)	22.1 (4.4)	22.0 (5.6)
Median (min, max)	20 (15, 44)	22 (16, 35)	21 (15, 44)
BMI Z-score group, n (%)			
Group 1: Patients <20 yrs and BMI Z-score (-2.9, -0.1)	17 (38.6)	2 (6.3)	19 (25.0)
Group 2: Patients <20 yrs and BMI Z-score (-0.1, -0.8)	5 (11.4)	15 (46.9)	20 (26.3)
Group 3: Patients <20 yrs and BMI Z-score (0.9, 2.0)	9 (20.5)	9 (28.1)	18 (23.7)
Group 4: Patients ≥20 yrs	13 (29.5)	6 (18.8)	19 (25.0)
HLA-DR4, n (%)			
DR4 information missing	2 (4.5)	0	2 (2.6)
Absent	15 (34.1)	11 (34.4)	26 (34.2)
Present	27 (61.4)	21 (65.6)	48 (63.2)
HLA-DR3, n (%)			
DR3 information missing	2 (4.5)	0	2 (2.6)
Absent	21 (47.7)	17 (53.1)	38 (50.0)
Present	21 (47.7)	15 (46.9)	36 (47.4)

Parameter	Teplizumab N=44	Placebo N=32	Total N=76
HLA-DR3/DR4, n (%)			
Both DR3 and DR4	11 (25.0)	7 (21.9)	18 (23.7)
DR3 only	10 (22.7)	8 (25.0)	18 (23.7)
DR4 only	16 (36.4)	14 (43.8)	30 (39.5)
Missing	2 (4.5)	0	2 (2.6)
Neither DR3 or DR4	5 (11.4)	3 (9.4)	8 (10.5)
Auto-antibodies positive (N), n (%)			
1*	1 (2.3)	0	1 (1.3)
2	12 (27.3)	7 (21.9)	19 (25.0)
3	11 (25.0)	5 (15.6)	16 (21.1)
4	12 (27.3)	14 (43.8)	26 (34.2)
5	8 (18.2)	6 (18.8)	14 (18.4)

Source: FDA statistical reviewer

Abbreviations: BMI, body mass index; HLA, human leukocyte antigen; ITT, intent-to-treat; SD, standard deviation

* A single patient was enrolled with 1 autoantibody detected, but the titer for the second autoantibody was borderline between positive and negative. This subject was permitted to enroll in the study at the Investigator's discretion.

Body Mass Index Z-Score

Body mass index (BMI) z-score is used in children to control for the effects of age, height, and sex on BMI. Whereas BMI was mostly balanced across groups, for patients younger than 20 years of age, the BMI-for-age z-score (BMI-z), was lower at baseline amongst patients treated with teplizumab. There is some evidence that higher BMI-z predicts more rapid T1D onset (Barker et al. 2007; Viner et al. 2008; Ferrara et al. 2017). Therefore, the lower BMI-z at baseline among teplizumab patients may favor teplizumab. Similar to age, however, it is unclear whether BMI-z affects the risk of progression to T1D in multiple-antibody-positive individuals once metabolic disturbances are present.

Human Leukocyte Antigen (HLA) Subtypes

As discussed in Section 2.1, HLA class II genes, responsible for presentation of antigens to the immune system, account for approximately half of the genetic susceptibility of T1D risk. In the TN-10 study, the presence or absence of DR4 and DR3 were balanced between treatment groups. In addition, the combinations of these genotypes, displayed in the second part of Table 10, were balanced between groups, with some variation likely due to the small study size.

Number of Positive Autoantibodies

The relationship between autoantibody status and disease progression was discussed in Section 2.1. Because of its potential prognostic effect on the clinical outcome, the number of baseline positive autoantibodies was summarized by treatment arm. There was a baseline imbalance in treatment allocation across different numbers of positive autoantibodies. Teplizumab-treated patients had a lower number of islet autoantibodies (mean 3.3, median 3 autoantibodies) than placebo patients (mean 3.6, median 4 autoantibodies). This difference is also demonstrated by a lower proportion of patients with 4 or 5 islet autoantibodies at randomization in the

teplizumab arm (20/44 [45.5%]) compared with (20/32 [62.5%]) in the placebo arm. Overall, there were more teplizumab patients who had 2 or 3 autoantibodies at baseline and fewer teplizumab patients who had 4 or more at baseline. This difference may favor teplizumab if the expected rate of conversion to clinical T1D is slower in the group with fewer positive autoantibodies at baseline.

Reviewer comment: Given the small size of the TN-10 study, baseline imbalances in important disease characteristics are not unexpected. Additional sensitivity analyses conducted by the FDA statistical reviewer to address these imbalances supported the validity of the primary analysis; these are presented in Section 6.1.2.6.

Baseline Glycemic Status and C-peptide Concentrations

The diagnosis of T1D is a dichotomous (yes/no) outcome but is based on a progression of worsening glycemic status and decreasing C-peptide. The Applicant's assessment of baseline glycemic status and C-peptide concentrations demonstrates that the treatment groups were balanced at baseline with respect to these factors ([Table 11](#)).

Table 11. T1D-Related Clinical Characteristics at Baseline for TN-10

Characteristic	Placebo N=32	Teplizumab N=44	Total N=76
Glucose, mg/dL			
Mean (SD)	155.3 (22.9)	162.5 (22.3)	159.5 (22.7)
Median (min, max)	154.4 (103, 200)	164.6 (115, 207)	160.4 (103, 200)
C-peptide AUC in OGTT, nmol/L			
Mean (SD)	1.89 (0.72)	1.98 (0.85)	1.94 (0.79)
Median (min, max)	1.73 (0.7, 3.8)	1.77 (0.6, 4.4)	1.76 (0.6, 4.4)
HbA1c, %			
Mean (SD)	5.21 (0.26)	5.16 (0.33)	5.18 (0.31)
Median (min, max)	5.3 (4.3, 5.6)	5.2 (4.6, 6.1)	5.2 (4.3, 6.1)

Source: Sponsor's TN-10 CSR

Abbreviations: AUC, area under the curve; CSR, clinical study report; HbA1c, hemoglobin A1c; ITT, intent to treat; OGTT, oral glucose tolerance test; SD, standard deviation; T1D, type 1 diabetes

6.1.2.5 Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Teplizumab is administered for a 14-day course by health care professionals. No difference in compliance was observed. Rescue medication is not relevant to this product. Concomitant medications to treat symptoms of cytokine release syndrome are not expected to affect the efficacy results.

6.1.2.6 Efficacy Results - Primary Endpoint

Please see Dr. Wang’s statistical review for additional information about the efficacy results. Dr. Wang recommends approval of this BLA.

Forty-three patients met the primary endpoint (T1D diagnosis) prior to the study cutoff date. The majority, 79% (34/43) of patients met criteria for T1D diagnosis by two consecutive OGTTs, representing 70% (14/20) of the T1D diagnoses in the teplizumab-treated group and 87% (20/23) of the diagnoses in the placebo group.

The median time to clinical T1D diagnosis was 49.5 months in the teplizumab group (95% CI: 32.1, NE [not estimable]) compared with 24.9 months in the placebo group (95% CI: 9.5, 48.6). The upper 95% confidence interval for the median time to T1D diagnosis analysis was not estimable because of the sample size, and the amount and distribution of censored data. A Cox proportional hazards (PH) model was used to analyze the time to T1D diagnosis, stratified by age and OGTT status at randomization. The results of the primary efficacy endpoint analysis are presented in [Table 12](#). The hazard ratio for the time to clinical T1D diagnosis was 0.41 (95% CI: 0.22 to 0.78) (p=0.0066). TN-10 demonstrated a delay in the onset of stage 3 T1D by a median of 2 years.

Table 12. Primary Efficacy Endpoint Analysis Results for TN-10

Parameter	Placebo N=32	Teplizumab N=44	Total N=76
Event numbers, n (%)			
Number of patients diagnosed with T1D	23 (72%)	20 (45%)	43 (57%)
Number of censored patients	9 (28%)	24 (55%)	33 (43%)
Censored due to reaching trial end ¹	8 (25%)	22 (50%)	30 (39%)
Censored due to discontinuation from study ²	1 (3%)	2 (5%)	3 (4%)
Time to event summary statistics			
Median time to T1D diagnosis, months	24.9	49.5	42.6
95% CI	(9.5, 48.6)	(32.1, NE)	(25.9, 55.2)
Primary analysis			
Hazard ratio (95% CI)			0.41 (0.22, 0.78)
P-value			0.0066

Source: FDA statistical reviewer.

Abbreviations: CI, confidence intervals; NE, not estimable; T1D, type 1 diabetes

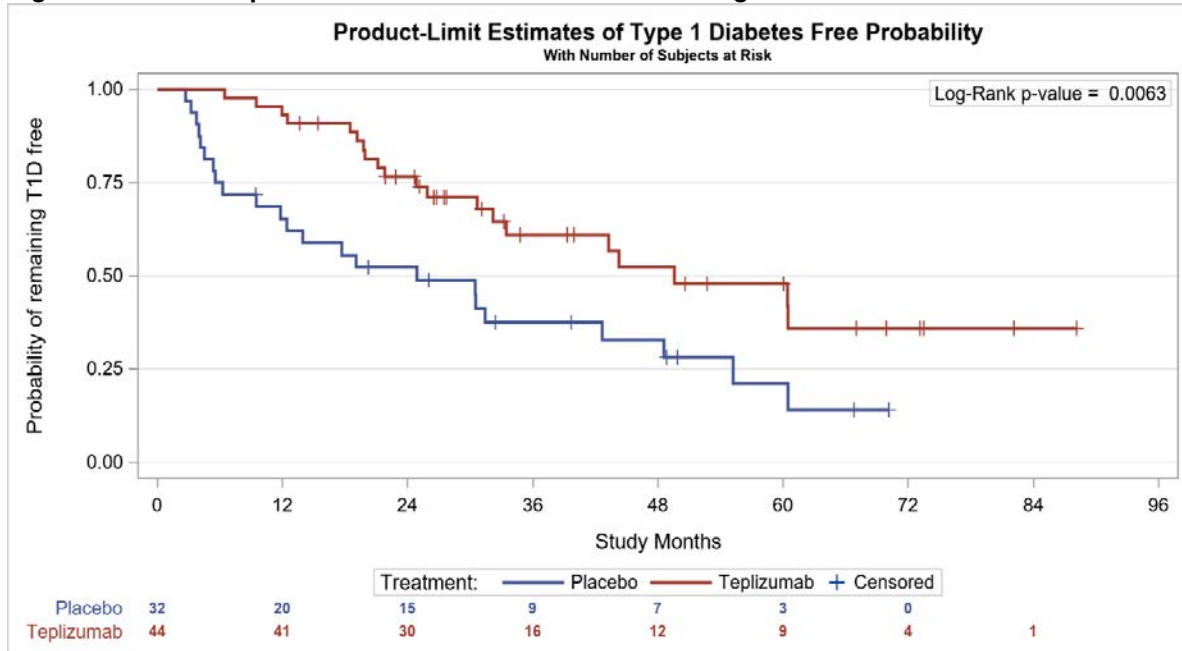
¹ Follow-up still ongoing at cutoff date

² For reasons other than T1D diagnosis

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The Kaplan-Meier (KM) plot was used to show the proportion of patients free of T1D by time since randomization ([Figure 6](#)).

Figure 6. TN-10: Kaplan-Meier Curves for Time to T1D Diagnosis



Source: FDA statistical reviewer
Abbreviations: T1D, type 1 diabetes

As the trial ended when 43 patients were diagnosed with T1D, the lengths of follow-up varied among patients, ranging from 9 months to 88 months. The median follow-up time was similar between the two treatment arms (50.6 months). The curves diverge in favor of teplizumab and the difference in T1D-free probability is greatest at 18 months and becomes smaller after that time. The two curves remain essentially parallel for the remainder of follow-up.

Sensitivity Analyses

Sensitivity Analyses for Baseline Imbalances

To address the concern that the imbalance at allocation between treatment groups in autoantibody count at randomization, which has a prognostic potential, may have impacted the results in favor of teplizumab, the FDA statistical reviewer performed an adjusted analysis by adding autoantibody count at randomization into the primary analysis model as a stratification factor. The adjusted analysis estimates the effect of teplizumab after adjusting for the covariate of antibody number at baseline. The hazard ratio from this analysis, 0.44 (95% CI: 0.22 to 0.87, $p=0.0175$), shown in [Table 13](#), is numerically higher than what was estimated in the primary analysis, but still statistically significant.

Similarly, the FDA statistical reviewer carried out an adjusted analysis by adding BMI at baseline into the primary analysis model as a stratification factor. The hazard ratio, 0.41 (95% CI: 0.21 to 0.78, p=0.006) as shown in [Table 13](#), was similar to what was estimated in the primary analysis, suggesting that BMI did not have a modulating effect on the efficacy outcome.

The FDA statistical reviewer performed an additional analysis by adjusting for both baseline positive autoantibody count and baseline BMI. The resulting hazard ratio was 0.42 (95% CI: 0.21 to 0.84, p=0.0136).

Because the primary analysis model included adjustment for age as a continuous variable as well as age strata (age greater or less than 18), the statistical reviewer did not perform an additional sensitivity analysis for baseline differences in age.

Table 13. TN-10. Primary Efficacy Endpoint Sensitivity Analysis for Impact of Imbalances in Prognostic Factors at Randomization (ITT Population)

FDA Reviewer's Analysis	
Sensitivity analysis for assessing the impact of imbalances in baseline positive autoantibody counts	
Hazard ratio (95% CI)	0.44 (0.22, 0.87)
Nominal p-value	0.0176
Sensitivity analysis for assessing the impact of imbalances in baseline BMI	
Hazard ratio (95% CI)	0.41 (0.21, 0.78)
Nominal p-value	0.0064
Sensitivity analysis for assessing the impact of both imbalance in baseline positive autoantibody counts and imbalance in baseline BMI	
Hazard ratio (95% CI)	0.42 (0.21, 0.84)
Nominal p-value	0.0137

Source: FDA statistical reviewer

Abbreviations: BMI, body mass index; CI, confidence interval; ITT, intent-to-treat

Sensitivity Analyses for Handling of Missing Data

In TN-10, the amount of missing data was small. At the clinical cutoff, 43 subjects were known to have had T1D onset, 30 patients were T1D-free, and 3 patients (2 in teplizumab and 1 in placebo group) had missing T1D status due to early discontinuation from the study. Three pre-planned sensitivity analyses and one FDA-performed sensitivity analysis with differing methods for imputing missing data ([Table 14](#)) produced similar results compared with the primary analysis. The statistical FDA reviewer also examined primary endpoint results by study site for the seven sites with the highest enrollment and found no concerns.

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Table 14. TN-10: Primary Efficacy Endpoint Sensitivity Analysis for Impact of Missing Data

Applicant's Pre-planned Sensitivity Analyses (SA)	
SA1: Set TTE to 1 year for placebo patients whose TTE <1 year	
Hazard ratio (95% CI)	0.43 (0.22, 0.81)
Nominal P-value	0.0089
Delay in Median (Months)	49.5-24.9=24.6
SA2: Set TTE to last evaluation for early dropouts who were T1D-free	
Hazard ratio (95% CI)	0.42 (0.22, 0.78)
Nominal P-value	0.0065
Delay in Median (Months)	44.3-22.0=22.3
SA3: A combination of SA1 and SA2	
Hazard ratio (95% CI)	0.43 (0.23, 0.81)
Nominal P-value	0.0086
Delay in Median (Months)	44.3-22.0=22.3
FDA Reviewer's Sensitivity Analysis	
SA4: Set TTE to last evaluation only for early teplizumab dropouts who were T1D-free	
Hazard ratio (95% CI)	0.44 (0.24, 0.83)
Nominal P-value	0.0113
Delay in Median (Months)	44.3-24.9=19.4

Source: FDA statistical reviewer.

Abbreviations: CI, confidence intervals; T1D, Type 1 diabetes; TTE, time to event.

Exploratory Analysis of Baseline T1D Progression Risk in Placebo Patients Compared to Natural History Experience

The natural history of the development of T1D has a predictable progression. Therefore, to further enhance confidence in the results of TN-10 we descriptively compared the rate of progression in the placebo arm of TN-10 to what would be expected in untreated individuals at a similar disease stage based on natural history studies.

The risk of progression to T1D observed in the placebo arm of the TN-10 trial was 25% at 6 months, 47% at 2 years, and 69% at 5 years, values that were comparable to data observed in natural history studies; to the extent they differed, progression tended to be more rapid in the natural history studies: 40% at 6 months, 60% at 2 years, and 75% at 4 to 5 years (Sosenko et al. 2009; Krischer 2013; Insel et al. 2015). In contrast, the risk of developing T1D in the teplizumab arm differed greatly, with a 6-month, 2-year, and 5-year risks of 0%, 23%, and 41%, respectively.

Data Quality and Integrity

Data quality and integrity were determined to be acceptable. There were several additional analyses conducted by FDA to address data quality including auditing of primary endpoint assessments, traceability assessments, and cross-validation of the submitted documents using the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets, performed by the statistical reviewer.

There were no integrity concerns or financial conflicts of interest.

Investigations into Primary Endpoint Ascertainment

TN-10 is notably a small trial. This section discusses additional information that provided confidence in the primary endpoint ascertainment.

First, we verified that there was not a delay between screening (qualifying OGTT) visit and randomization visit, as a difference between treatment arms in time to randomization from screening could bias results. There was a similar mean (32 teplizumab vs. 33 placebo) and median (34 teplizumab vs. 33 placebo) number of days between last screening OGTT and randomization visit, with similar standard deviations (11.7 days).

Next, we confirmed that all T1D diagnoses that were based on OGTT were traced back to OGTT results that confirmed the diagnosis, and that there were no missed OGTT tests that met the diagnostic criteria, but were not counted as T1D events. We also reviewed individual records (patient profiles) for both triggering and confirmatory events for the 10/44 (22.7%) patients for whom the primary endpoint was not determined by OGTT on both instances. Of these patients, 7 had either their triggering or confirmatory event determined by OGTT. Two diagnoses were adjudicated by a committee masked to treatment assignment. On FDA audit of the two patients requiring adjudication, the determinations were considered sufficient. In all but one patient, T1D onset was evident by initiation of insulin therapy or HbA1c >7%. The one patient who was marked as meeting the primary endpoint without clear evidence of disease onset was in the teplizumab arm and was reviewed as a protocol deviation in Section [6.1.2.2](#).

Additionally, we considered that a differential lag-time between treatment groups in scheduling and conducting the confirmatory test could bias the results. The mean number of days between the triggering event and confirmation event was similar between teplizumab-treated patients (30 days, standard deviation [SD] +/- 22, with range of 8 to 85 days) and placebo (32 days, SD +/- 39, with range of 1-169 days), although the median reflected a shorter time delay between the initial and confirmatory OGTT events for placebo group (15 days) vs. teplizumab (25 days).

Table 15. Time Delay in Days Between Initial and Confirmatory OGTT Events Diagnostic of T1D in TN-10 by Treatment Arm

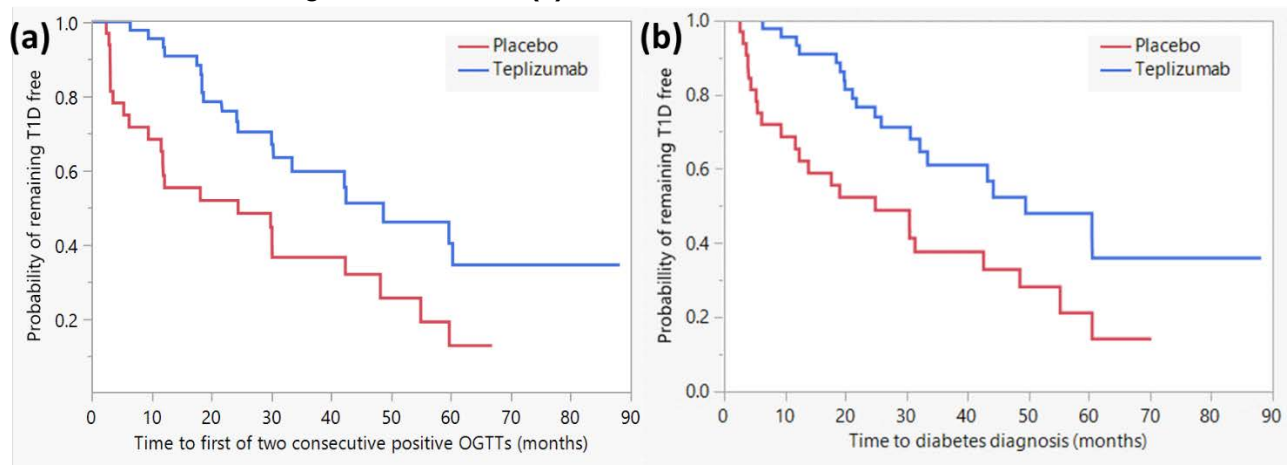
Parameter	Placebo N=23	Teplizumab N=19
Time of delay between events, days		
Mean	31.9	30.3
Median	15	25
Min	1	8
Max	169	85
SD	38.8	21.7

Source: FDA Clinical Reviewer

Abbreviations: OGTT, oral glucose tolerance test; SD, standard deviation; T1D, type 1 diabetes

We further explored this issue by noting that the majority of patients had their first event meeting diagnostic criteria occur at a scheduled visit (80% teplizumab-treated, vs. 91% placebo), while confirmatory events predominantly occurred on unscheduled visits in both arms: 90% teplizumab vs. 87% placebo. This finding may explain the lack of a 'step' pattern in the K-M curve shown in [Figure 6](#). Notably, the K-M analysis for time to the first of two consecutive positive OGTTs ([Table 7a](#)) is similar to the primary K-M ([Table 7b](#), and [Figure 6](#)), albeit with a more defined stepwise pattern likely related to the reporting of events at regularly scheduled protocol assessments. Thus, there is no evidence of bias due to differential confirmatory test lag-time between treatment groups.

Figure 7. K-M Curve Analysis of Time to First of Two Consecutive Positive OGTTs in Months (a) and Time to Diabetes Diagnosis in Months (b)



Source: FDA Clinical Reviewer generated from ADTTE.xpt
Abbreviations: KM, Kaplan-Meier; OGTT, oral glucose tolerance test; T1D, type 1 diabetes

Finally, the FDA clinical reviewer examined OGTT data to confirm that no TN-10 patients without onset of T1D by the end of the study met criteria for T1D before the study cutoff date.

Effects in Subpopulations

This section presents demographic subgroup analyses of TN-10 (age, sex, race/ethnicity) that are required by regulation. These data are then followed by effects in other subgroups of interest (based on disease characteristics).

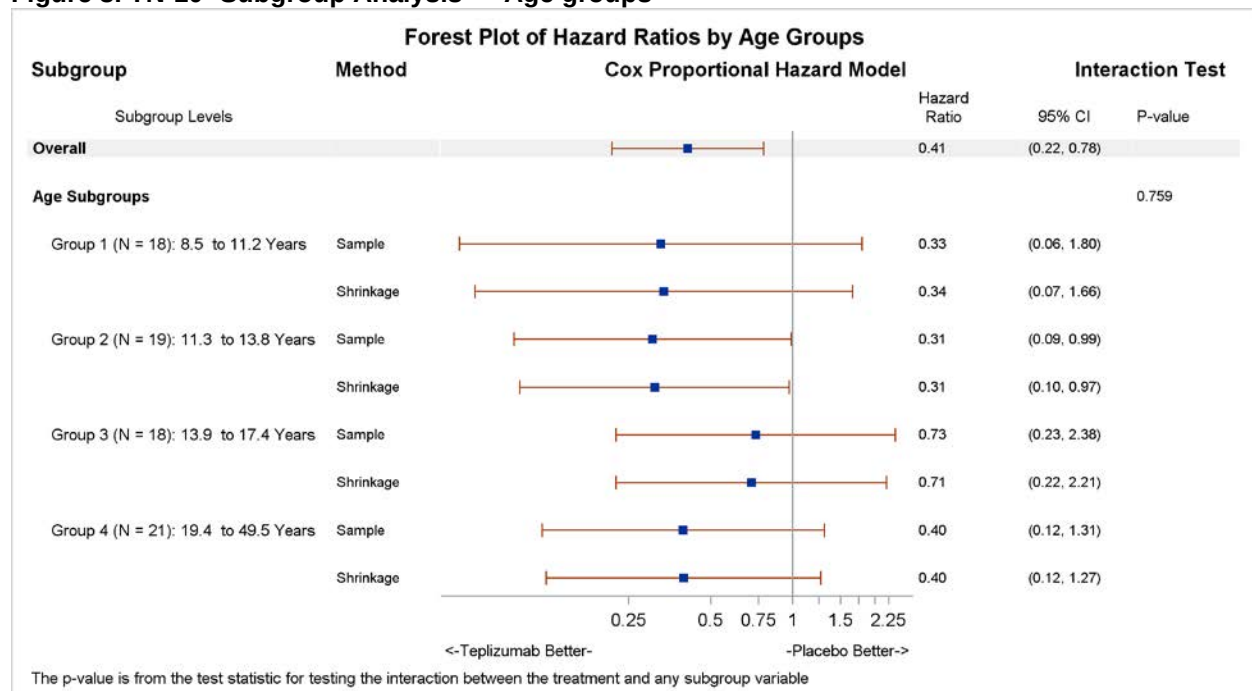
There were only two patients whose race was not White and four patients who participated at sites outside the US, hence subgroup analyses on race and geographical region were not carried out.

Pediatric patients (8 to 17 years of age) made up the majority (72%) of the TN-10 population. Therefore, we further divided the pediatric patient population into three groups using tertiles

of the study pediatric population age distribution (see [Figure 8](#) for patient counts and distributions among the groups).

In [Figure 8](#), for the overall population and each of the four age subgroups, the estimated hazard ratio of T1D onset and its 95% CI are plotted. All subgroup CIs have substantial overlap with the overall point estimate and indicate a consistency of findings across subgroups. No significant interaction was found between treatment and age subgroups at the 5% level (interaction test, $p=0.76$).

Figure 8. TN-10- Subgroup Analysis — Age groups

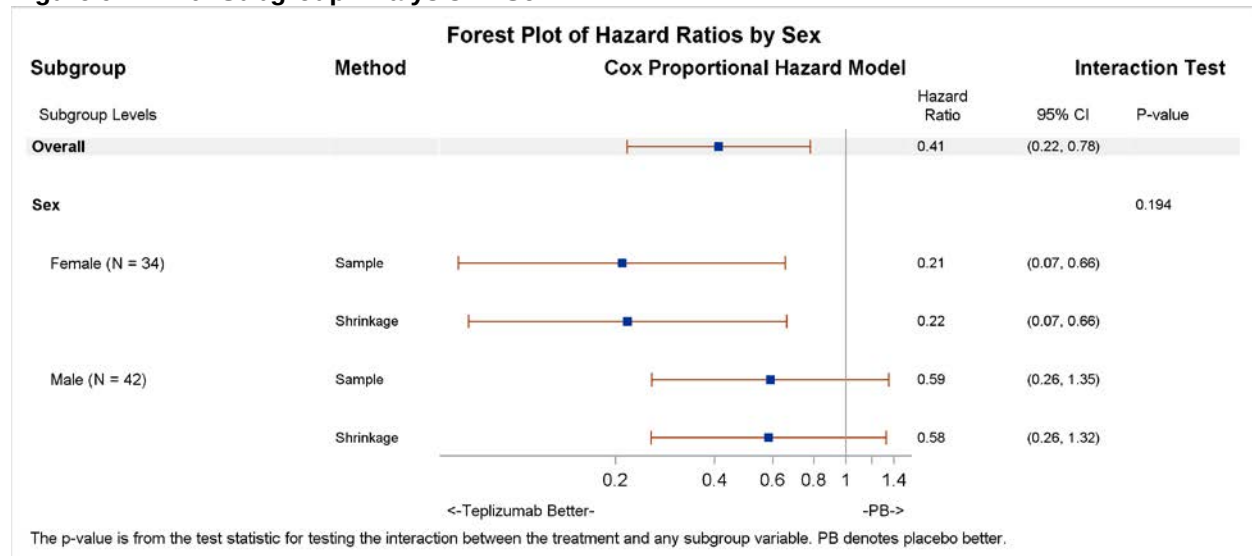


Source: FDA statistical reviewer
Abbreviations: CI, confidence interval

The statistical reviewer also performed a running group subgroup analysis to further investigate if the treatment effect of teplizumab (HR) was modulated by patient age. For this analysis, which broke TN-10 pooled study arms into 57 groups by age (with group 1 with the 20 youngest vs. group 57 with the oldest 20 patients), there was no clear directionality (data not shown).

[Figure 9](#) shows the subgroup analysis of treatment effect by sex. Although there was a trend for females experiencing greater treatment benefit than males, there was no significant interaction was found between treatment and sex at the 5% level (interaction test, $p=0.24$), indicating efficacy in both males and females.

Figure 9. TN-10: Subgroup Analysis — Sex



Source: FDA statistical reviewer
Abbreviations: CI, confidence interval, PB, placebo

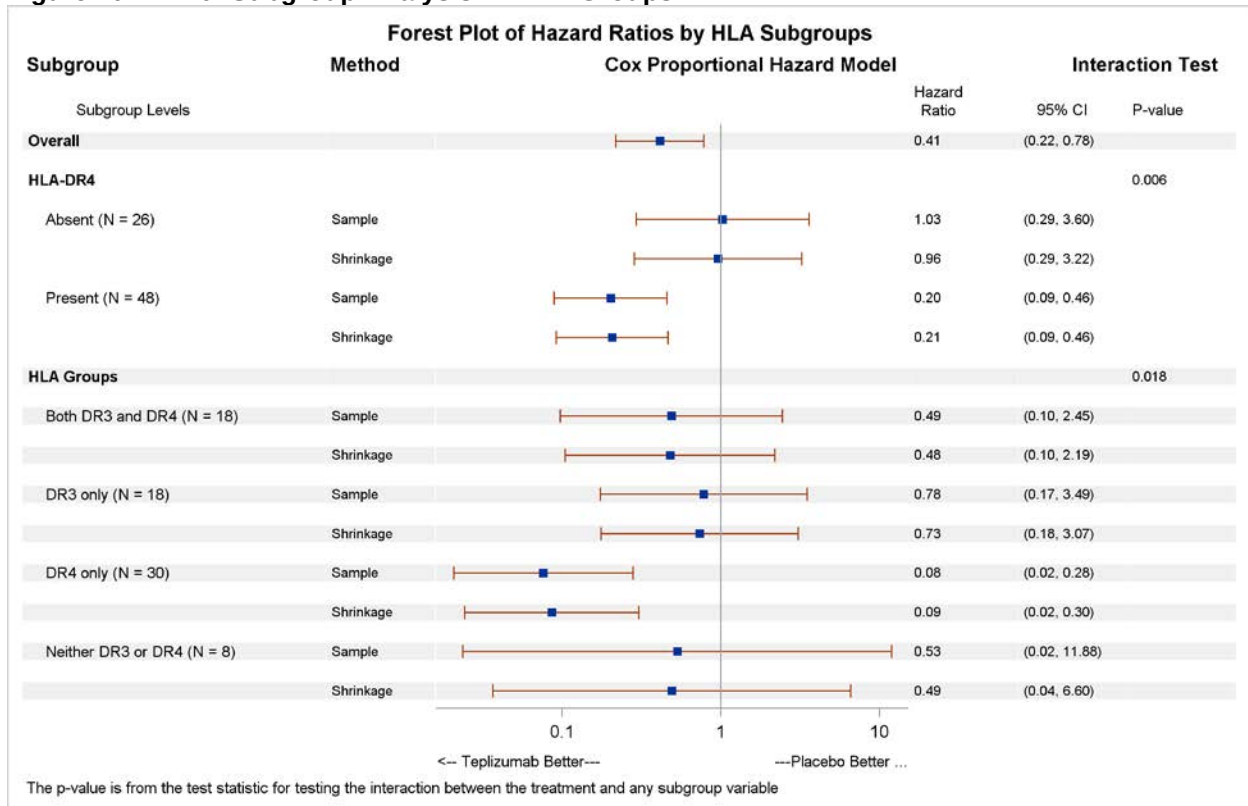
Effects in Other Subgroups

The presence or absence of specific human leukocyte antigen (HLA) gene type, islet autoantibody number, and BMI z-score were determined to be subgroups of interest.

