CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761183Orig1s010

Trade Name:	TZIELD injection
Generic or Proper Name:	teplizumab-mzwv
Sponsor:	Provention Bio Inc
Approval Date:	June 12, 2026

Indication:

TZIELD is a CD3-directed antibody indicated to:

- *Delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients 1 year of age and older with Stage 2 T1D.*
- *Delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D. This indication is approved under accelerated approval based on evidence of reduced C-peptide decline. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).*

Limitations of Use:

- *There is limited evidence of safety and effectiveness in patients aged 45 years and older with Stage 2 T1D.*
- *TZIELD is not effective as a disease modifying therapy in non-autoimmune dysglycemic conditions.*

CENTER FOR DRUG EVALUATION AND RESEARCH

761183Orig1s010

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APPLICATION NUMBER:

761183Orig1s010

APPROVAL LETTER

BLA 761183/S-010
BLA 761183/S-014

ACCELERATED APPROVAL
SUPPLEMENT APPROVAL

Provention Bio, Inc
Attention: Gargi Lakhwani
Regulatory Strategist – Associate Director, Global Regulatory Affairs
100 Morris Street
Morristown, NJ 07960

Dear Gargi Lakhwani:

Please refer to your supplemental biologics license applications (sBLAs), received July 21, 2025, for S-010, and December 23, 2025, for S-014, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tzield (teplizumab-mzwv) injection.

We acknowledge receipt of your major amendment dated November 24, 2025, which extended the goal date by three months for S-010. We also acknowledge receipt of your major amendment dated April 16, 2026, which extended the goal date by two months for S-014.

The Prior Approval sBLA, S-010, provides for updates to the Prescribing Information (PI) and Medication Guide (MG) to add an indication to delay the decline in endogenous insulin production in pediatric patients age 8 to 17 recently diagnosed with Stage 3 type 1 diabetes (T1D) and other information based on trial PRV-031-001 entitled, *A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed T1D (PROTECT).*

The Prior Approval sBLA, S-014, provides for updates to the PI to introduce alternative in-use syringe administration and provide updated compatibility information.

APPROVAL & LABELING

We have completed our review of these sBLAs, as amended. S-010 is approved under the provisions of accelerated approval regulations (21 CFR 601.41), and S-014 is also approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the PI and MG) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct a further adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If the postmarketing clinical trial fails to verify clinical benefit or is not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 8, 2026. This requirement is listed below.

4921-1 Complete study EFC18241, a randomized, double-blind, placebo-controlled trial to describe and verify the clinical benefit of teplizumab-mzwv in patients with Stage 3 type 1 diabetes (T1D). The trial should be

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

adequately powered to detect a treatment effect on the endpoint that will be used to describe and verify the clinical benefit.

Final Protocol Submission: August 2026
Trial Completion: June 2029
Final Report Submission: December 2029

Submit clinical protocols to your IND 100262 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open clinical trial required under section 506(c). One report will be a standalone submission, and the other report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval of the original BLA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761183/S-010 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval of the original BLA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that you provide detailed analyses of events of bone fracture reported from clinical study and post-marketing reports in your periodic safety report [i.e., the Periodic Adverse Drug Experience Report (PADER) required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format]. These analyses should show cumulative data relative to the date of approval of Tzield (teplizumab-mzwv) as well as relative to prior periodic safety reports.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Supendeep Dosanjh, Regulatory Project Manager, at Supendeep.Dosanjh@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mahtab Niyyati, M.D.
Associate Director of Therapeutic Review (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

MAHTAB NIYYATI
06/12/2026 03:38:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TZIELD safely and effectively. See full prescribing information for TZIELD.

TZIELD® (teplizumab-mzwv) injection, for intravenous use
Initial U.S. Approval: 2022

WARNING: Viral Reactivation

- **Serious, life-threatening cases of viral reactivation, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV) reactivation have been reported with TZIELD. Patients who are immunocompromised are at increased risk. Serious cases have also been reported in adults with higher body surface area or comorbid conditions, such as adrenal insufficiency or cardiovascular disease. The majority of serious cases occurred in patients who continued TZIELD treatment despite persistent, severe lymphopenia. Severe lymphopenia may be prolonged in adults. (5.1, 5.4)**
- **Test patients for active EBV and CMV infection prior to starting treatment. TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection). Adhere to lymphocyte count monitoring requirements and discontinuation recommendations. Monitor patients for signs and symptoms of viral reactivation following TZIELD treatment and for at least 2 months following the last infusion. If viral reactivation is suspected, discontinue TZIELD. (2.6, 4, 5.1, 5.4)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning	06/2026
Indications and Usage (1)	06/2026
Dosage and Administration (2)	06/2026
Contraindications (4)	06/2026
Warnings and Precautions (5)	06/2026

---------- INDICATIONS AND USAGE ----------

TZIELD is a CD3-directed antibody indicated to: (1)

- Delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients 1 year of age and older with Stage 2 T1D.
- Delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D. This indication is approved under accelerated approval based on evidence of reduced C-peptide decline. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Limitations of Use: (1)

- There is limited evidence of safety and effectiveness in patients aged 45 years and older with Stage 2 T1D.
- TZIELD is not effective as a disease modifying therapy in non-autoimmune dysglycemic conditions.

---------- DOSAGE AND ADMINISTRATION ----------

- Confirm Stage 2 T1D by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available (2.1).
- In patients who meet criteria for a diagnosis of Stage 2 T1D ensure the patient's diagnosis confirms an autoimmune origin and does not suggest insulin resistance due to obesity, type 2 diabetes (T2D) or dysglycemia due to other forms of diabetes.
- Confirm Stage 3 T1D by documenting at least one positive pancreatic islet cell autoantibody and peak C-peptide ≥0.2 pmol/mL on a mixed-meal tolerance test (MMTT) or alternative method if appropriate and MMTT is not available (2.1).
- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests and evaluate patients for active EBV and CMV infection, including assessment of viral load (e.g., polymerase chain reaction testing). Consider expert consultation for appropriate laboratory and clinical evaluation to assess for active EBV or CMV infection. Use of TZIELD is not recommended in patients with certain laboratory abnormalities. TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection) (2.2).
- Premedicate with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and (3) consider use of an antiemetic before each TZIELD dose for at least the first 5 days of the treatment course (2.3).
- Administer TZIELD by intravenous infusion once daily for 14 days (Stage 2) or 12 days (Stage 3). See full prescribing information for the recommended dosage, dosing schedule, minimum infusion duration according to age, and recommendations regarding missed doses (2.4, 2.5).
- See full prescribing information for recommendations on: monitoring lymphocyte counts, liver enzymes, bilirubin, and symptoms of viral reactivation; and discontinuing treatment (2.6).
- Must dilute TZIELD in 0.9% Sodium Chloride Injection, USP. See full prescribing information for detailed preparation and administration instructions (2.7).

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection: 2 mg/2 mL (1 mg/mL) single-dose vial (3).

---------- CONTRAINDICATIONS ----------

TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection) (4).

---------- WARNINGS AND PRECAUTIONS ----------

- *Cytokine Release Syndrome (CRS):* Premedicate, monitor liver enzymes and bilirubin during treatment, and discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN. If severe CRS develops, consider temporarily pausing or discontinuing TZIELD. (5.2).
- *Serious Infections:* Use of TZIELD is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after TZIELD treatment. If a serious infection develops, discontinue TZIELD (5.3).
- *Lymphopenia:* Monitor lymphocyte counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD (5.4).
- *Hypersensitivity Reactions:* If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly (5.5).
- *Vaccinations:* Administer all age-appropriate vaccinations prior to starting TZIELD. See the full PI for recommendations regarding live-attenuated, inactivated, and mRNA vaccines (5.6).

---------- ADVERSE REACTIONS ----------

Most common adverse reactions were lymphopenia, vomiting, rash, leukopenia, diarrhea, neutropenia, increased liver transaminase and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Provention Bio, Inc. at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm. To minimize exposure to a fetus, avoid use of TZIELD during pregnancy and at least 30 days prior to planned pregnancy (8.1).
- Lactation: A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: Viral Reactivation

- **Serious, life-threatening cases of viral reactivation, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV) reactivation have been reported with TZIELD. Patients who are immunocompromised are at increased risk. Serious cases have also been reported in adults with higher body surface area or comorbid conditions, such as adrenal insufficiency or cardiovascular disease. The majority of serious cases occurred in patients who continued TZIELD treatment despite persistent, severe lymphopenia. Severe lymphopenia may be prolonged in adults. (5.1, 5.4)**
- **Test patients for active EBV and CMV infection prior to starting treatment. TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection). Adhere to lymphocyte count monitoring requirements and discontinuation recommendations. Monitor patients for signs and symptoms of viral reactivation following TZIELD treatment and for at least 2 months following the last infusion. If viral reactivation is suspected, discontinue TZIELD. (2.6, 4, 5.1, 5.4)**

1 INDICATIONS AND USAGE

TZIELD is indicated to *[see Dosage and Administration (2.1)]:*

- Delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients 1 year of age and older with Stage 2 T1D.
- Delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D. This indication is approved under accelerated approval based on evidence of reduced C-peptide decline *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Limitations of Use:

- There is limited evidence of safety and effectiveness in patients aged 45 years and older with Stage 2 T1D.
- TZIELD is not effective as a disease modifying therapy in non-autoimmune dysglycemic conditions.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Patients with Stage 2 T1D

Select adult and pediatric patients 1 year of age and older with Stage 2 T1D for TZIELD treatment to delay the onset of Stage 3 T1D based on the confirmation of:

- At least two positive pancreatic islet cell autoantibodies, and
- Dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT):
  - If an OGTT is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate.

- **In adults aged 18 years or older**, recommend following the definition of dysglycemia used in clinical trials to diagnose dysglycemia prior to use of TZIELD due to the lack of specificity of other measures *[see Clinical Studies (14.1)]*.

Ensure the patient's diagnosis confirms an autoimmune origin and does not suggest insulin resistance due to obesity, type 2 diabetes (T2D) or dysglycemia due to other forms of diabetes. These may include, but are not limited to, genetic forms of diabetes, maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), or diabetes secondary to medications or surgery.

Patients with Stage 3 T1D

Select pediatric patients aged 8 to 17 years recently diagnosed (within the last 8 weeks) with Stage 3 T1D for TZIELD treatment to delay the decline in endogenous insulin production based on confirmation of both of the following:

- At least one positive pancreatic islet cell autoantibody
- Peak C-peptide ≥0.2 pmol/mL on a mixed-meal tolerance test (if a mixed meal tolerance test is not available, an alternative method for measuring peak C-peptide ≥0.2 pmol/mL may be appropriate).

2.2 Laboratory and Infection Evaluation, and Vaccination Prior to Initiation

- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests. Use of TZIELD is not recommended in patients with the following conditions *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*:
  - Lymphocyte count less than 1,000 lymphocytes/mcL
  - Hemoglobin less than 10 g/dL
  - Platelet count less than 150,000 platelets/mcL
  - Absolute neutrophil count less than 1,500 neutrophils/mcL
  - Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
  - Active serious infection or chronic active infection other than localized skin infections *[see Warnings and Precautions (5.3)]*.

- Prior to initiating treatment, evaluate patients for active EBV and CMV infection, including assessment of viral load [e.g., polymerase chain reaction (PCR) testing]. Consider expert consultation for appropriate laboratory and clinical evaluation to assess for active EBV or CMV infection. Use of TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection). *[see Warnings and Precautions (5.1)]*.

- Administer all age-appropriate vaccinations prior to starting TZIELD *[see Warnings and Precautions (5.6)]*:
  - Administer live-attenuated (live) vaccines at least 8 weeks prior to TZIELD treatment.
  - Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment.

2.3 Important Premedication Instructions

Prior to each of the first 5 days of TZIELD infusion *[see Warnings and Precautions (5.2)]*:

- Premedicate with a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen
- Premedicate with an antihistamine, and
- Consider premedication with an antiemetic

If needed, administer additional premedication doses.

2.4 Recommended Dosage and Administration

Body Surface Area Dosage Calculation

The dosage of TZIELD is based on body surface (BSA) area, which is calculated using the Mosteller formula, below:

$$\text{BSA } (m^2) = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)}/3{,}600}$$

Using the patient's BSA, calculate the dose based on treatment day:

$$\text{Dose (mcg)} = \text{Daily dosage } (\text{mcg}/m^2) \text{ x BSA } (m^2)$$

Recommended Dosage and Administration in Patients with Stage 2 T1D

Administer TZIELD once daily for 14 consecutive days using BSA-based dosing per the schedule below:

Day(s)	**Daily Dosage**
Day 1	65 mcg/m²
Day 2	125 mcg/m²
Day 3	250 mcg/m²
Day 4	500 mcg/m²
Days 5 through 14	1,030 mcg/m

Administer TZIELD by intravenous infusion over a minimum of:

- 30 minutes in adult and pediatric patients aged 8 years and older.
- 2 hours in pediatric patients aged 1 to less than 8 years *[see Clinical Pharmacology (12.3)]*.

Recommended Dosage and Administration in Patients with Stage 3 T1D

Initiate treatment as soon as possible following Stage 3 T1D diagnosis but no later than 8 weeks from diagnosis.

Administer TZIELD by intravenous infusion over a minimum of 30 minutes, once daily for 12 consecutive days for each treatment course, for a total of two treatment courses, using the BSA-based dosing schedule below:

Day(s)	Daily Dosage
Day 1	106 mcg/m²
Day 2	425 mcg/m²
Days 3 through 12	850 mcg/m²

Second treatment Course:
Administer the second 12-day treatment course 6 months after the first treatment course.
If the second course is delayed, administer the second treatment course within 6 to 12 months after the first treatment course.

2.5 Recommendations Regarding Missed Doses

If a planned TZIELD infusion is missed, administer the missed dose as soon as possible and all remaining doses on consecutive days to complete the 14 total dose regimen in patients with Stage 2 T1D or each of the two 12-day treatment courses in patients with Stage 3 T1D.

Do not administer two doses on the same day.

2.6 Recommended Monitoring During Treatment with TZIELD

- Monitor lymphocyte count regularly (every 2-3 days) during TZIELD infusion and monitor for lymphocyte recovery following completion of TZIELD.
- If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, permanently discontinue TZIELD.
- Monitor patients for signs and symptoms of viral reactivation during TZIELD treatment and for at least 2 months following the last infusion. If viral reactivation is suspected, discontinue TZIELD *[see Warnings and Precautions (5.1)]*.
- Monitor liver enzymes and bilirubin during treatment. Discontinue TZIELD treatment in patients who develop elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN *[see Warnings and Precautions (5.2)]*.

2.7 Preparation and Administration Instructions

- Read this entire section carefully before preparing TZIELD.
- **Must dilute TZIELD prior to use.** This requires the preparation of 100 mcg/mL dilution followed by the preparation of an infusion solution.
- Start the infusion after preparation is complete.
- If the TZIELD infusion solution is not used immediately, store as instructed per corresponding infusion preparation method.

The following are preparation and administration instructions based on BSA dosing requirements *[see Dosage and Administration (2.4)]*:

TZIELD 100 mcg/mL Dilution Preparation:

- Prior to dilution, inspect TZIELD visually before use (the supplied solution is clear and colorless). Do not use TZIELD if particulate matter or coloration is seen.
- Prepare TZIELD using aseptic technique. Each vial is intended for one-time use only, discard any unused portion.
- If the calculated dose is:
  - 2,000 mcg or less, then prepare:
    - **One** sterile syringe (polypropylene (PP), polycarbonate (PC) or glass) **or**
    - **One** sterile glass vial with 18 mL of 0.9% Sodium Chloride Injection **or**
    - **One** ≤50 mL polyvinylchloride (PVC) with di-(2-ethylhexyl)phthalate (DEHP) infusion bag with 18 mL of 0.9% Sodium Chloride Injection.
  - Greater than 2,000 mcg, then prepare:
    - **Two** sterile syringes (PP, PC or glass) **or**
    - **Two** sterile glass vials with 18 mL of 0.9% Sodium Chloride Injection **or**
    - **Two** ≤50 mL PVC with DEHP infusion bags with 18 mL of 0.9% Sodium Chloride Injection.
- Remove the cap from the TZIELD vial – this is the preparation start time.
- Remove 2 mL of TZIELD from the single-dose vial and slowly add to the sterile syringes (PP, PC or glass), glass vial or PVC with DEHP infusion bag containing 18 mL of 0.9% Sodium Chloride Injection.
- Mix gently by slowly swirling the vial or rocking the infusion bag or syringe. The resulting 20 mL diluted TZIELD solution contains 100 mcg/mL of teplizumab-mzwv.
- If preparing a dose greater than 2,000 mcg, repeat the above process with second TZIELD vial and the glass vial, or PVC with DEHP infusion bag or syringe (PP, PC or glass) containing 18 mL of 0.9% Sodium Chloride Injection.

TZIELD Infusion Solution Preparation:

- Calculate the volume of TZIELD 100 mcg/mL dilution needed for the infusion.

$$\text{Volume of 100 mcg/mL dilution (mL)} = \frac{\text{Dose (mcg)}}{\text{100 mcg/mL}}$$

There are two different methods for preparation of the infusion: infusion bag (Method 1) or syringe (Method 2, for syringe pump infusion). Use the appropriate steps below depending on the selected method.

Method 1: Infusion bag for intravenous administration:

- Using an appropriately sized syringe *[see Compatible Materials for Administration (2.8)]*, withdraw the volume of TZIELD 100 mcg/mL dilution required for that day's calculated dose (for a calculated dose 2,000 mcg or less) or from both prepared 100 mcg/mL dilutions (for a calculated dose more than 2,000 mcg) *[see TZIELD 100 mcg/mL Dilution Preparation]*.
- Discard unused portion of remaining TZIELD dilution in the syringe, sterile glass vial or PVC with DEHP infusion bag.

- Slowly add contents of the syringe containing the TZIELD dose to a PVC with DEHP infusion bag containing 25 mL of 0.9% Sodium Chloride Injection (**for a calculated dose more than 2,000 mcg, add the cumulative volume for the calculated dose to a single infusion bag**). Gently rock the infusion bag to ensure that the solution mixes sufficiently. Do not shake.

Infusion bag administration:

- Prime the IV infusion set with the TZIELD infusion solution. Do not waste any infusion solution during the priming process.
- Infusion administration has a minimum duration of:
  - 30 minutes in adult and pediatric patients aged 8 years and older
  - 2 hours in pediatric patients aged 1 to less than 8 years
- Rate may be slowed for patient's tolerability.
- After infusion, flush the IV set with a volume of 0.9% Sodium Chloride Injection greater than or equal to the priming volume, to ensure full dose is administered. Same infusion rate should be used for flushing.
- If the TZIELD infusion solution is not used immediately, store at room temperature between 15°C to 25°C (59°F to 77°F). Discard if the infusion is unable to be completed within 6 hours of preparation.

Method 2: Syringe for intravenous infusion via syringe pump:

- Requires an appropriately sized sterile syringe (up to 60 mL) [i.e., infusion syringe] which is compatible with available syringe pump. The syringe pump should support rates as low as 1 mL/hour *[see Compatible Materials for Administration (2.8)]*.
- The final concentration range is 15 mcg/mL to 60 mcg/mL with a maximum infusion volume of 60 mL.
- To fit technical constraints of syringe pump, a lower volume may be used as long as the concentration is between 15 mcg/mL and 60 mcg/mL.

If the calculated dose is:

- 900 mcg or less:
  - Calculate the maximum volume that can be administered for the calculated dose (based on treatment day, dose and patient BSA) using a minimum infusion concentration of 15 mcg/mL.

$$\text{Volume}_{\text{Infusion}}(\text{mL}) = \frac{\text{Dose (mcg)}}{\text{Minimum infusion concentration 15 mcg/mL}}$$

  - Calculate the volume of 0.9% Sodium Chloride Injection to be added to the infusion syringe:

$$\text{Volume}_{\text{0.9\% Sodium Chloride Injection}}(\text{mL}) = \text{Volume}_{\text{Infusion}}(\text{mL}) - \text{Volume}_{\text{100 mcg/mL dilution}}(\text{mL})$$

- Greater than 900 mcg: the maximum infusion volume is capped at 60 mL.

$$\text{Volume}_{\text{0.9\% Sodium Chloride Injection}}\,(\text{mL}) = 60\ \text{mL} - \text{Volume}_{\text{100 mcg/mL dilution}}\,(\text{mL})$$

For all doses:
- Measure the appropriate volume of 0.9% Sodium Chloride Injection from above calculation into the infusion syringe.
- Using an appropriately sized syringe, withdraw the volume of TZIELD 100 mcg/mL dilution *[see Compatible Materials for Administration (2.8)]* required for that day's calculated dose (for a calculated dose 2,000 mcg or less) and add it to the infusion syringe. For a calculated dose more than 2,000 mcg, add the cumulative volume from both prepared 100 mcg/mL dilutions to a single infusion syringe *[see TZIELD 100 mcg/mL Dilution Preparation]*.
- Gently rock the infusion syringe to ensure that the solution mixes sufficiently. Do not shake.

Syringe administration:
- Prime the IV extension set with the TZIELD infusion solution. Do not waste any infusion solution during the priming process.
- Attach infusion syringe to a syringe pump.
- The infusion must be administered over a minimum of:
  - 30 minutes in adult and pediatric patients aged 8 years and older
  - 2 hours in pediatric patients aged 1 to less than 8 years
- **Do not manually push the syringe.**
- Infusion administration rate may be slowed for patient's tolerability.
- After infusion, flush the IV extension set with a volume of 0.9% Sodium Chloride Injection greater than or equal to the priming volume at the same infusion rate to ensure full dose is administered.
- If the TZIELD infusion solution is not used immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 12 hours, followed by a maximum of 6 hours at room temperature between 15°C to 25°C (59°F to 77°F) which includes infusion time. Discard if the infusion is unable to be completed within 15 hours of preparation.

2.8 Compatible Materials for Administration

Compatibility has been demonstrated with the materials listed in Table 1. Other materials should not be used.

Table 1. Compatible Materials for TZIELD Administration

Step	Equipment	Product Contact Material
Initial dilution	Containers	PP, PC, glass, PVC with DEHP IV bag
	Syringes	PP, PC, glass
Infusion with IV bags	IV bags	PVC with DEHP for all doses EVA bags for doses ≥ 240 mcg
	Infusion sets	PVC with DEHP

Infusion with syringe pump	Infusion dilution container	Syringe: PP, PC
	Syringes	PP, PC
	Infusion/extension sets	PE, PVC with or without DEHP

Abbreviations: PP=polypropylene, PC=polycarbonate, PVC with DEHP=polyvinylchloride with di-(2-ethylhexyl)phthalate, PE=polyethylene.

Use of in-line filter is not recommended. If necessary, use a polyethylene sulfone (PES) filter. Do not use light protected (colored) infusion sets.

3 DOSAGE FORMS AND STRENGTHS

Injection: 2 mg/2 mL (1 mg/mL) clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection) [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Viral Reactivation

Serious, life-threatening cases of viral reactivation, including EBV and CMV infections, have been reported with TZIELD. During and within 2 months of TZIELD treatment, if primary infection or reactivation of EBV or CMV occurs, it may present with increased severity, including EBV-associated lymphoproliferative disease and organ failure.

Patients who are immunocompromised, including patients with Down syndrome, may be at increased risk. TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection). The majority of serious viral reactivation cases occurred in patients who continued TZIELD despite persistent, severe lymphopenia. The duration of severe lymphopenia following TZIELD treatment may be prolonged in adults *[see Warnings and Precautions (5.4)]*.

Serious cases have also been reported in adults with higher body surface area or comorbid conditions, such as adrenal insufficiency or cardiovascular disease.

Prior to initiating treatment with TZIELD, evaluate patients for active EBV and CMV infection and confirm absence of active infection on assessment of viral load (e.g., PCR). TZIELD is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection) *[see Dosage and Administration (2.2)]*.

During treatment with TZIELD, regularly monitor lymphocyte counts *[see Dosage and Administration (2.6), Warnings and Precautions (5.4)]* and monitor patients for signs and symptoms of viral reactivation during treatment and for at least 2 months following the last infusion. If viral reactivation is suspected, discontinue TZIELD and obtain viral load (e.g., PCR) promptly. Consider appropriate expert consultation for diagnostic testing recommendations as some diagnostic tests may give inaccurate results following treatment with TZIELD, including

rapid heterophile antibody testing. If viral reactivation is confirmed, permanently discontinue TZIELD *[see Dosage and Administration (2.6)].* Consider appropriate expert consultation for the management of severe viral reactivation.

5.2 Cytokine Release Syndrome

Cytokine release syndrome (CRS) has been observed in TZIELD-treated patients. In a pool of clinical trials, CRS was reported in 5% of TZIELD-treated patients compared to 0.8% of control-treated patients. In the PROTECT study, CRS was reported in 9% of TZIELD-treated patients compared to 1% of placebo-treated patients during the treatment period and through 28 days after the last study drug administration. Manifestations of CRS in TZIELD-treated patients included fever, nausea (with or without vomiting), fatigue, headache, myalgia, arthralgia, increased ALT, increased AST, and increased total bilirubin. These manifestations typically occurred during the first 5 days of TZIELD treatment *[see Adverse Reactions (6.1)]*. To mitigate CRS:

- Premedicate with antipyretics, antihistamines and/or antiemetics prior to TZIELD treatment *[see Dosage and Administration (2.3)].*
- Monitor liver enzymes and bilirubin during treatment. Discontinue TZIELD treatment in patients who develop elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.
- Treat symptoms of CRS in TZIELD-treated patients with antipyretics, antihistamines and/or antiemetics. If severe CRS develops, consider:
  - Temporarily pausing TZIELD dosing for 1-2 days and if symptoms have resolved or significantly improved, subsequently administering the remaining doses on consecutive days to complete the full 14-day treatment course in patients with Stage 2 T1D or each of the two 12-day courses in patients with Stage 3 T1D, **or**
  - Discontinuing TZIELD treatment.

5.3 Serious Infections

Bacterial and viral infections have occurred in TZIELD-treated patients. In a pool of clinical trials, TZIELD-treated patients had a higher rate of serious infections (3.5%) than control-treated patients (2%), including gastroenteritis, cellulitis, pneumonia, abscess, sepsis *[see Adverse Reactions (6.1)].* Adults may have a longer duration of severe lymphopenia following TZIELD treatment, which may increase the risk for serious infections.

Use of TZIELD is not recommended in patients with active serious infection, or chronic infection other than localized skin infections. Monitor patients for signs and symptoms of infection during and after TZIELD treatment. If serious infection develops, treat appropriately, and discontinue TZIELD.

5.4 Lymphopenia

In a pool of clinical trials, 78% of TZIELD-treated patients developed lymphopenia compared to 11% of control-treated patients. For most TZIELD-treated patients who experienced lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pre-treatment values within two weeks after treatment completion and without dose interruption. Severe lymphopenia (<500 cells per mcL) lasting 1 week or longer occurred in 0.9% of

TZIELD-treated patients, 0.5% of TZIELD-treated patients permanently discontinued TZIELD because of lymphopenia *[see Adverse Reactions (6.1)]*.

In the PROTECT study, 51% of TZIELD-treated patients developed lymphopenia compared to 3% of placebo-treated patients. Severe lymphopenia lasting 1 week or longer occurred in 1.4% of TZIELD-treated patients.*[see Adverse Reactions (6.1)]*.

Severe lymphopenia following TZIELD treatment may be more prolonged in adults. Obtain a CBC prior to starting TZIELD and monitor lymphocyte counts during TZIELD treatment. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, permanently discontinue TZIELD.

5.5 Hypersensitivity Reactions

Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in TZIELD-treated patients *[see Adverse Reactions (6.1)]*. If severe hypersensitivity reactions occur, discontinue use of TZIELD and treat promptly.

5.6 Vaccinations

The safety of immunization with live-attenuated vaccines in TZIELD-treated patients has not been studied. Additionally, TZIELD may interfere with the immune response to vaccination and decrease vaccine efficacy.

- Administer all age-appropriate vaccinations prior to starting TZIELD *[see Dosage and Administration (2.2)]*.
- Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to any TZIELD treatment course, during treatment, or up to 6 weeks after completion of any treatment course.
- Live-attenuated vaccinations are not recommended within the 8 weeks prior to starting TZIELD treatment, during treatment, between treatment courses, or up to 52 weeks after completion of final treatment course.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the Prescribing Information:

- Viral Reactivation *[see Warnings and Precautions (5.1)]*
- Cytokine Release Syndrome *[see Warnings and Precautions (5.2)]*
- Serious Infections *[see Warnings and Precautions (5.3)]*
- Lymphopenia *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Placebo-Controlled Study in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 T1D (TN-10)

The data in Table 2 are derived from the placebo-controlled study (Study TN-10) in adult and pediatric patients aged 8 years and older with Stage 2 T1D *[see Clinical Studies (14.1)]*. These data reflect exposure of 44 patients of whom 93% completed the full 14-day treatment course.

Table 2 presents common (≥5%) adverse reactions that occurred during treatment and through 28 days after the last study drug administration in patients with Stage 2 T1D in Study TN-10. Adverse reactions observed in pediatric patients 8 years and older who received TZIELD were consistent with those reported in adult patients in this study.

Table 2. Common Adverse Reactions[1] in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 T1D (Study TN-10)[2]

Adverse Reaction	TZIELD N=44	Placebo N=32
Lymphopenia[3]	73%	6%
Rash[3]	36%	0%
Leukopenia[3]	21%	0%
Headache	11%	6%
Neutropenia[3]	5%	3%
Increased alanine aminotransferase	5%	3%
Nausea	5%	3%
Diarrhea	5%	0%
Nasopharyngitis	5%	0%

[1] That occurred during treatment and through 28 days after the last study drug administration.
[2] Adverse reactions that occurred in 2 or more TZIELD-treated patients
[3] Grouped term includes other related terms

Placebo-Controlled Trial in Pediatric Patients Aged 8 to 17 Years with Stage 3 T1D

In a 78-week placebo-controlled trial (PROTECT) in patients aged 8 to 17 years recently diagnosed with Stage 3 T1D, 328 patients were randomized to TZIELD or placebo daily by intravenous infusion for a 12-day course followed by another 12-day course 6 months later *[see Clinical Studies (14.2)]*.

Table 3 presents common adverse reactions (≥5%) that occurred during either of the two 12-day treatment courses and through 28 days after the last dose of study drug administration in the PROTECT trial.

Table 3. Common Adverse Reactions[1] in Pediatric Patients Aged 8 to 17 Years with Stage 3 T1D (PROTECT Study)

Adverse Reaction	TZIELD n=217	Placebo n=111
Course 1		
Lymphopenia[2]	51%	3%
Rash[2]	51%	9%
Leukopenia[2]	34%	3%
Nausea	34%	12%
Headache	29%	16%
Vomiting	26%	5%
Neutropenia[2]	23%	5%
Abdominal pain[2]	18%	11%
Pyrexia	16%	3%
Alanine aminotransferase increased	11%	0%
Diarrhea	10%	6%
Cytokine release syndrome	7%	1%
Hypotension	7%	6%
Aspartate aminotransferase increased	7%	1%
Hemoglobin decreased[2]	5%	4%
Chills	5%	0%

[1] Adverse reactions occurring in equal or more than 5% of participants in the TZIELD group, higher in TZIELD compared to placebo, in treatment course 1 through 28 days after the last dose.
[2]Grouped term includes other related terms.

No new adverse reactions were observed with the second course of TZIELD treatment. Incidence rates were similar than those reported during the first treatment course.

Pool of Five Controlled Clinical Studies in Stage 2 or Stage 3 T1D

Adverse reactions in TZIELD-treated patients were also evaluated in a larger pool of adult and pediatric patients who participated in five controlled clinical studies (including Study TN-10 described above):

- One study in patients with Stage 2 T1D (Study TN-10) *[see Clinical Studies (14.1)]*,
- Three placebo-controlled studies in patients with Stage 3 T1D,
- One open-label standard-of-care controlled study of TZIELD in patients with Stage 3 T1D.

In this pool:

- 773 patients received TZIELD (44 patients with Stage 2 T1D and 729 patients with Stage 3 T1D), and
- 245 patients received either placebo or standard of care control (32 patients with Stage 2 T1D and 213 patients with Stage 3 T1D).

In these studies, 436 patients received either a 14-day or 12-day dosing regimen of TZIELD with a total drug exposure that was comparable to the total drug exposure achieved with the recommended dosage *[see Dosage and Administration (2.4)]*, 168 patients received a 14-day course of TZIELD with a lower total TZIELD drug exposure, and 169 patients received a 6-day course of TZIELD with a lower total TZIELD drug exposure. The mean age of TZIELD-treated patients was 17.6 years (median 15 years), 62% were less than 18 years old (40% age 12 to 17; 21% age 8 to 11), 38% were 18 years and older (36% age 18 to 34; 2% age ≥35), and 64% were male. The population was 72% White, 26% Asian, 1% Black or African American, 1% were multiple or unknown race, and less than 1% American Indian or Alaska Native; 5% were Hispanic or Latino ethnicity.

Common Adverse Reactions

Cytokine Release Syndrome (CRS)

In Study TN-10, CRS was reported in 2% of TZIELD-treated patients compared to 0% of placebo-treated patients.

In the PROTECT Study, CRS was reported in 9% of TZIELD-treated patients compared to 1% of placebo-treated patients.

Of the 39 TZIELD-treated patients developed CRS (5% of all TZIELD-treated patients), in the pool of 5 clinical trials, 13% of the CRS cases were serious adverse reactions *[see Warnings and Precautions (5.2)]*. Liver transaminase elevations were observed in 56% of TZIELD-treated patients who experienced CRS; 64% were up to 2.5 times ULN, 32% were more than 2.5 to 5 times ULN, and 4.5% were greater than 5 -10 times ULN.

Serious Infections

In Study TN-10, serious infections (cellulitis, gastroenteritis, pneumonia, wound infection) were reported in 9% (4/44) of TZIELD-treated patients compared to 0% (0/32) of placebo-treated patients any time during or after the first dose of study treatment.

In clinical trials, serious infections were reported in 3.5% of TZIELD-treated patients compared to 2% of control-treated patients any time during or after the first dose of study treatment.

Rash and Hypersensitivity Reactions

Hypersensitivity reactions were reported with TZIELD treatment in Study TN-10. Serum sickness was observed in 2% (1/44) of TZIELD-treated patients compared to 0% (0/32) of placebo-treated patients. The patient who developed serum sickness had a prior history of positive anti-nuclear antibody and presented with arthralgias and elevated c-reactive protein and low C4 complement five days after completing their course of TZIELD; illness resolved in 2.5 months.

In the PROTECT Study, hypersensitivity reactions were reported in 1% of TZIELD-treated patients and 0% in the placebo group. One patient in the TZIELD group experienced delayed hypersensitivity. The patient had a prior history of allergic rhinitis and presented with symptoms

of rash and arthralgia 16 days after completing Course 1. The event resolved with antihistamine treatment.

In the pool of 5 clinical trials of patients with Stage 2 or Stage 3 T1D:

- Anaphylaxis (with hypoxia and bronchospasm) was observed in one TZIELD-treated patient who was hospitalized.
- Angioedema (periorbital and facial) was observed in 0.3% TZIELD-treated patients, compared to 0% in control-treated patients.
- Peripheral and generalized edema was reported in 1.6% of TZIELD-treated patients and 0% of control-treated patients.
- Rash was observed in 48% of TZIELD-treated patients compared to 15% in control-treated patients, with 33 excess cases of rash per 100 patients. The majority of events of rash observed with TZIELD treatment were not serious and resolved without intervention; although 0.3% (2/773) of TZIELD-treated patients had a serious rash compared to 0% (0/245) of placebo-treated patients.
- Urticaria was reported in 1.9% of TZIELD-treated patients and in 1.2% of control-treated patients.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions
In Study TN-10, rash occurred in 39% of TZIELD-treated patients who developed anti-teplizumab-mzwv antibodies and in 33% of TZIELD-treated patients who did not develop anti-teplizumab-mzwv antibodies *[see Clinical Pharmacology (12.6)]*.

In the PROTECT Study, rash occurred in 30% of TZIELD-treated patients who developed anti-teplizumab-mzwv antibodies and in 17% of TZIELD-treated patients who did not develop anti-teplizumab-mzwv antibodies *[see Clinical Pharmacology (12.6)]*.

Open Label Study in Pediatric Patients Age 1 to Less Than 8 Years with Stage 2 T1D
The safety of TZIELD was evaluated in a non-randomized, single arm, open-label, multicenter study in 23 pediatric patients age 1 to less than 8 years with Stage 2 T1D (*PETITE-T1D Study; NCT05757713)[see Clinical Pharmacology (12.3)]*. In this trial, 87% completed the full 14-day treatment course. The median age was 4.9 years (1 patient was less than 2 years old; 52% were 2 to less than 5 years old; 44% were 5 to less than 8 years old; range 1.7 to 6.8 years) and 52% were female. The majority of the population (96%) was White and one patient (4%) was Asian; 3 patients (13%) were Hispanic or Latino ethnicity. At baseline, 87% of participants had a first-degree relative with T1D. The majority (87%) were positive for 3 or more diabetes-related autoantibodies. The most common autoantibodies were anti-insulin (87%), anti-ICA (85%), anti-GAD65 (83%), anti-ZnT8 (74%), and anti-IA2 (68%). The median HbA1c was 5.5%.

Overall, the safety profile of TZIELD observed in pediatric patients less than 8 years of age with Stage 2 T1D was consistent with that observed in patients 8 years of age and older with Stage 2 T1D. The most common adverse reactions that occurred in patients less than 8 years of age were vomiting (52%) and diarrhea (30%).

Other Adverse Reactions

Lymphopenia

In Study TN-10, lymphopenia was reported in 73% of TZIELD-treated patients compared to 6% of placebo-treated patients. The average lymphocyte count nadir occurred at Day 5 of treatment, with recovery and return to baseline by Week 6 *[see Warnings and Precautions (5.4)]*.

In the PROTECT Study, lymphopenia was reported in 51% of TZIELD-treated patients compared to 3% of placebo-treated patients. Lymphocyte count nadir occurred at approximately Day 4 of treatment, with recovery and return to baseline by Week 4 *[see Warnings and Precautions (5.4)]*.

Neutropenia

In Study TN-10, neutropenia was observed in 7% of TZIELD-treated patients compared to 3% of placebo-treated patients.

In the PROTECT Study, neutropenia was observed in 23% of TZIELD-treated patients compared to 5% of placebo-treated patients.

Decreased Hemoglobin and Thrombocytopenia

In the pool of 5 clinical trials, decreased hemoglobin was reported in 27% of TZIELD-treated patients compared to 21% of placebo-treated patients, and thrombocytopenia was reported in 13% of TZIELD-treated patients compared to 5% of placebo-treated patients during the 14-day treatment course; recovery occurred within 2 to 4 weeks of treatment. In these clinical trials, 1.8% of TZIELD-treated patients discontinued treatment due to hemoglobin less than 8.5 g/dL (or a decrease of more than 2 g/dL to a value less than 10 g/dL), and 1% discontinued TZIELD due to platelet count less than 50,000 platelets/mcL.

Liver Enzyme Elevations

Liver enzyme and bilirubin elevations were observed in TZIELD-treated patients, both in the context of CRS and in patients without CRS. In the pool of 5 clinical trials, ALT increased was reported in 25% of TZIELD-treated patients compared to 11% of placebo-treated patients during the 14-day treatment course. On laboratory analysis, 5.1% of TZIELD-treated patients experienced a peak ALT more than 3 times the ULN compared to 0.8% of control-treated patients. Most liver enzyme elevations were transient and resolved 1-2 weeks after treatment; 98% resolved by week 14.

Procedure-Related Venous Thrombosis

Venous thrombus and thrombophlebitis have been reported in patients receiving teplizumab intravenously administered via peripherally inserted central catheter (PICC). In the pool of 5 clinical trials of patients, deep vein thrombus was reported in 0.4% of TZIELD-treated patients compared to 0 placebo-treated patients. One teplizumab-treated patient (4.3%) in the PETITE-T1D study experienced a deep vein thrombosis.

Other Laboratory Abnormalities
In the pool of 5 clinical trials, other laboratory abnormalities including decreased bicarbonate (15% in TZIELD-treated patients, compared to 7% in placebo-treated patients) and decreased blood calcium (19% in TZIELD-treated patients, compared to 13% in placebo-treated patients) were noted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available case reports from clinical trials with TZIELD are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on teplizumab-mzwv in nonclinical studies, monoclonal antibodies can be actively transported across the placenta, and TZIELD may cause immunosuppression in the utero-exposed infant *(see Clinical Considerations).* To minimize exposure to a fetus, avoid use of TZIELD during pregnancy and at least 30 days prior to planned pregnancy.

TZIELD is not active in rodents. In animal reproduction studies, mice were given a surrogate anti-mouse CD3 antibody subcutaneously during organogenesis through lactation. Pups born to dams administered the murine surrogate antibody during pregnancy showed a reduction in the adaptive immune response consistent with the expected pharmacology *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Report pregnancies to Provention Bio, Inc.'s Adverse Event reporting line at 1-800-633-1610 or visit https://ae.reporting.sanofi.

Clinical Considerations

Fetal/Neonatal Adverse Reactions
Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because teplizumab-mzwv may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to teplizumab-mzwv in utero. There are insufficient data regarding infant serum levels of teplizumab-mzwv at birth and the duration of persistence of teplizumab-mzwv in infant serum after birth to identify a specific timeframe to delay live virus immunizations in infants exposed in utero.

Data

Animal Data
In an embryo-fetal developmental toxicity study, pregnant mice were administered a murine surrogate anti-mouse CD3 antibody by subcutaneous injection at dose levels of 0, 0.03, 0.3, or 20 mg/kg on Gestation Days 6, 10, and 14. Increase in post-implantation loss occurred in the 20 mg/kg group, in the presence of maternal toxicity.

In a pre- and postnatal development toxicity study in pregnant mice, in which the murine surrogate antibody was administered every 3 days from gestation day 6 through lactation day 19 at doses of 0, 0.3, 3, or 20 mg/kg, no maternal toxicity or increased incidence of post-implantation loss was observed. Reductions in T cell populations and increases in B cells, and a reduction in the adaptive immune response to keyhole limpet hemocyanin (KLH) were observed in the offspring on postnatal days 35 and 84 at 20 mg/kg. The surrogate antibody was present in the offspring serum at level less than 1.5% that of maternal serum at the high dose. A trend towards reduction in fertility was observed in the offspring of dams administered the murine surrogate antibody at 20 mg/kg. The human relevance of this finding is unknown.

8.2 Lactation

Risk Summary

There are no data on the presence of teplizumab-mzwv in either human or animal milk, the effects on the breastfed child, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to teplizumab-mzwv are unknown.

Although the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TZIELD and any potential adverse effects on the breastfed child from TZIELD or from the underlying maternal condition, a lactating woman may interrupt breastfeeding and pump and discard breast milk during treatment and for 20 days after TZIELD administration to minimize drug exposure to a breastfed child.

8.4 Pediatric Use

The safety and effectiveness of TZIELD have been established to:

- Delay the onset of Stage 3 T1D in pediatric patients 1 year of age and older with Stage 2 T1D. Use of TZIELD for this indication is supported by evidence from an adequate and well-controlled study (Study TN-10) in adult and pediatric patients 8 years of age and older (including 29 pediatric patients) with Stage 2 T1D and from additional pharmacokinetic and safety data in 23 pediatric patients aged 1 to less than 8 years of age with Stage 2 T1D (PETITE T1D) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)]*.

- Delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D. Use of TZIELD for this indication is supported by an adequate and well-controlled study (PROTECT Study) in pediatric patients recently diagnosed with Stage 3 T1D *[see Clinical Studies (14.2)]*.

Adverse reactions observed in pediatric patients 1 year of age and older who received TZIELD were consistent with those reported in adults *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of TZIELD have not been established to delay the onset of Stage 3 T1D in pediatric patients younger than 1 year of age with Stage 2 T1D.

The safety and effectiveness of TZIELD have not been established to delay the decline in endogenous insulin production in pediatric patients less than 8 years of age years recently diagnosed with Stage 3 T1D.

8.5 Geriatric Use

Stage 2 T1D is largely a condition that occurs in pediatric and younger adult patients. Clinical studies of TZIELD to delay the onset of Stage 3 T1D did not include patients 65 years of age and older.

11 DESCRIPTION

Teplizumab-mzwv is a CD3-directed monoclonal antibody (humanized IgG1 kappa) that has a molecular weight of approximately 150 kilodalton (kDa) and is expressed from a recombinant Chinese hamster ovary (CHO) cell line.

TZIELD (teplizumab-mzwv) injection is supplied as a sterile, preservative-free, clear and colorless solution in a 2 mg/2 mL (1 mg/mL) single-dose vial for intravenous use. Each mL contains 1 mg of teplizumab-mzwv, dibasic sodium phosphate (0.26 mg), monobasic sodium phosphate (0.98 mg), polysorbate 80 (0.05 mg), sodium chloride (8.78 mg), and water for injection. The pH is 6.1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Teplizumab-mzwv binds to CD3 (a cell surface antigen present on T lymphocytes) and delays the onset of Stage 3 T1D in adult and pediatric patients aged 1 year and older with Stage 2 T1D and delays the decline in endogenous insulin production in patients aged 8 to 17 years recently diagnosed with Stage 3 T1D.

The mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.

12.2 Pharmacodynamics

Clinical studies have shown that teplizumab-mzwv binds to CD3 molecules on the surface of both CD4+ and CD8+ T cells during TZIELD treatment, with internalization of the teplizumab-mzwv/CD3 complex from the surface of T cells. Pharmacodynamic effects include lymphopenia in the absence of depletion of T cells with a nadir approximately on the 5th day of dosing, during a 14-day course (Stage 2) or 12-day course (Stage 3) of TZIELD treatment *[see Warnings and Precautions (5.4)]*.

Teplizumab-mzwv exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of teplizumab-mzwv have not been fully characterized.

12.3 Pharmacokinetics

Distribution

The central volume of distribution (Vd) of teplizumab-mzwv was 2.27 L in a 60 kg subject.

Elimination
Teplizumab-mzwv showed saturable binding and elimination. The clearance of teplizumab-mzwv is 2.66 L/day in a 60 kg subject.

Metabolism
Teplizumab-mzwv is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations
No clinically significant differences in the pharmacokinetics of teplizumab-mzwv were observed based on age (1 to 35 years old), sex, or racial groups (White, Asians).

Pediatric Patients 1 to Less Than 8 Years Old
No clinically significant difference in the AUC of teplizumab-mzwv was observed in pediatric patients aged 1 to less than 8 years compared to that in adult and pediatric patients aged 8 years and older. By extending the infusion duration from 30 minutes to 2 hours in pediatric patients aged 1 to less than 8 years, the C_{max} of teplizumab-mzwv was comparable to that in adult and pediatric patients aged 8 years and older.

Body weight
BSA-based dosing normalizes the exposure to teplizumab-mzwv across body weight.

12.6 Immunogenicity
The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of teplizumab-mzwv or of other teplizumab products.

In the placebo-controlled study in patients aged 8 years of age and older with Stage 2 T1D (Study TN-10) *[see Clinical Studies (14.1)]*, approximately 57% (24/42) of TZIELD-treated patients developed anti-teplizumab-mzwv antibodies after one 14-day course of TZIELD treatment, 46% (11/24) of whom developed neutralizing antibodies. There was a higher incidence of rash in TZIELD-treated patients who developed anti-teplizumab-mzwv antibodies (39%) compared to those who did not develop anti-teplizumab-mzwv antibodies (33%) *[see Adverse Reactions (6.1)]*.

Results from the analysis up to Week 52 from the PETITE-T1D study in patients 1 to less than 8 years of age with Stage 2 T1D, approximately 87% (20/23) of TZIELD-treated patients developed anti-teplizumab-mzwv antibodies, 70% (14/20) of whom developed neutralizing antibodies *[see Adverse Reactions (6.1)]*. There was a higher incidence of skin and subcutaneous tissue disorders (most of which were mild or moderate) in TZIELD-treated patients who developed anti-teplizumab-mzwv antibodies (70%) compared to those who did not develop anti-teplizumab-mzwv antibodies (33%) *[see Adverse Reactions (6.1)]*.

There is insufficient information to characterize the effects of ADA on pharmacokinetics, pharmacodynamics, or effectiveness of TZIELD in patients aged 1 year and older with Stage 2 T1D.

In the placebo-controlled study in patients 8 to 17 years of age with Stage 3 T1D (PROTECT Study) *[see Clinical Studies (14.2)]*, approximately 98% (172/175) of TZIELD-treated patients developed anti-teplizumab-mzwv antibodies after two 12-day courses of TZIELD treatment, 77% (132/172) of whom developed neutralizing antibodies. Following the second course of TZIELD treatment, ADA titers and neutralizing activity were higher, and geometric mean teplizumab-mzwv AUC and C_{trough} after the last dose decreased by 51% and 81%, respectively, compared to those in first course. There is insufficient information to characterize the effects of ADA on pharmacodynamics or effectiveness of TZIELD to delay the decline in endogenous insulin production in patients with Stage 3 T1D. There was a higher incidence of rash in TZIELD-treated patients who developed anti-teplizumab-mzwv antibodies (30%) compared to those who did not develop anti-teplizumab-mzwv antibodies (17%) *[see Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to assess the carcinogenic potential of teplizumab-mzwv.

No studies have been performed to assess the mutagenic potential of teplizumab-mzwv. As an antibody, teplizumab-mzwv is not expected to interact directly with DNA.

Fertility and reproductive performance were unaffected in female and male mice that received a murine surrogate anti-mouse CD3 antibody administered by the subcutaneous route at doses up to 20 mg/kg.

14 CLINICAL STUDIES

14.1 Delay Onset of Stage 3 T1D in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 Type 1D

The effectiveness of TZIELD to delay the onset of Stage 3 T1D was investigated in a randomized, double-blind, event-driven, placebo-controlled study (Study TN-10; NCT01030861) in 76 patients, 8 to 49 years of age with Stage 2 T1D. Stage 2 T1D was defined as having both of the following:

1. Two or more of the following pancreatic islet autoantibodies:
    - Glutamic acid decarboxylase 65 (GAD) autoantibodies
    - Insulin autoantibody (IAA)
    - Insulinoma-associated antigen 2 autoantibody (IA-2A)
    - Zinc transporter 8 autoantibody (ZnT8A)
    - Islet cell autoantibody (ICA)

2. Dysglycemia without overt hyperglycemia on oral glucose tolerance testing (OGTT) defined as:
   - Fasting plasma glucose ≥ 110mg/dL, and <126 mg/dL or
   - 2 hour plasma glucose ≥140mg/dL, and <200 mg/dL or
   - 30, 60, or 90 minute value on OGTT ≥200 mg/dL

   In patients 18 years of age and older: two consecutive OGTTs, each demonstrating dysglycemia without overt hyperglycemia (as defined above) were required.

In Study TN-10, patients were randomized to receive TZIELD or placebo once daily by intravenous infusion for 14 days. Patients in the TZIELD group had a total drug exposure that was comparable to the total drug exposure achieved with the recommended total TZIELD dosage *[see Dosage and Administration (2.4)]*.

The primary efficacy endpoint in Study TN-10 was the time from randomization to development of Stage 3 T1D diagnosis.

Baseline Patient Characteristics in Study TN-10

In Study TN-10, 45% were female; 97% White, 1% Asian, and 1% reported multiracial background; 3% were Hispanic or Latino ethnicity; and 95% were from the United States. The median age was 14 years. The age range was 8.5 to 49.5 years old (72% were <18 years old; 14% were ≥35 years old) (Table 4).

Table 4. Baseline Age Characteristics of Adult and Pediatric Patients 8 Years of Age and Older with Stage 2 T1D (Study TN-10)[1]

	TZIELD N=44	**Placebo N=32**
Age Group		
≥18 Years	34%	19%
<18 years	66%	81%
Pediatric Age Group Quartiles		
8 to <11 years	21%	25%
11 to <14 years	27%	31%
14 to <18 years	18%	25%

[1] Intent to treat (ITT) population

Baseline Disease Characteristics in Study TN-10

Table 5 displays the baseline disease characteristics in Study TN-10.