In the FDA subgroup analysis by HLA DR4, presence of HLA-DR4 was associated with a greater treatment effect (HR=0.2, 95% [0.09, 0.46], interaction test p-value = 0.006). This was also shown in the Applicant's analysis. The FDA statistical reviewer concluded that although the by-sample analysis is indicative of no treatment benefit in HLA-DR4-absent patients (HR=1.03, 95% [0.29, 3.6]), the shrinkage analysis showed that treatment benefit is established. In FDA's additional subgroup analysis of HLA type groupings, the p-value (0.018) was numerically significant for interaction test, indicating some quantitative differences in treatment effects across the HLA subgroups. However, it is important to note that absence of evidence of treatment effect in HLA DR4 absent TN-10 patients is not evidence of absence, especially in a study this small. The treatment effects for subjects with and without HLA DR3 were similar.

Reviewer comment: The HLA subgroup analyses were performed post hoc with very small subject numbers, and therefore the conclusions that can be drawn from these analyses are limited. However, this information may be useful for assessing the benefit/risk for an individual patient if HLA genotype information is available.

Figure 10. TN-10: Subgroup Analysis — HLA-Groups

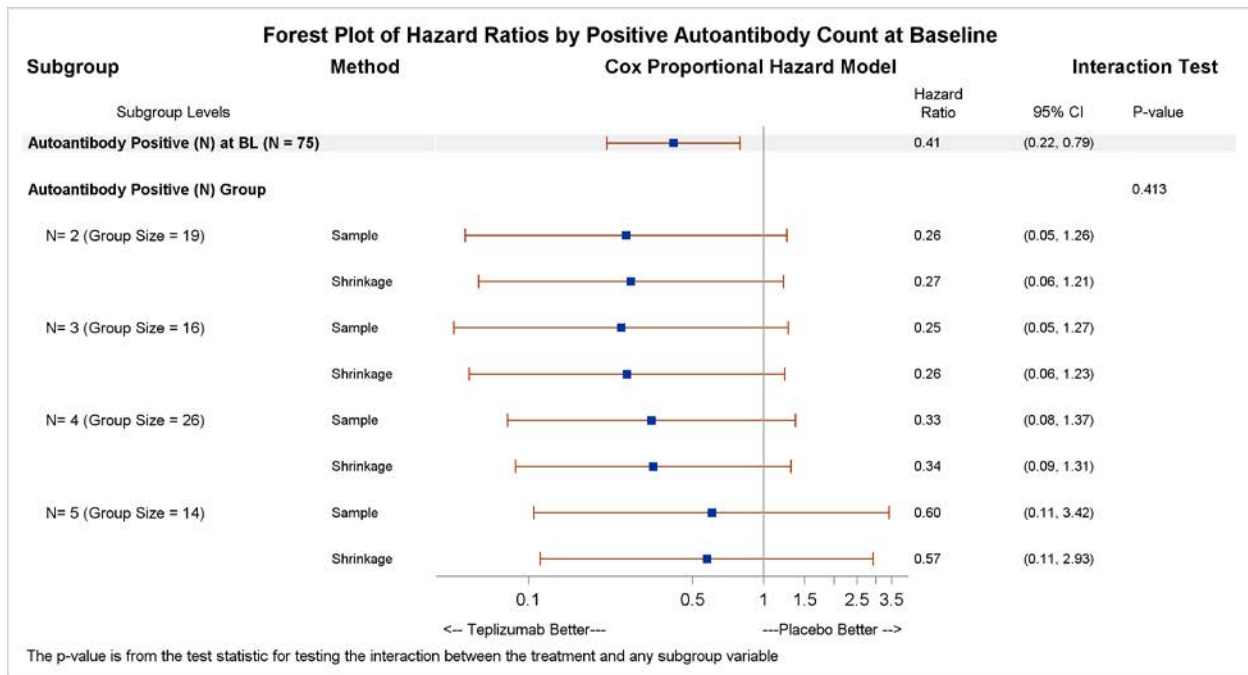


Source: FDA statistical reviewer

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen

Treatment effect by positive autoantibody count at baseline shows a trend for larger effect sizes with fewer positive autoantibodies at baseline ([Figure 11](#)). The confidence intervals, however, overlap, and the p-value for the interaction test was insignificant.

Figure 11. TN-10: Subgroup Analysis — Baseline Autoantibody Positive Count

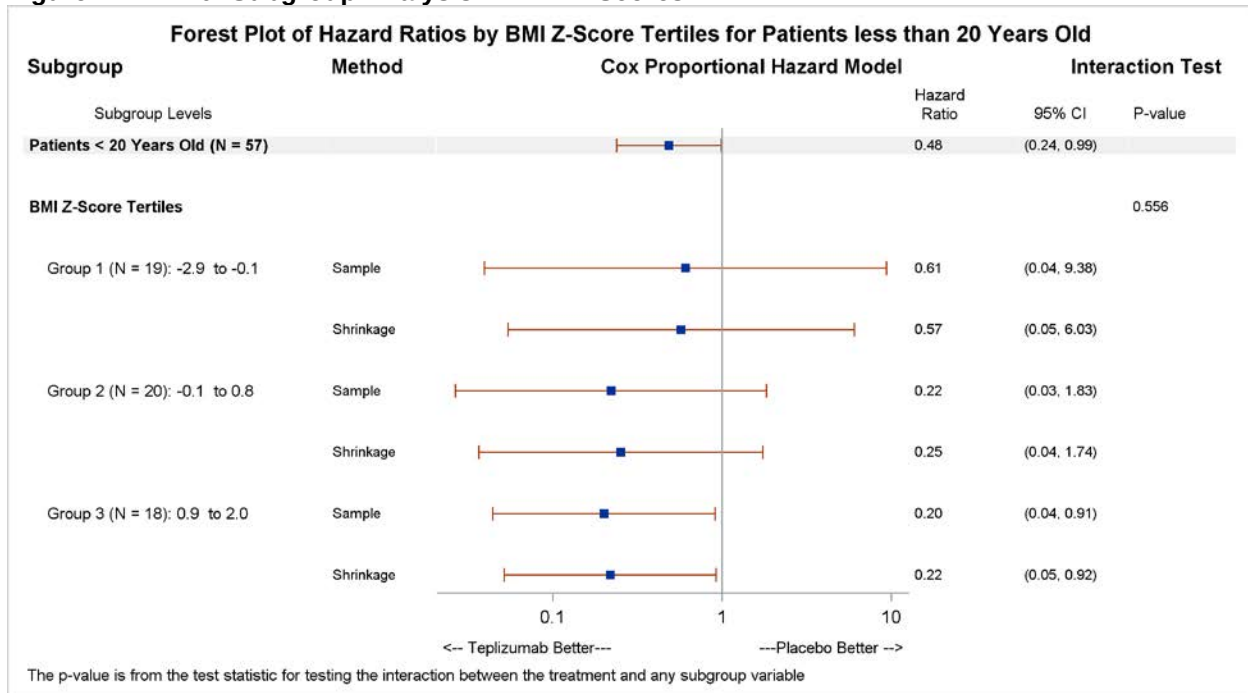


Source: FDA statistical reviewer

Abbreviations: BL, baseline; CI, confidence interval

As described in Section [6.1.2.4](#), patients under age 20 were divided into tertiles and a BMI z-score was derived for each patient. [Figure 12](#) shows a trend that larger effect size is associated with higher BMI z-scores. No significant interaction was found, however, between treatment and BMI z-score subgroups at the 5% level (interaction test p-value = 0.48).

Figure 12. TN-10: Subgroup Analysis — BMI Z-Scores



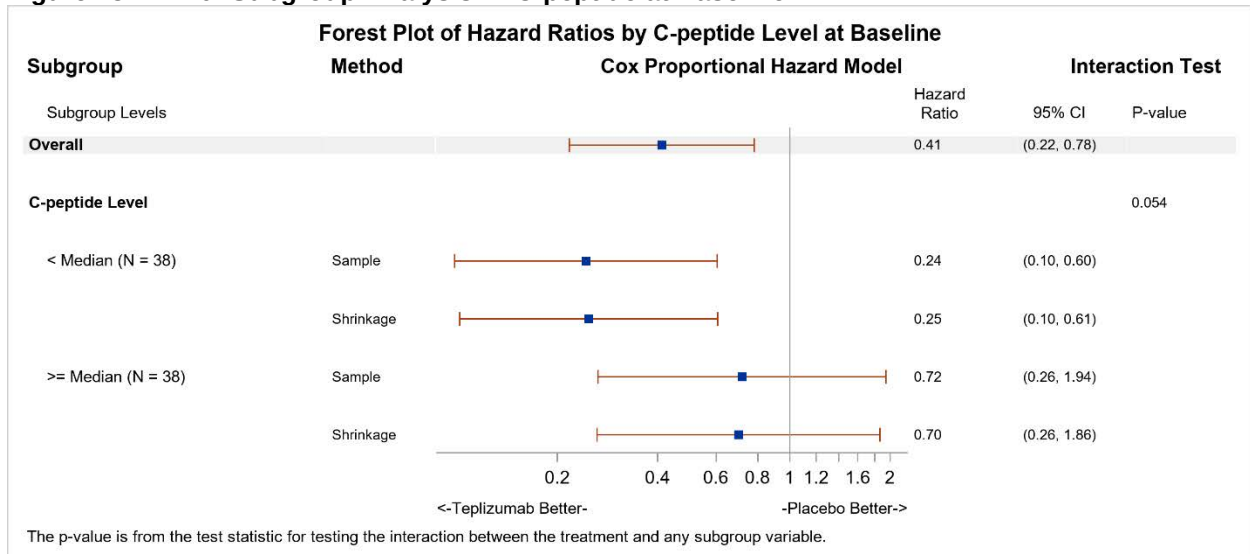
Source: FDA statistical reviewer

Abbreviations: BMI (body mass index); CI, confidence interval

Reviewer comment: The additional subgroup analyses performed by the FDA statistical reviewer demonstrated that there is lack of evidence that treatment effects differ across different BMI-z and positive autoantibody count at baseline, demonstrating that the baseline imbalances in these characteristics did not change the primary analysis conclusion.

An analysis by baseline C-peptide (<median; ≥median) suggested a stronger treatment effect in those with lower C-peptide at baseline but confirmed efficacy in both subgroups.

Figure 13. TN-10: Subgroup Analysis — C-peptide at Baseline

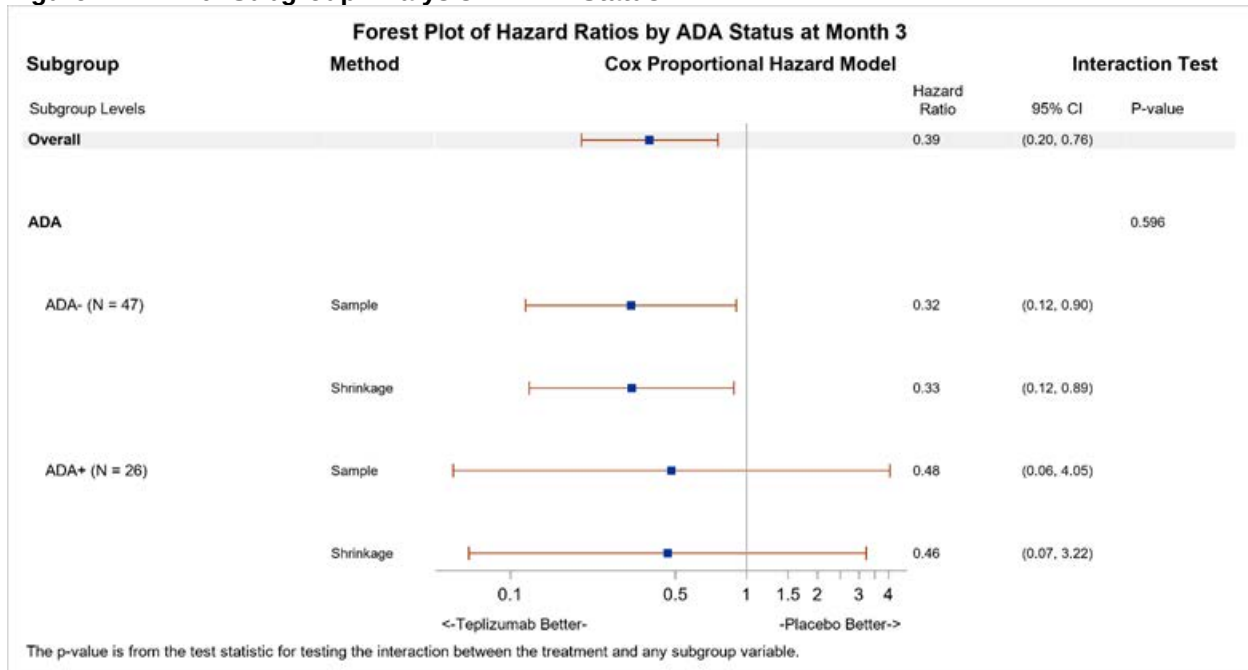


Source: FDA statistical reviewer
Abbreviations: CI, confidence interval

Subgroup Analysis of Anti-Drug Antibody (ADA) Effect on Efficacy

Anti-drug antibodies (ADA) were assessed in TN-10 and were found to be positive in 59% of patients at 3 or 6 months post-randomization. 72% of the ADA-positive patients were younger than 18 years. Immunogenicity as it relates to safety in the teplizumab development program is reviewed in Section [8.4.10](#). ADA positivity did not have an apparent effect on teplizumab's efficacy ([Figure 14](#)).

Figure 14. TN-10- Subgroup Analysis — ADA Status



Source: FDA Statistical Reviewer

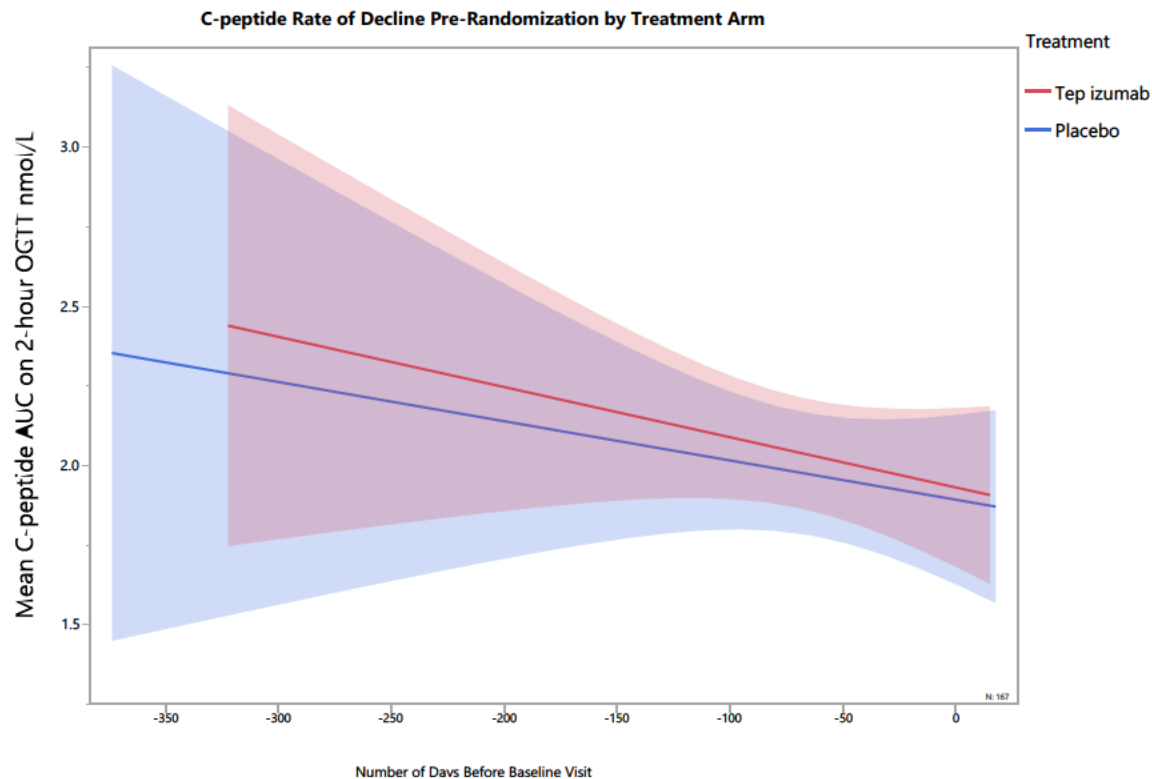
Note: This analysis included 73 TN-10 patients who had ADA status available at Month 3

6.1.2.7 Efficacy Results – Secondary and Other Relevant Endpoints

Published information on the rate of C-peptide decline in those with stage 2 T1D prior to enrollment in TN-10 showed that the pretreatment slope of C-peptide was -0.0233 pmol/mL/month (95% CI -0.0557, 0.0175) (Sims et al. 2021). For TN-10 participants randomized to placebo, the decline in C-peptide persisted, or worsened, during the first 6 months after enrollment, with no significant difference in pre- versus post-treatment slopes, even after correction for baseline age and C-peptide (Sims et al. 2021). These data are similar to the published rate of C-peptide AUC decline among those *newly diagnosed* with T1D. In an analysis of the collective placebo arms of new-onset T1D prevention trials, C-peptide AUC declined from baseline at a rate of -0.0245 pmol/mL/month (95% CI: -0.0271 to -0.0215) for the first 12 months post-diagnosis (Greenbaum et al. 2012).

The FDA clinical reviewer confirmed that prior to randomization in TN-10, the rates of Mean C-peptide AUC decline were similar between treatment arms ([Figure 15](#)).

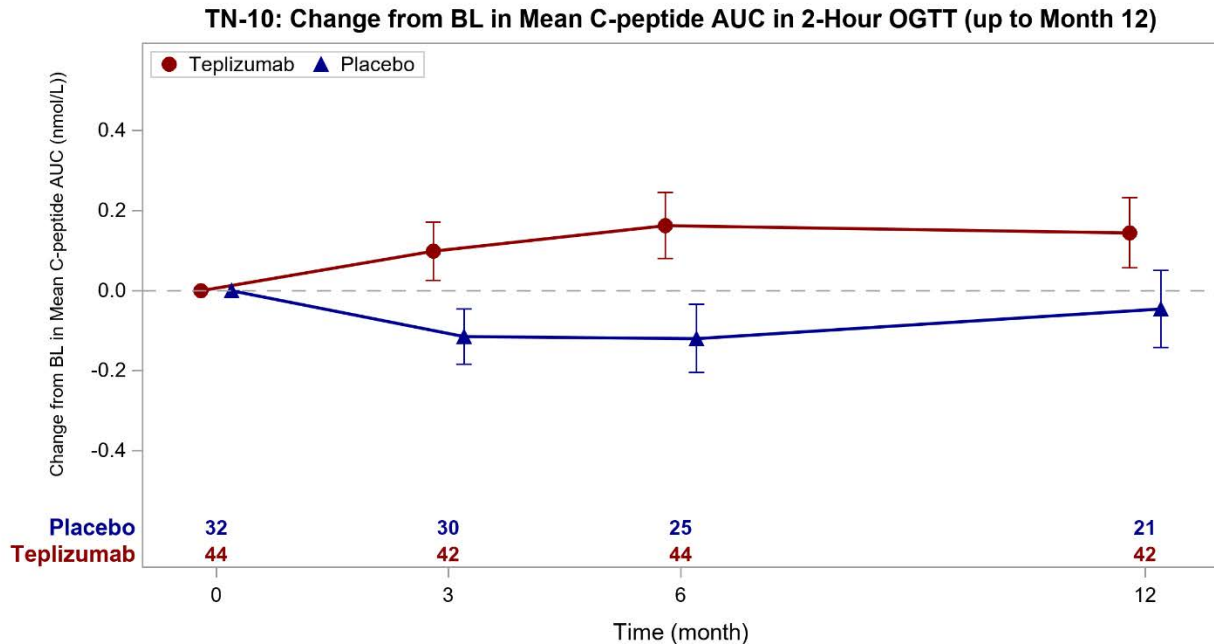
Figure 15. Exploratory Analysis — C-peptide Mean AUC Rate of Decline Pre-Randomization by Treatment Arm



Source: FDA Clinical Reviewer
 Abbreviations: AUC, area under the curve; OGTT, oral glucose tolerance test

In TN-10, after treatment we would expect further decline in C-peptide in the placebo arm, but an increase in C-peptide AUC in the teplizumab-treated patients if teplizumab is having the intended disease-modifying effect. [Figure 16](#) shows the comparison of C-peptide AUC change from baseline between the treatment groups. With the caveat of the informative censoring described previously (patients did not have C-peptide measurements once T1D was diagnosed) the early C-peptide trends in TN-10 (at 3 months) are suggestive that teplizumab is exerting a salutary effect on C-peptide.

Figure 16. Change From Baseline in Mean C-peptide AUC by Visit in TN-10 up to 12 Months Post-Randomization



Error bars indicate standard errors (SEs). The numbers of patients by group at each time are given above the x-axis.

Source: FDA Statistical Reviewer

Abbreviations: AUC, area under the curve; BL, baseline; OGTT, oral glucose tolerance test

6.1.2.8 Dose/Dose Response

41/44 patients in TN-10 received the intended 14-day course, therefore no dose-response data were available for this study.

6.1.2.9 Durability of Response and Persistence of Effect

On review of the K-M curve, the single 14-day treatment course was observed to primarily exert its effect during the first 12 to 18 months of follow-up, after which the curves for T1D development for treatment and placebo become parallel. The response to a second treatment cycle (e.g., after 12 months) was not tested in TN-10.

6.2. Meta-Analysis of Stage 3 Studies - Supportive Evaluation of Efficacy on C-peptide Data

In pre-submission meetings it was agreed that available C-peptide change from baseline data from teplizumab studies in new-onset T1D could serve as supportive evidence. Therefore, a five-study meta-analysis of the change from baseline in C-peptide AUC was performed with the inclusion of data from AbATE, Delay, Protégé, Encore, and Study 1.

[Table 3](#) summarizes key design features of the five studies, including the dosing regimen of teplizumab and C-peptide assessment schedule. [Table 16](#) summarizes the key inclusion criteria.

Table 16. Key Inclusion Criteria Across the ISE Studies

	Protégé	Encore	Study 1	AbATE	Delay
Age at entry	8-35 years	8-35 years	7.5-30 years	8-30 years	8-30 years
Time from T1D diagnosis to treatment	≤12 weeks	≤12 weeks	≤6 weeks	≤8 weeks	4-12 months
C-peptide level	detectable	detectable	≥0.2 nmol/L	≥0.2 nmol/L	≥0.2 nmol/L
Weight	≥36 kg	≥36 kg	N/A	≥25 kg	≥27.5 kg

Source: Modified from sponsor's table 3, ISE

Abbreviations: ISE, integrated summary of efficacy; T1D, type 1 diabetes

6.2.1. Individual Trials Included in Meta-Analysis

Protégé

The Protégé study was a dose-ranging study designed to assess the safety and efficacy of three teplizumab dosing regimens (a full 14-day course, a one-third dose 14-day course, and a 6-day course) of daily IV infusions compared with placebo (IV) given as two identical courses, 26 weeks apart. The study enrolled patients with newly diagnosed T1D who had experienced disease onset within the past 12 weeks, and patients underwent a 4-hour MMTT every 6 months for 2 years. The primary endpoint for Protégé was the proportion of patients who had both a total daily insulin dose of less than 0.5 units/kg/day and an HbA1c <6.5% at one year after randomization. The study was terminated early due to futility on its primary endpoint.

Encore

The Encore study was intended as a replicate study of Protégé. The primary endpoint for Encore was the proportion of patients who had both a total daily insulin dose <0.25 units/kg/day and HbA1c <7.0% at one year after randomization. The Encore study was terminated prematurely with 254 patients (64% of the planned 400 patients) enrolled after Protégé failed to demonstrate efficacy on the primary endpoint.

Study 1

Study 1 was a randomized, open-label study to test the safety and efficacy of a single course of teplizumab on the loss of insulin production over 2 years in patients with newly diagnosed T1D (within 6 weeks) compared to standard of care. Patients returned for a 4-hour MMTT every 6 months. The primary endpoint was change from baseline in the mean C-peptide 4-hour AUC in response to an MMTT at Month 24.

AbATE

The AbATE study was a randomized, open-label study that enrolled individuals diagnosed with T1D within 8 weeks of randomization. The study drug treatment group received two courses of

teplizumab: at randomization and at 12 months. Patients underwent a 4-hour MMTT every 6 months for 2 years. The parallel group control received standard of care. The primary endpoint was change from baseline in the mean C-peptide 4-hour AUC in response to an MMTT at Month 24.

Delay

The Delay study was a randomized, double-blind, placebo-controlled study that enrolled patients 4 to 12 months after their T1D diagnosis. Patients received one course of teplizumab and underwent a 4-hour MMTT every 6 months for 1 year. The primary endpoint was C-peptide AUC in response to an MMTT at Month 12.

6.2.1.1 Study Endpoints

The primary endpoint was the change from baseline in the mean C-peptide AUC. Because C-peptide AUC is typically log-normally distributed, values were transformed to $\log(\text{AUC}+1)$ for analyses. C-peptide has been discussed extensively elsewhere in this review (see Section [2.1](#) and [6.1.1.6](#)).

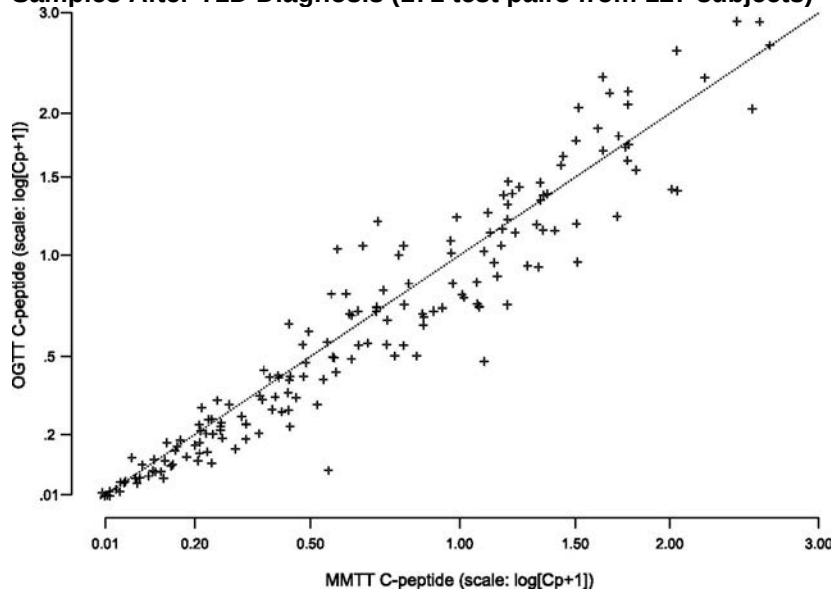
Three of the five studies assessed C-peptide for up to 2 years: Protégé, Study 1, and AbATE; the Delay study was designed for only 1 year of follow-up, and Encore was terminated early to provide C-peptide AUC data up to 1 year.

In the MMTTs, C-peptide measurements were taken at baseline, 15 minutes, and then every 30 minutes thereafter up to 4 hours.

Reviewer comment: The 4-hour MMTT is an acceptable method to assess the primary endpoint. Although both the 2-hour and 4-hour MMTT tests are considered the 'gold standard,' there is evidence that the 4-hour test is associated with less variability (Greenbaum et al. 2008; Boyle et al. 2016).

Whereas the MMTT is typically used *after* a diagnosis of T1D to assess stimulated C-peptide response, OGTTs (as used in TN-10) are typically used before a diagnosis of T1D in order to monitor for clinical diagnosis, and in a research setting, to measure stimulated C-peptide responses. As discussed in Section [6.1.1.6](#), 2-hour OGTTs were performed in TN-10 for the assessment of C-peptide AUC as a secondary endpoint. Concordance exists between an individual patient's AUC C-peptide response to 2 hour OGTT and a AUC C-peptide response to a 2 hour MMTT, when tests are performed proximally, as demonstrated in 171 OGTT-MMTT test pairs from 127 patients with T1D ($r = 0.96$) (Bogun et al. 2020).

Figure 17. Comparison of C-peptide AUC Means from Proximal 2-hour MMTT and 2-hour OGTT Samples After T1D Diagnosis (171 test pairs from 127 subjects)



Source: (Bogun et al. 2020)

Abbreviations: AUC, area under curve; MMTT, mixed meal tolerance test; OGTT, oral glucose tolerance test; T1D, type 1 diabetes

6.2.1.2 Statistical Methodologies

Study Selection

Participant-level data from five new- or recent-onset T1D studies were selected to be pooled for the meta-analysis. Study inclusion in the meta-analysis was based on the patient population (newly diagnosed T1D), the study design (i.e., randomized, controlled, or open-label standard of care), and assessment of C-peptide as measured by a 4-hour MMTT.

Individual Study Analyses

For each study, after multiple imputation (MI) was used to impute missing values, an analysis of covariance (ANCOVA) was used to estimate the treatment effect. The dependent variable was the change from baseline in $\log(\text{AUC}+1)$ at the last study visit (2 years for Protégé, AbATE, Study 1 in one meta-analysis, and 1 year for all five studies in another meta-analysis). Covariates were treatment, $\log(\text{baseline C-peptide AUC}+1)$, and age.

Meta-Analyses

To support the meta-analyses, the original study visits from the individual studies were unified to provide common windows.

By pooling individual participant data from the five completed studies, a one-stage random-effects model that combined and re-analyzed all studies simultaneously was proposed in the agreed-upon SAP. On the basis of the individual study analysis ANCOVA model, the meta-analysis model included two additional terms: a fixed-effect term indicating study identities, and a term for treatment-by-study interaction.

In their original plan for the one-stage meta-analysis, the Applicant proposed a random-effect approach analysis. The Applicant explained, however, that because all five completed randomized studies to date were included in the meta-analysis, the purpose of the analysis was to assess the effects of these specific studies on the outcome, such that fixed effects models would be more appropriate for the meta-analysis. The fixed-effects approach assumes that the between-study variance is zero, which is a strong assumption that rarely holds. The FDA disagreed with this approach and instead carried out a two-stage random effect meta-analysis to estimate the overall treatment effect that accounts for the between-study variances. The two-stage random-effects meta-analysis calculates each individual study weighted average treatment effect estimate separately, and then combines these in a traditional meta-analysis model. The weights were derived by the inverses of the sum of within-study and between-study variance components.