Table 5. Baseline Disease Characteristics of Adult and Pediatric Patients 8 Years of Age and Older with Stage 2 T1D (Study TN-10)[1]

	TZIELD N=44	Placebo N=32
Glucose, mg/dL[2]		
median (min, max)	165 (115, 207)	154 (103, 200)
HbA1c, %		
median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)
HLA-DR4		
Missing	5%	0
Absent	34%	34%
Present	61%	66%
HLA-DR3		
Missing	5%	0
Absent	48%	53%
Present	48%	47%
HLA-DR3/DR4		
Both DR3 and DR4	25%	22%
DR3 only	23%	25%
DR4 only	36%	44%
Missing	5%	0
Neither DR3 nor DR4	11%	9%
Autoantibodies Positive (N)		
1	2%	0
2	27%	22%
3	25%	16%
4	27%	44%
5	18%	19%
Autoantibody Type Positive		
GAD65	91%	88%
IAA	43%	34%
IA-2A	59%	75%
ICA	66%	88%
ZnT8	73%	75%

[1] Intent to treat (ITT) population

[2] The glucose data are area under the time-concentration curve (AUC) values from the oral glucose tolerance test

Abbreviations: HbA1c=hemoglobin A1c, SD=standard deviation, HLA = human leukocyte antigen, GAD65=Glutamic acid decarboxylase 65 (GAD) autoantibodies, IAA=Insulin autoantibody, IA-2A=Insulinoma-associated antigen 2 autoantibody, ZnT8A=Zinc transporter 8 autoantibody, ICA=Islet cell autoantibody

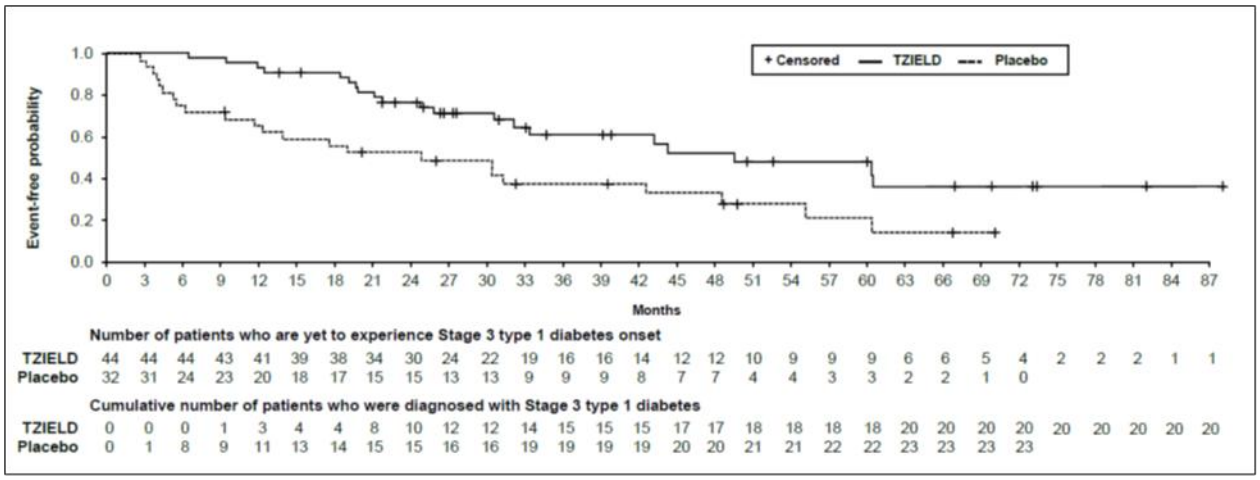
Efficacy Results in Study TN-10

In Study TN-10, Stage 3 T1D was diagnosed in 20 (45%) of the TZIELD-treated patients and in 23 (72%) of the placebo-treated patients. A Cox proportional hazards model, stratified by age and oral glucose tolerance test status at randomization, demonstrated that the median time from randomization to Stage 3 T1D diagnosis was 50 months in the TZIELD group and 25 months in the placebo group, for a difference of 25 months. With a median follow-up time of 51 months,

therapy with TZIELD resulted in a statistically significant delay in the development of Stage 3 T1D, hazard ratio 0.41 (95% CI: 0.22 to 0.78; p=0.0066) (Figure 1).

Study TN-10 was not designed to assess whether there were differences in the effectiveness between subgroups based on demographic characteristics or baseline disease characteristics.

Figure 1: Kaplan-Meier Curve of Time to Diagnosis of Stage 3 T1D in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 T1D by Treatment Group (Study TN-10)[1]



[1] ITT population

14.2 Delay Decline in Beta Cell Function in Pediatric Patients Aged 8 to 17 Years with Recently Diagnosed Stage 3 T1D

The PROTECT Study

The effectiveness of TZIELD to delay the decline in endogenous insulin production in patients recently diagnosed with Stage 3 T1D was investigated in a randomized, double-blind, placebo-controlled, multinational, multicenter study (PROTECT Study; NCT03875729) in 328 patients aged 8 to 17 years recently diagnosed with Stage 3 T1D (within 6 weeks of diagnosis). This trial enrolled patients with residual beta cell function, as indicated by peak stimulated C-peptide >0.2 pmol/mL on a mixed-meal stimulation test.

In the PROTECT study, patients were randomized to receive TZIELD or placebo once daily by intravenous infusion for a 12-day course followed by another 12-day course 6 months later (or at approximately 12 months for a subset of 28 patients) *[see Dosage and Administration (2.4)]*. The primary efficacy endpoint in the PROTECT study was the change from baseline in stimulated C-peptide at Week 78, as a marker of beta cell function.

Baseline Patient Characteristics in the PROTECT Study

In the PROTECT study, 43% of patients were female; 86% White, 3% Black or African American, 2% Asian, and 2% reported multiracial background; 6% were Hispanic or Latino ethnicity. The median age was 12 years (42% were <12 years old).

Baseline Disease Characteristics in the PROTECT Study

Table 6 displays the baseline disease characteristics in PROTECT Study.

Table 6. Baseline Disease Characteristics of Pediatric Patients 8 to 17 Years Recently Diagnosed with Stage 3 T1D (PROTECT Study)

	TZIELD N=217	**Placebo N=111**
HbA1c (%)	8.90	9.18
History of diabetic ketoacidosis, (%)	1%	4%
T1D-related Autoantibodies, (%)		
anti-GAD65	84%	87%
anti-IA-2	77%	78%
anti-ZnT8	75%	75%
anti-insulin	66%	77%
anti-ICA	52%	49%
Number of Positive T1D Autoantibodies, (%)		
0	<1%*	0%
1	5%	3%
2	18%	12%
3	22%	27%
4	30%	35%
5	25%	23%
HLA genotype: DR3, (%)**		
Positive	44%	51%
Negative	55%	49%
HLA genotype: DR4, (%)**		
Positive	64%	69%
Negative	36%	31%

Abbreviations: GAD=glutamic acid decarboxylase, HbA1c=hemoglobin A1c, HLA=human leukocyte antigen, IA=islet antigen, ICA=islet cell cytoplasmic autoantibody, ITT=intent to treat, T1D=type 1 diabetes, ZnT8=zinc transporter 8.

* This patient was randomized after testing positive for autoantibodies by the local laboratory. However, the central laboratory result for autoantibodies was negative.

** For these HLA genotype analyses, there were 215 TZIELD-treated patients and 109 placebo-treated patients.

A statistically significant difference in decline of C-peptide AUC from baseline at Week 78 was observed in TZIELD-treated patients compared to placebo (see Table 7).

Table 7. Change from Baseline in C-peptide ln(AUC+1) (pmol/mL) at Week 78 in Patients with Stage 3 T1D* (PROTECT Study)

	TZIELD N=217	Placebo N=111
Baseline, mean (SD)	0.54 (0.20)	0.53 (0.17)
Change from baseline, LSMean (95% CI)	-0.09 (-0.11, -0.07)	-0.22 (-0.25, -0.18)
Difference from placebo, LSMean (95% CI)	0.13 (0.08, 0.17)*	

Abbreviations: ANCOVA = Analysis of Covariance, AUC = Area Under the Curve, CI = Confidence Interval, ITT= intent to treat, LSMean = Least Squares Mean, SD = Standard Deviation
* Two-sided p-value < 0.0001.
Notes:
- Primary analysis; ITT population including all randomized participants.
- Baseline is defined as the most recent value collected prior to the first dose of study drug.
- The threshold value of 0.04 μg/L is used to populate below detectable C-peptide values.
- Missing data at Week 78 [29 (13%) in TZIELD arm; 23 (21%) in Placebo arm] are multiply imputed using a pattern-mixture model under the missing not at random assumption.
- Estimates and the p-value are obtained from an ANCOVA model with response variable change from baseline in C-peptide log (AUC +1) at Week 78 that includes treatment, age group at randomization, baseline C-peptide ln(AUC+1), and categorized peak C-peptide as independent variables.

Subgroup analyses of the primary endpoint by age group (age 8 to 11, 12 to 17 years), sex (males, females), race (White, other races), geographic region (North America, Europe), baseline insulin use (<0.5, ≥0.5 unit/kg/day), baseline peak C-peptide category (0.2-0.7, >0.7 pmol/mL), baseline HbA1c category (<7.5, ≥7.5%), timing of second course of TZIELD (month 6 or 12), number of positive T1D autoantibodies (1-2, ≥3), HLA genotype DR3 (positive, negative), HLA genotype DR 4 (positive, negative), and BMI z-score by quartile were carried out. The estimated treatment effect in maintaining C-peptide AUC was consistent among patients treated with TZIELD relative to placebo in patients in all subgroups.

16 HOW SUPPLIED/STORAGE AND HANDLING

TZIELD (teplizumab-mzwv) injection is a clear and colorless solution (2 mg/2 mL (1 mg/mL)) supplied in a single-dose vial as follows:

Carton Contents	NDC
1 single dose vial	NDC 73650-316-01

Refrigerate TZIELD vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Store upright. Do not freeze or shake the vials.

Once diluted, it is recommended that the product should be used immediately *[see Dosage and Administration (2.7)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Viral Reactivation

Inform patients that TZIELD may cause serious, life-threatening viral reactivation, including EBV and CMV infections. Instruct patients to contact their healthcare provider immediately if they develop any symptoms of viral reactivation (such as fever, malaise, or swollen glands) during or at least 2 months after TZIELD treatment *[see Warnings and Precautions (5.1)]*.

Cytokine Release Syndrome

Advise patients that TZIELD may cause cytokine release syndrome (CRS), which most commonly occurs during the first 5 days of treatment. Inform the patient that signs and symptoms of CRS may include fever, nausea, vomiting, fatigue, headache, muscle or joint pain, and increased transaminases or bilirubin. Instruct patients to contact their healthcare provider promptly if any of these symptoms occur. Inform patients that premedication will be given before each of the first 5 days of TZIELD infusion to help reduce the risk of CRS *[see Warnings and Precautions (5.2)]*.

Serious Infections

Advise patients that TZIELD may lower the immune system's ability to fight infections. Instruct patients to contact their healthcare provider immediately if they develop signs or symptoms of infection during or after TZIELD treatment. *[see Warnings and Precautions (5.3)]*.

Lymphopenia

Advise patients that a decrease in white blood cell counts (lymphopenia) is common with TZIELD treatment and in some instances it may be severe and may require discontinuation. Instruct patients to inform their healthcare provider immediately of fatigue, malaise, swollen glands, or signs of infection, as these may indicate lymphopenia. *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Advise patients that TZIELD may cause serious allergic reactions, including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking TZIELD and seek medical attention promptly if such symptoms occur *[see Warnings and Precautions (5.5)]*.

Vaccinations

Advise patient to receive all age-appropriate vaccinations prior to starting TZIELD. Instruct patients to contact their healthcare provider before receiving any vaccination prior to any TZIELD treatment course, during treatment, or after a treatment course. *[see Warnings and Precautions (5.6)]*.

Advise patient to contact their healthcare provider if planning any vaccination between treatment courses *[see Warnings and Precautions (5.6)]*.

Pregnancy

Advise patients to inform their healthcare provider of a known or suspected pregnancy. Inform patients that TZIELD may cause fetal harm and that use of TZIELD during pregnancy and at least 30 days prior to a planned pregnancy should be avoided Advise patients who are exposed to TZIELD during pregnancy to contact Provention Bio, Inc.'s Adverse Event reporting line at 1-800-633-1610 or visit https://ae.reporting.sanofi *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a lactating woman that she may interrupt breastfeeding and pump and discard breast milk during treatment and for 20 days after TZIELD administration to minimize drug exposure to a breastfed child *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Provention Bio, Inc.
Morristown, NJ 07960
A SANOFI COMPANY

U.S. License Number: 2170

MEDICATION GUIDE
TZIELD® (TEE-zeeld)
(teplizumab-mzwv)
injection, for intravenous use

What is the most important information I should know about TZIELD?

TZIELD may cause serious side effects, including:

- **Viral Reactivation**. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are common viruses that may stay inactive in your body after an initial infection. TZIELD may cause these viruses to become active again which, especially in people with a weakened immune system, can become serious and potentially life-threatening. These infections can happen during treatment with TZIELD and for up to 2 months after your last dose. Your healthcare provider will test you for active EBV and CMV infections before treatment with TZIELD. Contact your healthcare provider right away if you develop symptoms of an infection during or after treatment with TZIELD (such as fever, swollen glands, or fatigue).
- **Cytokine Release Syndrome (CRS).** Signs and symptoms of CRS problems may include:
  - fever
  - feeling tired (fatigue)
  - muscle and joint pain
  - nausea with or without vomiting
  - headache
  - increased liver enzymes in your blood

  These signs and symptoms may start during the first 5 days of TZIELD treatment. Tell your healthcare provider right away if you develop any signs and symptoms of CRS during treatment with TZIELD.
- **Serious Infections**: Treatment with TZIELD may lower your immune system's ability to fight infections, which may increase your risk of getting a serious infection. TZIELD is not recommended if you currently have a serious infection, or an infection that keeps coming back or does not go away (chronic infection), other than a minor skin infection. Contact your healthcare provider right away if you develop symptoms of an infection during or after treatment with TZIELD such as.
  - fever or chills
  - cough or shortness of breath
  - redness, warmth, or swelling of the skin
  - severe stomach pain or diarrhea
  - feeling tired
- **Decrease in white blood cells.** TZIELD may cause a decrease in a type of white blood cell called lymphocytes. A decrease in white blood cells is a serious, but common side effect that can affect your body's ability to fight infections. A decrease in white blood cell counts can happen after your first dose of any treatment course. Your white blood cell counts will start to go back to normal after your fifth dose of TZIELD. Some people may develop longer and more severe decreases in lymphocytes.

Your healthcare provider will do blood tests to check for active infections, verify your liver function and your complete blood counts before you start treatment and during treatment with TZIELD. During and after your treatment with TZIELD, your healthcare provider will check for side effects, and treat you as needed. Your healthcare provider may temporarily or completely stop your treatment with TZIELD, if you develop liver problems, have a serious infection or viral reactivation, or if your blood counts stay too low.

See "**What are the possible side effects of TZIELD?**" for more information about side effects.

What is TZIELD?

TZIELD is a prescription medicine used to:

- delay the onset of Stage 3 type 1 diabetes (T1D) in adults and children 1 year of age and older who have Stage 2 T1D
- delay the decline in insulin produced by the body (endogenous) in children 8 to 17 years of age who were recently diagnosed with Stage 3 T1D

- It is not known if TZIELD is safe and effective in children under 1 year of age who have Stage 2 T1D.
- It is not known if TZIELD is safe and effective in children under 8 years of age who have Stage 3 T1D.
- There is limited evidence of TZIELD being safe and effective in people 45 years of age and older with Stage 2 T1D.
- TZIELD is not effective as a disease modifying therapy in non-autoimmune dysglycemic conditions. These are conditions when your blood sugar goes too high and is not caused by your immune system.

Do not take TZIELD if you have a weakened immune system (immunocompromised) or have an active viral infection such as EBV or CMV infection.

Before or after receiving TZIELD, tell your healthcare provider about all your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section "**What is the most important information I should know about TZIELD?**"
- have a weakened immune system, including if you have Down syndrome.
- have a serious infection or an infection that does not go away or that keeps coming back (chronic).
- have recently received or are scheduled to receive an immunization (vaccine). TZIELD may affect how well a vaccine works. Tell your healthcare provider that you are receiving treatment with TZIELD before receiving a vaccine. Your healthcare provider will tell you when you can safely receive any vaccine before and after the treatment with TZIELD.
- are pregnant or plan to become pregnant. TZIELD may harm your unborn baby. **Do not** receive TZIELD during pregnancy and at least 30 days before a planned pregnancy.

  If you become pregnant while taking TZIELD, you are encouraged to report your pregnancy to the Provention Bio's Adverse Event reporting line at 1-800-633-1610 or visit https://ae.reporting.sanofi.
- are breastfeeding or plan to breast feed. It is not known if TZIELD passes into your breast milk and if it can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive TZIELD. If you are breastfeeding, you may consider pumping and throwing away your breast milk during treatment with TZIELD and for 20 days after receiving any TZIELD treatment.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive TZIELD?

- Your healthcare provider will recommend a 14-day treatment course if you have Stage 2 (T1D) or two 12-day treatment courses if you have Stage 3 type (T1D).
- TZIELD is given by a healthcare provider through a needle placed in a vein (intravenous infusion) in the arm.
- TZIELD is received as an infusion one-time a day, every day.
  - Each TZIELD infusion will last at least 30 minutes if you are an adult or your child is 8 years of age or older.
  - Each TZIELD infusion will last at least 2 hours if your child is 1 to less than 8 years of age.
- For the first 5 days of treatment, your healthcare provider will give medicines to be taken by mouth before starting the TZIELD infusion. These medicines include pain relievers (such as ibuprofen, naproxen or acetaminophen), an antihistamine, and possibly an anti-nausea medicine. These medicines may help reduce symptoms of CRS such as fever, headache, muscle and joint pain, or nausea, with or without vomiting. Vomiting and diarrhea may occur more frequently in children less than 8 years of age.
- If a scheduled infusion is missed, your healthcare provider will continue the treatment on the next scheduled day. Two infusions are not given on the same day.

Tell your healthcare provider if you think something will stop you from completing treatment with TZIELD.

What are the possible side effects of TZIELD?

TZIELD may cause serious side effects including:

- **See** "**What is the most important information I should know about TZIELD?**"
- **Allergic (hypersensitivity) reactions:** Serious allergic reactions can happen while receiving TZIELD. Your healthcare provider will watch you closely while you are receiving TZIELD and after your infusion for signs of a reaction. Tell your healthcare provider right away if you have any of the following symptoms of an allergic reaction:
  - fever, joint pain, swollen lymph nodes (serum sickness)
  - urticaria
  - vomiting
  - swelling of the face, lips, tongue, or throat (angioedema)
  - rash
  - trouble breathing

The most common side effects of TZIELD include:

- decrease in white blood cell counts
- vomiting
- rash
- diarrhea
- increase in liver enzyme levels
- headache

These are not all of the possible side effects of TZIELD. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. You may also report side effects to Provention Bio at 1-800-633-1610 or visit https://ae.reporting.sanofi.

General information about the safe and effective use of TZIELD.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about TZIELD that is written for health professionals.

What are the ingredients in TZIELD?
Active ingredient: teplizumab-mzwv.
Inactive ingredients: dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80, sodium chloride, and water for injection.

Manufactured by:
Provention Bio, Inc.
Morristown, NJ 07960
A SANOFI COMPANY

U.S. License Number: 2170

For more information, call 1-800-633-1610 or go to www.tzield.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 06/2026

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/

MAHTAB NIYYATI
06/12/2026 03:38:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s010

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

sBLA Clinical Review and Evaluation

Application Type	sBLA efficacy supplement
Application Number	sBLA 761183/S-010
Submit/Received Date	7/21/25
User Fee Goal Date	4/21/26
Division/Office	DDLO/OCHEN
Clinical Reviewer	Lauren Wood Heickman, M.D.
Cross Discipline Team Leader	Mahtab Niyyati, M.D.
Division Director	John Sharretts, M.D.
Review Completion Date	3/5/2026
Proprietary name/Established name	Tzield/teplizumab-mzwv (immunomodulator)
Applicant	Provention Bio, a Sanofi company
Dosage form/Proposed Dosing Regimen	Injection, administered as a two-course regimen, each course 12 days, with the second course given 6 to 12 months after the first Day 1: 106 mcg/m^2 Day 2: 425 mcg/m^2 Days 3 through 12: 850 mcg/m^2
Proposed Indication	To delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D
Recommended indication if Approved	To delay the decline in endogenous insulin production in pediatric patients 8-17 years of age recently diagnosed with Stage 3 T1D
Recommendation on Regulatory Action	Approval

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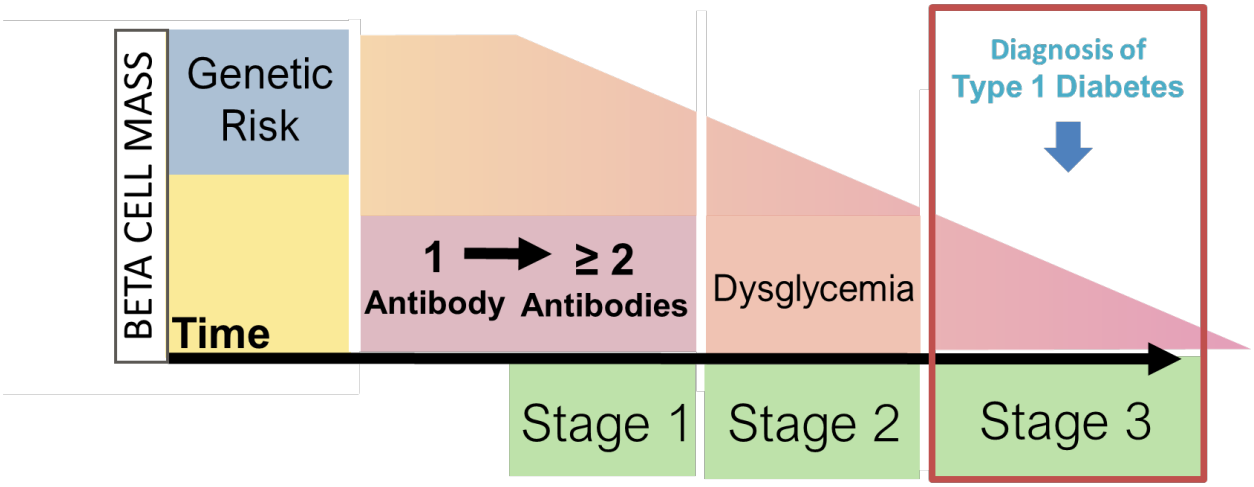
1 Executive Summary

1.1 Introduction

Type 1 diabetes mellitus (T1D) results from autoimmune destruction of pancreatic islet beta cells, leading to progressive deficiency in endogenous insulin production and dysregulated glucose homeostasis. T-cells are the primary effector mechanism for beta cell damage through loss of immune tolerance to self-antigens. T1D is a polygenic disorder with significant genetic predisposition, particularly involving Class II Human Leukocyte Antigen (HLA) genes (DR4-DQ8 or DR3-DQ2 haplotypes) responsible for antigen presentation.

The natural history of T1D follows a well-characterized, three-stage progression model as shown below. Stage 3 T1D is characterized by hyperglycemia and diagnosis of diabetes based on standard criteria. Patients with Stage 3 T1D require insulin to prevent hyperglycemia and diabetic ketoacidosis (DKA).

Figure 1. Type 1 Diabetes Disease Model



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

Longitudinal studies show that beta cell function decline accelerates dramatically in the 6 months before diagnosis and continues at this rapid rate for up to 12 months postdiagnosis, representing a critical therapeutic window for intervention.

As T1D is at present incurable, treatment goals focus on controlling blood glucose with exogenous insulin and device technologies. However, complex daily regimens require continuous attention to insulin dosing and timing, creating substantial burden for patients and families that affects nearly all daily activities.

FDA received a supplemental biologic licensing application (sBLA) from Provention Bio requesting marketing authorization for teplizumab-mzwv (Tzield) for a new indication to delay

Stage 3 T1D progression in adults and pediatric patients 8 years and older recently diagnosed with Stage 3 T1D.

Teplizumab is a first-in-class humanized anti-CD3 (cluster of differentiation 3) monoclonal antibody approved in November 2022 as Tzield to delay Stage 3 T1D onset in patients with Stage 2 T1D. The currently approved regimen involves a single 14-day intravenous (IV) treatment course with a 4-day ramp-up (65 to 500 μg/m²) followed by 1,030 μg/m² on Days 5 to 14, totaling 11.0 mg/m².

For the proposed Stage 3 T1D indication, the Applicant is seeking approval for a two-course regimen with the second course administered 6 to 12 months after the first. Each course involves 12 days of IV treatment with a 2-day ramp-up (106 μg/m² on Day 1, 425 μg/m² on Day 2) followed by 850 μg/m² on Days 3 to 12, with a total cumulative dose of 9.0 mg/m² per course.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness (SEE) based on teplizumab's ability to delay C-peptide decline in Stage 3 T1D patients with one adequate and well-controlled trial plus confirmatory evidence. Efficacy was evaluated in the PROTECT study, a randomized, double-blind, placebo-controlled trial that demonstrated a statistically significant treatment effect on C-peptide area under the curve (AUC) at Week 78 (primary endpoint), with results robust to sensitivity analyses under plausible missing data assumptions and consistent across subgroups. Adequate confirmatory evidence for effectiveness was derived from previously conducted clinical trials in the Stage 3 T1D population evaluating C-peptide.

C-peptide, a 31-amino-acid polypeptide released equimolarly with insulin during proinsulin processing, serves as a measure of endogenous insulin secretion when assessed through mixed-meal tolerance testing (MMTT). CDER has previously agreed, both in formal meetings with Sponsors and at public workshops, that C-peptide is a reasonably likely surrogate endpoint (RLSE) to measure beta-cell function in new-onset Stage 3 T1D and can support regulatory submissions for studies of drugs with immunomodulatory mechanisms through the accelerated approval pathway. While higher C-peptide levels have been associated with improved glycemic control, reduced insulin requirements, decreased hypoglycemia risk, and fewer long-term diabetes-related complications, these associations are based on observational data and have not been confirmed in controlled interventional studies. A confirmatory trial will be needed to verify and describe the anticipated clinical benefits of teplizumab in Stage 3 T1D patients.

A delay in the decline of C-peptide represents slower loss of endogenous insulin production, which is expected to lower exogenous insulin requirements and result in one or more clinical benefits. While PROTECT's secondary and exploratory endpoints showed favorable trends in reduced daily insulin dose and glycated hemoglobin (A1C), based on pre-submission formal agreements, the trial was not designed to demonstrate effectiveness on these clinical and

validated surrogate endpoints and thus cannot support traditional approval. A post marketing requirement will be a confirmatory efficacy trial to verify and describe the clinical benefit of teplizumab in new-onset Stage 3 T1D patients, consistent with the regulatory requirements of the accelerated approval pathway. The confirmatory trial has been agreed upon with the Agency and is in the early stages of patient enrollment. There is high confidence that the Applicant will conduct and complete the trial on time. The confirmatory trial will enroll subjects from (b) (4) clinical sites in (b) (4) countries with an estimated last patient last visit in 2029 and final report submission within approximately 4 years of trial initiation. Based on evaluation of the status of the confirmatory trial, the disease context, and available treatment options, the review division considers the confirmatory trial for this accelerated approval to be underway.

1.3 Benefit-Risk Assessment

The PROTECT study, a phase 3 randomized, controlled trial in Stage 3 T1D patients ages 8 to 17, diagnosed within the previous 6 weeks, and with C-peptide levels ≥0.2 pmol/L, was designed to demonstrate statistically significant preservation of C-peptide compared to placebo. Results showed a least squares [LS] mean difference 0.1253 pmol/mL ($p<0.001$) at Week 78 following two courses of teplizumab administered 6 to 12 months apart. Results were robust across sensitivity analyses under plausible missing data assumptions.

Prespecified secondary endpoints (insulin use, A1C, time in range [TIR] obtained from continuous glucose monitoring (CGM) data, and hypoglycemia) showed numerically favorable trends. Exploratory post hoc analyses showed a numerical increase in the cumulative duration of partial clinical remission in the teplizumab group relative to placebo.

While the magnitude of treatment effect associated with these trends remains uncertain, even small improvements in glycemic control, reductions in exogenous insulin requirements, or prolonged partial remission represent meaningful benefits given the high disease burden and absence of available disease modifying therapies for this population. Based on the observed C-peptide preservation in PROTECT, with treatment effects maintained through at least 78 weeks, these clinical benefits are expected to persist for approximately 1.5 to 2 years following treatment. While the full impact on long-term microvascular complications cannot be assessed within the typical timeframe of clinical trials, epidemiological studies suggest that preserved C-peptide levels correlate with reduced rates of retinopathy and nephropathy in T1D. Thus, observational data suggest preserving beta-cell function during the critical post-diagnosis period, coupled with improved glycemic control, may confer long-term benefits in reducing microvascular complications.

The benefit-risk assessment in this review is considered in the context of the specific patient population that the drug will be indicated to treat. The Applicant proposed a broader target population, including patients aged 8 years and older with any duration of Stage 3 T1D or any baseline C-peptide levels, but did not provide sufficient evidence demonstrating benefit for this

expanded population.

The risks of teplizumab in the intended population are similar to the risks identified for the already approved Stage 2 population, as the safety results in the PROTECT study were consistent with previously conducted clinical trials. In the Stage 3 population, similar to the Stage 2 population, teplizumab has a limited duration of therapy (is not intended as a chronic treatment). Known risks are limited to the dosing period and include cytokine release syndrome (CRS), lymphopenia, hypersensitivity, serious infections, and Epstein-Barr virus (EBV) reactivation (primarily transient viremia and, in one case, serious infectious mononucleosis). In PROTECT, a minimal increase in herpes zoster (0.9% versus 0%) was observed, and no cases of cytomegalovirus (CMV) reactivation or infection were seen. No new safety signals were identified in the PROTECT population, which included subjects who received a second course of teplizumab six months or one year after the first course. Importantly, PROTECT excluded immunocompromised patients.

Although no serious cases of viral reactivation occurred in PROTECT, there have been five postmarketing spontaneously reported serious adverse events (SAEs) of EBV infection/reactivation, including one case of severe EBV reactivation with serious lymphoproliferative disorder requiring rituximab. In addition, we are aware of a spontaneously reported case of a death of a patient that occurred within weeks of receiving teplizumab. Although the autopsy report stated the death was of natural causes, and EBV was not diagnosed, it cannot be definitively proven that EBV reactivation did not contribute to the fatal outcome.

The extent to which the serious EBV risk observed in postmarket surveillance extends to the PROTECT population is unclear, given that the two serious cases resulting in LPD occurred in immunocompromised individuals, a population that differs substantially from the non-immunocompromised pediatric Stage 3 T1D patients studied in PROTECT. Moreover, most serious cases (4 of 7; 66%) occurred in patients who continued teplizumab treatment despite persistent, severe lymphopenia – contrary to the drug's labeled discontinuation recommendations.

Nevertheless, these postmarket data indicate that EBV infection or reactivation may be a safety risk in certain populations, particularly immunocompromised individuals, and necessitate labeling strategies to manage risk. Similar considerations apply to possible infection or reactivation of other latent viruses (e.g., CMV or herpes viruses). We recommend adding a boxed warning (BW) to alert healthcare providers and patients to the serious risks associated with EBV infection or reactivation, particularly in immunocompromised individuals. The BW should emphasize the need for vigilant monitoring, early detection, and appropriate clinical intervention to reduce the likelihood of severe complications or fatal outcomes. The label will be modified to strengthen monitoring recommendations for lymphopenia to ensure treatment is discontinued should persistent severe lymphopenia occur. Additionally, viral reactivation

continues to be evaluated in the ongoing 10-year long-term safety study and in the ongoing confirmatory trial to further to characterize this risk.

In summary, we have concluded that the target population for the proposed indication should be consistent with the population evaluated in PROTECT where SEE has been established: specifically, pediatric patients aged 8 to 17 years with recently diagnosed T1D (diagnosed within approximately 6 weeks) who have sufficient residual beta cell function (C-peptide AUC ≥0.2 pmol/L on MMTT). The benefit-risk assessment is favorable for this narrow population based on several considerations as follows.

While the trial demonstrated statistically significant effects on C-peptide preservation, the clinical meaningfulness of this effect-including anticipated improvements in glycemic control, reductions in insulin requirements, and prolonged partial remission- will be evaluated in a currently underway confirmatory trial. The target population consists of recently diagnosed pediatric patients with preserved beta cell function who stand to gain the most benefit from disease modification during a critical window when intervention may alter disease trajectory. The absence of any approved disease-modifying therapies for Stage 3 T1D, combined with the substantial lifetime burden of the disease and patient-identified need for treatments that preserve beta cell function, supports approval in this specific population.

The known risks of teplizumab in PROTECT (including CRS, lymphopenia, hypersensitivity, serious infections, and viral reactivation) were manageable in the studied population. No serious cases of viral reactivation occurred in the pediatric study population during the trial. The serious viral reactivation events identified in postmarket surveillance occurred predominantly in populations not represented in PROTECT – specifically adults and immunocompromised individuals. The limited treatment duration (two 12-day courses) reduces cumulative exposure compared to chronic immunosuppressive therapies and the proposed risk mitigation strategies—including a BW emphasizing the serious risks of viral reactivation in immunocompromised individuals, contraindications for immunocompromised patients, screening requirements for (b) (4) viral infections prior to treatment, and monitoring protocols for early detection of reactivation—are expected to reduce the likelihood of serious outcomes.

1.4 Regulatory Considerations

While C-peptide preservation has been accepted as a RLSE for accelerated approval, traditional approval would require a demonstration of clinical benefit on validated endpoints.

Teplizumab's original approval for Stage 2 T1D met the regulatory standard for traditional approval by demonstrating a clinically meaningful benefit (delaying Stage 3 onset by approximately 25 months). Disease modifying drugs, at least to date, have not shown the ability to reverse the autoimmune destruction of beta cells. In Stage 3 T1D, patients are not expected to achieve insulin independence because of the advanced stage of beta cell loss. Even demonstration of temporary insulin independence is not feasible because current clinical practice rarely involves discontinuing insulin, even when patients achieve tighter A1C targets

(≤6.5 or 7.0%), with the intent of reducing the risk of DKA as beta cell loss progresses. Therefore, for patients who are exogenous insulin-dependent, demonstration of clinical benefits beyond insulin independence are required, but have been challenging to achieve in adequately powered trials within a reasonable timeframe.

Stage 3 patients in the early years of their disease generally have reasonably good glycemic control and less hypoglycemia. Most patients achieve glycemic goals (A1C <7%) during the first year regardless of treatment due to the "honeymoon period." Furthermore, severe hypoglycemia rates are relatively low (5 to 10 events per patient-year [PY]), making it difficult to adequately power studies for clinically meaningful hypoglycemia endpoints in the peri-onset period. With respect to trial design issues, use of treat-to-target background insulin therapy in this setting makes it difficult to demonstrate A1C differences, especially if the true treatment effect on A1C is small. The duration of trials to capture effects on diabetes complications would be prohibitively long.

The challenges of conducting clinical trials in new-onset T1D have been extensively discussed by the academic T1D community and presented to the FDA through Sponsor communications and two Critical Path Institute workshops (2021 and 2025) focused on regulatory considerations for T1D drug development.

C-peptide is a scientifically justified RLSE because it serves as a measure of endogenous insulin production, the primary pathophysiologic defect in T1D. Epidemiologic evidence demonstrates that higher C-peptide levels in T1D correlate with better glycemic control, reduced hypoglycemia risk, and lower rates of long-term microvascular complications of nephropathy and retinopathy. The availability of C-peptide as a RLSE and the accelerated approval regulatory pathway address trial feasibility challenges in Stage 3 T1D, where clinical outcome events are infrequent during the first 1-2 years of disease. While other clinically meaningful endpoints such as A1C and duration of partial clinical remission can be evaluated within the first 2 years of disease, they require larger sample sizes. By enabling approval based on a smaller trial of shorter duration rather than requiring large trials to demonstrate significance on other clinical endpoints, trials with C-peptide as a primary endpoint can be completed more quickly with fewer sites and reduced cost, and if negative, can avert the need for a larger confirmatory trial. This approach also provides earlier patient access to disease-modifying therapies that preserve residual beta cell function during a critical window immediately after diagnosis when such preservation is most achievable, while confirmatory trials are conducted to verify and describe the anticipated clinical benefits on outcomes such as glycemic control, hypoglycemia reduction, and reductions in number of required insulin injections over a longer duration of follow-up.

1.5 Patient Experience Data

Patient-reported outcome (PRO) data was submitted as an exploratory endpoint for the PROTECT study. The PRO data which showed some positive trends along with improvements in C-peptide, was not considered adequate (b) (4)

however, favorable trends were considered consistent with the other data supporting a favorable benefit-risk determination. Refer to Section 5.3.6.8 for a clinical review of the submitted PRO data.

2 Therapeutic Context

2.1 Analysis of Condition

T1D results from autoimmune destruction of pancreatic islet beta cells, leading to progressive insulin deficiency and dysregulated glucose homeostasis. T-cells serve as the primary effector mechanism for beta cell damage, with disease initiation occurring through loss of immune tolerance to self-antigens. The condition represents a polygenic disorder with significant genetic predisposition, particularly involving Class II HLA genes responsible for antigen presentation. Approximately 90% of T1D patients carry either DR4-DQ8 or DR3-DQ2 haplotypes, with about 30% having both, conferring substantial disease susceptibility (Redondo et al. 2018).

The natural history of T1D follows a well-characterized three-stage progression model (ADA Professional Practice Committee 2025). Stage 3 T1D represents the symptomatic phase following clinical diagnosis, when patients have progressed beyond the preclinical stages of autoantibody development (Stage 1) and dysglycemia (Stage 2) and require lifelong insulin therapy via multiple daily injections or pump delivery (Stage 3), creating risk for acute complications of hypoglycemia from insulin dosing errors or DKA if insulin doses are missed or inadequate. DKA affects approximately 7% (1 in 14) of U.S. pediatric patients annually, with rates of 1 to 15% per patient per year across studies (Maahs et al. 2015). Severe hypoglycemic events occur in 5 to 10% of pediatric patients annually, with highest rates in children under 6 years old (Cengiz et al. 2013). Adult patients experience severe hypoglycemia at rates approaching 19% per year in those over 40, with risk increasing with disease duration (Weinstock et al. 2013).

Microvascular complications (nephropathy, retinopathy, neuropathy) develop early, with one-third of patients showing early signs after just 8 years of disease duration at an average age of 21 years (Dabelea et al. 2017). T1D represents a leading cause of kidney failure and blindness, with nephropathy affecting T1D patients more severely than those with type 2 diabetes and contributing to approximately 60% of nontraumatic amputations. Macrovascular disease risk is substantially elevated, with cardiovascular events occurring earlier and more frequently than in age-matched nondiabetic populations. Patients diagnosed before age 10 demonstrate 30-fold higher cardiovascular morbidity compared to those diagnosed between ages 26 to 30. The Pittsburgh Epidemiology Study documented 1% annual cardiovascular event rates and 1.5% annual mortality in T1D patients under 40 with disease onset before age 17.

Despite advances in diabetes management technology, including CGM, mean A1C levels have

paradoxically increased in children and adolescents with T1D. The majority of people with T1D do not achieve recommended A1C goals, with only 19% of children and adolescents, and 28% of adults having A1C levels below 7.0%, the standard glycemic target recommended by the American Diabetes Association (Fang et al. 2025). The complex daily treatment regimen requires continuous attention to insulin dosing and timing, creating substantial burden for patients and families that pervades nearly all daily activities. The combination of worsening glycemic control, increasing disease incidence in the youngest age groups, and aging of the longest-duration patient population contributes to growing public health impact.

The immediate postdiagnosis period (typically 3 months postdiagnosis), often termed the "honeymoon phase," represents an important therapeutic opportunity. During this time, most patients retain some endogenous insulin production capability, reducing exogenous insulin requirements for glycemic control. This residual beta cell function provides the biological rationale for disease-modifying interventions in Stage 3 T1D, as therapies that preserve residual beta cell function during the postdiagnosis period when many patients retain some level of endogenous insulin production (as measured by C-peptide levels) reduce exogenous insulin needs, and depending on the magnitude of treatment effect, may improve the patient's ability to achieve glycemic control with less daily exogenous insulin. Improvement in glycemic control has been associated with a reduction in complication status as shown in the Diabetes Control and Complications Trial [DCCT]) (Diabetes Control and Complications Trial Research Group 1993), while the reduction in exogenous insulin needs means that patients may achieve glycemic targets with a decreased frequency of hypoglycemia. C-peptide is consistently recommended as a primary outcome measure for new- or recent-onset T1D trials (Palmer et al. 2004).

2.2 Analysis of Current Treatment Options

The mainstay of medical therapy for T1D is exogenous insulin, which is required for survival. Also approved for T1D is an adjunctive therapy, pramlintide, an amylin-mimetic. Both exogenous insulin and pramlintide can help improve glycemic control, but they do not alter the underlying pathophysiology of T1D.

Adjunctive approaches to T1D care include technologies such as CGM systems, which offer real-time glucose data, and emerging automated insulin delivery systems that deliver insulin based on glucose levels. However, insulin therapy, while required for survival, 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), over 80% of children and adolescents and over 70% of adults with T1D in the United States do not meet A1C goals (Fang et al. 2025).

Pancreatic islet-cell transplant has been used to restore beta-cell function, and in 2023, Lantidra, the first allogeneic (donor) pancreatic islet cellular therapy, was approved for the

treatment of adults with T1D who are unable to approach target A1C because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

Currently, there are no approved drugs or biologics that are considered disease-modifying agents, i.e., therapies that affect the underlying pathophysiology of T1D for the Stage 3 T1D population. FDA recognizes there is an unmet need for patients with Stage 3 T1D to help achieve glycemic goals and improve quality of life and treatment satisfaction.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The initial BLA (BLA 761183) for Tzield (teplizumab) was submitted to FDA in November 2020. Following the complete response letter issued by FDA in July 2021, the BLA resubmission was completed in February 2022. BLA 761183 was approved on November 17, 2022, for the delay of onset of Stage 3 T1D in adults and pediatric patients aged 8 years and older with Stage 2 T1D. It has also been approved for the same indication in the United Arab Emirates and Israel in 2024, and in Kuwait, Canada, and the United Kingdom in 2025.

3.2 Summary of Presubmission/Submission Regulatory Activity

Initial Development (2006 to 2012)

On July 25, 2006, IND 100262 was filed by MacroGenics, Inc., for teplizumab's indication of treatment of recent-onset T1D. Orphan-drug designation (#06-2296) was granted by the FDA on September 29, 2006, for this indication. This clinical program was halted in 2010 after the Protégé trial failed to demonstrate an effect on the primary outcome (proportion of subjects meeting the combination endpoint of A1C of <6.5% and daily insulin dose <0.5 units/kg/day at 12 months) and also failed to demonstrate a statistically significant effect on the secondary outcomes (including C-peptide AUC).

End-of-Phase 2 Discussions (December 2018)

In May 2018, teplizumab was acquired by Provention Bio, Inc., and in December 2018, FDA provided guidance on the Phase 3 clinical development program for the Stage 3 T1D indication at a Type B End of Phase 2 meeting. The Agency agreed with the overall study design and dosing regimen for the PROTECT study (PRV-031-001) and accepted C-peptide AUC measured at Week 78 by 4-hour MMTT as a reasonable primary endpoint for the PROTECT study. The Agency at the time noted that although C-peptide AUC is considered an endpoint reasonably likely to predict a clinical benefit in the Stage 3 T1D population, it is not considered a validated surrogate for clinical benefit, and the Agency cautioned that to support a traditional approval, there should be clinically meaningful differences versus placebo in the secondary clinical

endpoints in the PROTECT study. FDA acknowledged that one potential approval pathway could consist of the PROTECT study as a single adequate and well-controlled (AWC) trial plus confirmatory evidence from other Phase 2/3 clinical trials, though they emphasized that further discussions would be needed once PROTECT results became available. The Agency also agreed that combined safety data from PROTECT and the Protégé study could provide an adequate safety database, while recommending collection of robust long-term efficacy and safety data through at least 4 to 5 years.

Pre-sBLA Meetings and Pathway Clarification (August to September 2023)

Following completion of the PROTECT study, a Type B pre-sBLA meeting was held on August 29, 2023. FDA reviewed the PROTECT results, which demonstrated statistical significance on the primary C-peptide endpoint but failed to show statistical significance or clinically meaningful changes on key secondary clinical endpoints including exogenous insulin use, A1C change from baseline, clinically significant hypoglycemia, and TIR. The Agency clearly communicated that the data did not meet the standard for traditional approval because PROTECT showed statistical significance only on a RLSE (C-peptide) rather than on clinical endpoints. FDA recommended the accelerated approval pathway as the most suitable approach, emphasizing that this would require a postmarketing confirmatory study to verify clinical benefit. Despite the Applicant's arguments (b) (4) FDA maintained that such an approach (b) (4) would not meet traditional approval standards.

Confirmatory Study Design and Final Pathway Agreement (2024)

The previous regulatory interactions culminated in two Type C meetings (January 30, 2024, and December 18, 2024) focused specifically on designing the confirmatory postmarketing study required to support an accelerated approval. Through these discussions, along with written responses issued in July 2024 and an advice letter in September 2024, FDA and the Applicant reached agreement on the design and conduct of the confirmatory study. The Agency confirmed that the proposed two primary endpoints for the postmarket confirmatory trial (A1C change from baseline and total days without prandial insulin use) could be considered clinically meaningful for an AWC trial.

4 Summary of Findings From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Below is a summary of review findings from relevant disciplines. A nonclinical review was not conducted since no new pharmacology/toxicology information was submitted (the dose and population are similar to the approved indication).

Chemistry, Manufacturing, and Controls

The Office of Pharmaceutical Quality Assessment-III reviewer recommended approval as there are no new chemistry, manufacturing, and controls changes to teplizumab and despite changes in the dosing regimen (from one to two courses), the maximum dose remains within the approved dose range requiring no additional safety assessment of process-related impurities. The immunogenicity evaluation confirmed the adequacy of the previously validated immunogenicity assays for this new indication.

Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review focused on evaluating use of the to be manufactured teplizumab product (AGC Biologics), new immunogenicity findings from the PROTECT study, and the adequacy of the new dosing regimen (12 versus 14 days, and 2 versus 1 course). The OCP review team recommended approval of two 12-day courses of teplizumab for slowing the decline in beta cell function in adults and pediatric patients aged 8 to 17 years with Stage 3 T1D.

Two different manufacturing sources were used in PROTECT—Eli Lilly and AGC Biologics (the to-be-marketed product). Among 217 teplizumab-treated participants, 83 received only the Eli Lilly product and 66 received only the AGC Biologics product, with 68 receiving Eli Lilly in Course 1 and AGC product in Course 2. Exploratory analyses by the Applicant detected no differences in efficacy or safety between the two products. The clinical pharmacology reviewer concluded that both formulations demonstrated statistically significant C-peptide preservation compared to placebo, despite lower exposure with the AGC product, supporting the conclusion that the current commercial Tzield (AGC Biologics) product is effective for the proposed dosing regimen in the intended population.

The OCP review also evaluated new immunogenicity findings from the PROTECT study, which evaluated antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) as well as their impact on pharmacokinetics (PK), PD, and efficacy. Teplizumab is highly immunogenic, and following completion of both treatment courses in PROTECT, nearly all subjects (98%) developed ADAs, with 77% also developing NAbs. Previous studies have shown a greater impact of ADA on teplizumab exposure (clearance increased by up to 438%) during Course 2, when a treatment course was repeated after 6 months. The PROTECT study also showed higher maximum ADA titers and individual postdosing titers following the second course. Reassuring analyses presented by the Applicant showed no impact of ADA or NAb positivity on efficacy as measured by change from baseline in C-peptide levels (Protégé, Encore, TN-10, PROTECT) and HbA1c (PROTECT), although the limited number of ADA negative participants prevented a definitive conclusion. Exploratory efficacy analyses conducted by the FDA pharmacometrics and statistical team revealed that a subgroup of subjects with higher ADA titers and lower Course 2 teplizumab exposure had consistent efficacy at Week 78 (as measured by C-peptide AUC change from baseline) versus those with higher exposures. The OCP review team found no

apparent differences in C-peptide AUC changes from baseline over time based on ADA titer levels or NAb status. The overall evidence suggests that the impact of immunogenicity on teplizumab exposure, particularly for Course 2, does not appear to impact efficacy.

5 PROTECT Study

The PROTECT study demonstrated a statistically significant treatment effect on C-peptide preservation (least squares mean [LSM] difference of 0.13 pmol/mL at 18 months) with lower exogenous insulin use compared to placebo. Although not statistically significant, favorable trends were observed across multiple secondary and exploratory endpoints, including TIR improvements. Additionally, a favorable trend in A1C reduction from baseline was observed not only at the prespecified Week 78 endpoint, but also at other postrandomization timepoints including Weeks 12, 26, 39 and 52. Furthermore, higher proportions of teplizumab-treated subjects achieved A1C goals (<6.5%), met criteria for partial clinical remission (A1C ≤6.5% and insulin dose ≤0.25 units/kg/day), and demonstrated favorable trends on PROs.

The PROTECT study was powered to detect differences in the primary C-peptide endpoint but not individual secondary endpoints. Therefore, the lack of statistical significance on secondary and exploratory endpoints was considered in context. For some of the prespecified endpoints (e.g., A1C, TIR), the confidence intervals surrounding the point estimates included a magnitude of benefit that would be considered clinically meaningful. FDA concluded that the trends in clinically meaningful secondary and exploratory endpoints are generally consistent with teplizumab's physiologic effect and support the use of C-peptide as a RLSE for accelerated approval, with the requirement to verify and describe clinical benefit associated with the observed magnitude of C-peptide preservation. This is consistent with the FDA draft guidance for industry *Expedited Program for Serious Conditions - Accelerated Approval of Drugs and Biologics* (December 2024), which states that accelerated approval may be granted based on a drug's effect on an RLSE, without requiring demonstration of favorable results on clinical endpoints in premarket trials.

FDA's evidentiary standard for effectiveness has been met based on the PROTECT study with confirmatory evidence from meta-analysis results showing a significant treatment effect of teplizumab versus comparator on C-peptide AUC change from baseline at 1 year, though not at 2 years. The 2-year analysis included significantly fewer patients, reducing statistical power, particularly with the two-stage random-effects model. Importantly, the estimated treatment effect was numerically similar between the 1- and 2-year analyses.

The slower C-peptide decline and trends in secondary and exploratory endpoints observed in the PROTECT study are consistent with results from other Stage 3 T1D programs testing drugs and biologics with various mechanisms of action. Despite mechanistic differences, these programs share a common therapeutic effect: slowing the decline of C-peptide.

5.1 Review Strategy

Efficacy Review Strategy

The efficacy review for this sBLA focuses on the PROTECT study as the single AWC trial in patients with Stage 3 T1D. PROTECT enrolled 328 pediatric patients (ages 8 to 17) recently diagnosed, within 6 weeks, with Stage 3 T1D. The primary endpoint was change from baseline in C-peptide AUC, a measure of beta cell function considered by the Division to be a RLSE for patients with Stage 3 T1D. In addition to confirming the primary efficacy analyses, the review team also evaluated secondary and exploratory endpoints from the PROTECT trial, including A1C, exogenous insulin use, CGM parameters, clinical partial remission rates, and severe hypoglycemic events to further characterize the potential clinical benefit associated with or expected based on the magnitude of C-peptide preservation seen in the PROTECT study.

Confirmatory evidence of effectiveness comes from a previously FDA reviewed meta-analysis of C-peptide results from five clinical trials in patients aged 8 to 35 with new- or recent-onset T1D. This meta-analysis was submitted and reviewed at the time of the original BLA and evaluated the effect of teplizumab treatment compared to control on changes from baseline in C-peptide AUC across five supportive studies in Stage 3 T1D (Protégé, Encore, AbATE, Delay, Study 1). At the time of the original BLA review for the indication of delay in onset of Stage 3 T1D, the FDA statistical reviewer verified the Applicant's meta-analysis of C-peptide results described above and concluded that teplizumab demonstrated a statistically significant impact on the rate of decline of C-peptide in Stage 3 T1D patients at 1 year of follow-up compared to control. Refer to the statistical review by Dr. Yu Wang dated June 28, 2021, and the clinical review by Dr. Lauren Wood Heickman dated July 2, 2021, for details, as the results will not be recapitulated in this review.

Teplizumab's robust findings of effectiveness in the delay of Stage 3 T1D onset in at-risk Stage 2 T1D patients (~25 months of insulin independence versus placebo), as well as supportive findings that C-peptide preservation was also observed in teplizumab-treated subjects with Stage 2 T1D, a population similar to patients with Stage 3 T1D but with less advanced disease, were also considered as confirmatory evidence of effectiveness for teplizumab's effect in slowing the decline in C-peptide because these data confirm the mechanism of action.

Longitudinal natural history T1D studies have demonstrated that impaired beta cell function (as measured by declining C-peptide) may start more than 5 years before diagnosis (Evans-Molina et al. 2018) of Stage 3 T1D, with a period of rapid stable C-peptide decline beginning 6 months before diagnosis that persists for ~12 months after (Bogun et al. 2020) Stage 3 T1D diagnosis.

In addition to the evidence regarding teplizumab's effect on C-peptide, the Applicant provided an integrated summary of efficacy (ISE) combining PROTECT with the five supportive studies and evaluating clinical endpoints of A1C, insulin use, and hypoglycemia events, in order to provide additional evidence that consistent trends in clinical endpoints that are clinically meaningful to patients with T1D have been observed across the teplizumab development

program, and that positive trends in these endpoints are associated with a slowed decline in C-peptide. The clinical team did not verify the results of the ISE as it was not prespecified and there were concerns regarding the pooling strategy.

The Applicant also provided data from a Scottish registry study conducted in patients with T1D, the Scottish Diabetes Research Network Type 1 Biorepository Study (SDRNT1BIO), as further support for C-peptide as an RLSE. This real-world study containing observational data was generally consistent with what is known about C-peptide, and it was not reviewed by the clinical reviewer.

The clinical and statistical reviewers determined that the data quality and integrity were acceptable. A final statistical analysis plan (SAP), Version 5.0, was submitted with important endpoint analysis decisions made prior to unblinding of the PROTECT study. The review division collaborated with the Office of Computational Science, which performed analyses to address data quality including auditing of primary endpoint assessments, traceability assessments, and the statistical reviewer performed cross-validation of the submitted documents using the Study Data Tabulation Model and Analysis Data Model datasets. There were no integrity concerns or financial conflicts of interest.