Handling of Missing Data and Sensitivity Analysis

The amount, pattern, and reasons for missing data were to be described for each study. Multiple imputation was to be used for the primary analysis. The pattern mixture multiple imputation for missing data was based on two missing data patterns. For patients with missed assessment(s) secondary to administrative reasons, missing data were imputed based on data from completers. For patients with missing data secondary to non-administrative reasons such as AEs, multiple imputation was based on data from retrieved dropouts. Retrieved dropouts are subjects in the same study who discontinued treatment but completed the studies and had C-peptide measured at the scheduled 1- or 2-year timepoints.

After multiple imputation had filled in missing values based on the approach described above, the modified dataset was to be used in the analyses. Rubin's rules for combining data from imputed datasets was used.

6.2.2. Study Results

6.2.2.1 Patient Disposition

[Table 17](#) summarizes study disposition by individual and pooled studies. Data from a total of 609 patients were included in the meta-analysis.

Table 17. Meta-Analysis: Study Disposition

Analysis	Teplizumab N=375 n (%)	Control N=234 n (%)	Total N=609 n (%)
By study			
AbATE	52 (13.9)	25 (10.7)	77 (12.6)
Delay	32 (8.5)	28 (12.0)	60 (9.9)
Encore	63 (16.8)	62 (26.5)	125 (20.5)
Protégé	207 (55.2)	98 (41.9)	305 (50.1)
Study1	21 (5.6)	21 (9.0)	42 (6.9)
Pooled			
Completed planned treatment course 1	337 (89.9)	229 (97.9)	566 (92.9)
Patients assigned a two-course regimen	227 (71.5) ¹	133 (71.9) ¹	360 (71.0) ¹
Completed planned treatment course 2	211 (93.0) ²	127 (95.5) ²	338 (93.9) ²

Source: FDA statistical reviewer.

Abbreviations: ISE, integrated summary of efficacy; MA, meta-analysis

¹ Percentage with respect to number of pooled patients

² Percentage with respect to number of patients with 2-course regimen

6.2.2.2 Demographic Characteristics

Pooled Dataset

In the pooled dataset, demographic characteristics were balanced across treatment groups and sufficiently representative of the US population with the exception of a limited number of Black or African American patients ([Table 18](#)).

Table 18. Pooled Demographics of Meta-Analysis Studies

Characteristic	Teplizumab N=375	Control N=234	Total N=609
Age, years			
Mean (SD)	16.9 (7.1)	16.6 (7.2)	16.8 (7.1)
Median (min, max)	15 (7, 35)	14 (8, 35)	14 (7, 35)
Sex, n (%)			
Female	145 (38.7)	86 (36.8)	231 (37.9)
Male	227 (60.5)	148 (63.2)	375 (61.6)
Unknown	3 (<1)	0	3 (<1)
Race, n (%)			
American Indian or Alaska Native	2 (<1)	0	2 (<1)
Asian	87 (23.2)	50 (21.4)	137 (22.5)
Black or African American	4 (1.1)	4 (1.7)	8 (1.3)
Other	5 (1.3)	1 (<1)	6 (<1)
Unknown	2 (<1)	0	2 (<1)
White	275 (73.3)	179 (76.5)	454 (74.5)
Country, n (%)			
US	186 (49.6)	122 (52.1)	308 (50.6)
Canada	6 (1.6)	1 (<1)	7 (1.1)
Other	183 (48.8)	111 (47.4)	294 (48.3)

Source: FDA statistical reviewer.

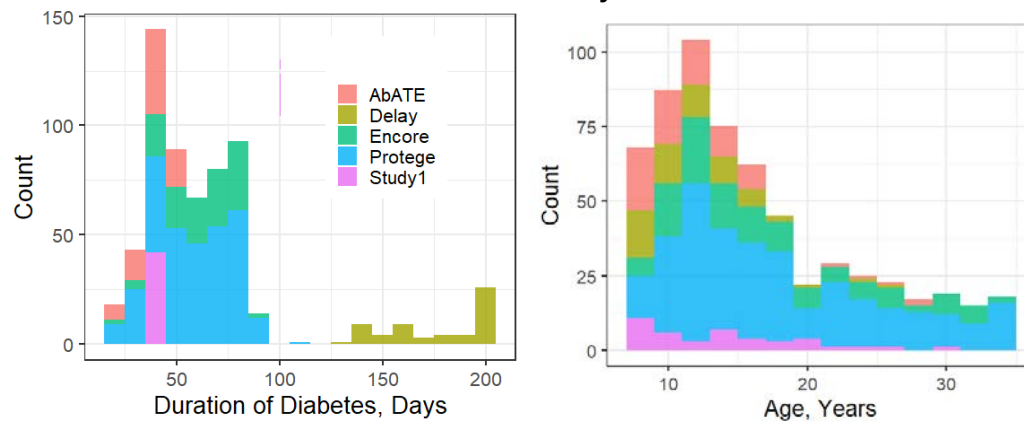
Abbreviations: ISE, integrated summary of efficacy; SD, standard deviation

Demographics and Baseline Characteristics by Individual Study

This section highlights some key differences among studies with respect to demographic and baseline characteristics. In Protégé and Encore patients were, on average, older with a higher proportion of 18- to 35-year-olds ([Figure 18](#)). The mean ages for AbATE, Delay and Study 1 (12 to 14 years) were more in line with the age of peak incidence of T1D (Maahs et al. 2010).

Duration since diabetes diagnosis also differed among the trials, in part due to the enrollment criteria listed in [Table 3](#). Most notably, the Delay study enrolled patients four to twelve months from diagnosis. The other studies enrolled patients 6 to 12 weeks from diagnosis. Abate and Study 1 enrolled patients with the shortest duration of T1D (6 to 8 weeks) compared to Protégé and Encore, which enrolled patients up to 12 weeks from diagnosis. Average insulin dose at baseline and baseline HbA1c also differed among the trials.

Figure 18. Histograms Demonstrating the Age Distribution and Duration of Diabetes at Time of Randomization for the Studies in the Meta-Analysis



Source: Reviewer generated

The enrollment criteria for baseline C-peptide also differed by study, with Protégé and Encore allowing slightly lower baseline C-peptide levels (detectable) compared with AbATE, Delay and Study 1 (which required ≥ 0.2 nmol/L stimulated C-peptide). In addition, the baseline body weight requirement for Protégé and Encore was higher than the other trials. Finally, the country of enrollment differed by study, with 100% of AbATE, Delay and Study 1 completed in the US, and only 27 to 31% of patients enrolled in Protégé and Encore from the US.

Reviewer comment: Heterogeneity was noted in the studies included in the ISE. The most notable heterogeneity was related to duration of T1D, age and country of recruitment, in part related to differences in design among the studies. These baseline factors may help explain the differences in efficacy conclusions noted among the individual studies. This heterogeneity among the trials was considered

in the establishment of the SAP and the planned random-effects model that incorporates both within-study and between-study variance into the analysis.

6.2.2.3 Meta-Analysis Efficacy Results – Primary Endpoint

Please see Dr. Wang’s statistical review for further information about the meta-analysis efficacy results.

[Table 19](#) summarizes mean AUC 4-hour MMTT C-peptide data availability at months 12 and 24. Note that because of the early termination of Encore, only 27.2% of the Encore study population provided month 12 C-peptide data.

Table 19. Meta-Analysis C-peptide Data Availability by Unified Visit Windows

Study	Baseline N	Month 12 n (%)	Month 24 n (%)
Protégé	305	279 (91.5)	195 (63.9)
Encore	125	34 (27.2)	
AbATE	77	72 (93.5)	70 (90.9)
Delay	60	58 (96.7)	
Study 1	42	42 (100)	33 (78.6)
Pooled population for 1-year analysis	609	485 (79.6)	
Pooled population for 2-year analysis	424		298 (70.3)

Source: The Applicant. FDA statistical reviewer replicated the analysis.

Data from the five studies that included 1-year follow-up data were pooled for analysis of the primary endpoint at 1-year. Additionally, the three studies that included 2-year follow-up data were pooled for the 2-year analysis. For the individual studies, an ANCOVA model included the change from baseline C-peptide log(AUC+1) at the 1-year time point or 2-year time point as the dependent variable and baseline C-peptide log(AUC+1), age, and treatment as covariates.

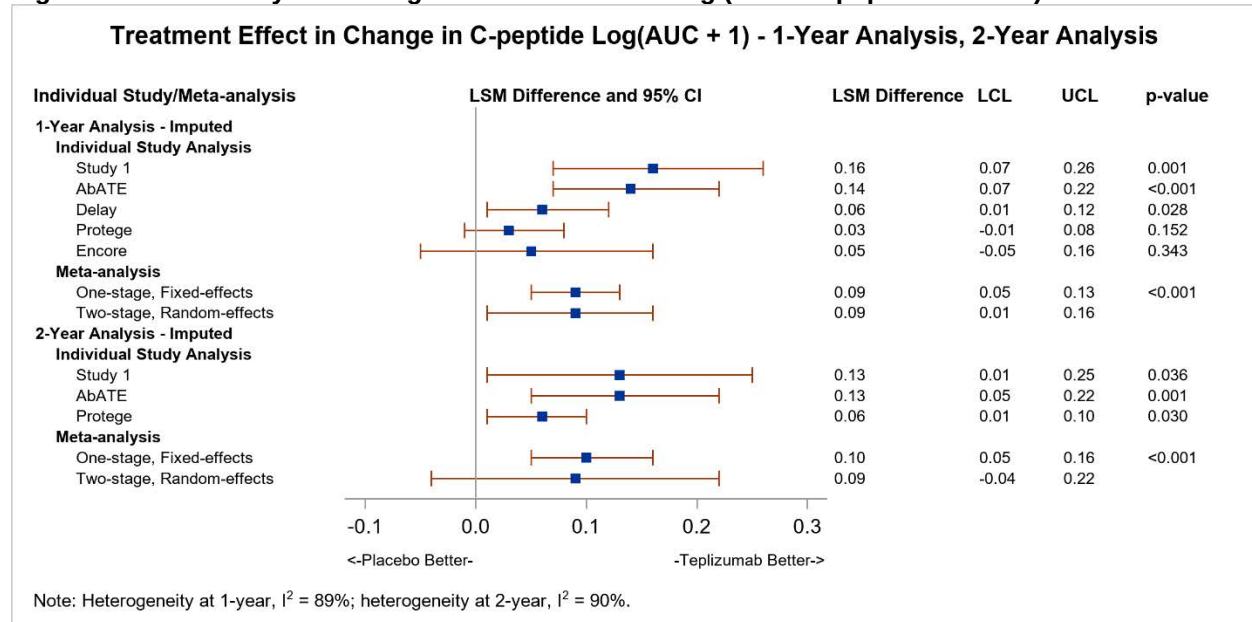
[Figure 19](#) displays both individual study analysis results and the meta-analysis results based on imputed data. The 1-year random effect meta-analysis results suggest that teplizumab improves preservation of C-peptide by 0.09 (95% CI: 0.01 to 0.16) on the scale of log(Mean C-peptide AUC+1), as compared with control. For results based on observed data please see Dr. Wang’s statistical review.

There was notable heterogeneity among the individual study C-peptide results. Study 1 and AbATE observed larger treatment effects than Delay. Protégé and Encore failed to demonstrate a statistically significant difference in C-peptide preservation. To account for this between-study variability, as was previously discussed, the FDA statistical reviewer performed a two-stage random effect meta-analysis to estimate the overall treatment effect. The overall treatment effect by this methodology were similar in size with the one-stage fixed effect model estimates (data not shown); however, the estimated overall treatment effect for the 2-year analysis was

not statistically significant, secondary to widened confidence intervals (0.09; 95% CI: -0.04 to 0.22).

Not shown, the majority of baseline C-peptide values (80%) were in the range of 0.2 to 1.1 nmol/L with mean of 0.6 nmol/L, which is expected for a recent onset T1D population.

Figure 19. Meta-Analysis: Change From Baseline in Log (Mean C-peptide AUC +1)



Source: FDA statistical reviewer.

Abbreviations: AUC, area under the curve; CI, confidence interval; LSM, least squares mean; LCL, lower confidence limit; UCL, upper confidence limit

Reviewer comment: I agree with Dr. Wang that FDA's evidentiary standard for effectiveness has been met, with confirmatory evidence from the results of the meta-analysis that showed a significant treatment effect of teplizumab vs. comparator on C-peptide AUC change from baseline at 1-year, but not 2-year. The 2-year analysis included significantly fewer patients compared to the 1-year analysis, decreasing statistical power, especially using the two-stage, random-effects model. Importantly, the estimated treatment effect was numerically similar between the 1- and 2-year analyses.

It is important to note that the parameter of interest in this analysis is change from baseline in C-peptide, regardless of the baseline value. Although inverse associations between higher stimulated C-peptide and lower HbA1c (Rickels et al. 2020) and rate of severe hypoglycemia (Sørensen et al. 2013a; Gubitosi-Klug et al. 2021) have been reported, there is no minimum change in C-peptide that is considered clinically meaningful.

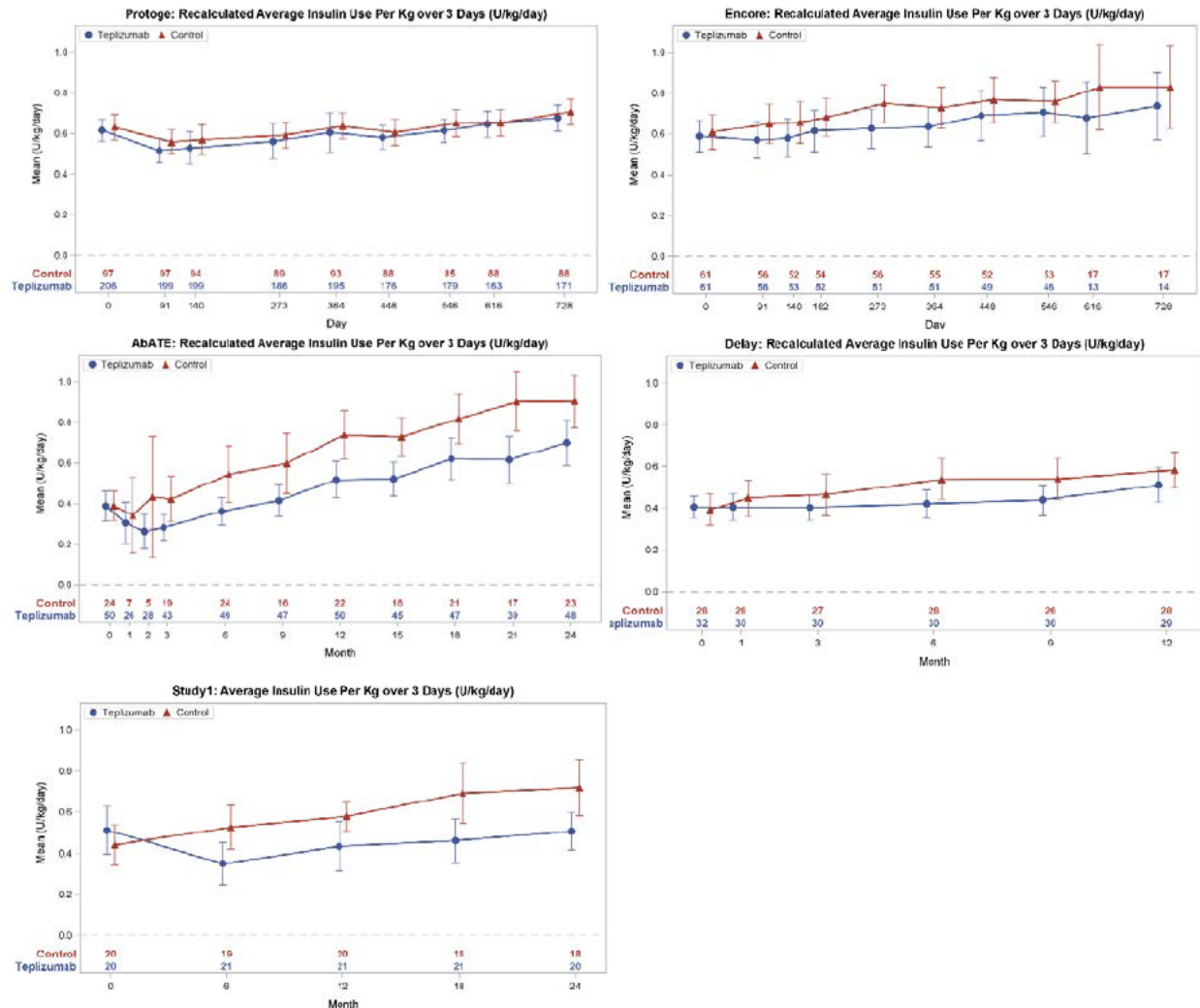
6.2.2.4 Meta-Analysis Efficacy Results – Secondary and Other Relevant Endpoints

Average Insulin Use and HbA1c

The Applicant submitted supportive data regarding average insulin use and HbA1c from the studies in the meta-analysis. Insulin use and HbA1c must be considered together because higher insulin usage will result in lower HbA1c and vice versa.

In all studies included in the meta-analysis, the average insulin use at each study visit was calculated by averaging documented insulin use over approximately 3 days before the visit in units/kg/day. These analyses were confirmed and replicated by the FDA statistical reviewer, with results by study presented in [Figure 20](#). In all studies except Protégé there is a trend towards lower insulin usage in the teplizumab group.

Figure 20. Average Daily Insulin Use (units/kg/day) by Visit for Individual Meta-Analysis Studies

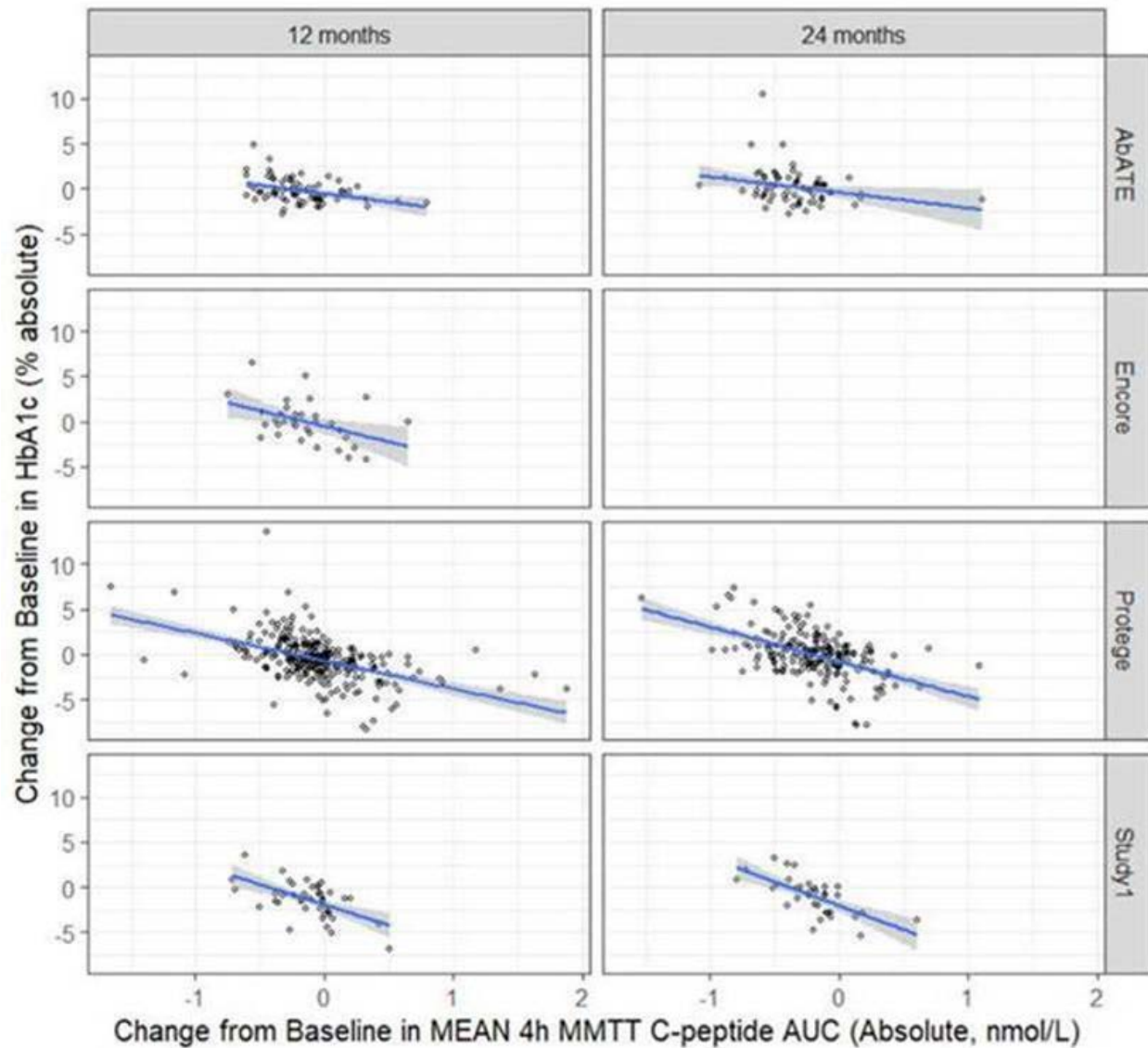


Source: FDA Clinical Reviewer

Additionally, an FDA exploratory analysis confirmed a negative linear relationship between C-peptide change from baseline and HbA1c change from baseline in each of the studies in the meta-analysis individually ([Figure 21](#)) and when pooled ([Table 22](#)). This relationship was statistically significant for each study and time period independently. A similar analysis was conducted by the Applicant and presented at the Advisory Committee (but was not submitted as a part of this Application).

Both analyses below were performed with pooled study level data from the teplizumab and comparator arms, 1-year data were available for Protégé, Encore, AbATE and Study 1, and 2-year data for Protégé, AbATE, and Study 1. The Delay study was excluded from this analysis given the patient population had a longer duration of T1D (4 to 12 months).

Figure 21. FDA Exploratory Analysis of Effect of Change From Baseline Mean C-peptide AUC on HbA1c Change From Baseline (%) at 12 months and 24 months by Study for Pooled Teplizumab and Comparator Treatment Arms



Source: FDA Clinical Reviewer

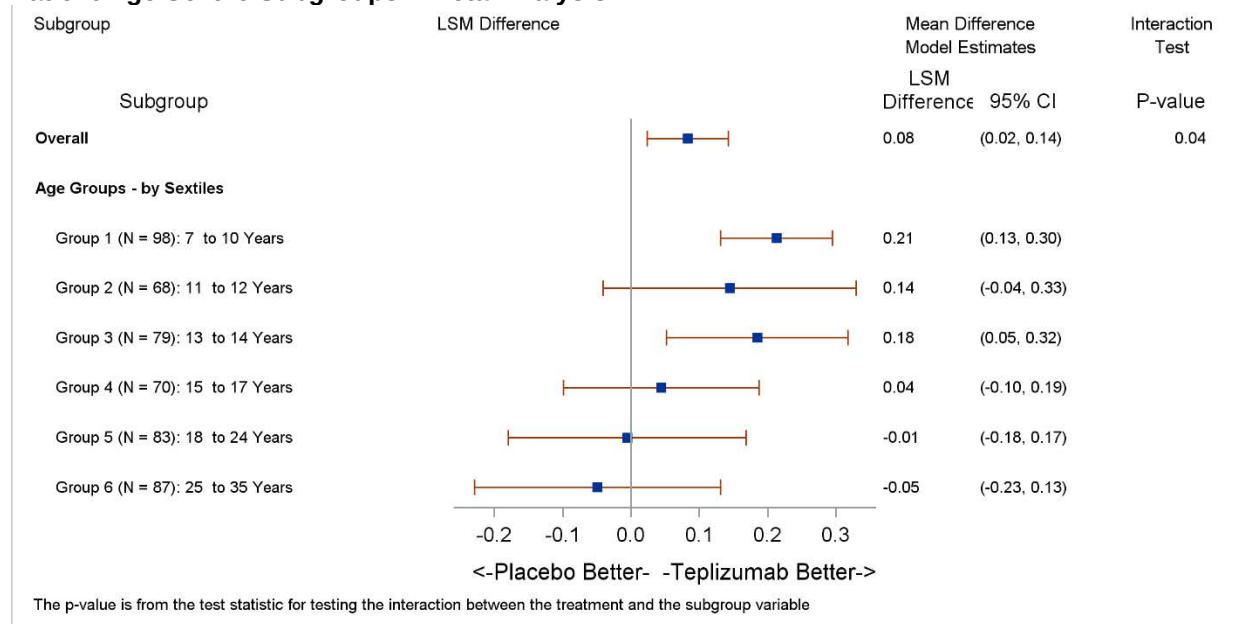
Abbreviations: AUC, area under the curve; HbA1c, hemoglobin A1c; MMTT, mixed meal tolerance test

Reviewer comment: These exploratory analyses strongly support a conclusion that the meta-analysis results of C-peptide change from baseline are predictive of a clinically meaningful effect and provide robust support for the use of C-peptide AUC change from baseline as confirmatory evidence of effectiveness.

Effect of Age on Change from Baseline in C-peptide

Figure 22 shows an exploratory analysis of the treatment effect of teplizumab by age sextile for the C-peptide meta-analysis.

Figure 22. Forest Plot of 1-Year Difference in Change From Baseline C-peptide AUC (nmol/L) by Patient Age Sextile Subgroups – Meta-Analysis



Source: FDA Statistical Reviewer

Abbreviations: AUC, area under the curve; CL, confidence limit; LSM, least squares mean

Reviewer comment: These data are suggestive of a lack of effect of teplizumab in older age groups; however, this finding was not observed in the TN-10 trial. Therefore, the evidence is insufficient to conclude that the use of teplizumab to delay on the onset of T1D should be limited to younger patients.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The efficacy evaluation for teplizumab is derived from one AWC in the population for teplizumab's intended use, TN-10, in patients at-risk of T1D, and by a meta-analysis in five phase 2/3 studies in new- or recent-onset T1D. Therefore, this section is not applicable to this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Discussions of benefit in the postmarket setting are deferred until the next review cycle because of the proposed Complete Response action for this BLA. The to-be-marketed product should be demonstrated comparable (PK or other method) to the clinical trial product in order to conclude that efficacy in the postmarket setting will be similar to the treatment effect observed in the clinical development program.

7.2.2. Other Relevant Benefits

There are no other relevant benefits that warrant discussion in this section.

7.3. Integrated Assessment of Effectiveness

There is substantial evidence of effectiveness on the basis of which it could fairly and responsibly be concluded that teplizumab will have the effect it purports to have under the conditions of use planned for labeling. Although the Applicant amended their proposed indication during the review cycle, at this time there is agreement on the appropriate indication as: to delay the onset of T1D in at-risk individuals who are ≥ 8 years of age who have two or more T1D-related autoantibodies (anti-GAD [glutamic acid decarboxylase], micro insulin, anti-IA-2, islet cell antibody [ICA], anti-ZnT8) and abnormal glucose tolerance on a 2-hour oral glucose tolerance test. Although TN-10 was limited to relatives of patients with T1D, the pathogenesis and risk of progression for stage 2 T1D individuals who are not T1D relatives are not considered to be significantly different from the at-risk population studied in TN-10, and therefore expansion of the treatment indication to include non-relatives is recommended, and was generally supported the Advisory Committee meeting.

The submitted evidence of effectiveness has met the statutory evidentiary standard, consisting of one AWC clinical trial (TN-10) demonstrating efficacy on delay of T1D, and confirmatory evidence consisting of a meta-analysis demonstrating improved C-peptide change from baseline compared to placebo or standard of care in a cohort of patients with new or recent onset T1D.

The primary endpoint in TN-10, delay of T1D, is an objective clinical endpoint directly measuring how a patient feels and functions. TN-10 was an event driven trial and was to be stopped when 40 subjects met the primary endpoint, to detect an effect size measured by a hazard ratio of 0.4 for teplizumab vs. placebo, with 80% power at a one-sided alpha level of 0.025.

A Cox proportional hazards (PH) model was used to analyze the time to T1D diagnosis. The hazard ratio for the time to clinical T1D diagnosis was 0.41 (95% CI: 0.22 to 0.78) with a low p

value of 0.0066. Sensitivity analyses addressing baseline imbalances in important demographic and disease characteristics, as well as sensitivity analyses to address missing data, were consistent with the primary efficacy analysis. No data quality or integrity issues precluding approval were noted.

Consistent with clinical practice, patients in TN-10 T1D were generally diagnosed with objective laboratory-based criteria and the study employed a second confirmatory test that improved the specificity of the primary endpoint. We also performed extensive exploratory analyses of the primary endpoint that further strengthened our confidence in the results. These included excluding bias in the time to confirmatory test from the triggering test, reviewing the individual patient level associated documentation with each clinical diagnosis of T1D, reviewing the DSMB minutes describing the T1D diagnosis for patients not diagnosed with two OGTT tests, and ensuring similar glycemic status at baseline between the two groups, as well as comparing the expected rate of T1D diagnosis in the placebo group to what would be expected based on natural history experience.

Subgroup analyses of the primary endpoint showed some differences in the magnitude of treatment effect among subgroups, but were largely consistent, especially in view of the small sample size. The most notable example was the analysis by HLA type. The subgroup analysis was suggestive of no treatment effect in patients with HLA DR4 absent, but the strength of this finding is insufficient to recommend restricting the indication to patients with HLA DR4 present.

The pre-specified secondary endpoint of C-peptide change from baseline could not be reliably interpreted because of informative censoring, but an exploratory analysis considering only the first 3 and 6 months post-baseline is strongly suggestive of a beneficial effect of teplizumab on C-peptide, and hence beta-cell function.

Limitations to TN-10 include its small sample size (see Advisory Committee discussion), but the trial accrued the pre-specified minimum number of events in order to detect a treatment difference. That 43 events of T1D were accrued with enrollment of only 73 patients speaks to the high-risk nature of the study population. With 73 patients, however, there is a higher chance that baseline imbalances could affect the efficacy conclusions. Indeed, we found a baseline imbalance in the percentage of patients age 18 or older vs. younger patients, among other important imbalances. Also, with a treatment that often has predictable adverse events, e.g., pyrexia and rash, there is a potential for unintentional unblinding that could bias the results. The FDA analyses attempted to address these concerns using the sensitivity and exploratory analyses as noted above, but it remains possible that unknown confounders had an impact on the efficacy assessment. Without a second AWC clinical study, the concern about concluding effectiveness when in fact there is none, is increased. Along the same lines, it is well known that many phase 2 studies that have demonstrated striking treatment effects that were not able to be substantiated in phase 3. There are a number of explanations for this

phenomenon, including chance, i.e., a random 'high.' With the entire treatment effect in TN-10 driven by perhaps a half-dozen subjects, we must acknowledge the concern here, as the TN-10 results could represent a false positive result despite all of the considerations described above. We note, however, that the positive results on the C-peptide meta-analysis provide significant protection from the false-positive, as the findings are fairly strong. Despite these concerns, we believe that the single study is justified because of the rarity of the population of at-risk individuals and the challenge of conducting a second study. Over seven years were needed just to enroll TN-10 (ten years overall). At this time, general population screening for risk of T1D is uncommon outside of research studies.