Compliance With Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (FDA guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018)).

Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators* (February 2013).

5.2 PROTECT Study Design and Conduct

The PROTECT study (PRV-031-001) was an 18-month, double-blind, multinational, placebo-controlled trial evaluating teplizumab efficacy and safety in children and adolescents (ages 8 to 17) with newly diagnosed Stage 3 T1D. The study enrolled 328 participants diagnosed within 6 weeks of randomization who had residual beta cell function (peak stimulated C-peptide ≥0.2 pmol/mL) and at least one positive T1D-related autoantibody. Participants were randomized 2:1 to receive either teplizumab (n=217) or placebo (n=111), stratified by peak C-peptide levels and age groups.

The treatment regimen consisted of two 12-day courses administered approximately 6 months apart, though COVID-19 pandemic restrictions necessitated protocol amendments that delayed the second course to 12 months for 28 participants (16 in the teplizumab group and 12 in the placebo group). The majority (88%) of participants received two courses, and 80% of participants received the second treatment course at month 6.

The PROTECT study's conduct was complicated by a manufacturing change that resulted in participants receiving teplizumab from two different manufacturers (Eli Lilly or AGC Biologics). For any individual participant, the same product was administered for a full 12-day treatment course (either Course 1 or Course 2). Among the 217 PROTECT participants treated with teplizumab, 83 received the Eli Lilly product only (66 in both courses and 17 in a single course), and 66 received the AGC Biologics product only (57 in both courses and 9 in a single course). An additional 68 participants received the Eli Lilly product in Course 1 and the AGC product in Course 2.

Exploratory analyses conducted by the Applicant did not detect any difference in efficacy or safety by the particular product administered. The FDA clinical pharmacology review team similarly concluded that C-peptide efficacy data from the PROTECT study supported the Applicant's conclusion that the current commercial Tzield (AGC Biologics) product is effective for the proposed dosing regimen in the intended population.

Protocol Amendments

The original protocol (Version 1.0, dated December 31, 2018) underwent three amendments during the study conduct, resulting in Versions 2.0, 3.0, and 4.0. The primary endpoint methodology remained unchanged across versions, with Version 3.0 representing the most significant changes to the study due to COVID-19 adaptations and the implementation of a modified dosing schedule (MDS), a critical adaptation to maintain study integrity during the COVID-19 pandemic when subjects were not able to receive the second course of drug at 6 months. The PK/PD substudy added in Version 4.0 provided comparative data between different teplizumab products (Eli Lilly versus AGC Biologics).

Table 1. Summary of PROTECT Protocol Amendments

Version/Amendment Date	Changes
1.0 → 2.0/September 2, 2019	• Primary analysis: Repeated measures → ANCOVA • Added time in range (TIR) endpoint and insulin discontinuation criteria • Enhanced safety monitoring
2.0 → 3.0/May 12, 2020	• Modified Dosing Schedule (MDS) implementation due to COVID-19 restrictions and SARS-CoV-2 testing requirements for safety • Enhanced missing data methodology
3.0 → 4.0/December 10, 2020	• PK/PD substudy implementation to address product comparability • ECG substudy removal (FDA waiver) • AESI changed to align with other studies

Abbreviations: AESI, adverse event of special interest; ANCOVA, analysis of covariance; ECG, electrocardiogram; PD, pharmacodynamic; PK, pharmacokinetic

5.3 PROTECT-Efficacy

5.3.1 Disposition

In total, 422 participants were screened and 328 were randomized and included in the intent-to-treat population used for the primary efficacy analysis.

Approximately 296 randomized participants (90%) completed the trial, with 195/217 (89.8%) in the teplizumab group and 101/111 (91.0%) in the placebo group completing the study. Treatment discontinuation occurred in 30 (13.8%) participants in the teplizumab group and 15 (13.5%) participants in the placebo group. In the teplizumab group, 5 (2.3%) participants discontinued from the study due to adverse events of cytokine release syndrome and protocol-defined liver aminotransferase elevations. Other than a higher number of discontinuations in the teplizumab arm due to adverse events, no other patterns of treatment and study discontinuation were noted, and the statistical reviewer concluded that given the analysis plan for missing data, discontinuations were unlikely to have an impact on missing data. Of participants who discontinued treatment, 8/30 (26.7%) teplizumab-treated and 5/15 (33.3%) placebo-treated participants discontinued the study, and a similar proportion of subjects who discontinued treatment in each arm were followed-up for efficacy and safety (retrieved dropouts).

5.3.2 Protocol Violations/Deviations

Several categories of protocol deviations were noted across both treatment arms in the PROTECT study, including informed consent issues, failure to collect continuous glucose monitoring data, missing insulin/blood glucose diaries, and procedural issues with the MMTT. Both teplizumab and placebo arms experienced similar types of deviations, with several subjects in the teplizumab arm experiencing treatment-related deviations including incorrect study drug preparation, IV tubing issues, and dose calculation errors leading to underdosing. These treatment-specific deviations in the teplizumab arm could potentially introduce some

variability in drug exposure (underdosing) but were not noted to an extent that would hinder the trial's ability to accurately assess the drug's efficacy and safety profile. There were several selection criteria violations leading to delayed subject randomization by 1 to 4 days (i.e., subjects were randomized within ~6.5 weeks of T1D diagnosis versus within the protocol-specified 6 weeks of diagnosis). These violations were related to rescheduling due to the subject not fasting or late laboratory results and were reported for nine teplizumab and two placebo subjects. These minor protocol screening deviations were not considered to be significant enough to influence interpretation of the PROTECT trial findings through the inclusion of these subjects.

Additionally, the COVID-19 pandemic impacted the conduct of the PROTECT study, with multiple subjects requiring modified dosing schedules (MDS) due to pandemic-related disruptions. The underlying reasons for COVID-19 deviations were primarily site closures, shelter-in-place orders, patient/family reluctance to travel due to infection concerns, and inability to perform in-person procedures. These deviations were well-documented, were noted in both treatment arms, and the MDS was a contingency initiated as a protocol amendment, and the clinical pharmacology reviewer's MDS subgroup analyses (presented later) showed similar treatment effect in subjects receiving the MDS regimen.

5.3.3 Baseline Characteristics and Demographics

The PROTECT study enrolled 328 participants with newly diagnosed Stage 3 T1D, with demographics generally well-balanced between treatment arms. Specifically, baseline characteristics that may impact beta cell decline and potentially confound C-peptide endpoint interpretation, included age (mean 12.1 years), C-peptide AUC (mean 0.74 pmol/mL), body mass index, A1C levels, insulin dose (mean 0.426 units/kg/day), T1D duration since diagnosis, and HLA genotype status, which were balanced between the two arms. The study population was predominantly White (86.3%) with balanced age stratification (41.5% aged 8 to 11 years, 58.5% aged 12 to 17 years), and participants had received their T1D diagnosis a mean of 5.31 weeks prior to randomization. Key disease severity indicators were also generally comparable between groups, including baseline C-peptide levels, insulin requirements, body mass index z-scores, and the number of positive T1D autoantibodies (mean 3.6).

Table 2. Baseline Demographic and Disease Characteristics

Demographics	**Teplizumab (N=217)**	**Placebo (N=111)**
Age, years - Mean (SD)	12.0 (2.5)	12.3 (2.6)
Age group, n (%)		
8-11 years	90 (41.5)	46 (41.4)
>11-17 years	127 (58.5)	65 (58.6)

Demographics	**Teplizumab (N=217)**	**Placebo (N=111)**
Sex - male, n (%)	119 (54.8)	69 (62.2)
Race - n (%)		
White	189 (87.1)	94 (84.7)
Black or African American	5 (2.3)	6 (5.4)
Asian	4 (1.8)	3 (2.7)
American Indian or Alaska Native	1 (0.5)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.9)
Ethnicity - Not Hispanic or Latino, n (%)	193 (88.9)	101 (91.0)
Country - United States, n (%)	126 (58.1)	56 (50.5)
Disease characteristics		
T1D duration, weeks - mean (SD)	5.37 (0.73)	5.20 (0.81)
Baseline C-peptide AUC, pmol/mL - mean (SD)	0.74 (0.37)	0.72 (0.32)
Baseline peak C-peptide >0.7 pmol/mL, n (%)	157 (72.4)	84 (75.7)
Insulin use at baseline, units/kg/day - mean (SD)	0.45 (0.31)	0.38 (0.25)
HbA1c at baseline, % - mean (SD)	8.9 (1.7)	9.2 (1.9)
HbA1c >9% at baseline, n (%)	95 (43.8)	57 (51.4)
Number of positive T1D autoantibodies - mean (SD)	3.53 (1.2)	3.65 (1.1)
HLA DR4 positive, n (%)	137 (63.7)	75 (68.8)
HLA DR3 positive, n (%)	96 (44.7)	56 (51.4)
History of DKA, n (%)	2 (0.9)	4 (3.6)
BMI at baseline - mean (SD)	18.9 (3.5)	19.1 (3.6)

Source: Reviewer's analysis of adsl.xpt, OCS Analysis Studio, Custom Table Tool.
Demographic or disease characteristics that were not reported are excluded from table
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Race for multiple, other are excluded from table
Abbreviations: AUC, area under the curve; BMI, body mass index; DKA, diabetic ketoacidosis; HLA, Human Leukocyte Antigen; SD, standard deviation; T1D, type 1 diabetes

Table 2 provides a general outline of the baseline demographic and disease characteristics overall and by treatment arm. One notable baseline imbalance was identified in A1C distribution, with a higher proportion of placebo participants having A1C >9% at baseline (55.5%) compared to teplizumab participants (46.1%), a baseline imbalance that could potentially indicate greater baseline disease burden in the placebo arm or create challenges for demonstrating treatment effects on the key secondary endpoint of A1C change from baseline. However, this imbalance is unlikely to significantly bias the C-peptide primary endpoint results given that the analysis adjusts for baseline C-peptide stratification and other important disease characteristics including baseline A1C. Furthermore, the statistical analysis for the key secondary endpoint of change from baseline in A1C incorporates baseline A1C as a covariate in the analysis model, ensuring that treatment comparisons are adjusted for this baseline imbalance.

Critically, the PROTECT study population's restriction to children and adolescents aged 8 to 17 years with T1D duration ≤6 weeks and baseline peak C-peptide >0.2 pmol/mL limits generalizability to the Applicant's intended broader indication population, which includes patients with Stage 3 T1D, who are aged 8 years and older (without an upper age limit). This broader population includes individuals who may have longer disease duration, lower residual

beta cell function, and different disease progression patterns Additionally, the PROTECT study did not include adults, a population for which the Applicant has not demonstrated sufficient evidence of effectiveness of teplizumab on C-peptide preservation. PROTECT's enrollment criteria may have selected for a study population with more preserved beta cell function and potentially greater treatment responsiveness than the broader population, which includes patients with baseline peak C-peptide <0.2 pmol/mL, those with longer disease duration, and adults.

5.3.4 Primary Endpoint

PROTECT Primary Endpoint

The primary endpoint was change from baseline in C-peptide AUC following a 4-hour MMTT at Week 78, intended to demonstrate preservation of beta cell function as a RLSE. C-peptide AUC measurements were obtained at randomization and Weeks 26, 52, and 78 using standardized 4-hour MMTT protocols, which represent a validated method for assessing stimulated beta cell function in this population.

The PROTECT study was powered to detect an absolute difference in LSM C-peptide AUC of −0.14 pmol/mL (equivalent to a 40% difference in geometric mean AUC C-peptide levels at Week 78) that was considered meaningful by the Applicant based on a 2014 analysis of the DCCT (Lachin et al. 2014). This analysis found that a 50% relative increase in peak C-peptide (the maximal C-peptide during a 2- or 4-hour mixed-meal stimulation test) among the group intensively treated with insulin was associated with a lower risk of severe hypoglycemia (by ~8%), lower A1C, lower insulin use, and a reduction in long term microvascular complications (retinopathy risk decreased by 25%), with a continuous relationship between C-peptide and outcomes. The relationship held for hypoglycemia and retinopathy even after adjusting for baseline A1C, suggesting that C-peptide preservation confers independent clinical benefit. Since academic researchers in the T1D field no longer consider peak C-peptide as the best measure of treatment response for clinical trials in Stage 3 T1D, with mean AUC now considered to be more informative, to justify powering the PROTECT study to detect a 40% difference in geometric mean AUC C-peptide levels at Week 78 (from baseline), the Applicant provided an analysis showing a linear relationship between C-peptide AUC and peak C-peptide (RR ~0.93) and support from previous teplizumab trials, which showed that a 40% increase in the geometric mean C-peptide AUC from a 4-hour MMTT at 18 months translated to a 58% higher peak C-peptide value of 0.74 pmol/mL (or ln(AUC+l) versus placebo 0.41 pmol/mL in subjects aged 8 to 17 years in the Protégé trial, thus considering a 40% increase in mean C-peptide AUC to meet or exceed the 50% relative increase in peak C-peptide considered to be clinically meaningful by the Applicant based on the DCCT findings. In addition, sustained C-peptide secretion ≥0.2 nmol/L over the first year of follow-up for adolescent and adult patients diagnosed with Stage 3 T1D within the last 5 years was associated with a 50% reduction in severe hypoglycemia prevalence (from ~65% to ~30%) and improved A1C compared to those whose C-peptide fell below this level or was undetectable (Steffes et al. 2003).

Since C-peptide AUC data do not follow normal distributions and are skewed to the right; standardized C-peptide AUC was normalized by the log transformation using ln(AUC+1) in order to proceed with analysis models based on normality assumptions (e.g., analysis of covariance, mixed model for repeated measures [MMRM]). To account for baseline factors known to be associated with C-peptide rate of decline, C-peptide analyses were adjusted for randomization stratification factors of age group at randomization (8 to 12 years versus >12 to 17 years) and screening peak C-peptide category (0.2 to 0.7 pmol/mL versus >0.7 pmol/mL), and baseline C-peptide AUC was included as a covariate in the model. The FDA statistical team used a similar model to the Applicant's.[1]

Handling of Missing Data

The proportion of participants with missing C-peptide AUC data at Week 78 was 20.7% and 13.4% for the placebo and teplizumab groups, respectively. The placebo and teplizumab groups showed generally similar patterns of missing C-peptide data. The most common reason for missing data at Week 78 was study discontinuation due to withdrawal of consent in both groups (7.2% placebo versus 5.1% teplizumab). Multiple imputation was conducted on missing data using several approaches including using retrieved dropouts for treatment completers to account for subjects with early study discontinuation or study completion without Week 78 data.

As shown in Table 3, at Week 78, the difference between the two treatment groups (teplizumab versus placebo) in the LS mean change from baseline was 0.13 pmol/mL (95% CI: 0.08 to 0.17 pmol/mL) (p<0.001), indicating a slowing in the rate of C-peptide decline observed in the teplizumab treated group when compared to placebo.

Table 3. Primary Analysis of Change From Baseline in C-Peptide Log (AUC+1) (pmol/mL) at Week 78, ITT Population

Parameter	Teplizumab N=217	Placebo N=111
Baseline		
Missing data (n)	0	0
Mean (SD)	0.54 (0.20)	0.53 (0.17)

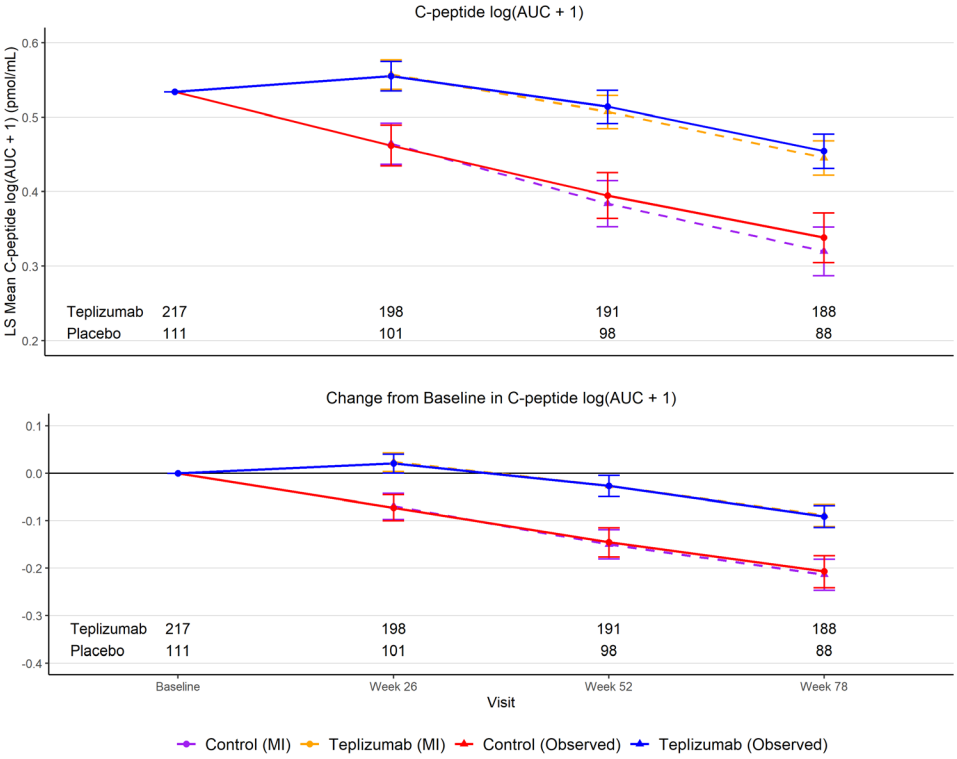
[1] The Applicant did not include screening peak C-peptide, a PROTECT study stratification factor, as a covariate in their analysis model due to the collinearity between baseline C-peptide AUC and screening peak C-peptide. The FDA statistical team incorporated screening peak C-peptide as a covariate for their primary confirmatory analysis, and did not find it modified the model or altered the results.

Parameter	Teplizumab N=217	Placebo N=111
Week 78		
Missing data, n (%)	29 (13.3)	23 (20.7)
Retrieved dropouts†, n (%)	6 (5.4)	16 (7.4)
CFB, LSMean* (SE)	-0.09 (0.01)	-0.22 (0.02)
Difference from placebo, LSMean* (CI)		0.13 (0.08, 0.17)
Two-sided p-value		$<10^{-5}$

Source: FDA Statistical Review; *Statistical Analysts' analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4.*
† Retrieved dropouts are defined as subjects who prematurely discontinued treatment, but have Week 78 C-peptide AUC measurements collected
* The LSMean estimates were derived from an ANCOVA model with response variable CFB in C-peptide log (AUC+1) at Week 78, and covariate adjustment for treatment, baseline C-peptide log (AUC+1), age group at randomization (≥8 to 12 years vs. >12 to ≤17 years), and screening peak C-peptide category (≥0.2 to ≤0.7 pmol/mL vs. >0.7 pmol/mL). Missing data were multiply imputed based on the primary pattern-mixture model, with a 0 lower bound.
Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; CFB, change from baseline; CI, 95% confidence interval; ITT, intent-to-treat; LS, least square; N, number of randomized participants; SD, standard deviation; SE, standard error

Figure 2 below displays the FDA statistician's plot of LS means of C-peptide log (AUC+1) and change from baseline in C-peptide log (AUC+1) over time by treatment arms. The estimates based on observed data (solid line) and imputed data (dashed line) from the FDA statistical review were similar. While the placebo arm demonstrated a steady, continuous decline, the teplizumab arm displayed a slight upward trend until Week 26, followed by a decline that almost paralleled the rate observed in the placebo arm, though its mean C-peptide AUC values remained consistently higher than placebo at all postbaseline visits.

Figure 2. LS Means for C-Peptide Log (AUC+1) and LS Means for "Change From Baseline in C-Peptide Log (AUC+1)" Over Time, Based on Observed and Imputed Data



Source: FDA Statistical Review; Statistical Analysts' analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4.Note: The table on the bottom of each plot displays the number of observed data at each timepoint for teplizumab arm and placebo arm. Multiple imputation was performed at each visit based on the primary pattern mixture model
Abbreviations: AUC, area under the curve; LS, least square; MI, multiple imputation

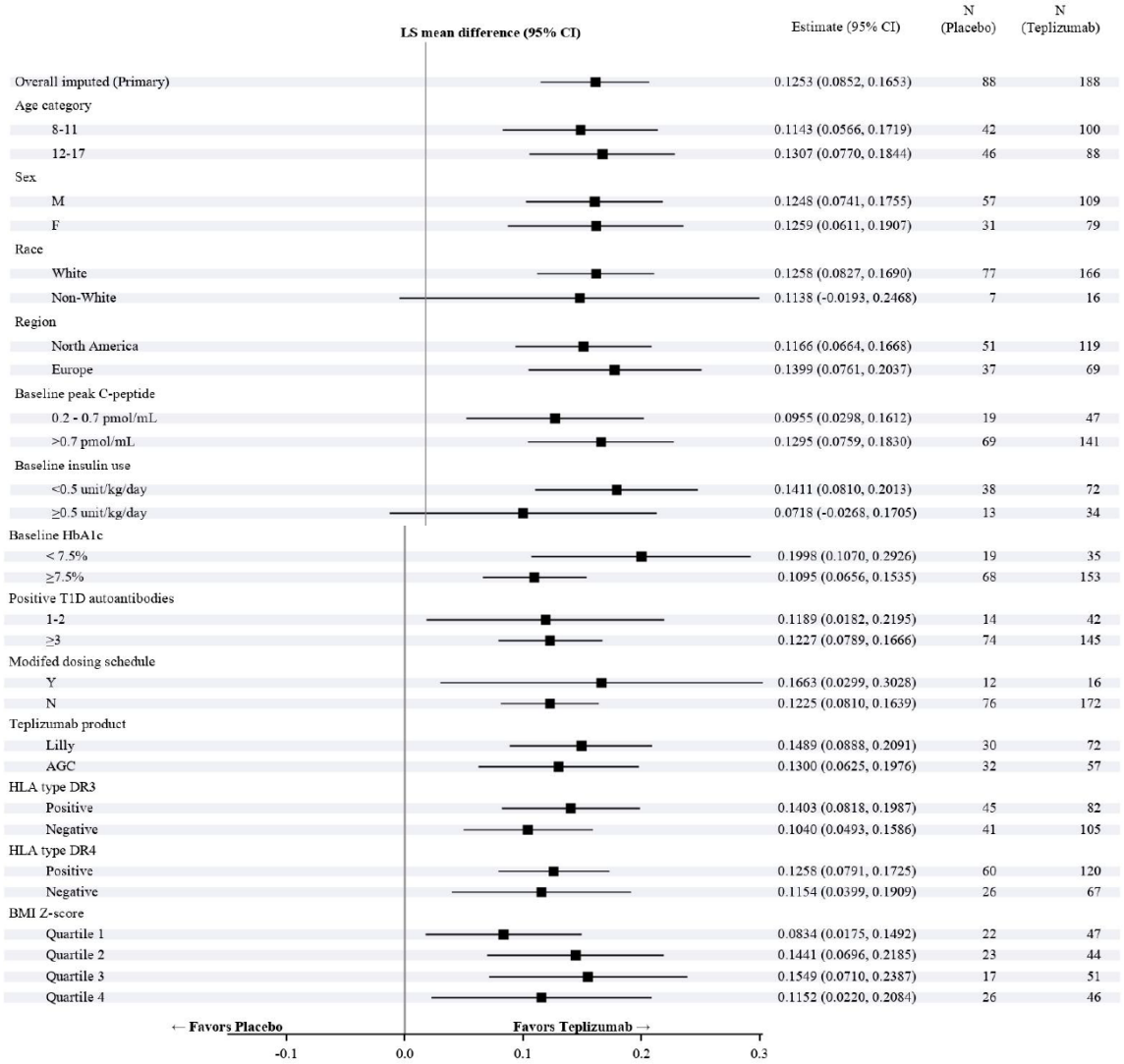
Prespecified sensitivity analyses included control-based imputation, tipping point analysis, and MMRM analyses supported the robustness of the primary outcome. Sensitivity analyses addressing baseline imbalances in important demographic and disease characteristics, as well as sensitivity analyses to address missing data, were consistent with the primary efficacy analysis. Please see the separate statistical review for details.

5.3.4.1 Subgroup Analysis

The Applicant's prespecified subgroup analyses did not demonstrate any notable differences in treatment effects based on baseline characteristics selected for their potential to modify the treatment effect. These are shown in Figure 3 below.

Of note, clinical pharmacology reviewer's analyses of the MDS (second course given at 12 months) compared to the original protocol-specified dosing regimen (second course given at 6 months) demonstrated comparable efficacy based on C-peptide preservation, showing no difference in treatment effect whether the second course was administered at month 6 or 12.

Figure 3. Forest Plot of Subgroup Analysis of Change From Baseline in ln(AUC+1) C-Peptide (pmol/mL) at Week 78 (ITT Population)



Source: Applicant's Figure 14.2.1.4, PROTECT CSR
Note: Baseline was defined as the most recent value collected before the first doe of study drug.
Note: Missing data were multiply imputer using a pattern-mixture model under the assumption of missing not at random.
Abbreviations: AUC, area under the curve; BMI, body mass index; F, female; HbA1c, hemoglobin A1c; HLA, human leukocyte antigen; ITT, intent-to-treat; M, male; T1D, type 1 diabetes

5.3.5 Key Secondary Endpoints

Key secondary endpoints included:

- Exogenous insulin use at Week 78 (units/kg/day): participants self-reported detailed information on number, dose and type of insulin injections/boluses in an eDiary.[2]
- Change from baseline in A1C at Week 78.[3]
- Time in range at Week 78, defined as percentage of time with blood glucose 70 to 180 mg/dL, derived from CGM data.[4] Notably, the PROTECT study did not collect CGM data at baseline (prerandomization) and instead started CGM data collection at Week 2 (after Course 1 treatment) so this endpoint was not baseline adjusted.
- The rate (number of events/study follow-up time) of clinically important hypoglycemic episodes measured by either CGM or SMBG through Week 78, self-reported by participants in an eDiary throughout the trial including:
  - Level 2 hypoglycemia, defined as blood glucose <54 mg/dL, (i.e., Level 2 hypoglycemia as defined by the American Diabetes Association), and
  - Level 3 hypoglycemia also known as severe hypoglycemia, defined as a hypoglycemia event of severe cognitive impairment requiring external assistance (such as seizure, syncope, severe confusion with or without a confirmatory low BG reading) (i.e., American Diabetes Association Level 3 Hypoglycemia)

Handling of Missing Data for Secondary Endpoints

For the key secondary endpoint of average daily insulin use, data was considered missing if a participant did not have insulin data for at least 3 of the 7 days prior to a visit window for each time point and for TIR on CGM, participants were required to have at least 3 days of ≥8 hours of CGM data during a 14-day CGM collection period in order to calculate a daily average percentage TIR, otherwise it was considered missing. For all key secondary endpoints except for hypoglycemia rates (i.e., an endpoint where imputation of missing data would not be reasonable as lack of hypoglycemia events should not be considered missing), missing data was imputed according to the same methodology as the primary endpoint analysis.

[2] Patients self-reported this information over 7-day periods prior to study visits at Weeks 12, 26, 39, 52, 65, and 78, with data considered valid only if participants provided at least 3 days of insulin data, otherwise classified as missing.
[3] A1C was measured via laboratory collection at Screening, Day 1, and Weeks 12, 26, 39, 52, 65, and 78, with analysis by central laboratory.
[4] Collected approximately 7 times throughout the study requiring minimum 8 hours of CGM data per day and at least 3 days of valid daily TIR data per visit to avoid classification as missing.

Reliance on participant self-reporting (eDiary) led to a substantial amount of missing data which introduced uncertainty in the assessment of insulin use and hypoglycemia. For the CGM-based TIR endpoint, there was also a high level of missing data at Week 78 related to nonadherence with reliably wearing the CGM device. Although there were positive trends on these endpoints consistent with a pharmacodynamic effect of teplizumab the large amount of missing data precludes drawing reliable conclusions.

Table 4 presents the results for key secondary and exploratory endpoints. The 4 key secondary endpoints did not reach statistical significance. However, trends of lower exogenous insulin use with similar A1C were observed in the teplizumab treatment arm, along with a numerically higher TIR with an estimated difference between the 2 treatment arms of 4.71% (95% CI: −1.72 to 11.15%). The prespecified hypoglycemia endpoint was neutral.

Table 4. PROTECT Study—Results for Key Secondary and Exploratory Endpoint Analyses*

Key Secondary Efficacy Endpoints at Week 78	Placebo (N=111)	Teplizumab (N=217)
Avg insulin use (units/kg/day), n (%)	50 (45)	98 (45)
LSMean (95% CI)	0.593 (0.47, 0.72)	0.463 (0.36, 0.56)
LSMean diff (95% CI), p-value		-0.131 (−0.28, 0.02); p=0.085
Change from baseline A1C (%), n (%)	100 (90)	192 (88)
LSMean (95% CI)	-1.89 (−2.16, −1.62)	-1.98 (−2.17, −1.78)
LSMean diff (95% CI), p-value		-0.09 (−0.42, 0.24); p=0.606
Time in range[a] (%), n (%)	63 (57)	140 (65)
LSMean (95% CI)	62.22 (57.60, 66.84)	67.35 (64.10, 70.60)
LSMean diff (95% CI), p-value		4.71 (−1.72, 11.15); p=0.151
Level 2 hypoglycemia, n (%)	111 (100)	217 (100)
Event rate (95% CI)	4.24 (3.06, 5.89)	4.68 (3.70, 5.91)
Rate ratio (95% CI)		1.10 (0.74, 1.64); p=0.634
Level 3 hypoglycemia, n (%)	111 (100)	217 (100)
Event rate (95% CI)	0	0

Exploratory/Post Hoc Efficacy Analyses at Week 78	Placebo (N=111)	Teplizumab (N=217)
Post hoc analysis of severe hypoglycemia adverse events (level 3 hypoglycemia from eDiary and CTCAE Grade ≥3 hypoglycemia AE from eCRF)		
Incidence n (%)	18 (16.2)	29 (13.4)
Number	110	62
Rate (event/person-year)	0.67 (0.37, 1.20)	0.19 (0.12, 0.31)
Post hoc analysis of level 2 hypoglycemia (level 2 hypoglycemia from eDiary and CTCAE Grade 2 hypoglycemia AE from eCRF)		
Incidence n (%)	92 (82.9)	179 (82.5)
Number	2006	3077
Rate (event/person-year)	10.85 (8.19, 14.35)	9.95 (8.15, 12.15)
Post hoc analysis of 'clinically important hypoglycemia events' (Level 2 and 3 hypoglycemia from eDiary and CTCAE Grade ≥2 hypoglycemia AE from eCRF		
Incidence n (%)	92 (82.9)	179 (82.5)
Number	2070	3125
Rate (event/person-year)	11.27 (8.52, 14.90)	10.11 (8.28, 12.35)
Proportion of participants meeting insulin discontinuation criteria[b]		
n/N (%)	4/50 (8.0%)	12/98 (12.2%)

Source: Modified version of Applicant's clinical overview (Table 4) and Table 19 from PROTECT CSR
*Analyzed using an ANCOVA model including treatment group and randomization stratification factors (age group and screening peak C-peptide category). The same covariates were included in the model for change from baseline HbA1c (%) at week 78, with the addition of baseline HbA1c (%) as a covariate. The covariates were agreed to at the time of the initial SAP submission and were generally acceptable. The key secondary hypoglycemia endpoint was analyzed and tested between treatment groups using a negative binomial model including treatment group and randomization stratification factors (age group and screening peak C-peptide category) as covariates.
[a] Daily average of the percentage of time in a 24-hour day blood glucose is ≥70 but ≤180 mg/dL (>3.9 to ≤10.0 mmol/L), assessed using CGM at Week 78.
[b] HbA1c ≤6.5% and insulin daily dose ≤0.25 units/kg/day.
Treatment LSMean Diff, difference in LSMean = teplizumab - placebo.
Note: For incidence, participants with multiple events are counted only once for each level of hypoglycemia.
Abbreviations: A1c, glycated hemoglobin A1c; AE, adverse event; ANCOVA, analysis of covariance;CI, confidence interval; CTCAE, Common Terminology Criteria For Adverse Events; eCRF, electronic case report form; LS, least square

5.3.5.1 A1C Change From Baseline to Week 78

Both treatment groups demonstrated substantial A1C reductions from approximately 9% at baseline to 7% at Week 78. The LSM changes from baseline were −1.98% for teplizumab versus −1.89% for placebo, with a statistically nonsignificant difference of −0.09% (95% CI: −0.42 to 0.24%; p=0.606). Additionally, a favorable trend in A1C reduction from baseline compared to placebo was observed at all postbaseline timepoints, with point estimates ranging from 0.19 to -0.29% from Week 12 to Week 52. Notably, the lower bound of the 95% confidence interval for A1C reduction was ≤ -0.5% at Weeks 26, 39, and 52, suggesting that the treatment difference reached the clinically meaningful threshold.

Several factors may have limited the ability to detect between-group differences in this endpoint. The protocol-mandated treat-to-target insulin titration strategy may have masked A1C differences, particularly given the modest treatment effect. Specifically, increased insulin

use in the placebo arm could have compensated for lower endogenous insulin production, reducing observable A1C differences between groups. Additionally, the high variability in baseline A1C values (ranging from 4.8% to 14.6%) may have influenced the direction and magnitude of the observed treatment effect. In newly diagnosed T1D, baseline A1C primarily reflects the recency of insulin initiation rather than underlying disease severity or progression, adding further complexity to interpretation.

Despite these limitations, the small favorable trends observed for the A1C endpoint are generally consistent with a modest treatment effect likely related to preservation of endogenous insulin production. The data suggest that teplizumab's beta-cell preservation effects may enable subjects to achieve glycemic targets with lower exogenous insulin requirements supporting the pharmacodynamic effect of teplizumab.

Exploratory endpoints provided additional supportive evidence. A higher proportion of teplizumab-treated subjects achieved A1C <6.5%, and a lower proportion experienced A1C >9% postbaseline. These findings provide additional support for the favorable modest trend observed in the key secondary A1C endpoint.

5.3.5.2 Average Daily Insulin Use

The teplizumab group maintained stable insulin requirements from baseline to Week 78 (0.447 to 0.446 units/kg/day), while the placebo group showed increased insulin requirements (from 0.383 to 0.598 units/kg/day). The estimated LSM difference between teplizumab and placebo of −0.131 units/kg/day (95% CI: −0.280 to 0.018; p=0.085) at Week 78.

However, significant missing data concerns limit interpretability of this endpoint. Missing data rates were substantial, with 42% missing at baseline and 38% missing at Week 78. Analysis of missing data patterns revealed several demographic imbalances between subjects with available versus missing data:

Age: The group with available data had a higher proportion of younger subjects (46.6% versus 37.2% aged 8 to 11 years), suggesting age-related differences in study completion or data collection compliance.

Race: There was a complete absence of Black/African American participants in available data compared to the missing data group (0% versus 6.1%).

Sex: The sex distribution was relatively balanced (59.5% versus 55.6% male), indicating sex was not a major factor in missing data at Week 78.

Disease severity markers: Beta-cell function (as measured by peak C-peptide strata) and baseline A1C (9.03% versus 8.97%) were similar between subjects with missing versus available insulin use data, suggesting baseline disease severity was comparable and not a major predictor of data availability.

This pattern of missing data appears to be driven primarily by demographic factors rather than disease severity, which limits the generalizability of the insulin use findings but suggests the missing data mechanism may not be related to treatment efficacy.

5.3.5.3 Time In Range

The teplizumab group showed numerically higher TIR at Week 78 with an estimated difference of 4.71% (95% CI: −1.72 to 11.15%; p=0.151). This difference exceeds the 3% threshold considered clinically meaningful by international consensus for CGM metrics in clinical trials (Battelino et al. 2023). However, PROTECT did not include baseline TIR measurements limiting data interpretation.

Post hoc analyses provided supportive evidence. An analysis using Week 2 as baseline yielded similar results (3.61% difference). Additionally, a favorable trend in TIR was observed at all postbaseline timepoints, with TIR numerically higher in the teplizumab group versus placebo, consistent with the TIR secondary endpoint at Week 78. Furthermore, the proportion of participants achieving the clinically relevant target of >70% TIR was numerically higher in the teplizumab group compared to the placebo group, though this difference was not statistically significant. These trends in TIR improvement at Week 78 are generally consistent with the known physiologic effect of slowing beta-cell decline.

However, substantial missing data limits the strength of these conclusions. Missing data rates reached 55% at Week 78. Analysis of missing data patterns revealed that patients with higher residual beta-cell function were more likely to maintain CGM compliance, and female subjects had higher rates of missing TIR data. The combination of substantial missing data and lack of baseline-adjusted measurements limits the ability to draw definitive conclusions from this endpoint.

5.3.5.4 Hypoglycemia

In PROTECT, hypoglycemic events were reported by the participants and/or caregivers in the eDiary and classified as Level 2 and Level 3 events. The primary analysis of clinically important hypoglycemic events, based on eDiary-reported events, found no Level 3 events. The estimated rate of Level 2 events was 4.68 events/patient-year (95% CI: 3.70 to 5.91) in the teplizumab group compared with 4.24 events/patient-year (95% CI: 3.06 to 5.89) in the placebo group. The estimated rate ratio of Level 2 events (teplizumab versus placebo) was not statistically significant (1.10 [95% CI: 0.74 to 1.64]; p =0.634).

Post Hoc Sensitivity Analysis Integrating Multiple Data Sources

Hypoglycemia was also reported as an adverse event by the investigators in the electronic case report form (CRF) and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. To provide a more comprehensive evaluation of clinically important

hypoglycemic events, a post hoc sensitivity analysis integrated both the eDiary and the adverse event CRF data. In this analysis, "clinically important hypoglycemic events" were defined as:

- Level 2 hypoglycemic events: Level 2 events from the eDiary or CTCAE Grade 2 (40 to 54 mg/dL) hypoglycemia adverse events from the adverse event CRFs.
- Level 3 hypoglycemic events: Level 3 events from the eDiary or severe hypoglycemic adverse events (CTCAE Grade ≥3) (i.e., blood glucose ≤39 mg/dL) events from the adverse event CRFs.

Results of the post hoc hypoglycemia analysis are previously shown in Table 4. The Applicant removed duplicate or overlapping hypoglycemic events between the eDiary and adverse event CRF. Since no eDiary-reported hypoglycemic events were classified as Level 3, all Level 3 events in this sensitivity analysis were severe hypoglycemic adverse events (Grade ≥3).

Results of Post Hoc Analysis

For Level 3 hypoglycemic events, the estimated rate was 0.19 events/patient-year (95% CI: 0.12 to 0.31) in the teplizumab group versus 0.67 events/patient-year (95% CI: 0.37 to 1.20) in the placebo group. The estimated rate ratio was statistically significant (0.29 [95% CI: 0.13 to 0.62]; p=0.002), favoring teplizumab.

For Level 2 hypoglycemic events, the estimated rates were similar between groups but trended favorably for teplizumab: 9.95 events/patient-year (95% CI: 8.15 to 12.15) in the teplizumab group versus 10.85 events/patient-year (95% CI: 8.19 to 14.35) in the placebo group. The rate ratio was 0.92 (95% CI: 0.65 to 1.29; p=0.623).

For Level 2 and 3 hypoglycemic events, or "clinically important hypoglycemia events", the estimated rates were similar between groups, but trended favorably for teplizumab: 10.11 events/patient-year (95% CI: 8.28 to 12.35) in the teplizumab group versus 11.27 events/patient-year (95% CI: 8.52 to 14.90) in the placebo group. The rate ratio was 0.90 (95% CI: 0.64 to 1.27; p=0.538).

Interpretation and Limitations

Although the clinical team agrees that the hypoglycemia definitions used in this additional analysis are clinically relevant, the results were sensitive to the case definition and dataset employed, raising concerns about the robustness and consistency. The prespecified primary analysis showed no difference in Level 2 events and no Level 3 events in either group, while the post hoc analysis integrating adverse event data showed a statistically significant reduction in Level 3 events with teplizumab. Additionally, the Applicant's exploratory analyses for both Level 2 hypoglycemic events and "clinically important hypoglycemia events" (a combination of Level 2 and Level 3) showed favorable trends for teplizumab. Although not statistically significant, favorable trends across multiple hypoglycemia analyses, including those using more sensitive

detection methods (i.e. incorporating hypoglycemia adverse events in addition to eDiary data), support a potential favorable impact on hypoglycemia. Given the lack of alignment between the prespecified and post hoc analyses, the results are not conclusive regarding any benefit of teplizumab on the rate of hypoglycemia events.

5.3.6 Exploratory Endpoints

The PROTECT study evaluated multiple exploratory efficacy endpoints intended to assess disease burden and the clinical meaningfulness of teplizumab's C-peptide preservation effects. The section below presents the Applicant's results. The statistical reviewer confirmed that the statistical methodology was appropriate and did not independently verify results using the datasets.

In general, exploratory analyses should not be relied upon to support conclusions of clinical benefit. The ability to draw conclusions from exploratory endpoint analyses in PROTECT was particularly limited due to the large amount of missing data for both insulin use and CGM data and the post hoc nature of some of the analyses.

A summary is provided below. Additional detail follows is subsequent sections.

- Maintenance of clinically significant stimulated peak C-peptide ≥0.2 pmol/mL during MMTT which the Applicant suggests in observational studies has been associated with better metabolic outcomes in patients with T1D within 5 years of diagnosis (Mortensen et al. 2010; Sorensen et al. 2013; Lachin et al. 2014; Harsunen et al. 2023). At Week 78, a higher percentage of teplizumab-treated participants maintained peak C-peptide ≥0.2 pmol/mL, compared to placebo (92.7% and 74.2%), respectively.
- Partial clinical remission or "honeymoon period" prolongation. At Week 78, a higher percentage of teplizumab-treated participants versus placebo met the criteria for insulin discontinuation (A1C ≤6.5% and insulin dose ≤0.25 units/kg/day) or freedom from exogenous insulin at Week 78 (12.2% versus 8%) and discontinued exogenous insulin at Week 52 (2.8% versus 0.9%) and Week 78 (1.4% versus 0.9%). Exploratory analyses conducted by the Agency on this endpoint showed that although a similar proportion of subjects without partial clinical remission at baseline achieved partial clinical remission least once during the study: 59/217 (27.2%) teplizumab subjects and 29/111 (26.1%) placebo subjects, with a larger proportion of teplizumab subjects (34%) versus placebo (14%) having 3 or more postbaseline visits meeting these criteria.
- Comprehensive glycemic assessments including TIR, hyperglycemia/hypoglycemia exposure, glycemic variability, and clinically important hypoglycemic episodes.
- PROs measuring quality of life, hypoglycemia fear, treatment satisfaction, and family impact. There was a greater perception of diabetes control and treatment satisfaction as measured by Diabetes Treatment Satisfaction Questionnaire (DTSQ)-Teen, and greater

treatment satisfaction as measured by DTSQ-Parent instruments, and a positive trend was seen on most PROs measured.

- Additional FDA-conducted exploratory analyses evaluating proportion of subjects achieving A1C goals with differing thresholds (<5.5%, <6%, <6.5%) showed favorable trends at postbaseline timepoints for teplizumab-treated subjects.

5.3.6.1 Exploratory Analyses for Age, Duration of T1D, and C-peptide Threshold

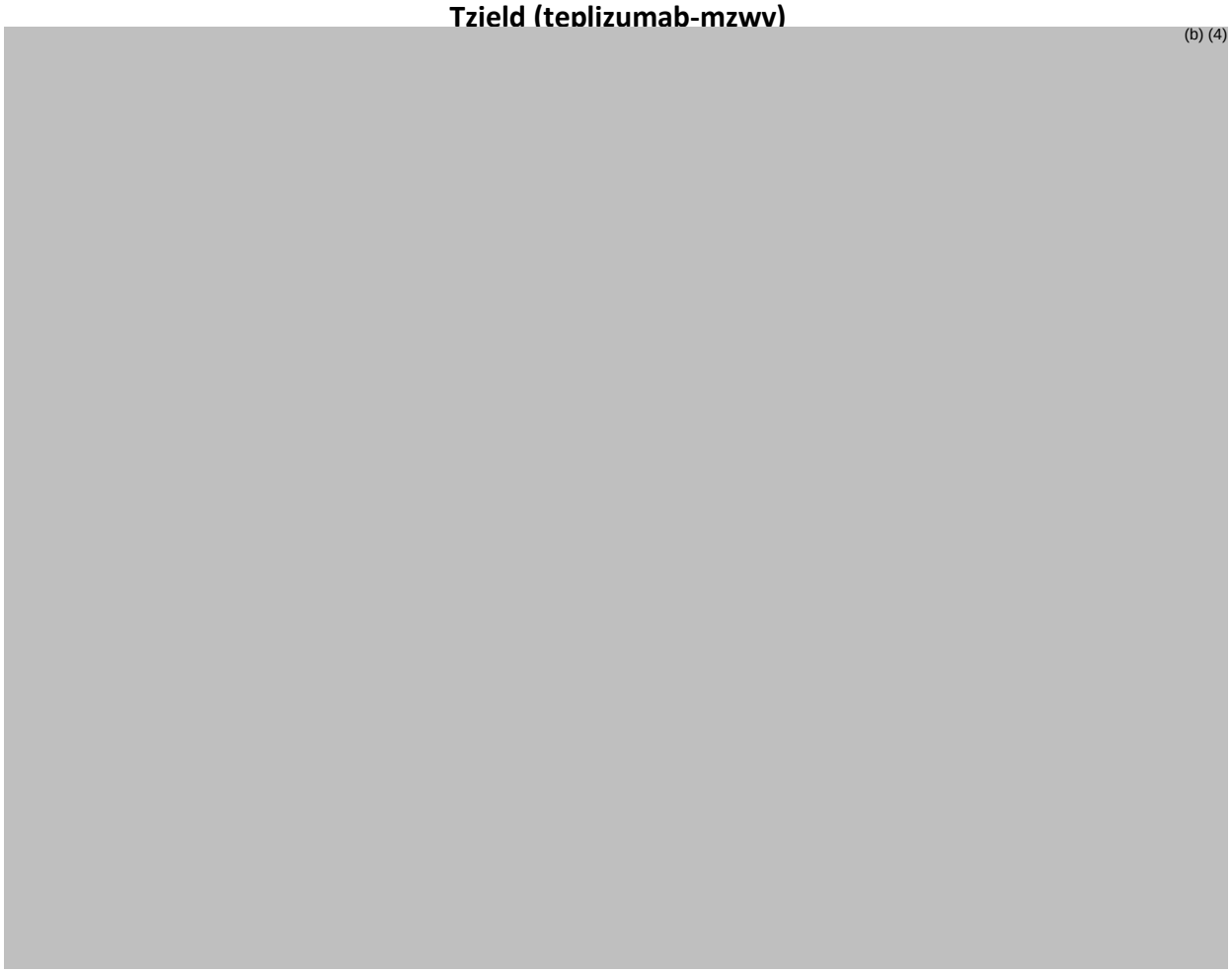
During the review, the Agency identified that the Applicant had not provided sufficient evidence for extrapolating findings from the PROTECT study to the broader proposed indication. The PROTECT study enrolled a specific population: pediatric subjects aged 8 to 17 years, with residual beta cell function (peak C-peptide ≥0.2 pmol/mL on MMTT) with T1D diagnosis within the last 6 weeks. In contrast, the Applicant's requested indication encompasses Stage 3 T1D patients aged 8 years and older (including adults) with any baseline beta cell function or duration of T1D. The Agency needed additional evidence to support extrapolating the pediatric C-peptide results and favorable trends in some clinically meaningful endpoints from the narrower PROTECT population to this broader indicated population.

To determine whether the PROTECT study findings could be extrapolated to this broader population, the Agency recommended that the Applicant provide subgroup efficacy analyses evaluating three key factors: (1) age (<18 versus ≥18 years), (2) baseline peak C-peptide (<0.2 versus ≥0.2 pmol/mL), and (3) T1D diagnosis duration (<6 versus ≥6 weeks). The Agency also requested follow-up analyses in narrower subpopulations among patients with peak C-peptide ≥0.2 pmol/mL, stratified by both age (<18 versus ≥18 years) and T1D duration (6 to 8 weeks, 8 to 12 weeks, or >12 weeks). To conduct these analyses, the Applicant incorporated data from five supportive studies (AbATE, Delay, Encore, Protégé, and Study 1) using both individual study evaluations and pooled meta-analytic approaches (1-stage and 2-stage meta-analyses). The Applicant's analyses showed the following:

5.3.6.1.1 Age Subgroup Analysis

(b) (4)

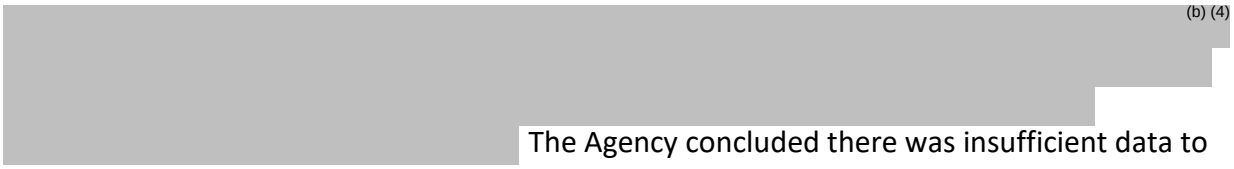
(b) (4)



Given these limitations in the adult data, extrapolation from pediatric findings to adult populations presents substantial challenges and uncertainties. The Agency determined that the justification was inadequate to support broadening the indication to the adult Stage 3 T1D population. The Agency noted that upon completion of the confirmatory trial in Stage 3 T1D patients aged 1 to 25 years, if benefit is confirmed, the Applicant may have evidence to support a favorable benefit-risk assessment in adults.

5.3.6.1.2 Baseline Beta Cell Function Subgroup Analysis

(b) (4)



The Agency concluded there was insufficient data to extrapolate efficacy from the PROTECT study to this population.

5.3.6.1.3 T1D Duration Subgroup Analysis

The Applicant's exploratory subgroup analysis by T1D duration showed varying treatment effects based on time from diagnosis. Using a one-stage analysis model, subjects diagnosed

within 6 weeks of treatment (N=115) showed a treatment effect of 0.1087 (95% CI: 0.01196, 0.20537), while those diagnosed within 6 to 12 weeks (N=406) showed a lower point estimate of 0.0796 (95% CI: 0.02708, 0.1322).

An additional exploratory analysis requested by the Agency examined more granular time intervals (6 to 8 weeks and 8 to 12 weeks from T1D diagnosis). This analysis suggested continued treatment effect with longer T1D durations but with diminishing efficacy over time, showing smaller point estimates (~0.06 to 0.07) compared to the PROTECT study (0.12).

However, in the subset of 184 subjects treated within 8 weeks of diagnosis, the treatment effect was 0.1064 (95% CI: 0.03527, 0.17757), which was similar to those diagnosed within 6 weeks (0.11). This finding supports inclusion of patients diagnosed within 8 weeks in the indicated population.

5.3.6.2 Partial Clinical Remission

At Week 52, 1 (0.9%) participant in the placebo group and 6 (2.8%) participants in the teplizumab group were not using exogenous insulin. At Week 78, 1 (0.9%) and 3 (1.4%) participants, respectively, were not using exogenous insulin.

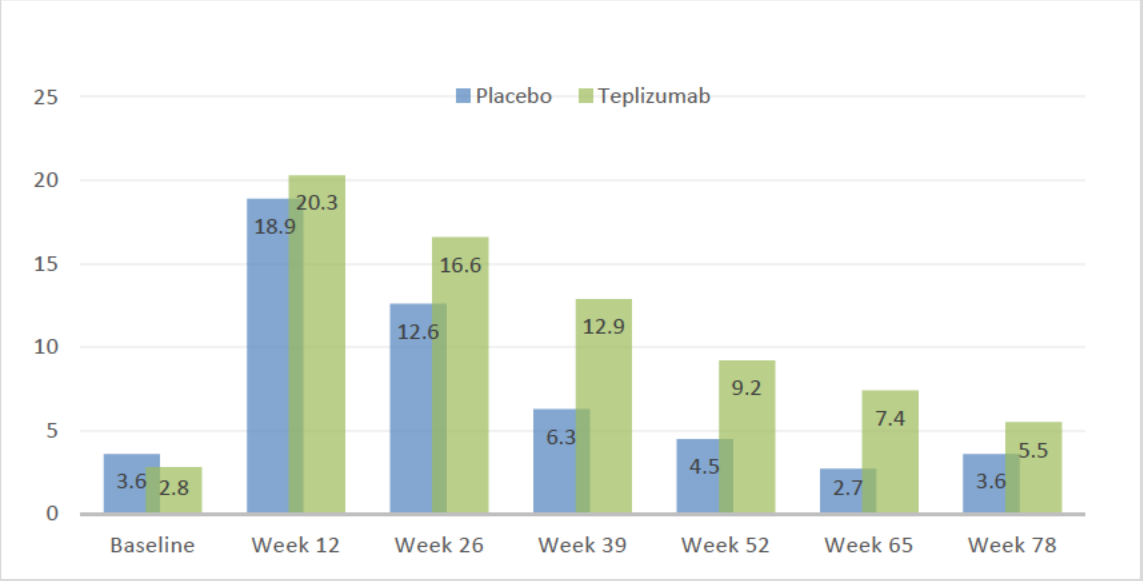
During the PROTECT study, it was recognized that assessing the number of participants able to discontinue insulin use was challenging because discontinuation of insulin is seldom performed in clinical practice due to the metabolic complications. Instead, patients often continue using low doses of insulin even if glycemic targets are achieved. For this reason, the study protocol was amended to add as a prespecified exploratory endpoint the criteria for insulin discontinuation developed in consultation with expert clinicians: A1C ≤6.5% and insulin dose ≤0.25 units/kg/day.