The confirmatory evidence provided in the BLA was based on effects on the biomarker C-peptide that directly measures endogenous insulin secretion and thus, beta cell function. Prior to the onset of T1D, there is a well characterized steady rate of decline reflective of the autoimmune destruction of the insulin-producing beta cell, in both the at-risk and new-onset T1D populations, who have differing stages of disease along the same continuum. The C-peptide meta-analysis was conducted using a pool of trials in new- or recent-onset T1D, which is a population with more advanced disease than TN-10's population but with similar pathophysiology. As a disease-modifying therapy, teplizumab is expected to improve beta-cell function in patients with T1D, and in patients who do not yet have T1D, delay diagnosis.

Although the meta-analysis was planned post hoc, the similarity of the patient populations, follow-up times, and C-peptide assessments render the meta-analysis valid. The meta-analysis demonstrated a significant treatment effect of teplizumab vs. comparator on C-peptide AUC change from baseline to 1-year after accounting for variations in effects among studies. The FDA analysis demonstrated that teplizumab significantly improved preservation of C-peptide as compared with control at 1-year. The estimated treatment effect at 2-years was similar to the estimate at 1-year but was not statistically significant. The smaller number of patients included in the 2-year analysis reduced statistical power. Given the significant results at 1-year, the meta-analysis was considered confirmatory evidence of efficacy by both clinical and statistical FDA review teams.

Taken together the results of TN-10 and the C-peptide meta-analysis support a conclusion of effectiveness in delay of onset of TN-10 through preservation of beta-cell function, although we cannot conclusively make this connection because of the lack of C-peptide follow-up data in patients diagnosed with T1D in the TN-10 trial.

TN-10 demonstrated a delay in the onset of stage 3 T1D by approximately 2 years. The median time to clinical T1D diagnosis was 49.5 months in the teplizumab group compared with 24.9 months in the placebo group. Our determination that this treatment effect is valued by patients was based on a literature review conducted by the FDA reviewer as well as the Open Public Hearing portion of the Advisory Committee meeting. A delay in the onset of T1D may help

patients avoid diabetic ketoacidosis, which has been associated with impaired cognitive function in newly diagnosed pediatric T1D patients, as compared to age-matched patients with T1D without diabetic ketoacidosis (DKA) (Jessup et al. 2015). In addition, a delay in the onset of T1D may reduce the significant disease burden associated with living with T1D on both the patient and caregivers, and result in an improved quality of life (Kalyva et al. 2011). Moreover, an older age at diagnosis may result in improvement in glycemic control, given literature suggesting that HbA1c levels are higher in patients with younger age at onset than in those with later onset (Rawshani et al. 2018). Younger age of onset of T1D (<7 years) has also been associated with worse cognitive function as compared to older age of onset of T1DM (>7 to 17 years) (Ferguson et al. 2005). Although patient preference assessments were not included in this application for review, a recent publication reported that among parents of children with T1D, when told to assume their youngest child would develop T1D within 6 months to 2 years, most (98% of those surveyed) would consider treatments to delay progression and indicated their willingness to accept side effects of a novel treatment for a delay in insulin dependence (DiSantostefano et al. 2020).

If approved, teplizumab would be the first treatment available to delay T1D and the first approved 'disease-modifying' therapy directed at the underlying pathophysiology of autoimmune T1D. Despite the introduction of newer and faster-acting insulin analogues and advances in glucose monitoring and insulin-delivery technologies, many patients with T1D fail to achieve glycemic control (Foster et al. 2019), contributing to the lifetime burden of long-term end-organ complications. Although not demonstrated in the clinical development program, it is not unreasonable to expect that delay of onset of T1D may delay the adverse effects of dysglycemia. Furthermore, there is now evidence that, after controlling for duration of T1D, age of diagnosis has a significant effect on cardiovascular morbidity and mortality (Rawshani et al. 2018).

While acknowledging the clinical meaningfulness of the delay of T1D, some members of the advisory committee noted that the confidence around the estimate of a 2-year delay is low, and we agree that is a reasonable concern. Importantly, however, at the Open Public Hearing we heard discussion that any delay in diagnosis of T1D would be meaningful to patients and families because of the high burden of managing T1D and decreased quality of life. It is thus, not necessary, in our view to conduct a second AWC clinical study to confirm the magnitude of delay.

A given individual patient will ultimately never know whether teplizumab had an impact on the disease course, unless, perhaps, that patient never develops diabetes. This issue is more relevant for a chronic therapy for which a patient is exposed to potential harms from the drug for unclear benefit and must face the decision about whether to accept therapy, and less relevant for a single course treatment such as teplizumab.

Finally, we would be remiss if we did not note that the value of repeated courses of treatment for the delay of T1D with teplizumab is unknown.

8. Review of Safety

8.1. Safety Review Approach

The safety review approach was previously discussed in Section [5.1](#). The primary safety analysis presented in this review is based on a pooled dataset (ISS) comprised of TN-10 in the at-risk population and four additional studies in patients with new- or recent-onset T1D (AbATE, Delay, Protégé, and Encore) (see [Table 3](#) for an overview of these studies).

8.2. Review of the Safety Database

Total exposure is summarized in [Table 20](#), for both TN-10 and the mISS. The total exposure was agreed upon between the Applicant and division prior to BLA submission.

In TN-10, total observation length was greater for the teplizumab group vs. the placebo group. The estimates of incidences of AEs may therefore be biased against teplizumab. Nonetheless, the majority of AEs occurred early in the observation period, and bias introduced by differential observation time is expected to be minimal.

In the mISS, 729 patients were exposed to at least one dose of teplizumab (not including the 18 patients from Delay exposed during the open label extension), with a total of 641 patient-years of exposure. 213 patients were enrolled in control arms. Time on study was not different between teplizumab and control, and the percentage of completers was high in each group (88.5% for teplizumab and 93% for control).

Table 20. Total Exposure — TN-10 and mISS

TN-10	Teplizumab N=44	Placebo N=32
Total observation time, ¹ patient-years	133	68
Follow-up time, days		
Median (IQR)	888 (656, 1519)	598 (185, 1230)
Final disposition, n (%)		
Completed study ²	41 (93.2)	29 (90.6)
Loss to follow-up	0 (0.0)	1 (3.1)
Other	2 (4.5)	2 (6.2)
Withdrawal by subject	1 (2.3)	0 (0.0)
Follow-up time, n (%)		
More than 2 years	31 (70.5)	15 (46.9)
Up to 2 years	11 (25.0)	5 (15.6)
Up to 1 year	2 (4.5)	12 (37.5)
At least 42 days	44 (100)	32 (100)
mISS (without TN-10)	Teplizumab N=729	Control N=213
Total observation time ¹ , patient-years	641	184
Follow-up time, days		
Median (IQR)	189 (182, 536)	189 (182, 387)
Final disposition, n (%)		
Completed study ³	645 (88.5)	198 (93.0)
Loss to adverse event	4 (0.5)	0 (0.0)
Loss to follow-up	28 (3.8)	6 (2.8)
Other	10 (1.4)	3 (1.4)
Protocol violation	1 (0.1)	0 (0.0)
Withdrawal by subject	41 (5.6)	6 (2.8)
Follow-up time, n (%)		
More than 2 years	272 (37.3)	85 (39.9)
Up to 1 year	50 (6.9)	16 (7.5)
Up to 2 years	407 (55.8)	112 (52.6)
At least 42 days	723 (99.2)	213 (100)

Source: FDA Clinical Reviewer, generated from ADSL.xpt.

Abbreviations: ADaM, Analysis Data Model; ADSL, ADaM Subject Level Analysis Datasets; IQR, inter-quartile range; ISS, integrated summary of safety; mISS, modified ISS

¹ Observation time only includes the time from first study treatment until the second cycle was administered. If the second cycle was not administered, end of overall observation period was used.

² Completed study was defined as either completing follow-up at the censoring date or becoming diagnosed with stage 3 T1D.

³ Completed study was defined as completing follow-up period designated by the study per [Table 3](#).

Reviewer comment: total exposure including patients with new- or recent-onset T1D is adequate to assess safety of teplizumab; in general, safety is expected to be similar between these subpopulations.

8.2.1. Relevant Characteristics of the Safety Population

The safety population for TN-10 was identical to the ITT population. Therefore, patient demographics and baseline characteristics for the safety analyses are identical to those presented in [Table 9](#), [Table 10](#), and in Section [6.1.2.3](#).

The patient demographics of the mISS are generally consistent with the TN-10 population although slightly more diverse with more Asian patients and fewer patients from the US ([Table 21](#)). The teplizumab and control groups appear balanced with respect to important demographic variables. There is a lower percentage of teplizumab subjects from the US, but this finding is not expected to have an impact on safety assessment.

Table 21. Demographics — mISS

Characteristic	Teplizumab N=729	Control N=213	P-value
Age, years			0.057
Median (min, max)	15 (8, 35)	14 (8, 35)	
Body weight, kg			0.01
Mean (SD)	57.11 (17.09)	53.74 (15.25)	
BMI, kg/m ²			0.135
Mean (SD)	21.06 (4.05)	20.59 (4.00)	
BSA, m ²			0.008
Mean (SD)	1.60 (0.29)	1.54 (0.27)	
Gender, n (%)			0.833
Male	470 (64.5)	135 (63.4)	
Race, n (%)			0.489
White	510 (70.0)	158 (74.2)	
Asian	200 (27.4)	50 (23.5)	
Not White or Asian	19 (2.6)	5 (2.3)	
Ethnicity, n (%)			1.0
Not Hispanic or Latino	689 (94.5)	201 (94.4)	
Country of participation, n (%)			0.028
United States	282 (38.7)	101 (47.4)	

Source: FDA Clinical Reviewer, generated from ADSL.xpt

Abbreviations: ADaM, Analysis Data Model; ADSL, ADaM Subject Level Analysis Datasets; BMI, body mass index; BSA, body surface area; ISS, integrated summary of safety; mISS, modified ISS; SD, standard deviation

8.2.2. Adequacy of the Safety Database

The safety database is adequate with respect to size, dose, duration of treatment, patient demographics, and disease characteristics with reference to the US target population. Although subjects were predominantly white and non-Hispanic/Latino, race/ethnicity is not expected to impact the safety of teplizumab, and the safety database is sufficient to establish safety and efficacy in the intended use population in the US.

8.3. Adequacy of Applicant's Clinical Safety Assessments

In general, the schedule of clinical evaluations that were conducted to assess the safety of teplizumab and the timing of evaluations ([Table 6](#)) appeared to be adequate for the evaluation of safety in the teplizumab development program. An important exception is that patients in TN-10, once diagnosed with T1D, were not assessed for safety post-diagnosis. As described previously, the protocol allowed for safety follow-up for a minimum of two years, but it appears

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patients did not attend these follow-up visits. In non-TN-10 studies, AEs and SAEs were followed up until events improved/returned to baseline.

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the submission was found to be adequate. Throughout the review, there were several instances where adverse event information and laboratory information were cross-checked with original CRFs for quality and verification. The key safety findings presented in this BLA were reproducible and confirmed using the submitted datasets. In addition, the adverse event dataset verbatim terms were evaluated for adequate matching to preferred terms for both TN-10 and ISS datasets. Three clinical sites were inspected and the quality reports from OSI also support the validity of the clinical data (see Section [4.1](#) for additional information).

8.3.2. Categorization of Adverse Events

Except where otherwise noted (e.g., cytokine release syndrome analyses), the Applicant used the standard medical dictionary for regulatory activities (MedDRA Version 23.0) to capture and categorize AEs. The grading scale used to assess severity was the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. Grading for studies were unified based on CTCAE version 3.0, where studies with CTCAE grading (TN-10, Protégé, and Encore) remained as coded and grading for other studies (AbATE and Delay) was converted (mild to grade 1, moderate to grade 2, severe to grade 3, SAE to grade 4 and death to grade 5).

The Applicant's translation of verbatim terms to preferred terms and their categorization of preferred terms was acceptable.

Treatment-emergent AEs were defined as adverse events that occurred after the first dose of the investigational product was administered or taken regardless of whether or not the AE was considered drug related. The censoring time was not until the next dose was to be administered (e.g., after 6 to 12 months) or study completion. Although this methodology is appropriate for detection of adverse events that may develop over time, it is not appropriate for AEs that are not likely to occur once exposure to drug is no longer present. Therefore, FDA also performed analyses defining treatment-emergent as events that occurred within 28 days of the last dose of study treatment, and in some cases, the 14-day infusion period.

The Applicant's coding risked diminishing safety signals through splitting of terms; this issue was noted in particular with respect to laboratory abnormality terms (e.g., hemoglobin decreased) and corresponding clinical conditions (e.g., anemia) which were not grouped for analyses. The FDA analyses use queries to address this problem.

Adverse events were assessed by frequency which is appropriate for a single treatment-course therapy.

Adverse events of special interest (EOSI) were pre-specified by the Applicant based on safety concerns identified in other anti-CD3 or T-cell engaging immunotherapies, data from the literature, and preclinical data from the teplizumab development program. The FDA also considered infection, cytokine-release syndrome (CRS), lymphocytopenia, allergic/hypersensitivity reactions, rash, and liver function test abnormalities as EOSIs.

8.3.3. Routine Clinical Tests

Routine clinical testing has been described previously ([Table 6](#)) and appeared to be adequate for the evaluation of safety in the teplizumab development program. Because of the frequent use of local laboratories during the studies in the ISS, the Applicant used the New England Journal of Medicine (NEJM) laboratory to generate the normal ranges and upper limit of normal (ULN) in the dataset for adult patients, and the laboratory normal ranges/ULN in Harriet Lane Handbook for Pediatrics 2017 for pediatric patients.

8.4. Safety Results

8.4.1. Deaths

There were three deaths reported in the teplizumab development program. All three deaths were reported for patients with T1D who were randomized to teplizumab, with two deaths occurring during the follow-up period of the Protégé trial and one occurring in the follow-up period of the Protégé Extension Study. Therefore, death was reported in 0.4% of 791 patients randomized to teplizumab (including the 18 Delay subjects randomized to teplizumab in the open label extension) who were included in the safety dataset compared with 0 of 227 patients in the placebo or control group. It should be noted that the observation time was reasonably balanced, with 93% of the teplizumab-treated patients followed for up to 2 years and 39% followed for greater than 2 years, compared with 89% of placebo patients followed up to 2 years, and 41% followed for greater than 2 years.

A 20-year-old female patient with T1D from the Protégé trial died from DKA approximately 9 months after her last dose of teplizumab. This event is discussed further in Section [8.5.6](#).

A 27-year-old male died of complications related to an anterior wall myocardial infarction 15 months after receiving the last dose of study drug. A 24-year-old female died of unknown causes 26 months after the last dose of study drug. On review of this patient's narrative, an acute episode of abdominal pain, vomiting, and diarrhea treated by a local doctor preceded her death.

Reviewer comment: There were numerically more deaths reported in the teplizumab-treated patients compared with the comparator group. On review of individual events, it is unlikely these deaths are causally related to teplizumab

because of the long latency between dosing and the events. Furthermore, the etiologies were disparate and inconsistent with the mechanism of action of the drug.

8.4.2. Serious Adverse Events

8.4.2.1 TN-10

All serious adverse events (SAEs) in TN-10 were reviewed individually with review of CRFs, patient narratives and in some cases, patient profiles with individual laboratories. To evaluate serious adverse events, FDA MedDRA queries were used in addition to preferred terms, and terms included in the query for serious adverse events are listed in [Table 34](#) in [Appendix B](#).

In TN-10, ([Table 22](#)) seven patients in the teplizumab group (15.9%) and one placebo patient (3.1%) reported SAEs. One patient had two SAEs (dizziness and ankle fracture) in the teplizumab group. All SAEs required hospitalization and occurred after drug treatment was discontinued.

Immunosuppression is a safety issue of interest for teplizumab, and the cluster of four serious infections is notable, although the latency of the onset of two of the events relative to treatment start makes a causal relationship less likely. All resolved without sequelae. One infection was particularly severe and notable. A 15-year-old male presented 40 days after his last dose of teplizumab with severe, complicated, bilateral pneumonia with hypoxemia requiring care in an intensive care unit. The pathogen was not identified. The event was considered resolved after approximately 2 months. The severity of the pneumonia in a previously healthy adolescent suggests a compromised immune response, which may have been drug related. One event of serum sickness is also notable and discussed below. The other SAEs reported in TN-10 appear to be isolated events and are unlikely to be related to teplizumab dosing.

Table 22. Serious Adverse Events by Preferred Term — TN-10

Preferred Term	Patient Age/Sex	Teplizumab N=44 [# events] n (%)	Placebo N=32 [# events] n (%)	AE Onset Relative to Treatment Start (Days)
All Infections		[4] 4 (9.1)	[0] 0 (0)	-
Cellulitis	11/F	[1] 1 (2.3)	[0] 0 (0)	1861
Gastroenteritis	49/M	[1] 1 (2.3)	[0] 0 (0)	39
Pneumonia	15/M	[1] 1 (2.3)	[0] 0 (0)	60
Wound infection	44/F	[1] 1 (2.3)	[0] 0 (0)	204
Ankle fracture	12/M	[1] 1 (2.3)	[0] 0 (0)	711
Dizziness	12/M	[1] 1 (2.3)	[0] 0 (0)	521
MSK chest pain	41/M	[1] 1 (2.3)	[0] 0 (0)	160
Pelvi-ureteric obstruction	15/F	[0] 0 (0)	[1] 1 (3.1)	278
Serum sickness	12/M	[1] 1 (2.3)	[0] 0 (0)	22

Source: FDA Clinical Reviewer. Includes all serious events reported in adae.xpt
Abbreviations: AE, adverse event; F, female; M, male; MSK, musculoskeletal

A 12-year-old male was reported to have an SAE of ‘serum sickness’ 5 days after completion of a 14-day course of teplizumab, based on elevated C-reactive protein, erythrocyte sedimentation rate, and reduced C4 complement. Symptoms included arthralgias and fever, with laboratory data suggesting a recent streptococcal infection. The event resolved after approximately 2.5 months with a waxing and waning course. In retrospect, the patient was determined to have had a positive antinuclear antibody (ANA) prior to study treatment, and this finding raised the possibility that there was an underlying rheumatologic condition that may have been contributory (Karmacharya et al. 2015; Bayer et al. 2019). A causal relationship with teplizumab cannot be excluded. See also Section [8.5.2](#).

8.4.2.2 SAEs - Full ISS

[Table 23](#) presents SAEs that were more frequently reported by patients in the teplizumab group after at least one dose of treatment and that were reported by at least two patients, using the full ISS.

Table 23. Serious Adverse Events Reported During the Entire Follow-Up Period (Any Time After Treatment Administration) in At Least Two Patients in the Teplizumab Group with Risk Difference >0.1, — Full ISS

SAE	Teplizumab N=773 n (%)	Placebo N=245 n (%)	RD	Relative Risk	95% CI
Diabetic ketoacidosis*	20 (2.5)	2 (0.8)	1.8	3.17	(0.8, 13.5)
Infection*	26 (3.4)	5 (2.0)	1.4	1.65	(0.6, 4.2)
Hypoglycemic seizure	6 (0.8)	0 (0.0)	0.8	-	-
Cytokine release syndrome	5 (0.6)	0 (0.0)	0.6	-	-
Hypoglycemia*	13 (1.7)	3 (1.2)	0.5	1.37	(0.4, 4.8)
Hepatic injury*	4 (0.5)	0 (0.0)	0.5	-	-
Rash	2 (0.3)	0 (0.0)	0.3	-	-
Splenic rupture	2 (0.3)	0 (0.0)	0.3	-	-
Allergic reaction, hypersensitivity*	2 (0.3)	0 (0.0)	0.3	-	-
Suicidal ideation, intentional overdose, self-injury, suicide*	2 (0.3)	0 (0.0)	0.3	-	-
Lymphopenia*	2 (0.3)	0 (0.0)	0.3	-	-
Fall, dizziness, balance disorder*	2 (0.3)	0 (0.0)	0.3	-	-
Abdominal pain*	2 (0.3)	0 (0.0)	0.3	-	-
Pyrexia*	2 (0.3)	0 (0.0)	0.3	-	-
Fracture*	4 (0.5)	1 (0.4)	0.1	1.27	(0.1, 11.3)
Leukopenia*	4 (0.5)	1 (0.4)	0.1	1.27	(0.1, 11.3)

Source: Reviewer generated using ADAE.xpt. SAEs marked with an asterisk* represent queries that may include multiple terms
Abbreviations: CI, confidence interval; ISS, integrated summary of safety; RD, risk difference; SAE, serious adverse event

DKA is discussed in Section [8.5.6](#).

Aside from diabetes complications (DKA, hypoglycemia), the SAEs in the full ISS are qualitatively similar to the non-serious AEs (Section [8.4.5](#)). An exception is that SAEs of infections in the ISS were observed more frequently in teplizumab treated patients, 3.4%, compared with 2% of control patients, consistent with the finding in TN-10. Of interest, an SAE of hepatic amebiasis occurred in a 15-year-old male randomized to teplizumab. At the time of his hospitalization, his lymphocyte count was low in the context of elevated total leukocyte count and neutrophils, normal eosinophils, and elevated blood glucose. The event was considered resolved at the time of hospital discharge. It is possible that immunosuppression from teplizumab treatment contributed to the event.

Other notable SAEs of infection include four infections reported during or soon after teplizumab administration that required anti-infectives and either an ER visit or hospitalization. These were staphylococcal sepsis, anal abscess, epididymitis, and bronchitis. All four events were associated with lymphopenia and reported during the time period when immunosuppression related to teplizumab would be expected.

There were 4 teplizumab-treated patients who were diagnosed with SAEs of viral gastroenteritis, gastritis, or infection of unknown origin, observed within 1 week of teplizumab

dosing, all with presentations that have significant overlap with CRS (fever, nausea, vomiting, +/-rash) without a specific pathogen identified.

SAEs of CRS, which occurred in five patients in the teplizumab group and no patients in the comparator group, are likely drug related. CRS is discussed in detail in Section [8.5.1](#). Similarly, lymphopenia is known to be caused by teplizumab dosing, and SAEs of lymphopenia were reported by two patients in the teplizumab group and no patients in the comparator group. Please see Section [8.5.3](#) on lymphopenia. Hepatic enzyme abnormalities may occur as a part of CRS through the effect of cytokines on the liver, an issue that is discussed in more detail in Section [8.5.1](#). There were two SAEs each of hepatic enzymes increased in the teplizumab group vs. none in the comparator group. As shown in [Table 25](#), transaminase elevations were a commonly reported reason for treatment discontinuation.

Two patients were reported to have SAEs of drug hypersensitivity in the teplizumab group vs. none in the comparator group. One of these events was related to teplizumab, occurring in the context of CRS-like symptoms, and one event was remote to teplizumab dosing (approximately 17 months after dosing) and noted immediately after subcutaneous immunotherapy in the context of allergic disease. There were two serious reports of rash in the teplizumab group vs. none in the comparator group. Neither of these rashes appeared to be consistent with a clinically important event such as Stevens-Johnson syndrome, with one event occurring concurrently with CRS and the other severe rash occurring approximately 11 months after teplizumab dosing, too remote to be drug related. Cases of rash and hypersensitivity are further reviewed in Section [8.5.2](#).

Not shown in the table, an SAE of 'subclavian vein thrombosis' was reported for a 25-year-old patient, who had a peripherally inserted central catheter (PICC) placed in her left subclavian vein for study drug administration. Although this SAE is not directly caused by teplizumab, it is associated with the procedure for venous access needed to administer the drug.

Most SAEs resolved without sequelae, there were two events reported to have resolved with sequelae, phlegmon in a placebo patient, and biliary dyskinesia in a teplizumab-treated patient which occurred approximately 1 year after the last dose of teplizumab. Any SAEs that were listed as "not recovered/not resolved" were further investigated. One teplizumab-treated patient reported an SAE of sensorineural hearing loss with symptoms noted approximately 100 days after the last study drug and was determined upon neurosensory assessment to have permanent 50% hearing loss bilaterally. This was the only reported hearing-related adverse event reported in the ISS. There were two other SAEs marked as not resolved, uncontrolled hyperglycemia (teplizumab-treated patient with T1D with elevated glucometer readings) and microalbuminuria, reported in a placebo patient.

Some other isolated SAEs warranted further scrutiny, but after review of individual narratives, we determined that most were not reasonably attributed to treatment. The PTs for the SAEs are listed in [Table 34](#).

Reviewer comment: Infection secondary to immunosuppression is an important safety issue of interest for teplizumab. There were a few infectious events that were temporally related to teplizumab dosing and consequently, temporally related to immunosuppression, with reported low lymphocyte and/or neutrophil counts reported at the time of infection. It is important to note that some of these events could have been CRS rather than infection, as constitutional symptoms and fever have the potential to be confused for infection. All infectious SAEs resolved without sequelae and none were associated with long-term complications.

Despite these uncertainties, these data do not justify the Applicant's proposed labeling statement that teplizumab (b) (4)

Several other SAEs were notably in the same categories as non-serious events, e.g., CRS, lymphopenia etc. lending plausibility to a positive causality assessment.

For other SAEs, there are too few events to draw meaningful conclusions.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

This section discusses AEs that led to discontinuation of teplizumab treatment. According to the teplizumab study protocols, teplizumab dosing was to be fully withdrawn if certain clinical laboratory criteria were met ([Table 24](#)). In other words, drug infusions would not be resumed if any of the conditions in [Table 24](#) were met, and the subject would be considered as having met protocol-specified withdrawal criteria.

Reviewer comment: The withdrawal criteria were reasonable although perhaps somewhat conservative. There are implications for safety in the postmarket setting because similar withdrawal criteria will need to be applied in the postmarket setting to expect similar safety profiles in patients using teplizumab.

Table 24. Prespecified Discontinuation Criteria for Studies Included in ISS

Parameter	TN-10	AbATE	Protégé	Encore
Bilirubin	>1.3 mg/dL on Day 1; ≥2.0 mg/dL on other days	>1.3 mg/dL on Day 1; ≥2.0 mg/dL on other days	>2 times ULN	>2 times ULN
AST/ ALT/ LDH	AST level >2 times ULN on Day 1 AST, ALT or LDH ≥3.0 times ULN on other days.	AST level >2 times ULN on Day 1 AST, ALT or LDH ≥3.0 times ULN on other days.	AST or ALT >3 times ULN	AST or ALT >3 times ULN
Platelet count	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days	<140,000 on Day 1; <100,000 on other days
Neutrophils	<1000 cells/mm ³ (grade 3)	<1,000 cells/mm ³ (grade 3)	<1,000 cells/mm ³ (grade 3) on 2 consecutive evaluations performed on different days	<1,000 cells/mm ³ (grade 3) on 2 consecutive evaluations performed on different days
Hemoglobin	≤8.5 g/dL or a drop in ≥2 g/dL compared with prior to infusion to a value <10.0 g/dL	≤8.5 g/dL or a drop ≥2 g/dL to <10 g/dL	<8.5 g/dL or a reduction of >2 g/dL from pre-treatment level	<8.5 g/dL or a reduction of >2 g/dL from pre-treatment level
Coagulation	INR >0.1 above ULN	INR >1.3	N/A	N/A

Clinical Review
Lauren K. Wood Heickman, MD
BLA 761183
Tzield/Teplizumab (PRV-031)

Parameter	TN-10	AbATE	Protégé	Encore
Adverse Events	Grade 3 or above, except for: Lymphopenia Hypoglycemia Hyperglycemia Fatigue/malaise Insomnia Cheilitis Dry skin Nail changes Hot flushes/flushes Headache Myalgia Flu-like symptoms	Grade 3 or above, except for: Lymphopenia Hypoglycemia Hyperglycemia Fatigue/malaise Insomnia Cheilitis Dry skin Nail changes Hot flushes/flushes Headache Myalgia Flu-like symptoms	Grade 3 or above, except for: Lymphopenia Low WBC count Hypoglycemia or symptoms and signs of a hypoglycemic episode Hyperglycemia or symptoms and signs related to hyperglycemia Fatigue/malaise Insomnia Cheilitis Dry skin Nail changes Hot flushes/flushes Headache Myalgia Flu-like symptoms	Grade 3 or above, except for: Lymphopenia Low WBC count Hypoglycemia or symptoms and signs of a hypoglycemic episode Hyperglycemia or symptoms and signs related to hyperglycemia Fatigue/malaise Insomnia Cheilitis Dry skin Nail changes Hot flushes/flushes Headache Myalgia Flu-like symptoms

Source: Reviewer. The protocol for Delay was not available.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; Grading based on CTCAE, Common Terminology Criteria for Adverse Events; HGB, Hemoglobin; INR, international normalized ratio; ISS, integrated summary of safety; LDH, lactate dehydrogenase; NCI, National Cancer Institute; ULN, upper limit of normal; WBC, white blood cell

In addition, the protocols generally required discontinuation of teplizumab if any CTCAE grade 3 or above events occurred, other than events that were related to teplizumab's mechanism of action (e.g., lymphopenia, fatigue, malaise, hot flashes, flu-like symptoms).

In TN-10, one patient in the teplizumab group (elevated ALT and pruritic rash) and two patients in the placebo group (both with hyperbilirubinemia) were withdrawn secondary to these AEs. All AEs were related to the laboratory test criteria for drug discontinuation, and all resolved after dosing discontinuation.

AEs leading to withdrawal in the mISS dataset, during the first cycle are shown in [Table 25](#). A greater number of subjects discontinued study treatment in the teplizumab group: 91/729 (12.5%) compared to the control group 6/213 (2.8%). A majority of these AEs were related to the laboratory criteria for dosing discontinuation described above. All of these AEs resolved.

In the teplizumab group 5/91 (5.5%) of the AEs leading to withdrawal during the first cycle required hospitalization (CRS, two cases of transaminase increases, hypersensitivity reaction, hepatitis A) compared to the control group (multiple drug resistant tuberculosis, complication of pregnancy) 2/6 (33%). When looking at AEs leading to withdrawal during the second cycle, two cases were reported in teplizumab-treated subjects (severe neutropenia, infection of unknown origin) compared to no cases in controls.

Table 25. Adverse Events Leading to Treatment Discontinuation with Risk Difference At Least 1% — mISS

Preferred Term	Teplizumab N=729 [# events] n (%)	Control N=213 [# events] n (%)	Risk Difference n (%)
Decreased white blood cells ¹	[11] 11 (1.5)	[1] 1 (0.5)	1
Decreased hemoglobin ²	[14] 13 (1.8)	[0] 0 (0)	1.8
Transaminase elevations	[41] 41 (5.6)	[2] 2 (0.9)	4.7
Cytokine release syndrome	[7] 7 (1)	[0] 0 (0)	1
Thrombocytopenia	[7] 7 (1)	[0] 0 (0)	1

Source: ADAE.xpt.

Abbreviations: ISS, integrated summary of safety; mISS, modified ISS

¹ Includes leukopenia, lymphopenia, and neutropenia

² Includes decreased hemoglobin and anemia

mISS population (Omitting TN-10)

Only events occurring in treatment cycle 1, or treatment cycle 1 follow-up included.

Only events occurring in more than one subject are shown.

Reviewer comment: A large portion (51%) of discontinued patients met withdrawal criteria related to transaminase elevations. As reviewed in Section [8.4.6.2](#), elevations in transaminases were frequently observed with recovery despite continued dosing of teplizumab, and there were no signals observed for drug-induced liver injury. In the case of drug discontinuations solely related to hepatic enzyme elevations, it is unclear if discontinuation criteria were too

conservative given the data provided. It cannot be determined, however, whether the protocol-specified withdrawal criteria may have prevented more serious or permanent harms from continued dosing. Therefore, similar withdrawal criteria should be used in the postmarket setting. With this approach, it is estimated that approximately 10% of patients will not be able to tolerate the full course of teplizumab therapy.