In clinical practice, these thresholds are typically used to define subjects with partial clinical remission, commonly referred to as the “honeymoon period.” Additionally, A1C ≤6.5% represents the diagnostic threshold for the diagnosis of diabetes, and insulin dose ≤0.25 units/kg/day has been previously defined as a dose level safely applied to individuals without diabetes in the Diabetes Prevention Trial of Type 1 (DPT-1) and is considered a low dose of insulin. A similar criterion was assessed as primary endpoint in the Protégé study (A1C <6.5% and insulin <0.5 units/kg/day at Week 52) and the Encore study (A1C <7.0% and insulin <0.25 units/kg/day at Week 52).

The proportions of participants who met the insulin discontinuation criteria based on observed data are graphically represented by visit in Figure 4. Based on the observed data, higher proportions of participants in the teplizumab group than the placebo group met the prespecified criteria for insulin discontinuation at each evaluated postbaseline timepoint. At Week 78, this criterion was met by 12/98 participants (12.2%) in the teplizumab group and by 4/50 participants (8.0%) in the placebo group. Uncertainties related to this exploratory

endpoint include interpretation of binary endpoints in the context of a continuous variable and the substantial missing insulin use data.

Figure 4. Proportion (%) of Participants Who Met Insulin Discontinuation Criteria of A1C ≤6.5% and Insulin Dose ≤0.25 Units/kg/Day by Visit (ITT Population) With Missing Data Imputed as a Nonresponse



Source: Reviewer generated from Applicant's Table from PROTECT CSR
Abbreviations: HbA1c, hemoglobin A1c; ITT, intent-to-treat

Additionally, given that achieving criteria at a single time-point is of unclear significance, while achieving criteria at consecutive timepoints is more meaningful (as it implies a period of partial clinical remission), the FDA requested additional exploratory analysis to better understand the duration of time each individual subject fulfilled the partial clinical remission criteria as a proxy for the honeymoon period. The Applicant performed several post hoc analyses for the subpopulation of PROTECT participants not meeting the clinical remission criteria at baseline (but who achieved it at a postbaseline timepoint), including a summary of the number of visits (out of 7) where partial clinical remission criteria were achieved.

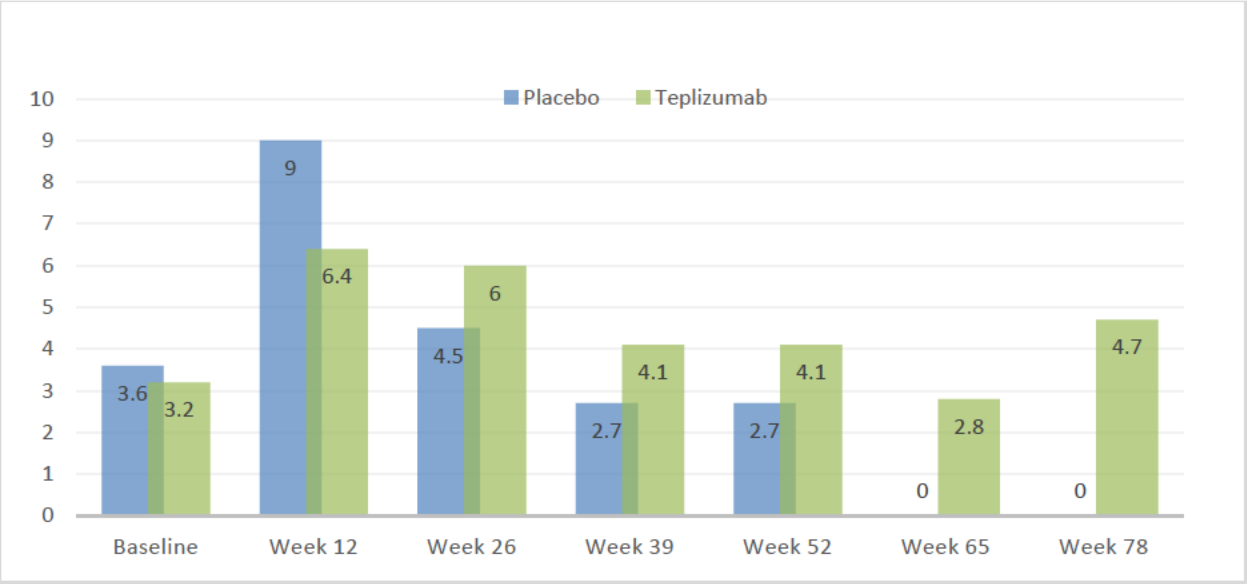
A similar proportion of patients was identified by arm who did not meet partial clinical remission at baseline but achieved it at least once during the study: 59/217 (27.2%) teplizumab subjects and 29/111 (26.1%) placebo subjects. In these subjects, most placebo subjects experienced criteria for partial clinical remission at a single postbaseline visit (66%) and only 14% had 3 or more consecutive visits meeting honeymoon criteria, versus the teplizumab group, where a larger proportion (34%) of those experiencing honeymoon had 3 or more postbaseline visits meeting these criteria. In subsequent responses to information requests, the duration of time meeting partial clinical remission criteria was described, with the teplizumab group generally showing a higher mean (SD) number of days of 230.2 (149.4) compared to 141.7 (133.7), a difference of approximately 3 months. In general, while trends suggest that

teplizumab use was associated with a longer period of partial clinical remission among subjects that did not meet insulin discontinuation criteria at baseline, the Agency had challenges interpreting this exploratory endpoint due to the large amount of missing insulin use data and the post hoc nature of the analysis incorporating postrandomization variables. Additionally, this type of analysis should be conducted in the confirmatory trial in order to further describe and understand these findings in addition to implementation of strategies to reduce missingness for these variables in order to better capture and approximate the duration of partial clinical remission by treatment arm.

5.3.6.3 Proportion of Subjects Who Transitioned to Basal Insulin Only (Discontinued Prandial Insulin)—Post Hoc Analysis Requested by FDA

A key secondary efficacy endpoint in PROTECT was exogenous insulin use at Week 78 using self-reported data in an eDiary at baseline and Weeks 12, 26, 39, 52, 65, and 78. As a post hoc analysis requested by the Agency, the Applicant described the proportion of subjects by treatment arm who discontinued prandial insulin injections and transitioned to basal insulin only. As shown in Figure 5, when subjects with missing data counted as nonresponse, there was a trend toward a numerically higher proportion of teplizumab-treated participants not taking bolus insulin for at least one day (defined as marking “I didn’t take any insulin yesterday” on the eDiary module during the 7-day reporting window prior to each visit) at Week 26 and all subsequent timepoints. However, pump data showed no trend for basal insulin only use, which appeared balanced between arms. The insulin eDiaries were only completed for 7 days prior to each visit, resulting in sporadic data with limited information on the duration of time off bolus insulin that could be evaluated from the collected data. Given the high degree of missing insulin use data and the discordant findings between pump and injection diaries regarding basal insulin only use, there is substantial uncertainty in interpreting this exploratory analysis. It is also unclear whether these data represent the subgroup of subjects experiencing fewer insulin requirements during the “honeymoon period.”

Figure 5. Proportion (%) of Participants Reported to be Insulin Free on Pump Data by Visit (ITT Population) With Missing Data Imputed as a Nonresponse

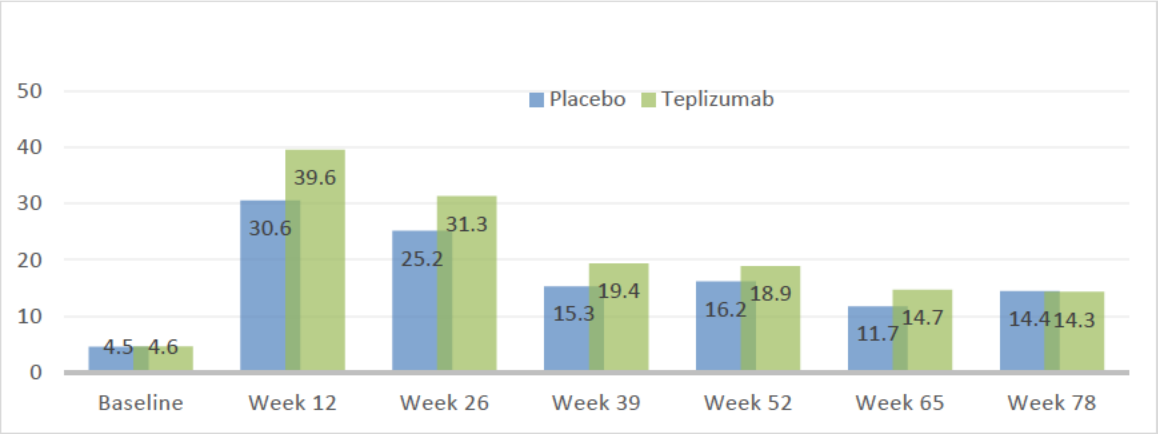


Source: Reviewer generated from data submitted by Applicant in response to IR
Note: Not taking insulin defined as subjects who reported not taking any insulin ("I didn't take any insulin yesterday") on yesterday's insulin diary for at least one day during the 7-day reporting window prior to randomization (baseline) and each visit.
Note: Analysis visit windows defined in the statistical analysis plan are used in this summary.
Abbreviations: ITT, intent-to-treat

5.3.6.4 Proportion of Subjects Achieving A1C <7%, <6% and <5.5% by Study Visit-Post Hoc Analysis Conducted by FDA (Intent-to-Treat Population, Observed Data)

The Applicant performed several exploratory A1C threshold analyses that evaluated the proportion of subjects achieving a combination endpoint of A1C <6.5%, <7.0% and <7.5% with an insulin daily dose either <0.5 or <0.25 units/kg/day. Due to the high level of missing insulin use data, a similar post hoc analysis was conducted by the clinical reviewer that examined only A1C data (with missing data counted as nonresponder) to evaluate whether the trend toward higher proportions of teplizumab subjects achieving A1C ≤6.5% and insulin dose ≤0.25 units/kg/day was driven by insulin use data or was due to improved A1C. This approach was taken because of uncertainties in interpreting the exploratory binary endpoint of partial clinical remission due to substantial missing insulin use data, as discussed above. Figure 6 shows the proportion of participants achieving A1C <6.0% by visit. This and other A1C thresholds tested (<7% and <5.5%) suggested early treatment benefits for teplizumab that diminished over time, providing supportive evidence for the drug's physiologic effects while highlighting the progressive nature of Stage 3 T1D.

Figure 6. Proportion (%) of Subjects With A1C <6.0% by Visit (ITT Population) With Missing Data Imputed as a Nonresponse



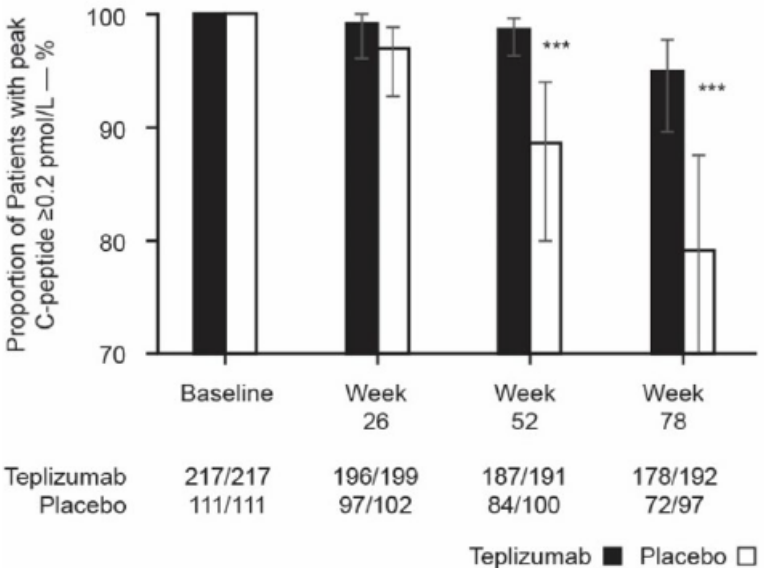
Source: Reviewer generated from Applicant's Table from PROTECT CSR
Abbreviations: HbA1c, hemoglobin A1c; ITT, intent-to-treat

Additionally, at the most clinically relevant threshold of A1C <7%, teplizumab demonstrated consistently higher proportions of participants achieving target glycemic control from Week 12 through Week 65, with the largest treatment effect observed at Week 26 (72.4% versus 59.5%, risk difference of 12.9%). Similarly, for the more stringent A1C <6% threshold, teplizumab showed numerical advantages through Week 65, with peak benefit at Week 12 (39.6% versus 30.6%, risk difference of 9.0%). The A1C <5.5% threshold, representing near-normal glycemic control, showed modest early benefits for teplizumab, particularly at Week 12 (14.3% versus 8.1%), though absolute proportions remained low in both groups throughout the study. While these exploratory analyses cannot independently establish clinical benefit, they suggest that teplizumab-treated subjects reached glycemic goals more frequently than placebo-treated subjects.

5.3.6.5 Peak C-Peptide

Per the Applicant, the proportion of participants retaining more residual beta cell reserve and function was higher with teplizumab than with placebo at postbaseline timepoints, as shown in Figure 7. At Week 78, more teplizumab-treated participants maintained peak C-peptide ≥0.2 pmol/mL, compared to placebo (92.7% and 74.2%, respectively). The adjusted proportion estimates were 0.949 and 0.792, respectively, and the estimated odds ratio of teplizumab/placebo was 4.9 (95% CI: 2.3 to 10.5).

Figure 7. Proportion of Subjects With Peak C-Peptide Levels ≥0.2 pmol/mL on MMTT by Visit (Observed Data)



Source: Figure 14, PROTECT CSR
Note: Error bars indicate 95% CIs. Percentages are based on the number of nonmissing observations in each treatment group. Estimates are obtained from a generalized linear model for repeated measures using logit link function that includes treatment, visit, age group at randomization, and baseline peak C-peptide as fixed effects, and a treatment by visit interaction term.
Abbreviations: CI, confidence interval.

5.3.6.6 The Relationship Between C-peptide Preservation Defined as Peak Stimulated C-Peptide ≥0.2 pmol/mL at Week 78 and Improvements in Metabolic Function—Post Hoc Analysis Requested by FDA

To further understand whether subjects in PROTECT who preserved C-peptide following treatment showed improvements in metabolic function (secondary efficacy endpoints: A1C levels, clinically important hypoglycemic events, TIR), the Agency requested an exploratory responder analysis. Responders were defined as those with peak C-peptide ≥0.2 pmol/mL at Week 78 compared to those with peak C-peptide <0.2 pmol/mL at Week 78 for both treatment arms. Of note, the sample size of the subgroup with C-peptide <0.2 pmol/mL at Week 78 was only 39, which included 14 in the teplizumab arm, and randomization was not preserved.

The Applicant conducted an exploratory analysis utilizing peak C-peptide levels at Week 78 stratified into quartiles. This post hoc analysis demonstrated that the subgroup of subjects (regardless of treatment group), who exhibited greater C-peptide preservation at Week 78 demonstrated lower A1C levels, greater percentage of TIR, and experienced the lowest hypoglycemic event rates at Week 78. The Agency noted that this exploratory analysis had several limitations in that the subgroups were defined based on a postrandomization variable, and there was a higher proportion of participants present in the higher quartiles (e.g., Quartiles 3 and 4) in the teplizumab-treated group, while the proportion of participants in the placebo group decreased from tile 1 through Quartile 4. While this post hoc analysis may suggest a favorable relationship between the magnitude of C-peptide preservation (in either the

teplizumab or placebo arm) and clinical endpoints including A1C, TIR, and hypoglycemia, the data interpretation is limited for the reasons mentioned above.

5.3.6.7 Interpretation of the Magnitude of Treatment Effect on C-Peptide

Placebo-controlled interventional trials in Stage 3 T1D have consistently used the LSM change from baseline in C-peptide (natural logarithm of AUC+1, in pmol/mL) after MMTT as a primary endpoint to assess β-cell preservation. The magnitude of treatment effect varies by drug class and mechanism.

The LSM difference in C-peptide (ln[AUC+1) observed in the teplizumab program of 0.13 pmol/mL at 18 months, appears to be generally similar to the 12-month treatment effect for other therapies currently in Phase 3 trials for Stage 3 T1D (Jacobsen et al. 2020). For example, at 12 months, low-dose anti-thymocyte globulin (ATG) (2.5 mg/kg IV) had an LSM difference in C-peptide (ln[AUC+1]) of 0.14 pmol/mL (P=0.0003) (Haller et al. 2018), and golimumab's 12-month LSM difference in log(AUC+1) C-peptide was 0.20 pmol/mL (95% CI, 0.07 to 0.33; p=0.002) (Quattrin et al. 2020). The American Diabetes Association and the European Association for the Study of Diabetes consider teplizumab, low-dose ATG, and golimumab to be the most promising immunotherapies for β-cell preservation in recent-onset T1D (Holt et al. 2021).

Consistent with the findings of the PROTECT study, at a similar degree of C-peptide preservation, other programs did not demonstrate a significant difference in A1C versus placebo (for golimumab, mean change in A1C 0.47% versus 0.56%; p=0.8) or a difference in rate of American Diabetes Association Level 2 or 3 hypoglycemia. The challenges with interpretation of the A1C change from baseline and hypoglycemia endpoints are discussed in Section 1.4 and Section 5.3.5.1 of this review and will not be recapitulated here.

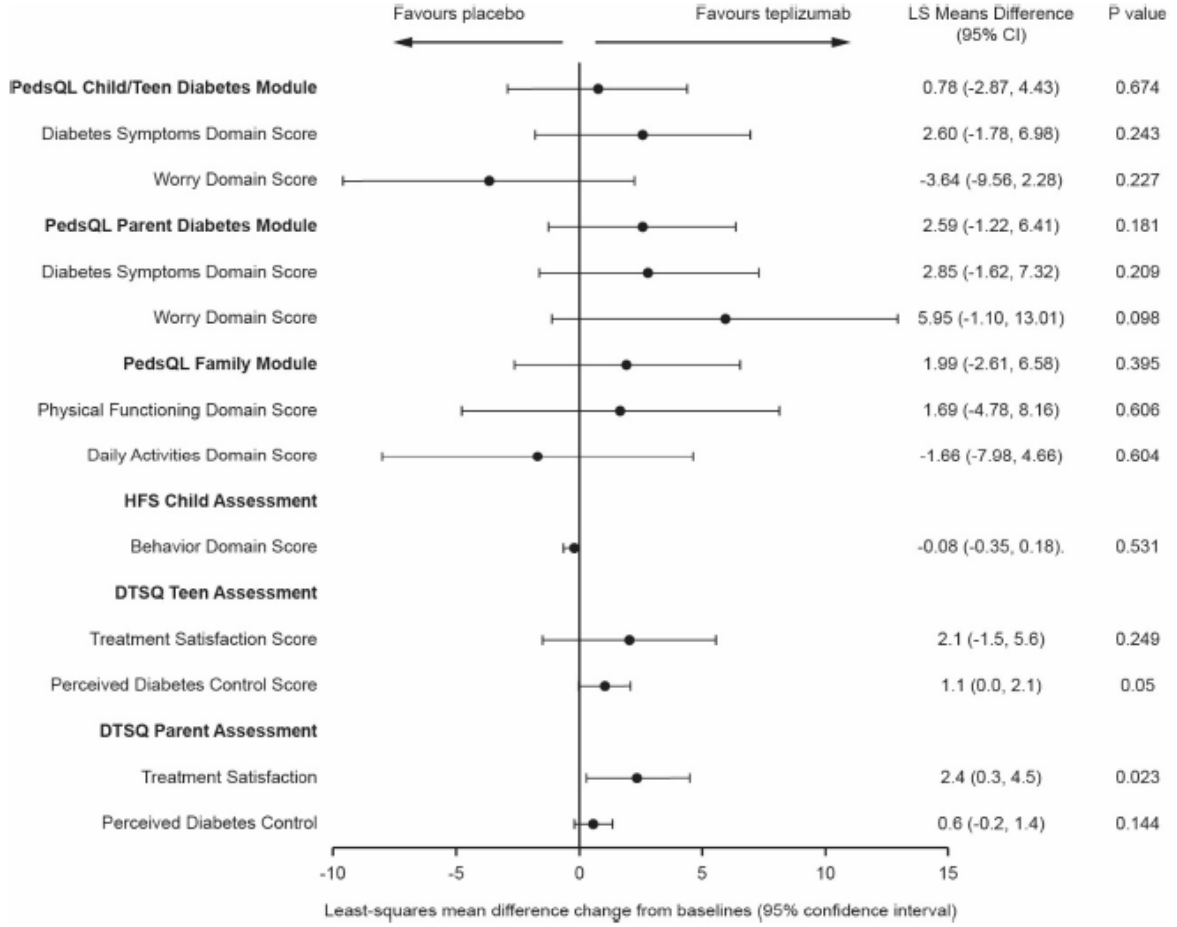
What has been consistently shown in these programs in conjunction with C-peptide preservation, consistent with teplizumab's Stage 3 T1D program, are trends for lower insulin requirements in the treatment group versus placebo and trends of higher rates of partial remission (defined in a variety of ways). For example, insulin use at 12 months was 0.07 units/kg/day versus 0.24 units/kg/day in placebo subjects (p=0.001) and higher rates of insulin dose–adjusted A1C ≤9 was achieved in 43% of golimumab-treated participants versus 7% with placebo. For low-dose ATG, insulin use was 0.36 units/kg/day versus placebo 0.48 units/kg/day (p=0.001), and insulin dose–adjusted A1C ≤9% achieved in 55% of low-dose ATG-treated participants versus 29% with placebo (Haller et al. 2018; Quattrin et al. 2020). Prolongation of the honeymoon period or partial clinical remission has been described by patients and families of patients with T1D as a desirable treatment effect of disease-modifying therapy. Patients achieving partial clinical remission in natural disease history have demonstrated superior metabolic control throughout the first year after diagnosis, with lower A1C levels and daily insulin requirements from diagnosis until one-year postdiagnosis (p<0.001) (Cimbeketal.2021).

5.3.6.8 Patient Reported Outcomes

The PRO assessment utilized validated instruments including the PedsQL™ 3.2 Diabetes Module (measuring diabetes-specific quality of life), PedsQL™ 2.0 Family Impact Module (assessing family burden), Hypoglycemia Fear Scale (evaluating hypoglycemia-related anxiety), and DTSQ for teens and parents (measuring treatment satisfaction and perceived control). Data were collected at seven study visits over 78 weeks and analyzed using MMRM with treatment group, visit, baseline scores, and interaction terms as fixed effects. The analysis strategy appropriately handled missing data and provided LSM differences with 95% confidence intervals for between-group comparisons.

The Agency's analysis of the primary PRO tables generally aligns with the Applicant's summary presented in Figure 8 which reported trends favoring teplizumab. The most consistent favorable trends emerged in treatment satisfaction measures, with statistically significant improvements in both teen and parent DTSQc treatment satisfaction at Week 12 and parent DTSQ treatment satisfaction at Week 78. The perceived diabetes control measures also showed favorable trends for teplizumab, reaching statistical significance for teens at Week 78 and parents in the DTSQc analysis. However, many other PRO domains showed only numerical trends without statistical significance, and some measures (particularly in quality-of-life domains) showed minimal between-group differences.

Figure 8. Applicant's Forest Plot of LS Mean Difference in Patient Reported Outcomes (ITT Population)



Source: Applicant's Figure 3, clinical overview
Abbreviations: CI, confidence interval; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HFS, Hypoglycemia Fear Scale; ITT, intent-to-treat; LS, least square; PedsQL, Pediatric Quality of Life Inventory

Favorable trends were observed in treatment satisfaction and diabetes control perceptions. The consistent pattern in PRO results across multiple satisfaction measures and the alignment between teen and parent assessments support the conclusion that preservation of C-peptide may confer clinical benefit. However, the clinical review team notes important limitations: these PRO instruments lack validation specifically in newly diagnosed pediatric T1D populations, effect sizes are generally modest, and many comparisons did not reach statistical significance.

5.3.7 Confirmatory Evidence

In addition to the PROTECT trial data and analyses, the Applicant provided two efficacy analyses containing integrated assessments of effectiveness from multiple studies conducted with teplizumab in the Stage 3 T1D population:

(1) The original 5-study C-peptide meta-analysis submitted with the original BLA (without modification or inclusion of PROTECT), intended as confirmatory evidence

(2) A 6-study integrated analysis called the "ISE" including the five trials from the original meta-analysis plus the PROTECT study, evaluating efficacy endpoints of peak C-peptide, A1C, exogenous daily insulin use, hypoglycemic adverse events, proportion of participants meeting insulin discontinuation criteria and the correlation between these metabolic endpoints and change in C-peptide. (b) (4) .

The original 5-study C-peptide meta-analysis was reviewed by the statistical and clinical reviewers as part of the original BLA submission and review and will not be recapitulated in this review. In summary, per the Applicant, in all 5 supportive studies, teplizumab consistently led to higher C-peptide at the last study visit (1 year for Delay and Encore; 2 years for Protégé, AbATE, and Study 1) compared to control, despite similar baseline C-peptide by treatment arm. The difference between teplizumab and control was significant in all the studies except in Encore, which was terminated early by the Applicant before its completion, resulting in a large amount of missing data.

At the time of the original BLA, the statistical reviewer conducted sensitivity analyses applying control-based imputation that also showed results consistent with the meta-analysis. During the original BLA review, the Agency determined that the meta-analysis showed a statistically significant difference in C-peptide at 1 year, but on FDA's analysis, did not reach statistical significance at year 2. Given the consistent results for teplizumab's ability to preserve C-peptide across studies included in the Stage 3 T1D clinical program, and based on the PROTECT study and the 5-study meta-analysis findings, results from this 5-study meta-analysis were considered to be adequate confirmatory evidence, sufficient to support an accelerated approval in the context of a favorable benefit-risk assessment. As the SEE is based on the primary endpoint of C-peptide (a RLSE), there remains the requirement to verify and describe the anticipated benefit of teplizumab's magnitude of effect on C-peptide in the Stage 3 T1D population.

The 6-study integrated analysis evaluated pooled efficacy endpoints including A1C, insulin use, hypoglycemic events, insulin discontinuation criteria, and C-peptide maintenance (b) (4) This supplementary 6-study meta-analysis and "ISE SAP" submitted at the time of the sBLA was not agreed upon by

the Agency in advance of this submission. Additionally, the Division had concerns with the pooling and comparability of the studies included in the ISE analyses, and since the planned analyses were not prespecified, the Applicant's analyses were not verified by the Agency during this review.