8.4.4. Significant Adverse Events

Significant adverse events are discussed in Section [8.5](#).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

To evaluate ‘common’ adverse events, FDA MedDRA queries were used in addition to preferred terms, and terms included in the query for ‘common’ adverse events are listed in [Table 35](#) in [Appendix B](#).

[Table 26](#) displays the most frequent adverse events occurring in the full ISS pool during the 14-day treatment period. We also evaluated TN-10 and the mISS separately and found similar results (data not shown). Exploratory analyses of time to event for AEs that informed the basis for our review strategy (to evaluate the 14-day treatment period only) are shown in [Figure 32](#) in [Appendix B](#). Nevertheless, when AEs were evaluated over the entire follow-up period, the frequency of reported AEs appeared similar to the analysis shown in [Table 26](#), confirming that most teplizumab-related AEs were limited to the time of exposure (14-days).

During the treatment period (14-day course) a majority of patients reported at least one AE (>95%). Leukopenia and lymphopenia were the most frequently reported AEs. All reported AEs are expected based on teplizumab’s mechanism. Overall, the pattern of AEs observed demonstrate that adverse reactions caused by teplizumab treatment generally consist of low white blood cell count, rash, transaminase elevations, and other constitutional symptoms likely related to CRS (e.g., pyrexia). Transaminase elevations, CRS, rash, and lymphopenia are discussed in more detail in Sections [8.4.6.2](#), [8.5.1](#), [8.5.2](#), and [8.5.3](#), respectively. Other AEs such as chemistry panel abnormalities are probably drug related. With respect to severity, we examined the CTCAE severity rating for certain adverse events of interest, e.g., thrombocytopenia and hypocalcemia. All were reported as grade 1 or 2. In addition, all reportedly resolved without sequelae.

Table 26. Adverse Events in the Full ISS (TN-10 + ISS), 14-Day Treatment Period, Reported by At Least 10% of Patients in the Teplizumab Group, Ordered by Risk Difference

Adverse Event	Teplizumab N=773 n (%)	Placebo N=245 n (%)	Risk Difference n (%)	Relative Risk	Relative Risk 95% CI
Lymphopenia*	594 (76.8)	23 (9.4)	67.4	8.2	(5.5, 12.1)
Leukopenia*	635 (82.1)	59 (24.1)	58.0	3.4	(2.7, 4.3)
Rash*	344 (44.5)	22 (9.0)	35.5	4.9	(3.3, 7.5)
Transaminases elevated*	189 (24.5)	26 (10.6)	13.9	2.3	(1.6, 3.4)
Neutropenia	185 (23.9)	29 (11.8)	12.1	2.0	(1.4, 2.9)
Pruritus*	117 (15.1)	13 (5.3)	9.8	2.8	(1.7, 5.1)
Thrombocytopenia*	102 (13.2)	11 (4.5)	8.7	2.9	(1.6, 5.3)
Pyrexia	120 (15.5)	17 (6.9)	8.6	2.2	(1.4, 3.6)
Blood bicarbonate decreased	116 (15.0)	16 (6.5)	8.5	2.3	(1.4, 3.8)
Nausea*	106 (13.7)	15 (6.1)	7.6	2.2	(1.3, 3.7)
Anemia*	211 (27.3)	52 (21.2)	6.1	1.3	(1, 1.7)
Hypocalcemia*	143 (18.5)	31 (12.7)	5.8	1.5	(1, 2.2)
Headache*	136 (17.6)	35 (14.3)	3.3	1.2	(0.9, 1.8)
Hyponatremia*	158 (20.4)	43 (17.6)	2.8	1.2	(0.9, 1.6)

Source: Reviewer, ADAE.xpt.

Abbreviations: ISS, integrated summary of safety

* Events with an asterisk represent queries that include multiple terms

Adverse events with a risk difference favoring teplizumab are omitted

Reviewer comment: The AEs listed in [Table 26](#) are appropriate for section 6 of the Prescribing Information: Adverse Reactions.

Vomiting, chills, and fatigue were also reported more frequently by teplizumab treated patients vs. controls but at a frequency less than 10% (8.3% vs. 2.4%; 7% vs. 1.6%; and 8.7% vs. 4.5%; respectively). Hyperbilirubinemia was noted at a slightly higher frequency in teplizumab-treated patients (3.9%) compared to controls (2.4%).

Reviewer comment: These AEs are likely drug related and associated with cytokine release. These events should be reported in text format under the main Adverse Reaction table in section 6 of the Prescribing Information.

8.4.6. Laboratory Findings

As noted previously, routine laboratory safety assessments included complete blood count (CBC) with differential, coagulation tests, chemistry panels, liver tests, Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) viral loads and serologies, and urine pregnancy tests in females, and are presented in detail in [Table 6](#).

FDA analyses were conducted for laboratory data related to teplizumab's mechanism of action. Absolute lymphocyte count data was analyzed by trend over time along with neutrophil, platelet, and INR. Lymphocyte data are presented below. The other parameters demonstrated a similar trend with the greatest deviation from normal around Day 5 to 8 with recovery soon

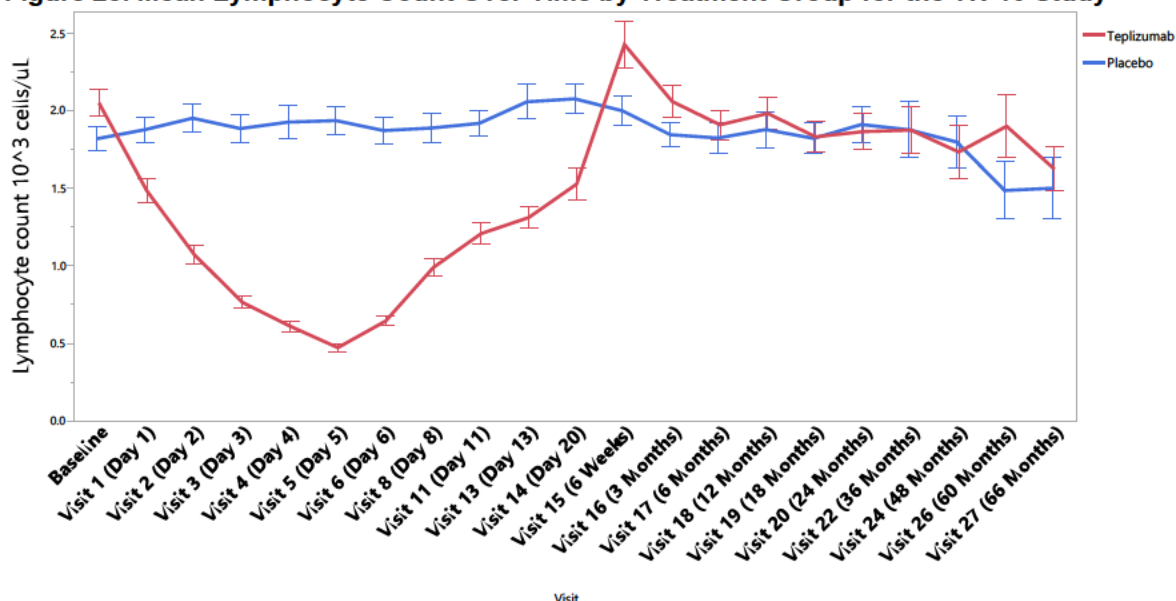
after. Peak ALT, AST, alkaline phosphatase (ALP) and total bilirubin were evaluated by longitudinal trend and by outlier analysis, based on the degree of elevation above the upper limit of normal (ULN). Important findings were limited to changes in lymphocyte counts and hepatic enzymes/bilirubin which are discussed in the next two sections.

Other analyses of laboratory data (analyses of central tendency) conducted by the Applicant were unremarkable and are not presented.

8.4.6.1 Lymphopenia

Lymphopenia is known to result from drugs that modulate T-cell function. In TN-10, there was a decline in lymphocyte count during the treatment course with nadir at Day 5, which recovered and returned to baseline by Week 6, even while dosing continued ([Figure 23](#)).

Figure 23. Mean Lymphocyte Count Over Time by Treatment Group for the TN-10 Study



Source: Reviewer generated from ad b.xpt dataset, TN-10.
Error bar indicates 1 standard deviation from the mean.

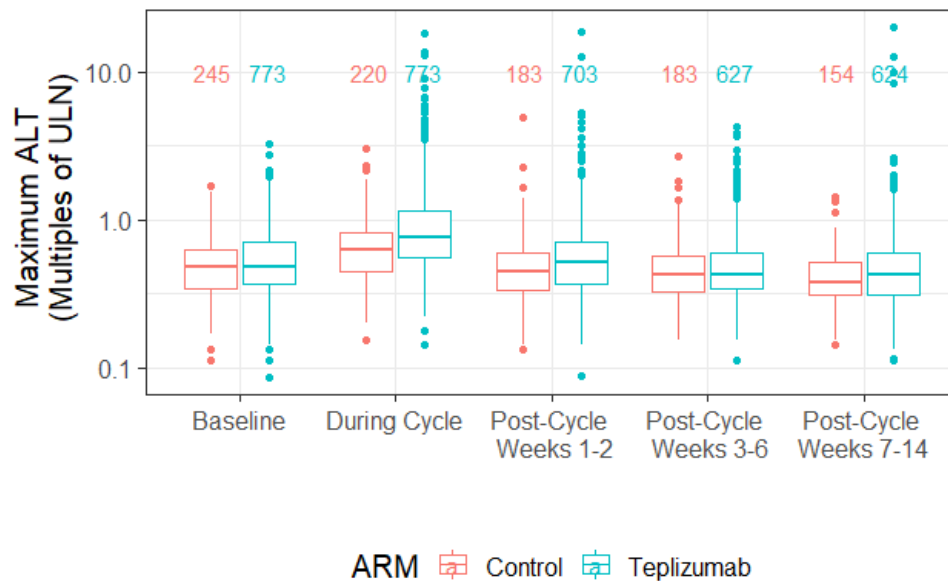
A similar pattern of lymphocyte decline and rebound was observed, with nadir at Day 5 and recovery at Week 6 in the mISS (data not shown).

Reviewer comment: An analysis of adverse events with the term lymphopenia is reviewed in Section [8.5.3](#).

8.4.6.2 Hepatic Enzyme Elevations

In the clinical studies, hepatic enzyme and bilirubin concentrations were generally measured daily during infusion periods, frequently for the 6 months (e.g., every 2 to 6 weeks), then every 12 weeks afterwards. The FDA analyzed bilirubin, ALT, and AST by time for the first treatment cycle. The maximum value for each patient and time period was selected (i.e., if a patient had daily labs drawn during the treatment cycle, only the highest value was selected). The data were normalized by the laboratory-reported upper limit of normal, pooled, and plotted to inspect longitudinal trends in ALT ([Figure 24](#)), AST, and bilirubin (not shown).

Figure 24. Observed ALT on a Semi-Log Scale, by Time Period — Full ISS



Source: Reviewer generated from ad b.xpt dataset.

Abbreviations: ALT, alanine transaminase; ISS, integrated summary of safety; ULN, upper limit of normal
Includes full ISS (TN-10 and supporting studies).

Visits were filtered to include main study visits, and exclude visits following a second cycle of treatment

ALT was balanced between treatment groups at baseline. A difference in the median and interquartile range (IQR) between treatment arms was observed during the treatment cycle but did not persist beyond 1 to 2 weeks post-treatment. [Figure 24](#) also suggests a difference in the occurrence of ALT >10X ULN for teplizumab-treated patients starting during treatment and persisting beyond 7 to 14 weeks, but there are approximately 3 times more teplizumab-treated patients than controls. Importantly, the observed ALT abnormalities (i.e., ALT >5X ULN and 10X ULN) resolved either by the end of observation, or before the start of a second treatment cycle.

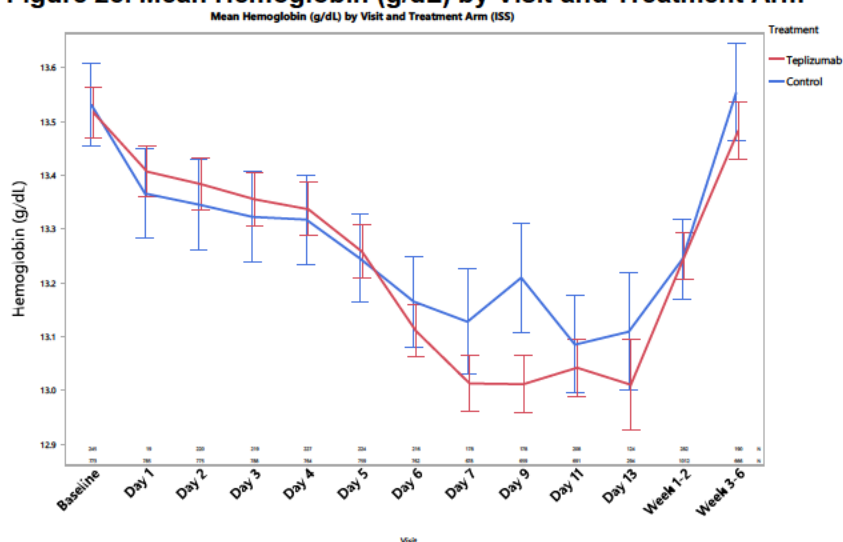
There were two SAEs each of hepatic enzymes increased in the teplizumab group vs. none in the comparator group. Both patients had normal hepatic enzymes at baseline, and the SAE lead to drug discontinuation. One patient's clinical course was consistent with CRS, with fever noted at the time of AST and ALT elevations (both $\geq 4 \times \text{ULN}$) following the 12th infusion of teplizumab, without bilirubin elevation. ALT and AST elevations resolved within 3 months without intervention. The other patient with an SAE related to hepatic enzyme elevations was noted to have Peak ALT, AST and total bilirubin were approximately $8 \times \text{ULN}$, $6.5 \times \text{ULN}$, and $>1.5 \times \text{ULN}$. This 10-year-old male patient completed 5 days of teplizumab before asymptomatic hepatic enzyme elevations were noted, leading to hospitalization workup for viral hepatitis was negative, with resolution of hepatic enzyme elevations within 2 weeks of drug discontinuation.

In addition to the two SAEs, there were two cases, in two patients with bilirubin $>2 \times \text{ULN}$ concurrent with ALT $>3 \times \text{ULN}$ which are reviewed in Section [8.5.4](#).

8.4.6.3 Hematologic Parameters

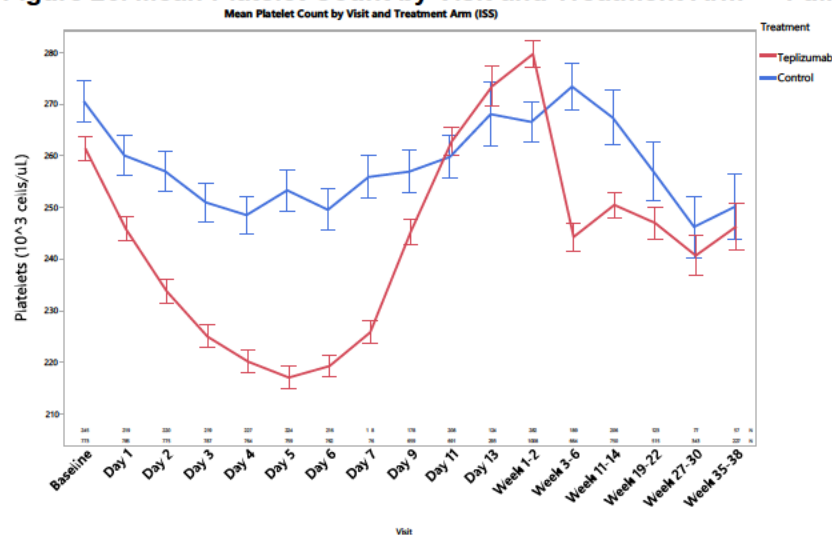
There were elevations from baseline in laboratory results (including hemoglobin, platelets, and Prothrombin Time/International Normalized Ratio (PT/INR) with nadir (Hemoglobin, Platelets) and peak (PT/INR) timing between visits 5 to 8, when the full dose of teplizumab had been reached, with recovery during the dosing period before the last dose of teplizumab. [Figure 25](#) and [Figure 26](#) below show the trend in hemoglobin and platelets for the ISS studies, and PT/INR for TN-10 is shown in [Figure 27](#).

Figure 25. Mean Hemoglobin (g/dL) by Visit and Treatment Arm — Full ISS



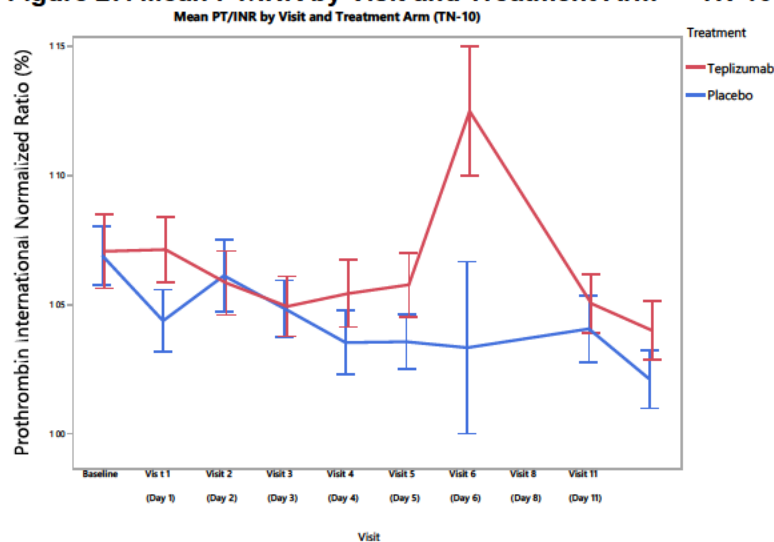
Source: Reviewer generated from ad.b.xpt dataset
Abbreviations: ISS, integrated summary of safety

Figure 26. Mean Platelet Count by Visit and Treatment Arm — Full ISS



Source: Reviewer generated from ad b.xpt dataset
Abbreviations: ISS, integrated summary of safety

Figure 27. Mean PT/INR by Visit and Treatment Arm — TN-10



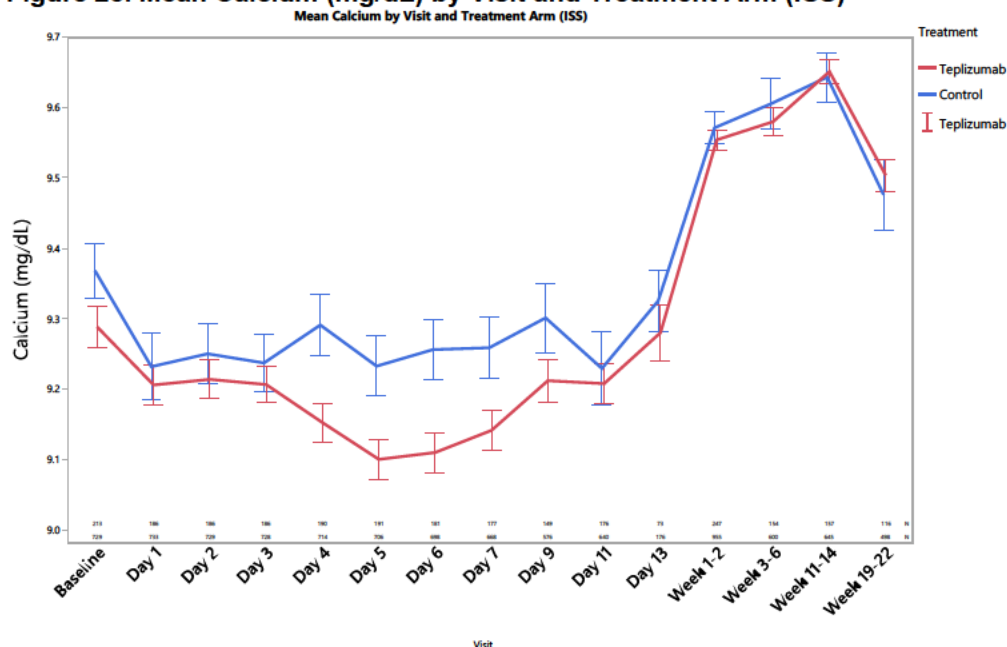
Source: Reviewer generated from ad b.xpt dataset TN-10
Abbreviations: PT/INR, prothrombin time/international normalized ratio

Lymphocyte count decline is presented in Section [8.4.6.1](#). A similar decline with recovery prior to the end of the 14-day treatment course were observed for other leukocyte cell lines; including neutrophils, monocytes, basophils in the TN-10 and ISS studies (data not shown). The eosinophil count elevations were observed in TN-10 and the ISS (not shown), with improvement to baseline by the 6-week follow-up visit.

8.4.6.4 Chemistry Parameters

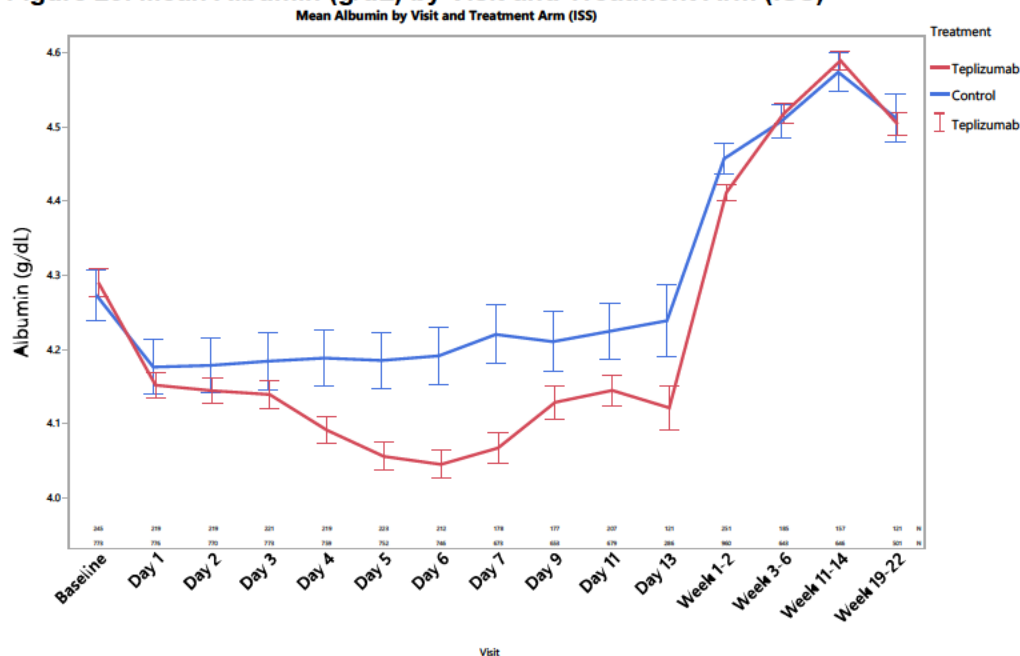
FDA analyses included the assessment of electrolytes (sodium, potassium, and calcium), and markers of renal function (BUN [blood urea nitrogen], Creatinine) during the teplizumab treatment and follow-up period for the pooled studies in the ISS. Transient changes were observed with liver function test parameters including ALT, AST, ALP, and bilirubin, presented in Section 8.4.6.2. Chemistry parameter outliers were low in frequency, and generally balanced between treatment arms. Calcium and albumin were the only chemistry parameters with notable differences between treatment arms during the dosing period for the study. There was a decrease in calcium with nadir day 5 and recovery before the end of the dosing period in teplizumab-exposed subjects (Figure 28). Mean blood albumin levels also decreased in the teplizumab arm during the dosing period, with recovery by week 1 to 2 of follow-up (Figure 29). There were no noted differences between treatment arms for serum sodium, chloride, potassium, creatinine, and bicarbonate during the treatment period (data not shown).

Figure 28. Mean Calcium (mg/dL) by Visit and Treatment Arm (ISS)



Source: Reviewer generated from ad b.xpt dataset
Abbreviations: ISS, integrated summary of safety

Figure 29. Mean Albumin (g/dL) by Visit and Treatment Arm (ISS)



Source: Reviewer generated from ad b.xpt dataset
Abbreviations: ISS, integrated summary of safety

8.4.7. Vital Signs

Changes in blood pressure, heart rate and temperature are potential effects of teplizumab treatment because of its capacity to cause CRS. It should be noted that BP measurements were not performed in triplicate or with the use of standardized equipment and the studies were not designed or conducted to rigorously assess blood pressure.

The Applicant provided a description of the changes in vital signs during treatment with teplizumab and concluded that “no clinically significant differences between treatment groups were observed” (ISS 4.1.1 Vital Signs). [Table 27](#) shows the results of the Applicant’s ‘clinically significant event’ analysis of the ISS vital signs, which were verified by the FDA reviewer.

Reviewer comment: As shown in [Table 27](#), there are small differences between teplizumab and control in clinically relevant cutoffs for blood pressure, heart rate, and most notably for temperature, so I disagree with the Applicant that “no clinically significant differences between treatment groups were observed”.

Table 27. Vital Signs, Applicant's ISS 'Clinically Significant Event' Analysis

Parameter	Teplizumab N=7911 n (%)	Control N=245 n (%)
Systolic blood pressure		
<80 mmHg	50 (6.3)	12 (4.9)
>140 mmHg	133 (16.8)	38 (15.5)
Diastolic blood pressure		
<45 mmHg	167 (21.1)	45 (18.4)
>90 mmHg	110 (13.9)	27 (11.0)
Heart rate		
<45 beats	20 (2.5)	5 (2.0)
>90 beats	502 (63.5)	144 (58.8)
Temperature		
<35°C	61 (7.7)	12 (4.9)
>37.5°C	224 (28.3)	52 (21.2)

Source: Sponsor's ISS Table 5.1

Abbreviations: ISS, integrated summary of safety

Further blood pressure analyses were requested of the Applicant. For these analyses, hypotension was defined³ as any systolic blood pressure <90 mmHg for children and adults ≥10 years of age and a systolic blood pressure <70 mmHg + (2 x age in years) for children younger than age 10. Overall, the incidence of hypotension during the course 1 treatment period was not different between treatment arms, with 180 of 773 teplizumab-treated patients (23.2%) compared with 56 of 245 control patients (22.9%) with hypotension identified by the analysis.

The Applicant also conducted an analysis of blood pressure data for the 39 patients who experienced adverse events of CRS. For these patients, the mean maximal drop in SBP was 25 mmHg (range 5 to 55) compared to the mean for the ISS population (17 mm Hg). For the patients with CRS events, hypotension events were noted to be more frequent on day 5 of the 14-day dose cycle.

Because of experience with the use of OKT3, the first FDA-approved anti-CD3 monoclonal antibody, hypertension and volume overload were of interest for the FDA review of this BLA and additional analyses were requested by the FDA during the review cycle. To identify hypertension in children, the Applicant used a simplified definition of stage 2 hypertension that takes into account the guidelines from the NHLBI Fourth Report, with hypertension in ages younger than 10 years defined as a systolic blood pressure >130 mmHg and for children and adults ≥10 years, a systolic blood pressure >140 mmHg (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Results demonstrated slightly more control patients 32/245 (13.1%) than teplizumab-treated patients 92/773 (11.9%) with hypertension events during the first course of teplizumab.

³ Adapted definition of hypotension in children provided by the Pediatric Advanced Life Support guidelines (Kleinman et al. 2010)

Reviewer comment: Teplizumab does not appear to cause meaningful blood pressure changes in most patients, but for teplizumab-treated patients with events of CRS, there were more dramatic maximal drops in SBP (~25 mmHg) noted, usually on day 5 of teplizumab. As changes in vital signs did not appear to persist beyond the dosing period, labeling mitigation measures such as blood pressure monitoring during infusion should be sufficient. Hypotension and hypertension/volume overload are discussed further as AESIs in Section [8.5.7](#).

8.4.8. Electrocardiograms

Electrocardiograms (ECGs) abnormalities are not expected for a monoclonal antibody product. Based on the Applicant's summary, there were no clinically significant ECG findings reported in the two studies where ECGs were specifically conducted after teplizumab dosing (Encore and TN-10). In TN-10 triplicate ECGs were performed at baseline and 12-month follow-up visits. In Encore, triplicate ECGs were performed at baseline and on day of dosing, before and 60 minutes after the infusion of teplizumab or placebo. The Applicant concluded that available nonclinical and clinical data demonstrate no evidence of any effect of teplizumab on cardiac repolarization.

The FDA clinical reviewer reviewed the cardiac adverse events (AESOC "Cardiac Disorders"). There was no signal for an increase in cardiac adverse events. A single death due to cardiac arrest was discussed previously.

8.4.9. QT

The Applicant requested a waiver to conduct a thorough QT (TQT) study. Via an email to the Division on July 7, 2020 (documented in DARRTS on June 25, 2021, the interdisciplinary review team for QT agreed with the request to waive a TQT study. They stated, "large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies. (Refer to ICH E14 Q&A (R3), section 6.3)."

8.4.10. Immunogenicity

Anti-drug antibodies (ADA) were identified in 50 to 92% of patients in Protégé, Encore and TN-10, during the first course of teplizumab across the various treatment regimens, and the incidence of ADA was as high as 90% when a second course was administered.

Type III hypersensitivity reactions, like serum sickness or vasculitis, are observed with monoclonal antibody therapies and are mediated by the formation of antigen-antibody complexes. Depending on the form, clinical manifestations may include fever, rash, arthralgias,

glomerulonephritis and lymphadenopathy. Timing of serum sickness is generally delayed, occurring weeks after the start of treatment, because the development of anti-drug antibodies precedes clinical manifestations. In addition, onset may be noted upon re-exposure to drug.

The Applicant performed an analysis of risk of serum sickness and vasculitis in patients who were either ADA antibody positive or negative, in Protégé ([Table 30](#)), Encore and TN-10 ([Table 31](#)). The Applicant reported that rash occurred more frequently in patients treated with teplizumab than with placebo or control comparator, but a correlation with development of ADA was not consistent across trials: ADA positivity did appear to increase the risk of AEs related to skin and subcutaneous disorders (rash) among ADA positive patients in Protégé in the first but not the second treatment cycles. In TN-10 there was a single case of serum sickness in an ADA positive patient, and there was a slightly higher frequency of rash in ADA positive patients.

Table 28. Immune-Related AEs by ADA Status for Protégé Segment 2, 14-Day Regimen

	COURSE 1 (number of events/total subjects (percent))				COURSE 2 (number of events/total subjects (percent))			
	ADA+	ADA-	Placebo ADA+	Placebo ADA-	ADA+	ADA-	Placebo ADA+	Placebo ADA-
Serum sickness	0/135	0/70	0/10	0/88	0/129	0/41	0/14	0/74
Skin & Subcutaneous disorders	59/135 (43.7)	19/70 (27.1)	1/10 (10.0)	7/88 (8.0)	12/129 (9.3)	7/41 (17.1)	0/14	2/74 (2.7)

Source: Applicant Table 26, ISI
Abbreviations: ADA, anti-drug antibodies; AE, adverse event

Table 29. Immune-Related AEs by ADA Status for TN-10

	Number of events/total subjects (percent)			
	Teplizumab ADA+	Teplizumab ADA-	Placebo ADA+	Placebo ADA-
Serum sickness	1/26 (3.8)	0/18	0/2	0/29
Skin & Subcutaneous disorders	10/26 (38.5)	6/18 (33.3)	0/2	0/29

Abbreviations: ADA=anti-drug antibodies; TEAE=treatment-emergent adverse event.
Source: ISI Tables 6.1.3.1, 6.1.3.2, 6.1.3.3, 6.1.3.5, 6.1.3.7, 6.1.3.9, and 6.1.3.11

Source: Applicant Table
Abbreviations: ADA, anti-drug antibodies; AE, adverse event

Reviewer comment: The data support the conclusions that teplizumab is immunogenic, potentially with clinical consequences of a greater risk of rash.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cytokine Release Syndrome

CRS was identified as an AESI (adverse event of special interest) for teplizumab because of its mechanism of action and given that CRS was frequently observed with OKT3, teplizumab's non-humanized precursor. In addition, nonclinical data from chimpanzees dosed with teplizumab demonstrated dose-dependent increases in circulating cytokines (TNF- α , IL-2, IL-6, IFN- γ) with peak levels 6 hours post-dose. T-cell agonists, including agonistic anti-CD3 antibodies like OKT3 and teplizumab, activate T-cells directly with subsequent secretion of cytokines that may cascade to other inflammatory cells. In addition, antibodies with an intact Fc receptor may activate monocytes and macrophages, resulting in cytokine production. Teplizumab, in contrast to OKT3, has been humanized in order to minimize Fc receptor binding, and thus there is a reduced risk of immune cell activation.

Symptoms of CRS include pyrexia, malaise, rash, headache, fatigue, arthralgias, myalgias, and nausea. Severe cases may include respiratory failure, hypotension requiring vasopressors, cardiac dysfunction, renal failure, elevated transaminases, and disseminated intravascular coagulation and multi-organ failure. Clinical signs and symptoms of CRS have been observed within minutes or hours of the first dose, and up to 14 days after infusion

Relevant cytokines include TNF- α , IL-2, IL-6, and IFN- γ . In the teplizumab development program, patients with new-onset T1D were observed to have peak serum TNF- α and IL-6 concentrations, following the second dose of teplizumab. Please see the consult from DHM1 for an additional discussion of CRS.

For purposes of the evaluation of CRS, the Applicant used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 CRS grading system. This grading method is based on clinical symptoms, the need for intervention (yes/no), and the intensity of intervention.

An overview of the CTCAE grading of CRS is presented in [Table 30](#). For additional details please refer to [Table 36](#) in [Appendix B](#).

Table 30. CTCAE Version 3.0 CRS Grading System

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 3.0	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; pressor or ventilatory support indicated

Source: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0
Abbreviations: CRS, cytokine release syndrome; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs, nonsteroidal anti-inflammatory drugs; IV, intravenous

In the ISS, there were 41 CRS cases reported during the first treatment cycle: 39 in the teplizumab group and 2 in the control group ([Table 31](#)). The majority (82%) of CRS cases were grade 1 and 2. The remaining 7 cases were grade 3, and 5/7 of the grade 3 cases were also reported as SAEs. An excess of 4.2 cases (95% CI: 2.3 to 6.1) of any grade of CRS was observed per 100 patients treated. The excess cases were primarily grades 1 and 2, with close to 1 excess case of grade 3 CRS per 100 patients.

Among the cases in the teplizumab group, ten resulted in treatment interruption or permanent treatment discontinuation. All patients with grade 3 events discontinued treatment early with a median treatment duration of 4.5 days. The median duration of the CRS event was 3 days and started 3 days into the treatment cycle. All 7 of the CRS grade 3 events occurred within 6 days of initiating the first course of teplizumab and had a median duration of 5 days.

Characteristics of the patients experiencing CRS were broadly consistent with the overall treatment population, although slightly older patients and more males reported CRS: the majority of cases of CRS were reported in males (30/41 [73.2%]). The median age of patients with CRS was also older (19 years) than the median age of the ISS population (15 years).

Of note, the identification of two cases of CRS in the control group highlights the limitations in the specificity of the CTCAE grading method as control patients should not have true CRS.

Table 31. Cytokine Release Syndrome Cases by CTCAE Grading Criteria and Treatment Group, All Studies — Full ISS

Severity	Teplizumab N=773 n (%)	Control N=245 n (%)	RD (95% CI)	RR (95% CI)
Overall	39 (5)	2 (0.8)	4.2 (2.3,6.1)	6.2 (1.5, 25.4)
1	12 (1.6)	1 (0.4)	1.2 (0.2,4)	3.8 (0.5, 29.1)
2	20 (2.6)	1 (0.4)	2.2 (0.8,3.6)	6.3 (0.9, 47)
3	7 (0.9)	0 (0)	0.9 (0.2,1.6)	-

Source: Reviewer generated using ADAE.xpt.

Abbreviations: CI, confidence interval; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ISS, integrated summary of safety; RD, risk difference

Includes both TN-10 and studies in the mISS. Only includes events occurring before initiation of a second treatment period.

Increased liver transaminases have been associated with CRS and are likely related to cytokine effects on the liver. Concomitant liver transaminase elevations were observed in 22/39 (56%) of teplizumab-treated patients experiencing CRS. The majority (64%) of liver transaminase elevations among these patients were CTCAE grade 1 (1-2.5x ULN), 32% were grade 2 (>2.5-5.0x ULN), and 4.5% were grade 3 (>5-10x ULN). All events of liver transaminase elevations >2.5x ULN occurred in patients with grade 2 and 3 CRS events, suggesting a correlation with the severity of CRS.

CRS requiring intervention other than antipyretics was rare. There were two hospitalizations for Grade 2 CRS and one hospitalization for Grade 3 CRS. There were no fatal outcomes or ICU admissions. No patient required a vasopressor for symptoms of hypotension or experienced significant hypoxia. There were no serious morbidities associated with CRS on review of the CRS specific report forms as well as AE reports.

8.5.1.1 Additional Cytokine Release Syndrome Analyses

The understanding of drug-induced CRS has improved with the expansion of use of therapeutics that activate T-cells, and newer CRS grading systems, such as the American Society for Transplantation and Cellular Therapy (ASTCT) criteria, have been developed to address limitations of older grading systems. In newer grading methods, fever ($\geq 38.0^{\circ}\text{C}$) is a requisite for a diagnosis of drug-related CRS.

Compared with the CTCAE method, the analysis using the ASTCT criteria showed an overall higher absolute risk of CRS in both teplizumab-treated and placebo groups, but a lower relative risk of CRS from teplizumab vs. comparator ([Table 32](#)). The majority of cases were Grade 1, which is associated with the presence of fever alone. In control patients, however, 10.2% also were classified as having Grade 1 CRS suggesting low specificity of this method. Of the 103 patients with Grade 1 CRS in the teplizumab treatment group, 10 required dose interruption. Grade 2 CRS events were infrequent. As a reminder, no patient required a vasopressor for symptoms of hypotension or experienced significant hypoxia.

Concomitant lymphopenia (defined as below the lower limit of normal) was also observed in the majority (88%) of patients with CRS events. However, the lymphopenia in the context of CRS was not more severe than that observed in the overall population.

Table 32. Analysis of Cytokine Release Syndrome by ASTCT Grading Criteria and Treatment Group, All Studies — Full ISS

Severity	Teplizumab N=773 n (%)	Control N=245 n (%)	Risk Difference (95% CI)	Relative Risk (95% CI)
Overall	130 (16.8)	25 (10.2)	6.6 (2,11.2)	1.7 (1.1, 2.5)
1	103 (13.3)	21 (8.6)	4.8 (0.5,9)	1.6 (1.0, 2.4)
2	27 (3.5)	4 (1.6)	1.9 (-0.2,3.9)	2.1 (0.8, 6.1)
Fever + Hypoxia	2 (0.3)	0	0.3 (-0.1,0.6)	-
Fever + Hypotension*	21 (2.7)	4 (1.6)	1.1 (-0.9,3)	1.7 (0.6, 4.8)
Fever + Hypoxia + Hypotension*	4 (0.5)	0	0.5 (0,1)	-

Source: Reviewer generated using DHM1 consult reviewer dataset.

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; CI, confidence interval; DHM1, Division of Hematologic Malignancies 1; ISS, integrated summary of safety

* Hypotension as defined by the Pediatric Advanced Life Support Guidelines (Kleinman et al. 2010): systolic blood pressure <86 mmHg for children age ≥8 years <9 years, <88 mmHg, for age ≥9y but <10 years, children and adults ≥10 years <90 mmHg
Includes both TN-10 and studies in the mISS. For patients with more than one CRS event, only worst grade shown. Only includes events occurring before initiation of a second treatment period.

Reviewer comment: Both the CTCAE and ASTCT methods of CRS grading showed an increased risk of CRS with teplizumab treatment vs. controls. This finding, in addition to the mechanism of action of teplizumab and the known risk of CRS with OKT3, is strongly suggestive of a causal relationship between teplizumab and CRS. The majority of events of CRS were considered mild, although some led to treatment discontinuation (about 1/3 using the CTCAE grading system). No patient experienced irreparable harm, however. Therefore, at this time the risk of CRS seems appropriate for labeling in the Warnings and Precautions section of the Prescribing Information. Additionally, CRS should be included as a safety issue of interest in postmarketing safety study(s) to further characterize the risk.

Mitigation steps used in the protocols to reduce the risk and/or symptoms of CRS included ramp-up dosing, pretreatment with ibuprofen, or similar non-steroidal anti-inflammatory (NSAID) and antihistamine. The same premedications should be continued in the post-marketing period and be recommended in section 2 of the Prescribing Information, if approved. Given the low incidence of severe CRS, few patients requiring hospitalization, and no patients requiring escalation of care, the DHM1 consultants did not recommend additional premedication, e.g., corticosteroids as prophylaxis in this population.

8.5.2. Hypersensitivity/ Rash

Anaphylaxis and serum sickness or vasculitis are two major acute infusion reactions that can be caused by monoclonal antibody therapies. These adverse reactions are less common with humanized monoclonal antibodies, but remain a concern (Isabwe et al. 2018). Patients with underlying autoimmune diseases, e.g., T1D, appear to be at a higher risk of drug hypersensitivity reactions than the general population (Karmacharya et al. 2015; Isabwe et al. 2018; Bayer et al. 2019). The Applicant identified hypersensitivity reactions as an EOSI. FDA conducted a standard MedDRA query for hypersensitivity-related AEs occurring during or following the first treatment cycle.

Our review revealed a low frequency of hypersensitivity AEs (with preferred terms “hypersensitivity” and “drug hypersensitivity”) 7/773 (0.9%) in the teplizumab group, vs. 2/245 (0.8%) in the control group. Two of the cases of hypersensitivity were reported as SAEs. One was likely related to study drug treatment: a 17-year-old male patient developed generalized cutaneous rash, fever, chills, nausea, and vomiting within 3-4 hours of teplizumab administration. The patient was hospitalized and treated with acetaminophen, loratadine, and IV hydrocortisone and discharged from the hospital the following day. Around the time of hospitalization, this patient also experienced laboratory abnormalities including low lymphocytes, neutrophils, platelets. Therefore, it is important to note that the clinical manifestations and timing of onset of this event could also be indicative of CRS. The other reported SAE associated with hypersensitivity occurred in a 26-year-old male approximately 204 days after the last dose of teplizumab and was reported immediately after receiving immunotherapy for allergic rhinitis. This event is unlikely to be related to drug administration.

There were two cases of angioedema (swelling face, periorbital edema) among teplizumab-treated patients and none among controls. No anaphylaxis was reported, but there was an SAE which appears consistent with a serious allergic reaction: the event was reported as grade 3 CRS by the investigator. The event lead to drug discontinuation after acute onset of symptoms of fever, nausea, vomiting, rash, facial swelling, urticaria, and bronchospasm following the fourth infusion of study drug.

As previously discussed, rash was commonly reported. During the 14-day treatment period, 11 (1.4%) teplizumab-treated patients and 1 (0.1%) control patient experienced urticaria. The majority of rashes observed with teplizumab treatment were not serious and resolved without intervention. One event of rash was reported to be serious and appeared to be partly allergic in nature, associated with urticaria; the event resolved after 4 days despite continued teplizumab dosing.

Reviewer comment: Allergic reactions and drug hypersensitivity appear to be a potential risk of teplizumab therapy and should be included in the product labeling in Warnings and Precautions.

Rash is clearly drug-related, although seems to have multiple causal pathways including CRS, ADA positivity, allergic reactions, and other mechanisms of drug-hypersensitivity. There is no evidence, however, of serious rash with sequelae.

8.5.3. Lymphopenia

Lymphopenia is known to result from drugs that modulate T-cell function. Therefore, we examined changes in lymphocyte count using both laboratory data, presented in Section [8.4.6.1](#), and via AE reporting with a focus on serious AEs of lymphopenia.

Lymphopenia was the most frequently reported AE during the study, observed in 72.7% of the teplizumab treatment group and 6.3% of the placebo group with a risk difference of 65.6% (95 CI: 49.3 to 81.9). Overall, 84% were grade 2 or grade 3 lymphopenia. As shown in the laboratory analysis section, in TN-10, lymphocyte count nadir occurred at Day 5, with recovery and return to baseline by Week 6, with most returning to baseline before the end of the treatment period, even while dosing continued ([Figure 23](#)). Outlier analysis for lymphocyte data for ISS (including TN-10) revealed no cases of persistent severe lymphopenia.

Two events in the ISS were reported as SAEs, one of which appears to be based on the degree of lymphocyte nadir (0.15×10^3 cells/uL on Day 8 of teplizumab infusion). The other was associated with an infection (gastritis); both resolved without sequelae.

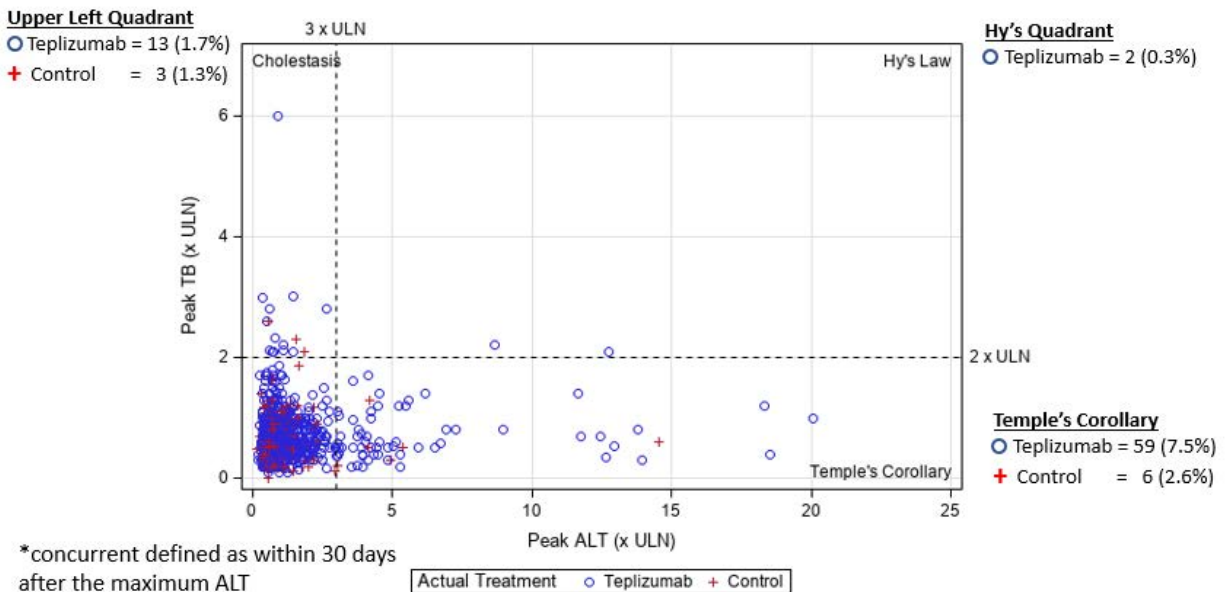
Reviewer comment: Overall, events of lymphopenia were predictable and transient. Besides the isolated SAE narratives above, no lymphopenia adverse events were serious. In addition to lymphopenia SAEs, any infection-related SAEs were reviewed for association with lymphopenia and are discussed in Section [8.4.2](#).

8.5.4. Evaluation of Potential Drug Induced Liver Injury

Maximum treatment-emergent values for all patients (full ISS) during the entire treatment and follow-up period were calculated for ALT and bilirubin and paired with each other if both laboratories were collected within 30 days ([Figure 30](#)). There were only two cases, in two patients with bilirubin >2X ULN concurrent with ALT >3X ULN. Both cases were determined to not be related to drug-induced liver injury and had alternative explanations (CRS and Hepatitis A).

Figure 30. Analysis of Maximum Concurrent ALT Plotted With Maximum Total Bilirubin by Patient

Maximum ALT xULN with concurrent* maximum Total Bilirubin x ULN



Source: Generated from 785 patients pooled from the ISS teplizumab treatment group and 233 control group patients with concurrent ALT and Tbili values.

Abbreviations: ALT, alanine transaminase; ISS, integrated summary of safety; ULN, upper limit of normal

Analysis includes courses 1 and 2 of treatment for pooled studies and includes the 18 patients from Delay who received both placebo and teplizumab.

8.5.5. Infections

8.5.5.1 General Infections

As noted previously, infection secondary to immunosuppression is an important safety issues of interest for teplizumab. In the full ISS, during the period of the 14-day teplizumab infusion, 38 patients (4.9%) reported any infection in the teplizumab group compared to 12 (4.9%) in the control group. During the first treatment cycle and follow-up period, 581 infections were reported by 309 patients (40.0%) in the teplizumab group compared to 17 infections among 99 patients (40.4%) in the control group.

As discussed previously, however, we found a higher incidence of serious infections in the teplizumab group compared to the control group. Additionally, the Applicant pre-specified CTCAE grade ≥ 3 infections (i.e., those requiring IV anti-infectives, invasive intervention, hospitalization, and/or resulting in death) as an EOSI. Such infections were reported by 3.0% of teplizumab patients and 2.0% of controls over all observation periods.

Reviewer comment: The reason for the similar frequency of general infections, but disproportionate frequency of serious infections, is unclear, but could be

related to misdiagnoses of CRS events as infections. Given the uncertainty it seems prudent to conservatively label the product and include a Warning and Precaution for a potential risk of serious infection.

8.5.5.2 Epstein-Barr Virus Reactivation

Reactivation of Epstein-Barr virus (EBV) has been observed with other immunotherapies affecting T-cell function. Cytotoxic (CD8+) T-cell exhaustion after teplizumab exposure is correlated with EBV reactivation (Long et al. 2016), and transient dose-related EBV reactivation has been observed in clinical studies with another anti-CD3 monoclonal antibody, oteelixumab (Keymeulen et al. 2021).

The Applicant conducted an exploratory MedDRA query for EBV⁴ and adjudicated each case as 'new infection' or 'reactivation' based on review of baseline status of seropositivity, AE listings, and clinical laboratory values. The adjudication of events was confirmed by the FDA clinical reviewer based on blinded review of the data.

At baseline, 76.6% of teplizumab patients and 72.3% of controls were noted to have evidence of prior EBV infection (as assessed by presence of EBV IgG antibody). The adjudication demonstrated a higher rate of EBV reactivation among teplizumab patients (4.5%) than controls (2.3%). Teplizumab treatment, however, did not appear to increase the risk of primary EBV infection, with slightly higher rates of new EBV infection in the control group (3.3%) compared with the teplizumab group (2.5%). Of the cases of EBV reactivation in the teplizumab group, 58% occurred within 30 days of teplizumab dosing.

8.5.5.3 Epstein-Barr Viremia and Lymphoproliferative Disorders

EBV-associated lymphoproliferative disorder (LPD) has been observed to be caused by drugs that suppress T-cell immune function. LPD is most commonly observed in the year following initiation of immunosuppressive therapies in solid organ transplant recipients (Green and Michaels 2013). EBV-associated LPD is more common in initially seronegative individuals who undergo organ transplantation and subsequently acquire a primary EBV infection (Walker et al. 1995; Nijland et al. 2016). In addition, chimpanzees dosed with teplizumab at 10 mg/kg (approximately 40x the human dose proposed) died secondary to non-neoplastic B-cell LPD resulting from T-cell immunosuppression and infection with an EBV-like virus.

⁴ PTs included Epstein-Barr viraemia, Epstein-Barr virus test positive, Epstein-Barr virus antibody positive, Epstein-Barr virus antigen positive, Epstein-Barr virus infection, Epstein-Barr virus infection reactivation, mononucleosis syndrome and infectious mononucleosis.

There were no events of LPD reported in the ISS population of patients with recent-onset T1D, or at-risk for T1D. We are aware of a single case of EBV-associated nonmalignant LPD noted in an islet cell transplant recipient dosed with teplizumab along with other immunotherapies (tacrolimus, sirolimus and etanercept). The confounding of chronic immunosuppressive therapies makes it unclear if teplizumab contributed to this event.

Higher peak quantitative EBV viral DNA titer is correlated with higher rates of post-transplant LPD (Green and Michaels 2013).

In the TN-10 study, EBV viral DNA was collected on Day 20, Week 6, and Months 3, 12, 24, 36, and 48. Nine patients in the teplizumab treatment group experienced increases in EBV viral DNA >3,000 copies/mL, a threshold selected by the Applicant, compared to none in the placebo group. All nine patients were noted to have increased EBV DNA titers at either the 20-day or 3-month visit after teplizumab dosing, with peak titer ranging from 3,045 to 32,325 copies/mL. A peak EBV viral DNA >1,000,000 copies/mL was noted in a single patient at Day 31, with resolution to <500 copies/mL 84 days later. Notably, all patients experienced a reduction in EBV viral load <1,000 copies/mL within 3 months postdosing, with continued reductions over time. One patient with EBV titers >3,000 copies/mL presented with pharyngitis, whereas the others were asymptomatic. The time course of EBV viral DNA increases observed in TN-10 mirrors the timeline of EBV viral reactivation observed in published T1D trials featuring the anti-CD3 monoclonal antibody, oteplizumab, where peak EBV titers were noted at Day 21 post-dose with subsequent recovery (Keymeulen et al. 2021).

Reviewer comment: It is reassuring that no events of LPD were reported in the ISS, despite follow-up times as long as seven years. Nevertheless, LPD remains a potential risk because of evidence of EBV viremia in some teplizumab-treated patients and the possible long-latency of LPD. In addition to labeling recommendations to prevent patients with active EBV or CMV infections from being treated with teplizumab, I recommend study of LPD in the postmarketing setting (via enhanced pharmacovigilance or an exposure registry). Further discussion of this issue is deferred to the next review cycle.

8.5.5.4 Other Notable Infections

Cytomegalovirus (CMV) is another common virus for which reactivation events are observed more commonly in immunocompromised hosts. There were very few adverse events of CMV infection within the mISS population, with 9/729 (1.2%) teplizumab-treated patients and 2/213 (0.9%) controls with 'Cytomegalovirus infection' or 'Cytomegalovirus test positive' events.

Herpes infections, which included the terms 'oral herpes' and 'herpes simplex', occurred in 7 of 773 teplizumab-treated patients (0.9%) and in 1 control patient (0.4%). VZV infections, which

were reported as 'varicella', 'herpes zoster', and 'varicella zoster virus infection' occurred in 9 teplizumab-treated patients (1.2%) and 1 control patient (0.4%).

Also, of interest, cases of tuberculosis were balanced between study arms with a single case of pulmonary tuberculosis, reported as an SAE in a teplizumab-treated patient approximately 151 days after treatment completion, and a SAE of disseminated pulmonary tuberculosis in a placebo patient 75 days after dosing.

Reviewer comment: Comparative rates of CMV, herpes virus, and VZV are all in favor of placebo (higher frequency in teplizumab) but absolute incidence is very small.

8.5.6. Diabetic Ketoacidosis

As discussed in Section [2.1](#), DKA is a substantial risk in children and adolescents with T1D and is caused by relative insulin insufficiency to metabolic need.

Importantly, there were no events of DKA in TN-10, in patients developing overt T1D, possibly reflecting the close follow-up of patients. All events of DKA occurred in the new- or recent-onset T1D trials. In the teplizumab development program, events of metabolic acidosis and DKA were identified by investigator-reported AEs that included PTs suggestive of possible DKA: Diabetic Ketoacidosis, Diabetic ketosis, Ketosis, and Ketoacidosis. The FDA analysis included assessment of the mISS pool during the entire follow-up period (including course 2 and follow-up period for patients in Protégé, Encore and AbATE given a second treatment course), and limited to course 1 and the course 1 follow-up period.

There was one fatal DKA event. On review of the DKA event, there are several features that lead to the determination that it was unlikely related to study drug. The DKA event occurred 9 months after the last dose of teplizumab, in a patient who had 6 DKA events preceding the event, including DKA prior to treatment with teplizumab. An insulin dose reduction from ~0.5 units/kg/day to approximately ½ the dose, 0.2 units/kg/day was observed prior to the onset of DKA episodes. Records from the first two DKA hospitalizations indicate disturbance of diet and insulin therapy were precipitating factors for DKA events, and substantial insulin dose increases were noted after the second hospitalization.

Over the entire duration of the follow-up period (course 1 and course 2), there were 32 episodes of DKA among 22 patients with a higher rate of DKA among teplizumab-treated patients 20/729 (2.7%) than among control patients 2/213 (0.9%). One DKA event in the teplizumab group was fatal as previously discussed.

The mean average time to event for the event analysis was 284.7 days after the last dose of teplizumab for the teplizumab-treated patients. The risk of DKA did not appear to be dose dependent (data not shown).

A detailed review of the narratives of DKA events among patients who were teplizumab-treated ([Table 37](#)) suggested that in many cases (30%), insulin dose was lowered prior to the DKA event; relative insulin insufficiency is a well-known cause of the development of DKA. For the two comparator patients, no insulin dose reduction was reported.

On further review of the narratives, we could identify in 80% of DKA cases a potential cause, i.e., a prior illness immediately preceding the DKA event, such as a viral upper respiratory illness, UTI, pyelonephritis, pneumonia. In one case, dengue fever was determined to be the preceding illness. Pump malfunction and investigator reported non-compliance were additional noted associated factors. Two patients also experienced DKA between diagnosis of T1D and screening for the study.

Table 33. Factors Associated With DKA Events — mISS

Characteristic	Positively Adjudicated N=20 n (%)
Insulin dose reduction	6 (30)
Insulin pump malfunction	3 (15)
Prior illness	8 (40)
Investigator-reported non-compliance	8 (40)
DKA episode between diagnosis and screening	2 (10)

Source: Reviewer generated table
Abbreviations: DKA, diabetic ketoacidosis; ISS, integrated summary of safety; mISS, modified ISS
The total number of events (N=20) includes DKA events in the teplizumab arm

Reviewer comment: There was a large difference in events of DKA not favoring the teplizumab group (20 vs. 2) among patients with T1D in the mISS population. This large of a difference is unlikely to be play of chance, but there is no clear mechanism how teplizumab could cause DKA. Teplizumab per se, may not be the cause, however, given that insulin dosing was disproportionately lowered for patients in the teplizumab group. The reason for this is unclear but could be related to inadvertent unblinding of treatment groups, especially because investigators had access to lymphocyte count monitoring information. In light of this uncertainty, DKA should be an adverse event of interest in postmarketing safety evaluations.

8.5.7. Hypotension and Hypertension/Volume Overload

As discussed previously, hypotension is a symptom of CRS. In addition, hypertension/volume overload was a safety concern for OKT3, teplizumab's non-humanized precursor.

We analyzed adverse events related to hypotension, including the following PTs: 'blood pressure decreased', 'diastolic blood pressure decreased', 'hypotension', 'orthostatic hypotension' in the ISS population. There were 30/773 (3.9%) teplizumab-treated vs. 8/245 (3.2%) control participants reporting hypotension-related terms during the first treatment cycle including the follow-up period. When this analysis was limited to the 28 days following any dose of study drug (the more appropriate analysis for this AE), the difference in frequency was more apparent: 20/773 (2.5%) among teplizumab-treated patients and 4/245 (1.6%) among controls. Importantly, however, there was no difference between groups in the frequency of syncope or presyncope.

An FDA MedDRA query was performed for events related to volume overload. Overall, there were more teplizumab patients 8/747 (1.1%) with MedDRA events related to volume overload (edema, non-pulmonary edema, fluid retention, overload) within 28 days of the last dose of study drug in comparison to 0 of the control.

Reviewer comment: AEs related to hypotension and volume overload were slightly more frequent among teplizumab-treated patients, but absolute incidence was low. These findings are consistent with the blood pressure analyses in Section [8.4.7](#).

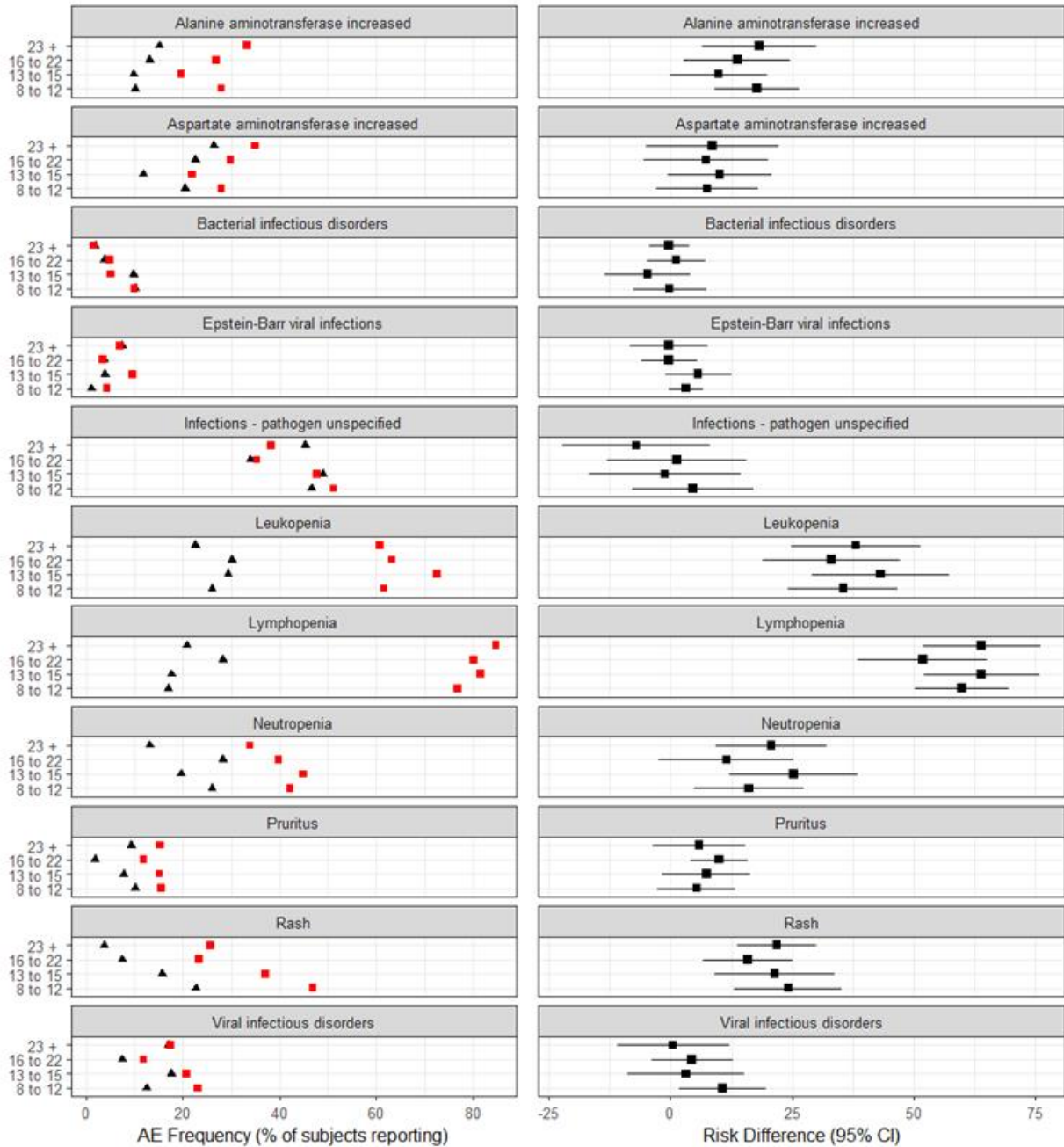
8.6. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroup utilizing the placebo-controlled pool were performed to evaluate whether significant adverse events (cytokine release syndrome, infections, cytopenias, hepatic enzyme elevations) differed importantly among subgroups.

Overall, the incidence of AEs in the full ISS (TN-10 and the supporting studies) were similar by quartiles of age ([Figure 31](#)). No treatment by age group interactions were observed.

Also shown in [Figure 31](#), there were no differences in safety findings among subgroups of sex (male and female) and race (White, Asian, Other). Note that the data were primarily from White patients, however, limiting conclusions.

Figure 31. Treatment-Emergent Adverse Event Analysis by Age, Sex, and Race Subgroups — ISS

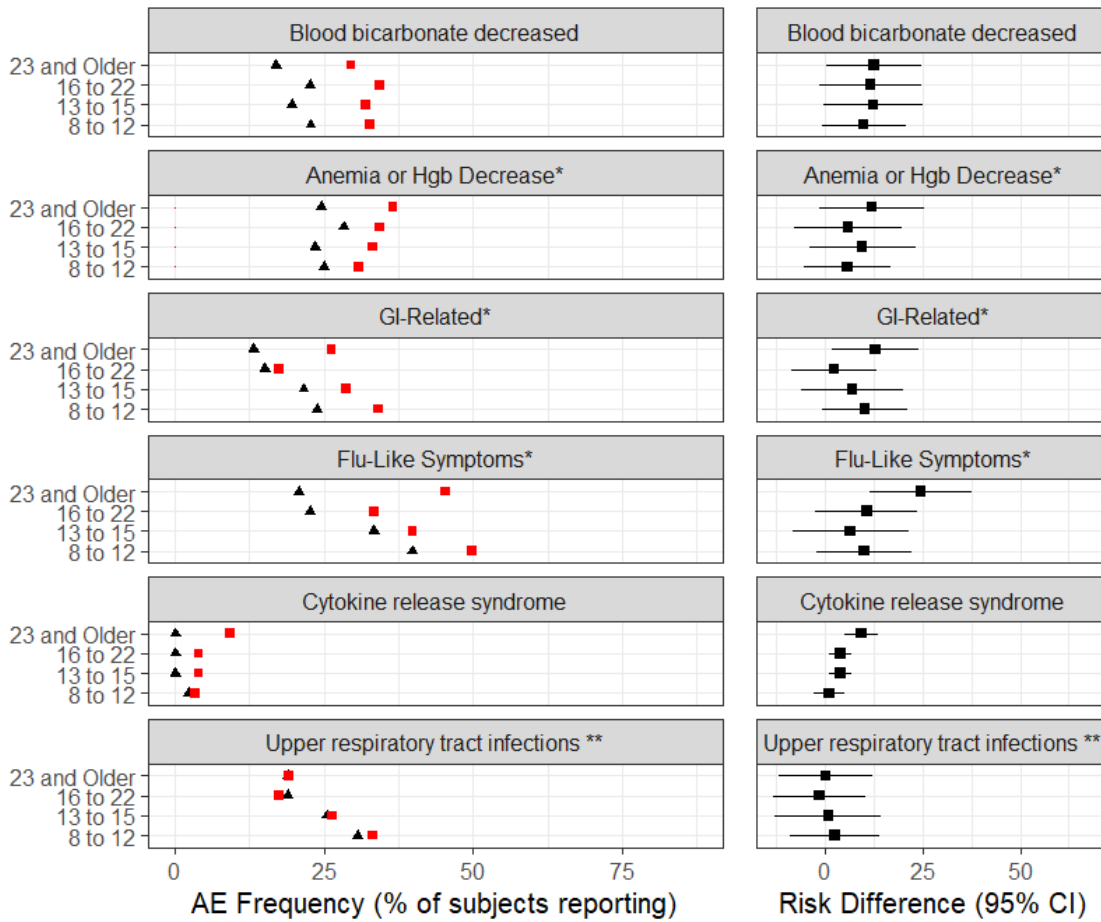


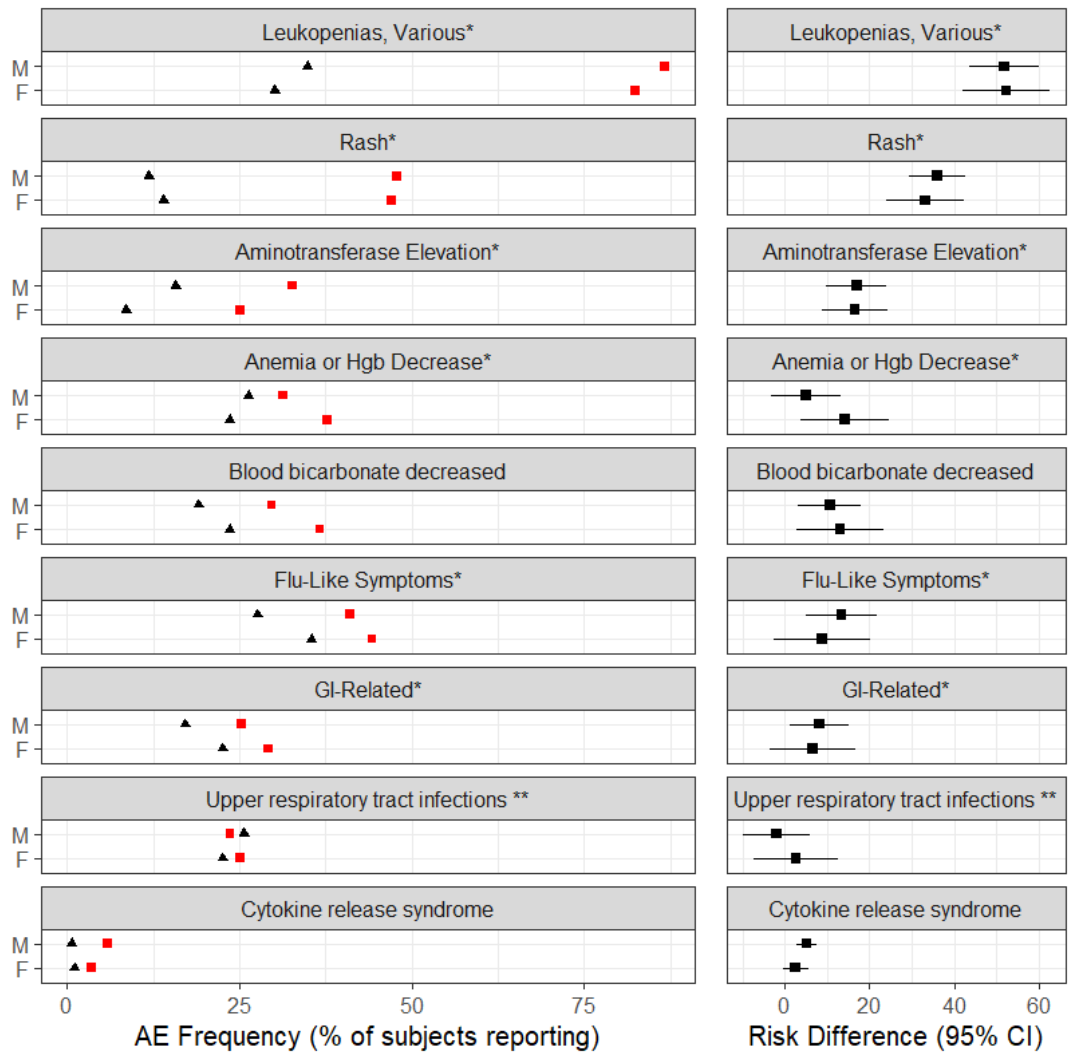
Clinical Review

Lauren K. Wood Heickman, MD

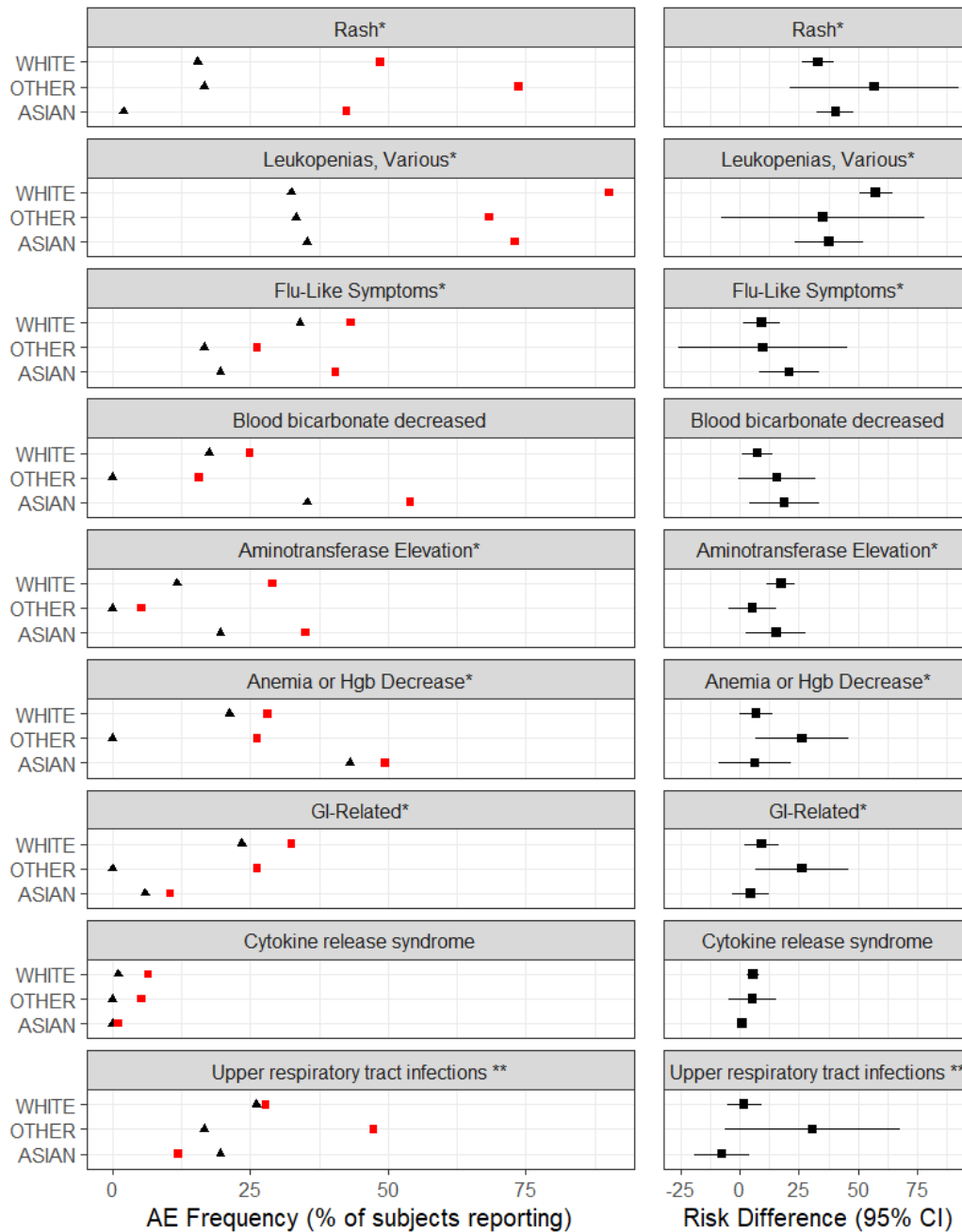
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Tzield/Teplizumab (PRV-031)





Clinical Review
 Lauren K. Wood Heickman, MD
 BLA 761183
 Tzield/Teplizumab (PRV-031)



Source: Clinical Reviewer Generated from adae.xpt, full ISS, limited to adverse events reported during course 1 treatment and follow-up period; Red squares=placebo, black triangles=teplizumab
 Abbreviations: AE, adverse event; CI, confidence interval

8.7. Specific Safety Studies/Clinical Trials

No other specific safety studies were conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

It is important to note that the clinical safety data submitted in the BLA are not sufficient to evaluate the potential risk of malignancy because of the short duration of follow-up as well as the relatively young age of the safety population. The longest trial duration available in publication is the 7-year follow-up of the AbATE trial (n=43), and this trial reported no malignancy among the 43 patients treated with two courses of teplizumab (given 1 year apart). In the ISS population, one malignancy was reported: a teplizumab-treated 21-year-old male was diagnosed with melanoma of the scalp with metastases to regional lymph nodes (supraclavicular and suprascapular). The patient had a history of dysplastic nevi and a pre-existing lesion that was not noted until after study entry. The affected tissue and lymph node metastases were excised, and no recurrence has been reported. Although it is extremely unlikely that teplizumab caused the malignancy, a contribution of teplizumab to a more rapid metastasis cannot be excluded.

Immunosuppressive therapies carry a theoretical concern for malignancies, as immunosuppression is known to impact anti-oncogenic immune activity (Wu and Shapiro 2011). OKT3, the progenitor mAb to teplizumab, has a labeled risk for post-transplant lymphoproliferative disorders, sometimes fatal. For OKT3, malignant lymphomas appear to develop early after transplantation, the majority within the first four months post-treatment (Swinnen et al. 1990). Therefore, this concern may be more relevant to chronic therapies using higher doses, such as in the setting of transplant rejection, than to therapies consisting of a single course of treatment.

Reactivation (1 to 4 months post-transplant) of EBV and CMV, and subsequent lymphoproliferative disorder (LPD) is a labeled risk for OKT3 therapy. There were observed EBV reactivations in the teplizumab development program. Most EBV reactivation events were reported early after treatment with teplizumab, with a minority of cases occurring more than 30 days after the end of treatment. However, no cases of LPD were observed in the teplizumab program, but there is a theoretical risk for the occurrence of LPD in the postmarket period.

Based on published reports in transplant patients, lymphoproliferative disorders occurred frequently within a year of transplantation (Opelz and Henderson 1993). Thus, the duration of follow-up (see Section [8.2.1](#)) for teplizumab was likely sufficient to detect a signal for LPD should it exist and be clinically important. The consultant from DHM1 estimated that the risk of LPD with teplizumab is <1%, so a registry study may not be practical, but instead, recommended addressing this theoretical risk through enhanced pharmacovigilance in the postmarketing period.

Nonclinical carcinogenicity or genotoxicity studies were not required to support this indication

given the short duration of treatment, as it was not considered appropriate to assess the long-term effects of treatment.

8.8.2. Human Reproduction and Pregnancy

Consultative review was provided by DPMH to assist with review of the human reproduction, pregnancy, and lactation data, as well as the Pregnancy and Lactation subsections of labeling.

There are no data on teplizumab and pregnancy outcomes in the published literature. A total of 13 pregnancies were reported in 12 teplizumab-treated women in the ISS. Two additional pregnancies were observed in Study 1 and Protégé Extension, which were not included in the ISS. Outcomes for the 15 pregnancies include 11 normal neonates, 2 elective terminations, 1 spontaneous abortion, and 1 unknown lost to follow-up. The last dose of teplizumab in relation to conception was ≤ 2 months for 4 pregnancies in teplizumab-treated patients, with 3 pregnancies reported without any complications, and one noted to have conception before treatment end, this pregnancy was electively terminated. The one pregnancy with adverse outcome (spontaneous abortion) was complicated by Graves' disease and T1D and occurred ~ 20 months after the last dose of teplizumab, making causality unlikely. None of the cases of abortion (elective or spontaneous) reported congenital malformations. Adherence to a contraceptive regimen was a requisite for participation in all teplizumab clinical studies.

There are no data on effects of fertility in humans. Fertility and reproductive performance were unaffected in female and male mice that received a murine analog of teplizumab administered by the subcutaneous route at doses up to 7 times the cumulative clinical dose based on body surface area. However, in offspring exposed to teplizumab in utero or via lactation in the pre- and postnatal toxicity study, a reduction in fertility was evident at 20 mg/kg (7 times the cumulative clinical dose based on BSA).

Two reproductive and developmental toxicity studies were conducted in mice using the surrogate murine antibody. In an embryofetal development study, fetal harm was observed at the highest dose (three doses administered at gestational day 6, 10, and 14) in pregnant dams (equivalent cumulative dose, based on BSA scaling, to 20 times the cumulative human dose). There was an increased incidence of post-implantation loss that included the loss of the entire litter for multiple females. The next lowest dose was deemed the NOAEL, which is 3/10th of the cumulative human dose. No gross abnormalities were noted in the viable pups. In a Prenatal and Postnatal Development study, the surrogate murine antibody was administered on gestational day 6 until lactational day 19. This is up to 12 doses assuming a 21-day gestational period. The highest dose administered (20 mg/kg, 60 mg/m²) was considered to be the NOAEL for the pregnant dam, which is $80 (60 \text{ mg/m}^2 \times 12 = 720. 720 \text{ (nonclinical)}/9 \text{ (clinical)} = 80\text{x margin})$ times the cumulative human dose based on BSA. The middle dose (3 mg/kg, 9 mg/m²) was considered to be the NOAEL for the offspring, as reductions in sperm count/motility and reduction in number of pregnancies was seen in the highest dose.

In summary, nonclinical data during pregnancy report increased resorptions of fetuses in mice exposed to the murine analog to teplizumab. Although there were no major congenital malformations (MCMs) or high rates of spontaneous abortion in pregnancies during the clinical trials, data are too limited to make any conclusions about reproductive safety. Teplizumab is being proposed for a relatively narrow indication, “for the delay and prevention of clinical type 1 diabetes in at-risk individuals.” This is not expected to be a large population but would include females of reproductive potential. DPMH recommends a postmarketing Single-arm Pregnancy Safety Study (SPSS) to assess major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age infants, and pregnancy complications such as preeclampsia and gestational diabetes in women exposed to teplizumab during pregnancy. This could be done as a stand-alone postmarketing requirement (PMR) or as part of a larger safety registry PMR.

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester and may interfere with immune response to infections and live vaccines, such as the rotavirus vaccine. To minimize exposure to a fetus, teplizumab should be administered at least 30 days (6 half-lives) prior to planned pregnancy. Females of reproductive potential should have a pregnancy test prior to treatment with teplizumab.

Studies of male and female mice pups on postnatal days 11 to 13 indicated exposure to teplizumab; however, because levels were not obtained at birth, the nonclinical reviewer concluded that there is insufficient information to determine if the detection of teplizumab in rat pups was related to in utero or lactational exposure. The DPMH review noted that ‘Human IgG is known to be present in human milk. The effects of exposure of teplizumab to the infant’s gastrointestinal tract and potential exposure to the infant are unknown. If teplizumab is present in human milk, it is likely that it will only be present in small amounts given the large molecular weight of the product and will likely to be destroyed in the infant’s gastrointestinal tract’.

DPMH recommends the following labeling language for section 8.2: Lactation: There are no data on the presence of teplizumab in human milk, the effect on the breastfed child, or the effects on milk production. Published data from other monoclonal antibodies generally indicate low passage of monoclonal antibodies into human milk and limited systemic exposure in the breastfed child. Although the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for [TRADENAME] and any potential adverse effects on the breastfed child from [TRADENAME] or from the underlying maternal condition, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 20 days after [TRADENAME] administration in order to minimize drug exposure to a breastfed infant.

8.8.3. Pediatrics and Assessment of Effects on Growth

Nonclinical chronic toxicity studies have only been done in sexually mature (six to seven weeks PNA) mice.

Safety in the pediatric population age 8 years and older is discussed extensively in this primary review. We did not find any efficacy or safety issues specific to the pediatric population. An impact on growth was not assessed in the safety program but is not expected for a monoclonal antibody targeting CD3. The agreed Pediatric Study Plan for the relevant IND states that the Applicant will request a deferral for the pediatric 0 to 8-year age group. If approved, to address the Pediatric Research Equity Act (PREA) a post-marketing requirement will be issued for an assessment in patients younger than age 8 years: an open-label, single-arm, 12 month study to evaluate the safety and PK of teplizumab in 15 to 20 pediatric patients 0 to 7 years of age with stage 2 T1D, with two T1D-related autoantibodies and dysglycemia on oral glucose tolerance testing.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Teplizumab will be administered via transfusion by health care personnel; therefore, intentional overdose is not expected. In the rare case of accidental overdose, exaggerated effects of CRS may occur, as previous studies that used doses up to 2 times higher than the proposed dose were with associated exaggerated effects of CRS.

No studies have been specifically designed to evaluate the potential for teplizumab to cause withdrawal and rebound. The safety data on teplizumab administration available for 1 to 2 courses of 6 to 14 days administered 6 to 12 months apart.

There are no relevant studies or information regarding a dependence or abuse potential of teplizumab. There was no Controlled Substance Staff (CSS) consult obtained or abuse potential assessed for this application given teplizumab is administered in a single 14-day course by a licensed medical provider in an outpatient healthcare setting, therefore was felt to have a low risk for abuse.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. No post-marketing data is available for teplizumab as it is not approved in any country at this time.

8.9.2. Expectations on Safety in the Postmarket Setting

The pooled safety population included in this Application included pediatric and adult patients

at risk of T1D age ≥ 8 years to young and mid-adulthood and represent a large portion of patients who would qualify for use of teplizumab in the postmarket setting. Subpopulations that are not adequately represented in the safety dataset adults, Black or African American patients, are not expected to have a different safety experience.

The indication statement will not include patients less than 8 years of age. Although we cannot be certain, we believe that off-label use is unlikely to occur in this population because of insurance reimbursement issues. Nevertheless, our review of the safety data did not identify safety risks that were more prominent or severe in younger patients to warrant any additional regulatory action to prevent off-label use. Another potential population in whom off-label use may be attempted is the stage 1 T1D population (2 or more T1D autoantibodies without evidence of dysglycemia). Although the safety profile would not be expected to differ between stage 1 and stage 2 patients, the benefit/risk assessment may be less favorable for stage 1 patients because they have a longer lead-time before anticipated progression to T1D. Natural history studies show 40% of stage 1 patients develop dysglycemia within 2 years, compared with 60% of stage 2 patients, who develop T1D within 2 years of detection of dysglycemia (Krischer 2013). Again, no additional regulatory approach to prevent off-label use is warranted.

Additionally, the long-term safety profile of teplizumab is unknown, because patients were followed for one to two years in each of the studies used to support safety, with an average exposure of 133 patient-years for the 44 teplizumab-treated patients in TN-10. The uncertainty with regards to long-term latent safety events like malignancy may be adequately addressed through the proposed 10-year registration study which is a requirement in the postmarketing period should teplizumab be approved.

Safety issues which could potentially arise in the postmarket setting are related to the ability of the healthcare provider to appropriately identify CRS and/or serious infection. This risk could be appropriately mitigated by clearly specifying symptoms of cytokine release syndrome and recommended treatment in labeling in order ensure that health care providers and patients are informed and take necessary steps to manage the risks.

The teplizumab clinical trials had broadly similar discontinuation criteria that provided a standardized approach to pausing or discontinuing drug treatment, with provisions to stop treatment for laboratory abnormalities including bilirubin and aminotransferase elevations, or abnormal platelet, neutrophil, hemoglobin, or coagulation parameters, and the occurrence of certain adverse events. If this approach to treatment discontinuation is applied in the postmarket setting, it is estimated that approximately 10% of patients will not be able to tolerate the full course of teplizumab therapy. We do not know if the protocol-specified withdrawal criteria may have prevented more serious or permanent harms from continued dosing. Therefore, similar criteria for treatment discontinuation should be used postmarketing.

8.9.3. Additional Safety Issues from Other Disciplines

There are no additional safety issues from other disciplines that warrant discussion.

8.10. Integrated Assessment of Safety

The safety of teplizumab was evaluated through a pooled dataset, the integrated summary of safety (ISS) dataset consisting of the TN-10 study, which provides clinical safety for the intended population of patients at-risk of T1D (N=76, 44 treated with teplizumab) plus 4 additional studies completed in patients with new- or recent-onset T1D. Thus, the majority of the exposure was in T1D patients, which is acceptable because the continuous nature of the disease allows applicability of safety findings from the new-onset T1D population to the at-risk population. The FDA performed safety analyses using a pooled dataset comprised of the ISS studies without TN-10 to evaluate for adverse events specific to the population with T1D (modified ISS, or 'mISS'). The submitted safety database was adequate for the proposed indication in the proposed at-risk population.

The safety profile for teplizumab appears similar in character to, but milder than, that of other T-cell stimulating monoclonal antibodies. Safety issues include cytokine release, infection, immunosuppression/lymphopenia, and rash, although many of these adverse events were self-limited, mild, or transient (limited to the 14-day dosing period).

There are no serious safety issues that rise to the level of a Boxed Warning or Contraindication. Potential serious risks include cytokine release, infection, and hypersensitivity reactions and should be described in the Warnings and Precautions section of the Prescribing Information.

Cytokine Release Syndrome

As with other drugs that modulate, or partially activate T-cell function, cytokine production has been observed following teplizumab treatment. Circulating cytokines were increased in a dose-dependent manner following teplizumab administration in nonclinical animal studies. Humanized monoclonal antibodies like teplizumab demonstrate notably less immune cell activation than non-humanized antibodies, and incremental dose increases were incorporated into teplizumab clinical studies as a strategy to reduce immune activation. Despite these strategies, clinically relevant cytokine release was still noted following teplizumab use in the clinical development program.

CRS events were identified in up to 5% of teplizumab-treated patients using the Applicant's analysis based on CTCAE version 3.0 criteria. DHM1 noted that the methodology for CRS grading used in the development program was somewhat obsolete/different than the current understanding of CRS. When newer criteria were adopted (the ASTCT grading system), a higher number of cases (~16% of teplizumab treated patients) were detected, although 10% of patients in the comparator arm also met criteria for CRS based on the presence of fever.

In general, the rates of severe CRS appear to be very low, regardless of the grading methodology used. The majority of cases of CRS were mild and self-limited without need for intervention beyond 24 hours (82%) and were responsive to antipyretics or interruption of drug infusion. All cases of CRS resolved without sequelae. There were 7 patients (0.9% of the teplizumab treatment group) who required hospitalization, symptomatic treatment past 24 hours, or both. No events required pressors or ventilator support, and all CRS events resolved without sequelae. The risk of CRS can be mitigated with labeling approaches and no REMS is recommended (see DRM memo).

Should teplizumab be approved, the label will need to be inclusive of the risks and include risk mitigation strategies that inform providers of common symptoms and timeline for recognition of important symptoms (symptoms may include fever, nausea, fatigue, myalgia, and malaise, and typically occurs during the first 5 doses), with median time to onset of CRS and recommendations to monitor for signs and symptoms as well as treatment if symptoms are detected (anti-pyretics [e.g., NSAIDs] or acetaminophen), antihistamines and/or anti-nausea medications). Importantly, if dyspnea, hypoxia, or hypotension occurs, the labeling should advise providers to consider a temporary pause of dosing for 1 to 2 days after improvement or until resolution of symptoms.

Infections

In clinical trials, patients treated with teplizumab had a higher rate of serious infections than placebo- or control- treated patients (3.4% vs. 2% for ISS) over the entire observation period, and this difference was more pronounced when analyzing the TN-10 trial alone. The rate of total infections (serious and nonserious) was not different between teplizumab treated patients or patients treated with placebo/control. On analysis of patient narratives of infection SAEs, a temporal relationship with lymphopenia was observed with several infections. It is important to note that symptoms of infection overlap with symptoms of CRS making distinguishing between the two difficult. Although an excess risk of serious infection with teplizumab is not certain based on the available data, temporary immunosuppression from teplizumab lends biologic plausibility. If approved, the Applicant's proposed label should be revised to strengthen the language about serious infections.

Hypersensitivity and Rash

Anaphylaxis and serum sickness are two major acute infusion reactions that can be caused by monoclonal antibodies and were investigated closely for teplizumab use, as immunogenicity was observed with teplizumab. The Applicant reported that 50-90% of patients developed anti-drug antibodies (ADA) during the first course of teplizumab across the various treatment regimens, and that the ADA incidence was as high as 100% when a second course was administered. An analysis of ADA status association with adverse events related to hypersensitivity (anaphylaxis, rash and serum sickness) revealed that the frequency of rash may

be higher in patients who are positive for ADA. Although rash was also observed at a 13-fold higher rate in the teplizumab group compared with the placebo group, the majority of rashes (with the exception of two SAEs) were generally non-serious and did not require additional intervention.

Overall, FDA analysis revealed a low frequency of reported hypersensitivity AEs: seven in the teplizumab group (0.9%) vs. two in the control group (0.8%), but there were some events consistent with anaphylaxis, bronchospasm, and angioedema in teplizumab-treated patients. There was one report of serum sickness in a patient treated with teplizumab in Study TN-10, that occurred in a patient who may have underlying risk (rheumatologic disease).

'Common' AEs

The most frequently reported treatment emergent adverse events (TEAEs) were lymphopenia and leukopenia, reported in $\geq 75\%$ of teplizumab-treated patients in the ISS studies during the 14-day treatment period. Both are expected pharmacodynamic effects based on nonclinical studies of teplizumab and clinical experience with teplizumab's non-humanized progenitor, OKT3. Rash was a common AE among teplizumab-treated patients (45%) but was self-limited and all cases resolved without sequelae. Transaminase elevations were also frequently reported AEs and were observed in $\sim 25\%$ of teplizumab-treated patients during the first treatment course and follow-up period. Similar to lymphopenia, transiently elevated transaminases were expected given teplizumab's mechanism and are attributed to the direct effects of cytokine release on the liver. On comprehensive review and outlier analysis of transaminase elevations, there was no signal for drug-induced liver injury with teplizumab use. Other cytopenias (neutropenia, thrombocytopenia, anemia) were also observed frequently, and similar to lymphopenia, recovery was noted within 2 to 4 weeks of treatment. Pruritis, pyrexia, nausea, and headache were all common and reported in $\sim 15\%$ of teplizumab-treated patients during the 14-day treatment period but were also noted at relatively high frequency among control patients (5 to 14%). Other electrolyte abnormalities, including blood bicarbonate decreased, hypocalcemia, and hyponatremia were all reported at higher frequencies in the teplizumab-treated safety population, and no events were considered severe.

Treatment Discontinuations

Approximately 10% of patients were unable to complete their treatment course with the majority of events related to protocol-driven laboratory drug discontinuation criteria. Laboratory abnormalities leading to drug discontinuation included transaminase elevations, hematologic parameters (lymphopenia, neutropenia, anemia, and thrombocytopenia) and cytokine release syndrome. Transaminase elevations accounted for half of drug discontinuations, occurring in 5.6% of teplizumab patients and 0.9% of control patients. It is unknown if adhering to prespecified drug discontinuation criteria prevented more serious adverse events during the clinical trials; therefore, a conservative approach to mitigate risk

should teplizumab be approved would be to incorporate a modified version of the discontinuation criteria included in the ISS studies into teplizumab's labeling.

Other Safety Issues

Certain safety findings identified within the teplizumab development program, e.g., DKA, are not expected to be adverse events observed in the intended patient population. Importantly, no patients in TN-10 presented with DKA at diabetes onset.

Long-Latency Risks: Uncertainties

During the safety review, potential longer-term risks were identified based on nonclinical findings from teplizumab in chimpanzees and safety events observed with OKT3, teplizumab's non-humanized precursor. These potential risks include lymphoproliferative disorders (LPDs) caused by Epstein-Barr virus (EBV) reactivation and or other malignancy due to immunosuppression. Nonclinical studies in chimpanzees demonstrated mortality related to T-cell immunosuppression and malignancy resulting from infection with EBV-like virus at high doses of teplizumab. A higher frequency of EBV reactivation was observed among teplizumab treated patients (4.5%) compared to control patients (2.3%) and EBV viral load assessments in TN-10 demonstrated mostly asymptomatic, transient EBV viral reactivations among a portion of patients treated with teplizumab. Although EBV-associated LPDs have been observed in drugs that suppress T-cell immune function, LPD incidence is associated with high degrees of immunosuppression (dose and duration dependent) and therefore, have a lower likelihood in a therapy with limited duration, as is being proposed with teplizumab. There were no cases of LPD detected during the teplizumab clinical development program in the ISS population. It is important to note that EBV-associated LPD and malignancy risks are only theoretical at this time as they are more likely to be associated with chronic immunosuppression. One mitigating strategy in the currently proposed label is to avoid teplizumab treatment in patients with active EBV (or CMV) infection, as CMV is a similar virus associated with long-term LPD risk. In order to address uncertainty related to long latency events, a 10-year exposure registry PMR may be considered to evaluate over time if there is an associated risk of malignancy with teplizumab use.

9. Advisory Committee Meeting and Other External Consultation

The Endocrine and Metabolic Drugs Advisory Committee (EMDAC) met on May 27, 2021 to discuss the findings from the teplizumab development program, and to specifically address the following questions. Note that only a brief summary is provided here, and the official transcript is publicly available.

Question 1 (Discussion)

The Applicant is seeking approval of teplizumab to delay T1D mellitus in at-risk individuals. Discuss the strength of the overall evidence presented herein to conclude that effectiveness has been established for teplizumab for the proposed indication.

Committee discussion:

For this question, the committee members discussed in detail the merits of the single adequate and well-controlled trial, TN-10. The majority agreed that TN-10 provided adequate evidence of efficacy, although this view was not unanimous. Several committee members mentioned they were reassured that the primary efficacy outcome (the delay of T1D in at-risk individuals) held up to multiple analyses by the FDA. Several committee members acknowledged that they believed there was a benefit associated with teplizumab use, but were not confident in the magnitude of the observed effect size of the 24 month delay given the small size of the study with notable baseline imbalances in age and genetics. There were comments about the small study limiting the ability to assess differential efficacy in subgroups, particularly noting the HLA analyses. There was not strong support for the use of the C-peptide meta-analysis as confirmatory evidence of effectiveness. One member stated that her view was because C-peptide is not a validated surrogate, and another stated that C-peptide is not convincing because the Protégé study failed its primary endpoint. They would also have considered measures of glycemic control in patients with stage 3 T1D supportive in this population, as the major effector of complications in T1D is related to glycemic control.

Question 2 (Discussion)

Discuss the clinical meaningfulness of the observed median 2-year delay of onset of T1D demonstrated in study TN-10.

Committee discussion:

The majority of the committee members acknowledged the unmet need and supported the clinical meaningfulness of a 2-year delay, but again expressed concern that the confidence in the estimate of 24 months is low. One member stated that the treatment effect is probably overestimated, while another stated that even less of a delay is still meaningful. This view seemed to be largely influenced by the Open Public Hearing speakers and their testimonials about quality of life. The patient representative also stated that any amount of delay would have been meaningful to her. Some members mentioned that any time

period of delay (even 6 months) appears to be meaningful for at-risk patients and their families. Some committee members mentioned that it is unknown whether this 2-year median delay will make an impact on the prevention of long-term complications of T1D.

Question 3 (Discussion)

Discuss your view of the safety issues identified in the clinical development program and the potential for unobserved, longer latency safety issues (e.g., malignancy) given the mechanism of action of teplizumab. Discuss whether these safety concerns can be adequately mitigated through labeling and/or required postmarketing studies.

Committee discussion:

A broad range of opinions were given about the safety findings. Overall, these ranged from a concern about the safety of the product in light of rates of serious adverse events, and diabetic ketoacidosis, to a concern about inadequate data to assess safety, to a view that the safety database was adequate for approval with postmarketing safety follow-up. There was concern noted that patients in TN-10 were not followed for safety after T1D diagnosis. The majority thought this deficiency could be addressed with a postmarket safety study, although one stated that the lack of data would be difficult to address through labeling. Several committee members acknowledged that uncertainty over long-latency adverse events of interest like malignancy could be adequately mitigated through rigorous post-marketing studies, and were reassured that with the limited exposure of teplizumab (a single 14-day course) the malignancy risk is likely low. Others, however, noted that if the drug ‘works’ then the immune system is being altered in such a way that could have an impact on safety, although it was unclear how. Additionally, the committee members expressed concern about the imbalance in risk of diabetic ketoacidosis (DKA) observed in teplizumab-treated patients the phase 2/3 studies in the new- or recent-onset population with T1D. Although they were reassured that DKA was not observed in TN-10 patients, several members of the committee mentioned that the Applicant and FDA should explore the risk of DKA further through continued study in the at-risk population after diagnosis of T1D, in order to ensure that this population too may not at some point be at excess risk of DKA (vs. untreated patients). In addition, the three deaths in the teplizumab development program were discussed in detail as safety issues worth investigating further, although another committee member commented that given the randomization ratio, the deaths observed in the teplizumab program in the population with T1D did not signal imbalance. The rheumatologist on the committee was overall reassured by the breadth of the safety data, since other immune-modulating immunotherapies in autoimmune

disorders primarily affecting pediatrics often have much smaller safety datasets, and the Applicant's inclusion of safety data for patients with stage 3 T1D, allowed for a robust amount of safety data in the teplizumab development program. Overall, the committee agreed that further postmarketing commitments or controlled studies would help to further characterize these safety issues.

Question 4 (Discussion)

The Applicant's proposed indication statement is "Teplizumab is for the delay of type 1 diabetes mellitus (T1D) in at-risk individuals." TN-10 was conducted in individuals ages 8 and older and enrolled relatives of patients with T1D with two or more positive autoantibodies and dysglycemia. Based on available data, discuss how the indicated population should be described to ensure that the expected benefit(s) of teplizumab will outweigh the risks of treatment. If you have any other recommendations for the indication statement, please provide them.

Committee discussion:

For this question, the majority of committee members agreed that the indication should not be restricted to relatives of patients with T1D, and instead should include both non-relatives and relatives meeting the criteria for stage 2 T1D as used in the TN-10 enrollment criteria (2 or more T1D-specific autoantibodies plus dysglycemia on OGTT). Some committee members also mentioned incorporating HLA DR4 present individuals in the labeling in order to advise patients and families of the most likely patient to benefit from therapy, while others cautioned the committee about restricting use to patients by subgroup analyses, which were not powered to detect treatment effect among groups.

Question 5 (Voting)

Does the information provided in the background documents and presentations by the Applicant and FDA, show that the benefits of teplizumab outweigh the risks in support of approval to delay type 1 diabetes mellitus? Vote yes or no. If you voted yes, provide your opinion on the appropriate indication statement, and discuss whether you recommend any post-marketing safety studies. If you voted no, provide your rationale, and provide recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of teplizumab.

Committee vote and discussion:

Ten members voted yes, and 7 voted no. The committee unanimously acknowledged significant unmet need in patients at risk of developing T1D and acknowledged and credited the moving testimonials from patients and family

members who discussed the clinical meaning of delay of T1D. The primary concern voiced was related to unclear efficacy (e.g. study not replicated, bias from baseline imbalances, uncertainty around the 2-year estimate, confirmatory C-peptide data not convincing). Only a small number of members cited safety concerns as their reason for voting no. Both those who voted yes and those who voted no stated these concerns as well as acknowledged the unmet need but came to different conclusions. Some committee members stated uncertainty, that more safety data, replication of efficacy, and diversity in the trial population would strengthen their certainty of the benefit of teplizumab in light of the risks.

Network of Experts Panel Meeting

During the review, the review team sought out experts in the care of children and adults with T1D to better understand provider practice with regard to the identification and monitoring of patients at-risk of developing T1D. As treatment options become available for patients with earlier stages of T1D, it is important to understand how clinicians plan to identify populations who would benefit from therapeutics meant to delay T1D. Specifically, the review team was interested in further understanding the current practice of identification of the stage 2 T1D population, and whether identification of these at-risk individuals through autoantibody screening is considered common clinical practice, and what information in the labeling of products intended to delay the onset of clinical T1D in this population would be useful to providers. Four experts were identified through the FDA Network of Experts (NoE) program who have experience in the care of patients with T1D. All selected experts were screened by the NoE staff for conflict of interest. In a virtual roundtable forum, the following questions were posed to the experts (answers summarized below):

1. Are you aware of the proposed 3 stage staging system for type 1 diabetes, and do you utilize this approach in your practice?
 - All of the experts in the group were aware of the staging system, and expressed familiarity with screening through the research setting, with some citing familiarity with TrialNet as a screening program. For the second part of the question, the consensus was that they currently do not utilize this approach in practice (outside of research) primarily because there are no therapies to offer patients identified as at-risk of T1D.
2. How do you identify patients with stage 2 type 1 diabetes? What antibody tests do you typically order for at-risk patients?
 - For this question, there were differing answers among the experts. Some identify patients who present with dysglycemia (for example, steroid-induced hyperglycemia, or stress-induced hyperglycemia), and some identify patients with other autoimmune conditions at risk of T1D who are noted to be antibody positive in the process of evaluation for underlying causes. Additionally, two of the experts identified TrialNet as a

screening program through which stage 2 patients are identified in their clinical practice. The approach to antibody testing varied according to the setting, with emergency rooms often testing only islet cell antibodies (ICA) or GAD-65, whereas the provider may also test for zinc transporter 8 (ZnT8) and insulin autoantibodies (IAA). One research-based physician consistently ordered a panel of 4 autoantibodies including: insulin, GAD65, islet tyrosine phosphatase 2 (IA-2), and ZnT8.

3. At what interval do you repeat autoantibody panels if you identify individuals at risk?
 - If one autoantibody is positive, most experts would repeat the autoantibody testing after one year, either by protocol (research) or through clinical monitoring, in order to monitor for risk of T1D.
4. Do you rely on any particular laboratory or notice any difference in performance among the available islet autoantibody tests?
 - For this answer, several different laboratories were mentioned (b) (4). For the ZnT8 autoantibody, one expert stated they use (b) (4), and another (who uses autoantibody determinations in research) uses the (b) (4). Otherwise, several providers mentioned they didn't have a preference, or were not aware of any difference in performance for the islet autoantibody tests. One expert also mentioned that at the time of autoantibody determination, often patients are in the hospital, and therefore the institution chooses the laboratory to perform the autoantibody testing. One expert that utilizes IAA for research mentioned that they noted some variability in the commercially available labs (b) (4) when used in the past, and currently uses the reference lab at his institution for clinical autoantibody determination. Another expert with research experience using autoantibodies, would often perform both standardized research assays and commercial assays (as they tended to return faster), and mentioned that these tests typically agreed with each other.
 - For autoantibody testing in research, the (b) (4) was mentioned by the expert involved in research, stating that some of the cutting-edge autoantibody assays have been developed at the (b) (4) over the years, as well as the (b) (4).
 - The Immunology of Diabetes Society Program was also mentioned as a source for assay comparisons as they have quantitative data comparing the sensitivity and specificity across different labs, through the testing of standardized samples.
5. What is your approach to follow-up of patients identified with preclinical type 1 diabetes?
 - The follow-up approaches detailed by experts all included education on the clinical symptoms of T1D and follow-up in clinic to obtain laboratory (HbA1c) and clinical assessments. Several experts mentioned they prescribed home glucometers.

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- One expert discussed that she instructs patients and their families on how to use a meter and to check blood glucoses twice daily (one fasting and one 2 hours postprandial) for 2 weeks in order to assess for dysglycemia, and following that, she usually recommends checking once weekly and contacting the office if any blood glucoses are >200 mg/dL, with follow-up in 3 months, then every 6 months thereafter.
 - One expert mentioned that the majority of patients at his institution are identified as at-risk through the TrialNet Pathway to Prevention Trial, and that most patients with stage 1 or 2 T1D are identified either through this program or another institution-based research program. Therefore, they follow clinical protocol of assessments, monitoring single-autoantibody positive patients once yearly by checking autoantibody assays, for patients with double autoantibodies they perform more formal assessments like oral glucose tolerance testing (OGTT), sometimes fasting blood glucoses, and HbA1c to follow for the development of dysglycemia.
 - The experts also mentioned their approach to identification and follow-up of these patients depends on the treatment options available. It was emphasized that providers currently have no available treatments to recommend to patients once they are identified as at-risk of T1D. Other experts mentioned that having a prevention measure would change the approach taken to these patients as it would be worthwhile to monitor more frequently and to see patients in clinic more frequently.
 - It was mentioned also that clear guidelines on when to start a disease-modifying treatment would be useful to help determine the frequency of autoantibody testing (and to mitigate over-testing). Some mentioned that they would not increase the frequency of autoantibody testing beyond their current practice, but instead would increase monitoring for dysglycemia in patients identified to have multiple autoantibodies.
6. Do providers read the FDA labels, and find them useful and what are the clinical organizations or clinical practice guidelines that you typically trust and rely on for additional information in clinical practice, outside of an FDA drug label?
- The experts largely stated that they read FDA labels, especially when reviewing side effect profiles and recommendations for monitoring.
 - The American Diabetes Association standards of clinical care (Pediatrics chapter, which includes a pre-diabetes for T1D section) currently recommends that family members be screened through a research program (this expert referenced TrialNet). Additionally, one expert mentioned that the ADA guidelines discuss that at this time family members/at-risk individuals aren't recommended to be screened outside of a research setting, in large part, because there are no therapeutics available to offer those identified as "at-risk" as far as an intervention.
 - Also, the International Society of Pediatric and Adolescent Diabetes (ISPAD) Guidelines, issued every 3 years, provide guidance on screening for at-risk patients.

- The American Academy of Pediatrics (AAP) Bright Futures program generally specifies the standard of care for preventative care for children at every age.
 - TrialNet, JDRF, Helmsley Trust, and the Milken Institute were also mentioned.
7. What information would you find useful in labeling for therapeutics intended to delay or prevent type 1 diabetes in high-risk individuals?
- Suggestions for labeling included defining the indication patient population well, specifically which antibodies need to be positive (and the titers) and the glycemic indices at the point of initiation. Most expert also mentioned clear monitoring guidance for side-effects including frequency of monitoring and mitigation actions (stop therapy, dose decrease recommendation, or specific treatment). Another expert mentioned it would be useful to identify how often to assess for transition to T1D once a patient has been treated. Additionally, one expert recommended including specific baseline characteristics (genetics, HLA type, antibody types) that would help the provider understand which type of patient would benefit most from therapy (younger, GAD-dominant, etc.).
8. What would you find clinically meaningful in a therapeutic? (direct quotes from all 4 experts)
- "In general, a 2- to 3-year delay actually has real clinical impact for these families."..."As I work with children, I imagine, what if I have a kindergartener that's a new onset? Managing that comes with all sorts of layers of problems. And if you can delay that until they're a second grader, that's a very different childhood, it's a very different family, and a very different support network, as very different support is needed for that child."
 - "I think from a clinical perspective, delaying clinical diabetes let's say for a year or more, prevention of DKA at presentation, I think both of those end goals I think would be clinically meaningful and relevant."
 - "I think that in the younger kids, a year or two delay I think would be significant. And of course, if we can reduce DKA, even by only 50%, that would be awesome."
 - "Delaying the diabetes and living with it for a shorter period of time is always a benefit."..." it's stressful for families, and a year less of living with diabetes is a better year."

Other Topics of Discussion

One expert mentioned the benefits of screening the general population for risk of T1D given the risk of DKA at onset of T1D can be as high as 60 to 70% depending on the population, and the DKA event at diagnosis is associated with adverse cognitive effects. Researchers at the (b) (4) have shown that in after single episode of DKA, there is a measurable cognitive deficit. Research is ongoing to identify at what age screening should occur, and many in the T1D autoimmunity research community and general pediatrics community are endorsing general

population screening efforts. Another expert described that most of the patients that do come in with new onset T1D do not have relatives and thought that screening the general population would be the best tool to prevent DKA, just as lipid screening is currently used in general pediatric screening guidelines. In addition, another expert mentioned that targeting newborn HLA haplotyping or genetic screening by another method, would narrow down the at-risk population for which future autoantibody screening would be indicated. Another expert mentioned that primary care doctors perform extensive screening for other diseases and thought that T1D autoantibody screening would be easy to incorporate into this screening paradigm. Another expert mentioned the importance of raising public awareness in our communities and considering more nationalized campaigns for improving T1D awareness as the rate of DKA has been cut by over 50% as a result of these campaigns.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling recommendations are discussed throughout this review; final labeling is deferred until the next review cycle.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended for this BLA.

Consideration was given to a communication plan only REMS that would provide education for patients and providers on the risks, diagnosis, and management of CRS after treatment with teplizumab, recommended by the DHM1 consult. On June 24, 2021, the review team met with DRM to determine if a REMS was necessary to ensure the benefit of teplizumab outweighed the risk of CRS. The review Division and DRM have determined that based on the data currently available, if approved, a REMS is not necessary to ensure the benefits of teplizumab outweigh its risks. The rationale for this decision was that the severity of the risk was not determined to reach a level requiring a REMS. It is also important to note that based on our safety analysis, the risk of CRS did not rise to the level of a boxed warning.

DRM and DDLO discussed potential FDA-driven communications close to the time of approval to highlight the novel treatment for patients at risk of T1D and to convey safety information.

12. Postmarketing Requirements and Commitments

This section discusses potential (Food and Drug Administration Amendments Act of 2007) FDAAA-related PMRs and PMCs. The Pediatric Research Equity Act (PREA) is discussed elsewhere in this review.

During the review we identified the following safety issues that may require a PMR safety study: CRS, infection, and longer latency events like LPD or other malignancy. The Applicant was notified of these potential PMR issues during the mid-cycle communication meeting. The Applicant also proposes to assess the risk of DKA in the postmarket setting. Final determination of postmarketing requirements and commitments are deferred until the next review cycle.

DPMH is also recommending a pregnancy study be performed in order to collect data for women and their offspring who are exposed to teplizumab during pregnancy in order to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

13. Appendix A

13.1. References

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13.2. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators.

Covered Clinical Study (Name and/or Number): TN-10

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>38</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>3</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14. Appendix B

Table 34. Preferred Terms With Events in SAE FDA Custom Query

FDA Query	Preferred Terms
Diabetic ketoacidosis	Diabetic ketoacidosis Diabetic ketosis Ketoacidosis Ketonuria Ketosis
Infection	Anal abscess Appendicitis Bronchitis Cellulitis Cholecystitis acute Dengue fever Gastritis viral Gastroenteritis Gastroenteritis viral Hepatitis A Infection Infectious mononucleosis Paronychia Pharyngotonsillitis Pilonidal cyst Pneumonia Pulmonary tuberculosis Pyelonephritis Sepsis Staphylococcal sepsis Tuberculosis Urinary tract infection Wound infection
Hypoglycemia	Hypoglycemia Hypoglycemic coma Hypoglycemic seizure Hypoglycemic unconsciousness
Hepatic injury	Alanine aminotransferase increased Aspartate aminotransferase increased Hepatitis A Hepatosplenomegaly

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FDA Query	Preferred Terms
Infection	Anal abscess Appendicitis Bronchitis Cellulitis Cholecystitis acute Dengue fever Gastritis viral Gastroenteritis Gastroenteritis viral Hepatitis A Infection Infectious mononucleosis Paronychia Pharyngotonsillitis Pilonidal cyst Pneumonia Pulmonary tuberculosis Pyelonephritis Sepsis Staphylococcal sepsis Tuberculosis Urinary tract infection Wound infection
Allergic reaction, hypersensitivity	Drug hypersensitivity Hypersensitivity
Suicidal ideation, intentional overdose, self-injury, suicide	Suicide attempt
Lymphopenia	Lymphopenia
Fall, dizziness, balance disorder	Dizziness Fall
Abdominal pain	Abdominal pain Abdominal pain upper
Pyrexia	Pyrexia
Fracture	Ankle fracture Facial bones fracture Fibula fracture Foot fracture Skull fracture Upper limb fracture
Leukopenia	Lymphopenia Neutropenia

Source: Clinical Reviewer
Abbreviations: SAE, serious adverse event

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Table 35. Preferred Terms With Events in TEAE FDA Custom Query

FDA Query	Preferred Terms
Lymphopenia	lymphocyte percentage decreased lymphopenia
Leukopenia	Eosinopenia Granulocytopenia Leukopenia Lymphopenia Monocytopenia Neutropenia Pancytopenia White blood cell count decreased
Rash	Application site rash Exfoliative rash Rash Rash erythematous Rash macular Rash maculo-papular Rash papular Rash pruritic Rash pustular
Transaminases elevated	Alanine aminotransferase increased Aspartate aminotransferase increased
Pruritus	Catheter site pruritus Infusion site pruritus Injection site pruritus Nasal pruritus Pruritus Rash pruritic
Thrombocytopenia	Pancytopenia Thrombocytopenia
Nausea	Nausea
Anemia	Anemia Erythropenia Hematocrit decreased Hemoglobin decreased Red blood cell count decreased
Hypocalcemia	Blood calcium decreased Hypocalcemia
Headache	Headache Migraine Procedural headache Tension headache
Hyponatremia	Blood sodium decreased Hyponatremia

Source: Clinical Reviewer
Abbreviations: TEAE, treatment-emergent adverse event

Table 36. CTCAE v.3.0 Grading System for Cytokine Release Syndrome

Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – <i>Select</i>; Ventricular arrhythmia – <i>Select</i>.						

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Source: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0
Abbreviations: CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events

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Table 37. Narrative Review of Individual DKA Events in Teplizumab-Treated Patients — mISS

Patient Characteristics	Study	# of Courses*	Characteristics of DKA Event	Days After Last Teplizumab Dose	Insulin Dose Available?
11y male, US, full 14 day regimen	AbATE	2	Insulin pump malfunction	265	Yes, lowered
9y female, US, full 14 day regimen	Delay	2	Insulin pump malfunction, history of 2 prior pump malfunctions	296	No
14y male, US, 6 day curtailed	Encore	1	Non-compliance with insulin	573	No
12y female, India, 6 day curtailed	Encore	2	Non-compliance with insulin	486	No
26y female, India, full 14 day regimen	Encore	1	UTI, interruption in insulin	157	Yes, lowered
16y female, India, 6 day curtailed	Encore	1	No reported illness or interruption in insulin, went on to get 2 nd course of teplizumab, followed until 538 days after course 2	34	No
26y male, India, ½ dose regimen	Encore	2	Weakness and weight loss x 1 month prior to hospitalization, no source of infection in narrative but treated with antibiotics (meropenem, amikacin, amoxicillin)	352	No
15y female, US, full 14 day regimen	Protégé	2	Infection, pyelonephritis	307	No
14y female, US, full 14 day regimen	Protégé	1	No infection or interruption in insulin documented, note, patient received 2 teplizumab infusions (withdrew due to GGT increased)	681	Yes, insulin dose increased from 0.6 to 1.6 units/kg/day 71 days prior to DKA
19y female, Ukraine, full 14 day regimen	Protégé	2	This patient had 5 DKA episodes and a fatality related to DKA approximately 289 days after the last dose of teplizumab. She was reported to have abnormal kidney function related to occupational exposure (linoleum) and was diagnosed with intercapillary glomerulosclerosis	65, 121, 216, 239, 285	Yes, insulin dose reduced (approximately 0.225 units/kg/day) prior to first DKA
14y female, India, 1/3 dose regimen	Protégé	1	Infection with pneumonia, second episode without infection or insulin interruption	86, 436	No
16y female, India, 6 day curtailed	Protégé	2	Infection with UTI, stress, noncompliance with insulin dosing reported	308	No
18y female, India, ½ dose regimen	Protégé	1	Infection: Renal abscess and sepsis	394	No

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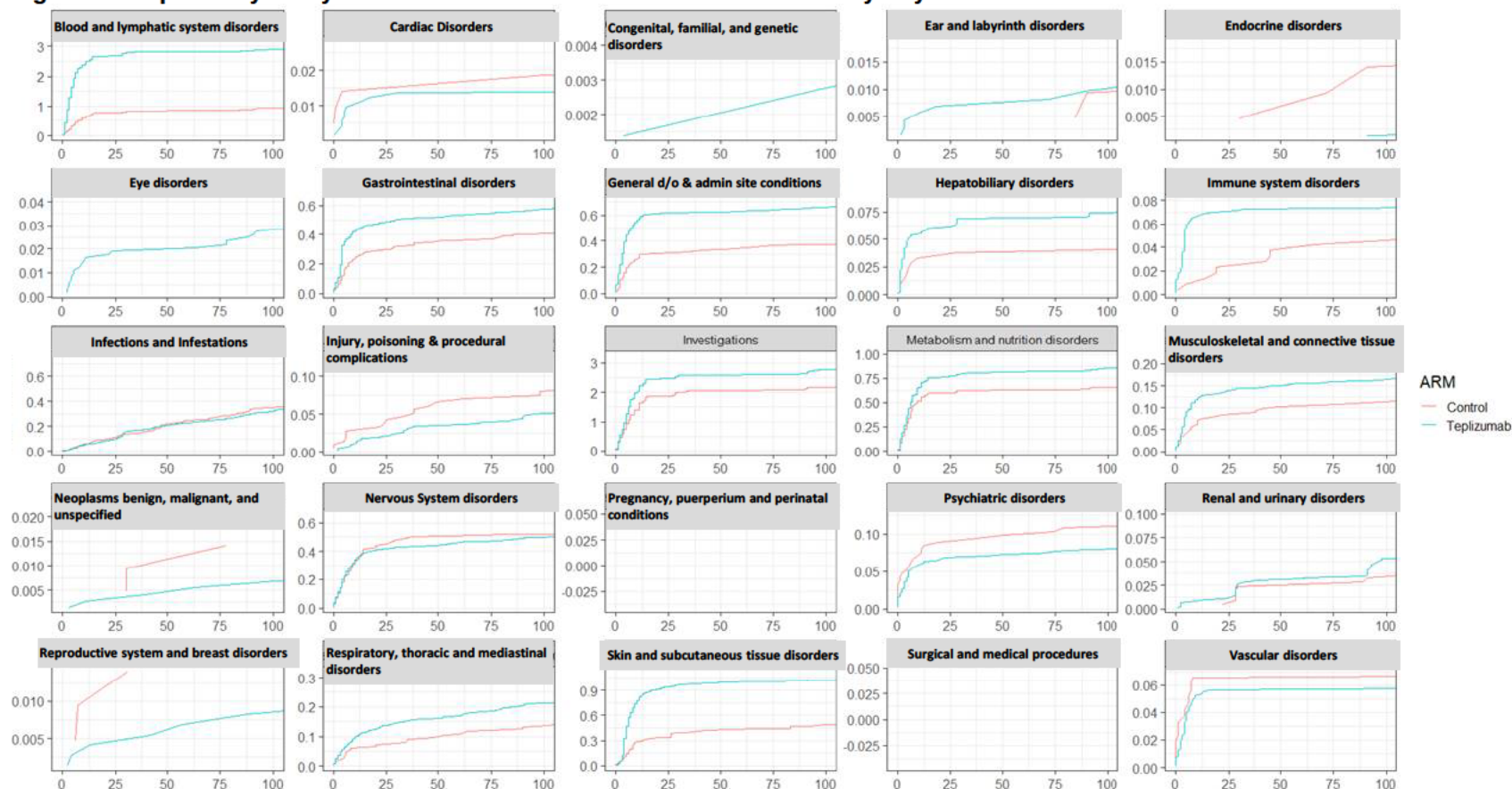
Patient Characteristics	Study	# of Courses*	Characteristics of DKA Event	Days After Last Teplizumab Dose	Insulin Dose Available?
19y female, India, 6 day curtailed	Protégé	2	DKA event requiring hospitalization between diagnosis and study screening, first episode of DKA without infection or evidence of poor compliance, second DKA episode occurred at time of preterm labor, in the peripartum period	311, 530	No
17y male, India, full 14 day regimen	Protégé	1	DKA event associated with overnight train journey, lack of sleep and fatigue. Based on the report, it is unclear if food intake or insulin administration was interrupted	50	Yes, no dose reduction was noted
14y male, Israel, full 14 day regimen	Protégé	2	Insulin pump malfunction	404	Yes, dose reduction from ~0.65 units/kg/day to 0.55 units/kg/day reported at preceding visit 2 months before DKA
9y male, Israel, full 14 day regimen	Protégé	2	All episodes of DKA had reports of non-compliance with insulin dosing, one episode associated with viral throat infection. Between diagnosis and screening for this study, the subject had ketoacidosis that required hospitalization.	239, 285, 340	Yes, dose reduction noted immediately after study drug, following DKA episodes insulin dose increased by 10
11y female, Poland, ½ dose regimen	Protégé	2	Both DKA episodes associated with insulin and diet noncompliance (reported) and HbA1c 13 and 13.8 preceding both events. Between diagnosis and screening for this study, the subject had ketoacidosis that required hospitalization.	294, 569	No
12y male, India, full 14 day regimen	Protégé	2	Infection: Dengue fever reported at time of DKA	516	No
10y female, India, full 14 day regimen	Protégé	1	Reportedly skipped insulin dose for the day. Note: this patient completed 2nd infusion cycle following this DKA event and continued to follow up for an additional 527 days without report of DKA	90	No

Source: Reviewer generated table

* Number of courses of teplizumab prior to DKA event

Abbreviations: F, female; M, male; US, United States; DKA, diabetic ketoacidosis; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; ISS, integrated summary of safety; mISS, modified ISS; UTI, urinary tract infection

Figure 32. Exploratory Analysis Cumulative Adverse Event Incidence Plot by Days From Randomization — mISS



Source: Reviewer Generated from adae.xpt and adsl.xpt, excluding TN-10, limited to the first 100 days from randomization, and adjusted for differences in exposure
Y axis is average number of cumulative events per patient. X axis is days from randomization
Abbreviations: mISS, modified integrated summary of safety, D/O, disorder

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/s/

LAUREN K WOOD HEICKMAN
07/02/2021 06:25:16 PM

LISA B YANOFF
07/02/2021 06:27:17 PM

i was directly involved in the review of this application and drafting of this memo. I concur with all of its conclusions.

ELLIS F UNGER
07/02/2021 06:31:19 PM

I participated in the drafting of this review memorandum and agree with its content and conclusions.