5.4 PROTECT-Safety

The safety review of the PROTECT trial, ongoing trials (120-day safety update), and postmarket reports revealed the following key findings:

PROTECT showed a higher rate of asymptomatic EBV reactivations in teplizumab-treated subjects without lymphoproliferative disease, consistent with previous data. No cases of CMV reactivation occurred, however a small imbalance in herpes zoster (0.9% versus 0%) was reported. Postmarket reports identified several serious EBV-associated infections within 1 to 2 months of treatment, including one severe case in a patient with underlying immunodeficiency; these more serious infections prompted risk mitigation measures including a boxed warning and contraindication for patients with preexisting immunodeficiency.

PROTECT showed a higher rate of CRS (8.8%) compared to previous studies (5% in original integrated safety analysis [ISS]), likely due to methodological differences in adverse event grading rather than increased toxicity. One delayed hypersensitivity event (rash/arthralgia) occurred at Day 28 in a teplizumab-treated subject, consistent with the known safety profile, and no anaphylaxis or angioedema events were reported. No evidence of higher serious infection rates was observed in PROTECT, with findings consistent with the previous safety database, and diabetic ketoacidosis was not observed. A numerical imbalance in fractures (4.6% teplizumab versus 0% placebo) was observed in PROTECT with low absolute rates, though this finding was not observed in the larger teplizumab safety database.

No malignancy events occurred in PROTECT; however, one low-grade glioneuronal neoplasm was reported in a 7-year-old female in the ongoing PETITE-T1D study approximately one year after teplizumab treatment. An independent pediatric neuro-oncology expert determined that pediatric low-grade gliomas typically have molecular drivers (most commonly MAPK pathway alterations) that cause tumor growth independent of immune response, are not associated with autoimmune conditions or immune therapies, and are not immunologically active. Based on the slow-growing nature and tumor size, the expert concluded the tumor was likely present at enrollment. Given the lack of malignancy signal in the overall program, the Applicant's causality assessment appears reasonable, and teplizumab's potential malignancy risk continues to be evaluated in the ongoing long-term safety registry study.

5.4.1 Safety Review Strategy

To date, the safety of teplizumab has been characterized by six randomized, controlled trials, including five studies in Stage 3 T1D (PROTECT, Protégé, Encore, AbATE, and Delay) and one study in Stage 2 T1D (TN-10). In total, data from 1,346 participants from six randomized, controlled studies were pooled into an integrated safety database. Of these, 990 received teplizumab.

The ISS previously reviewed by the Agency as part of the original BLA review, included data from four clinical trials conducted in Stage 3 T1D (Protégé, Encore, AbATE, Delay) and one trial conducted in Stage 2 T1D (TN-10). In this sBLA, the Applicant updated the previously submitted ISS to include safety data from two additional completed clinical trials: PROTECT (PRV-031-001) and Protégé Extension (CP-MGA031-02). For further details, see Table 9. The Applicant also summarized and submitted individual study safety data from two other completed studies, a single dose biocomparability study (PRV-031-004) in healthy volunteers and the TN-10 Extension (PRV-031-002). TN-10 Extension was not added to the pooled analysis since data pooling was completed before the database lock (February 28, 2025) and the sample size was small (n=6).

A "primary safety pool" consisting of the Delay (without the open-label period for 18 subjects), Protégé, Protégé Extension, Encore, and PROTECT studies served as the basis for the Applicant's safety analysis. While this pool was intended to represent only placebo-controlled trials in Stage 3 (recent, or new-onset) T1D, the Applicant also included Protégé Segment 1, which was an open-label segment of the Protégé Trial enrolling 38 subjects.

For the Agency's safety review strategy, the FDA clinical reviewer evaluated (1) the safety data from the PROTECT study, and (2) independently conducted safety analyses using a placebo-controlled safety pool (Delay, Protégé, Encore, and PROTECT) excluding open-label segments and noninterventional extensions. The placebo-controlled FDA safety pool was therefore used primarily to compare treatment-emergent adverse events (TEAE) and describe exposure-adjusted incidence rates for specific adverse events of special interest to account for differences in exposure duration by study and treatment arm to support the FDA's safety review.

The safety review strategy focused on two key areas: (1) identifying any new safety signals observed in the PROTECT study that are not currently described in the label, and (2) evaluating adverse events relevant to the newly indicated population (such as DKA and hypoglycemia) and safety signals occurring after a second treatment course.

5.4.2 Review of the Safety Database

Overall Exposure

The duration of follow-up for the FDA's safety pool is summarized in Table 5. For the Applicant's primary safety pool, the cumulative follow-up was 1,626.8 PY in the teplizumab group and 515.0 PY in the control group and the median duration of follow-up was longer in the teplizumab group (722.0 days) than in the control group (557.0 days). For the FDA's safety pool (limited to placebo-controlled trials), the cumulative follow-up was 1,425.4 PY in the teplizumab group and 483.5 PY in the control group.

Table 5. Duration of Follow-Up and Total Exposure, FDA's Safety Analysis

Duration of Study Follow-Up Categories, n (%)	Pooled Teplizumab N=856	Pooled Controls N=299
<1 year	60	19
≥1 year	796	280
≥2 years	284	89
≥3 years	7	3

Source: adsl.xpt N, number of subjects in treatment arm
Abbreviations: N, number of subjects with given treatment duration

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 U.S. target population of patients with Stage 3 T1D. 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 in the intended use population in the United States.

5.4.3 Adequacy of Applicant's Clinical Safety Assessments

Data Integrity and Submission Quality

The quality of the submission was found to be adequate. As with the original BLA 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 sBLA 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 PROTECT and the new ISS datasets.

Categorization of Adverse Events

The Applicant used the Standard Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 for adverse event capture and categorization, with harmonization of earlier studies that were originally coded using MedDRA Version 23.0. Severity assessment in PROTECT was conducted using the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 5.0, while other ISS studies used CTCAE Version 3.0 or converted grading scales (mild to Grade 1, moderate to Grade 2, severe to Grade 3, serious adverse events to Grade 4, and death to Grade 5) to ensure consistency across the development program.

The Applicant defined TEAEs using two complementary approaches to capture both immediate and delayed safety signals. The primary definition included all adverse events (AEs) occurring after first dose administration regardless of study duration or perceived drug relationship, while a secondary analysis focused on events within 28 days of last dose administration, based on teplizumab's terminal half-life (4±1.8 days) and pharmacodynamic recovery patterns (recovery of lymphocyte count within 28 days). Adverse events of special interest (AESIs) were prespecified based on known safety concerns with anti-CD3 and T-cell-engaging therapies, including infection, CRS, lymphocytopenia, allergic/hypersensitivity reactions, rash, and liver function abnormalities.

5.4.4 Safety Results

5.4.4.1 Deaths in Overall Development Program

No deaths occurred in the PROTECT study. In the teplizumab development program, there were a total of four deaths in teplizumab-treated subjects compared to none in control arms. One additional death was reported postmarketing in October 2025 via the FDA's Adverse Event Reporting System, as discussed above.

Three of the four deaths (occurring during Protégé and Protégé Extension) were reviewed extensively during the original BLA and were the subject of discussion at an Advisory Committee meeting. These deaths were considered unlikely to be causally related to teplizumab:

- A 19-year-old female subject with Stage 3 T1D from Ukraine enrolled in the Protégé trial died from DKA approximately 9 months after her last dose of teplizumab (approximately 15 months after study initiation). Notably, this subject had experienced DKA between screening and randomization and four additional times during the study, with A1C ranging from 12.9% to 17.3% from month 6 follow-up onward.
- A 27-year-old male subject in India with Stage 3 T1D died of complications related to an anterior wall myocardial infarction 14 months after receiving the last dose of study drug.
- A 24-year-old female subject in India died of unknown causes 26 months after the last dose of study drug. Review of this subject's narrative, revealed that an acute episode of

abdominal pain, vomiting, and diarrhea treated by a local physician preceded her death, which we suspect may be due to DKA; however, no additional information is available.

During the original review, the clinical reviewer noted that observation time was reasonably balanced, between treatment arms with 93% of teplizumab-treated subjects followed for up to 2 years and 39% followed for greater than 2 years, compared with 89% of placebo subjects followed up to 2 years, and 41% followed for greater than 2 years. However, due to randomization imbalances, there was approximately 3-fold more exposure-adjusted time following teplizumab subjects versus controls for the entire safety pool in the teplizumab clinical development program. Based on this analysis, the imbalance in deaths in the teplizumab program compared to controls was attributed to differential safety follow-up duration. Additionally, review of case narratives provided further support that the deaths occurring during the clinical trials were unlikely related to teplizumab, particularly given the long latency between dosing and the events and the etiologies inconsistent with the mechanism of action of the drug.

There was also a notable imbalance in baseline demographics for studies included in the Applicant's primary safety pool, where subjects from India comprised 21.9% (196/894) of the teplizumab group and 16.7% (50/299) of the placebo group. These imbalances were considered when evaluating deaths (and DKA rates). When analyzing only U.S. subjects or using safety analyses that allowed for more balanced geographic contribution to each treatment arm (FDA safety analysis #2), the rates of DKA and death were no longer considered notable. Refer to Section 5.4.4.6 for additional information on the evaluation of DKA as an AESI.

Additionally, the deaths that occurred in young adults from India (n=2) and Ukraine (n=1) occurred in resource-limited settings, which is consistent with global epidemiological data indicating that the majority of diabetes-related deaths in individuals under 25 years of age worldwide (97.5%) occur in patients from low to high-middle sociodemographic index countries, and the majority (73.7%) of all such deaths globally are attributed to T1D (GBD 2019 Diabetes Mortality Collaborators 2022).

This supplement also described a death that occurred during long-term follow-up in the TN-10 Extension study. A 21-year-old participant died by suicide during the TN-10 Extension study, approximately 9 years and 7 months after initial teplizumab exposure in the TN-10 study and 9 months and 17 days after the second course of teplizumab in the TN-10 Extension study. This participant had a documented history of anxiety and major depressive disorder with hospitalization approximately 1 year and 7 months prior to enrollment in the TN-10 Extension study. This case was reviewed and was not considered to be drug-related based on the available evidence.

5.4.4.2 Serious Adverse Events

In PROTECT, the proportion of participants experiencing SAE were similar between the teplizumab arm (5.5%) and the placebo arm (5.4%). Some notable findings are described below:

- On review of the preferred terms (PT) for SAE, there were 3 (1.4%) subjects treated with teplizumab with cytokine release syndrome SAEs. This is slightly higher rate than in the original ISS for BLA 761183 where 7/773 (0.6%) experienced SAEs of cytokine release syndrome.
- In PROTECT, there were no infection or infestation SAE in the teplizumab treated arm.
- One subject in the teplizumab arm had a Grade 4 SAE of suicide attempt by drug overdose approximately 179 days after the second 12-day course of teplizumab was completed, with another Grade 4 SAE of suicide attempt noted 2 months later. The narrative for this SAE was included in the submission and was reviewed. The timing of this event in relation to teplizumab administration (179 days) makes causality related to the drug unlikely. There was a different teplizumab-treated subject with Grade 3 SAEs of suicidal ideation reported 4 and 6 months following the second course of teplizumab. There were no SAEs of suicide attempt or suicidal ideation in placebo subjects in PROTECT.
- Other SAEs were reviewed and were not noted to have any notable clustering of PTs and also did not occur at a higher rate in the teplizumab arm than was observed in the original BLA safety database.

5.4.4.3 Discontinuation Due to Adverse Events

Consistent with the previous teplizumab clinical program, teplizumab-treated subjects had a higher discontinuation rate (6.8%, 15/217) compared to placebo (2.7%, 3/111) in the PROTECT study, with the majority of teplizumab discontinuations (60%, 9/15) attributable to protocol-specified laboratory criteria, primarily transaminase elevations. The rate of alanine aminotransferase (ALT)-related discontinuations in PROTECT (4.1%, 9/217) was consistent with the established teplizumab safety database from previous trials (5.6%, 41/729), indicating no new hepatotoxicity signal. These transaminase elevations are presumed to be related to cytokine release syndrome rather than direct hepatotoxicity, consistent with the known mechanism of teplizumab. The remaining discontinuations were due to either events unrelated to teplizumab (i.e., COVID-19 infection), events related to procedures involved in teplizumab administration (phlebitis), or known labeled risks including cytokine release syndrome (1.8%, 4/217), and delayed hypersensitivity (0.5%, 1/217), consistent with the established safety profile for teplizumab.

5.4.4.4 Treatment-Emergent Adverse Events

The majority (99.5%) of teplizumab-treated subjects and placebo (97.3%) subjects experienced TEAEs, with a higher proportion of teplizumab participants experiencing CTCAE Grade 3 and above TEAEs compared to placebo (56.7% versus 21.6%). The most common TEAEs in the PROTECT study included hypoglycemia (teplizumab group 69.6% versus placebo 73%), headache (43.3% teplizumab versus 18.9% placebo), nausea (42.4% teplizumab versus placebo 18.9%), rash (39.6% teplizumab versus 4.5% placebo), lymphocyte count decreased (33.6% teplizumab versus 4.5% placebo), and vomiting (31.8% teplizumab versus 13.5% placebo). Many of the TEAEs observed more commonly in the teplizumab group are known adverse reactions of teplizumab use (related to cytokine release) and were observed at a similar or lower rate than previously demonstrated in the prior teplizumab safety studies.

5.4.4.5 Adverse Events of Special Interest

The Agency's review of safety adverse events for the PROTECT trial was generally found to be consistent with the known safety profile for teplizumab. For the PROTECT trial, there were no events of DKA in either treatment arm, and unlike the previous safety database, there was no evidence for a higher rate of serious infection among teplizumab treated subjects. During the review, two postmarketing cases concerning for viral reactivations more serious than previously observed in the clinical program occurred prompting an analysis of the severity of viral reactivations, in the overall program in addition to the PROTECT study. There were several safety findings of interest in the PROTECT trial including a higher rate of CRS that appeared to be driven by mild to moderate CRS and fracture adverse events, discussed further below.

Other labeled adverse events of special interest (i.e., liver enzyme elevations, hypersensitivity reactions) and several safety events that are particularly relevant for the population of patients with Stage 3 T1D, such as hypoglycemia, and DKA, were reviewed for the PROTECT study and in the context of the larger clinical program.

5.4.4.5.1 Postmarket Suspected Unexpected Serious Adverse Reaction and Fatal Event

During the review, two critical postmarket cases were received for two adult patients treated with teplizumab:

A fatal case involved a 30-year-old male with autoimmune hypothyroidism, hypogonadism, prior cavernous malformation surgery, and recently diagnosed Stage 3 T1D who was treated off-label with teplizumab. Baseline laboratory results were suggestive of past exposure to EBV and CMV without active infection. The patient presented approximately 2 weeks after completing teplizumab treatment with progressive tonsillar hypertrophy, extensive cervical lymphadenopathy, and breathing difficulties. Laboratory evaluation revealed thrombocytopenia (platelets 95,000/µL), elevated liver enzymes (ALT 140 U/L, aspartate aminotransferase [AST] 65 U/L), and elevated lactate (3.3 mmol/L), initially attributed to a viral

syndrome and treated with antibiotics, antifungals, and steroids. The patient visited the emergency room on Days 27 to 28 post-treatment initiation with worsening symptoms, and experienced sudden death on Day 32 post-treatment initiation while normoglycemic. Although the clinical presentation—including the 10-day delay from treatment completion, fever, arthralgia, lymphadenopathy, hepatitis, and thrombocytopenia—was suggestive of a viral syndrome (e.g., EBV reactivation) viral testing was limited to respiratory panels and monospot (both negative), along with blood cultures. EBV or CMV reactivation was not confirmed by PCR testing. An autopsy report submitted on February 10, 2026, to the FDA, determined that the final pathologic diagnoses were undetermined natural causes, hypertensive cardiovascular disease, reactive splenomegaly, and elevated creatinine. While the autopsy results remain inconclusive and the ultimate cause of death is unclear, the clinical presentation of the patient is suggestive of a viral syndrome (e.g., EBV reactivation), and a contribution of teplizumab to the death cannot be ruled out. No clear evidence of an underlying immunodeficiency was identified.

Additionally, the Applicant informed the FDA of a SUSAR case involving severe EBV reactivation and biopsy-confirmed lymphoproliferative disorder (LPD) requiring rituximab treatment. The case involved a 44-year-old male with Down syndrome, history of Tetralogy of Fallot with surgical repair (with potential thymic disruption from cardiac surgery), and hypothyroidism who developed severe PCR-confirmed EBV reactivation (viral load 2,184,797 IU/mL) with clinical deterioration within 2 to 3 weeks of the teplizumab course, progressing to pneumonia, respiratory failure, hepatorenal syndrome, renal failure, and multiorgan failure requiring ICU care, intubation, and dialysis. Based on clinical presentation and biopsy findings showing EBV-associated lymphoproliferation, the patient was treated with rituximab for LPD/lymphoma. The patient was discharged from the hospital for continued at-home recovery (ongoing) approximately 4 weeks from the start of the illness.

The teplizumab infusion was complicated by persistent severe lymphopenia, with teplizumab infusions being paused after seven documented days of severe lymphopenia <500 cells/µL (though gaps in laboratory monitoring suggest this could represent 8 to 9 days of severe lymphopenia), then resumed for two additional doses after a 2-day pause once the lymphocyte count rose to >500 cells/µL (530 cells/ µL). Per Agency consultation with the Division of Hematological Malignancies 2, this case was consistent with EBV-associated LPD, specifically EBV-associated lymphoma, and it was noted that patient-specific factors (Down syndrome and past history of cardiac surgery with potential thymectomy) may have predisposed this patient to a baseline immunocompromised state and increased risk of LPD. Per the Applicant, prolonged severe lymphopenia (<500 cells/µL) lasting more than 1 week with continued treatment against labeled guidance, as well as the inability to fully exclude active EBV viral replication prior to treatment based on timing of laboratory evaluations are noted issues with this case. Specifically, limited pretreatment viral surveillance was performed prior to teplizumab (EBV IgM only; EBV IgG and EBV PCR were not performed) and this testing was performed approximately 4 months before the teplizumab course. Given this testing was performed so far in advance of treatment, active infection at the time of teplizumab initiation

could not be ruled out. The Applicant also notes that two additional patients with Down syndrome have been treated with teplizumab in 2022 and 2025. No EBV infection or any severe complications have been reported in the other two patients with Down syndrome, however one of these two patients had to discontinue treatment due to liver function elevation not related to EBV reactivation.

The SUSAR case prompted the Applicant to search[5] their pharmacovigilance database for additional cases of EBV reactivation from ongoing and completed clinical trials and postmarket data. As of the data cut-off of May 31, 2025, 732 patients were estimated to have been exposed to teplizumab in the postmarket setting. The Applicant's global pharmacovigilance database search identified a total of 10 cases (including the SUSAR described above but not including the fatal event) of EBV infection/reactivation, of which 7 were serious. Two cases involved LPD or suspected LPD based on histopathology reports and/or severe or life-threatening symptoms. One patient had Down syndrome as described above; the other was receiving chronic immunosuppression due to organ transplant rejection and had been treated with teplizumab's precursor product hOKT3γ1. One event had previously been reviewed as part of the original BLA, a 14-year-old female in the Protégé trial who was hospitalized with symptomatic infectious mononucleosis (confirmed by EBV serology) approximately 10 months after completing treatment with teplizumab. The search also identified four additional SAEs related to EBV reactivation, three occurring in adults >20 years and one in a female of unknown age, primarily presenting as infectious mononucleosis, some with elevated liver function tests. Of the 7 serious cases identified, 6 occurred within 1 month of completion of teplizumab, 5 cases either included immunocompromised patients or involved prolonged severe lymphopenia <500 cells/µL for 7 days or more with continuation of teplizumab treatment despite labeled guidance to discontinue, and at least 2 cases involved patients with elevated BSA (>2.0 m^2) and obesity (BMI >30 kg/m^2). Eight of the 10 cases had no identifiable condition leading to an immunocompromised state; however, all involved typical symptoms of EBV infection or infectious mononucleosis, including elevated liver function tests in some cases. Most required hospitalization, and all patients (with available follow-up data) recovered.

Notable individual cases from the pharmacovigilance report include:

- 14-year-old female in the Protégé study from the Czech Republic who had a SAE of infectious mononucleosis approximately 10 months after receiving a second course teplizumab. The subject ‘presented with typical symptoms of mononucleosis, and markedly elevated ALT 1071 IU/L and AST 537 IU/L (both >10x upper limit of normal [ULN]) in the context of normal bilirubin, and thrombocytopenia (platelets 130,000/µL). This event was

[5] Applicant’s search PTs: Preferred Term (PT) Epstein-Barr virus infection reactivation, Epstein-Barr virus infection, Epstein-Barr viraemia, Mononucleosis syndrome, Infectious mononucleosis, Epstein-Barr associated lymphoproliferative disorder, Epstein-Barr virus antibody positive, Lymphadenopathy, Epstein-Barr antigen positive, Epstein-Barr associated lymphoma, Epstein-Barr virus test positive (MedDRA Version 28).

consistent with EBV reactivation as her baseline EBV IgG was positive (indicating EBV exposure) with IgM seropositivity following infection. The subject was admitted to the hospital and treatment included IV methylprednisolone, penicillin, metamizole (a non-opioid analgesic and antipyretic), antihistamine, and oral NSAIDs. The event resolved and the subject was discharged from the hospital after 1 week. This case was reviewed in original BLA as the single severe EBV reactivation event in the teplizumab type 1 diabetes clinical program.

- A 32-year-old female patient who received hOKT3γ1 (teplizumab's precursor product) as an islet cell transplant recipient in an investigator-initiated study developed nonmalignant LPD presenting as lymphadenopathy, EBV-antibody positivity, and oropharyngeal pain approximately 1 month after completing a 12-day IV course of hOKT3γ1. The patient was also receiving three additional immunosuppressive agents at the time. According to the Applicant, the symptoms resolved following discontinuation of immunosuppression and treatment with antiviral therapy.
- A 58-year-old female with Stage 2 T1D from France, enrolled in a compassionate use program, with a BSA of 1.6 m^2, experienced mononucleosis syndrome and EBV reactivation following teplizumab treatment. Her medical history included autoimmune thyroiditis, Addison's disease, and adrenal insufficiency, and she was taking levothyroxine for hypothyroidism and fludrocortisone acetate and hydrocortisone for adrenal insufficiency and Addison's disease. During the 14-day teplizumab treatment course, she experienced persistent severe lymphopenia (<500 cells/ µL) with nadir noted on Day 4 at 140 cells/µL, Day 9 at 530 cells/µL, and Day 14, last day of treatment, at 390 cells/µL. Due to gaps in laboratory monitoring. Despite lymphocyte counts remaining <500 cells/µL, treatment was paused on Days 12-13 after approximately one week of documented lymphopenia <500 cells/µL, then teplizumab was resumed with a lymphocyte count of 390 cells/µL on the final day of treatment, contrary to labeled guidance to discontinue teplizumab if lymphocyte count remains <500 cells/µL for 7 days or longer. During teplizumab treatment, she also experienced several symptoms including rashes, mild transaminase elevations, asthenia, pain, and swelling of hands, with EBV PCR testing positive at that time. Approximately 3 weeks after her last dose of teplizumab, she was hospitalized with erythematous angina, odynophagia, fever, asthenia, and tonsillitis. At 2.5 months after the last dose, she developed mononucleosis syndrome characterized by fever, abdominal pain, diarrhea, and pseudomembranous tonsillitis, with both CMV and EBV PCR tests and serology returning positive. The patient was treated with symptomatic management including acetaminophen and corticosteroids (60 mg hydrocortisone daily at discharge) and subsequently recovered from the mononucleosis syndrome.
- 25-year-old male from the United States with Stage 2 T1D treated in the observational study OBS18117, with a BSA of 2.0 m^2 and weight of 81.1 kg who developed a serious adverse event of infectious mononucleosis approximately 8 days after completing a 14-day course of teplizumab, presenting with sore throat, headache and fatigue and was treated with ibuprofen or acetaminophen at urgent care and recovered without need for

hospitalization. The patient was exposed to a person with mononucleosis around the time of teplizumab treatment.

- A 21-year-old female patient with Stage 2 T1D from France, enrolled in a compassionate use program, with a BSA of 2.1 m^2 and weight of 86.5 kg (190.3 lbs), experienced a serious adverse event of CMV and EBV reactivation presenting with multiple symptoms including chills, palpitations, hypoesthesia, somnolence, lymphopenia, pruritic rash, fatigue, elevated liver enzymes and C-reactive protein, and increased hypersensitivity. During treatment, she experienced severe lymphopenia with a nadir of 490 cells/µL on Day 6 with recovery to 610 cells/µL by Day 14. Very few laboratories were performed during the infusion, so the duration of severe lymphopenia <500 cells/uL is unknown, but she could have experienced severe lymphopenia of up to 9 days based on the limited laboratories available. Treatment was completed without interruption. The patient's past medical history and the outcome of the viral reactivations were not reported.
- A 22-year-old female patient with Stage 2 T1D from China, with a BSA of approximately 1.8 m^2 and weight of 67.3 kg, experienced acute lymphadenitis, acute tonsillitis, and EBV infection. During treatment, she experienced severe lymphopenia with a nadir of 310 cells/µL on Day 8 which remained persistently <500 for ~ 2 weeks, with the first documented recovery >500 (520 cells/µL at day 28, approximately 2 weeks post-treatment). Treatment was completed without documented interruption despite the severe lymphopenia, representing approximately 2-3 weeks of potential severe lymphopenia post-teplizumab.
- A female patient of unknown age in the United States with possible Stage 2 Type 1 Diabetes and unknown BSA, developed a serious adverse event of EBV reactivation with elevated liver function tests approximately 2.5 weeks after her last dose of teplizumab. She initially presented with fever lasting approximately 10 days, sore throat, and shortness of breath that did not improve with outpatient antibiotic treatment using Augmentin and azithromycin. She visited the emergency room and was hospitalized after laboratory results showed liver function tests at two times the upper limit of normal, and white blood cells (WBC) of 10.2 with 58% lymphocytes. CT imaging revealed prominent nasopharyngeal tissue and visible chest lymph nodes. While both the respiratory viral panel and monospot tests were negative, EBV PCR testing was positive, confirming EBV reactivation. The patient's fever resolved two days after admission, and she was discharged from the hospital. The patient's age, medical history, concomitant medications, predisposing factors, the specific dose of teplizumab administered (or the patient’s BSA), or laboratory results from during the infusion were not reported.

5.4.4.5.1.1 Clinical Trial Findings - Viral Reactivation of Latent Viruses and Infectious Mononucleosis

In PROTECT, teplizumab-treated subjects showed minimal increases in herpes zoster (0.9% versus 0%) and no cases of CMV reactivation. Adverse events of lymphadenopathy occurred in 3.7% of teplizumab subjects and 1.8% of placebo subjects, with no cases associated with EBV or CMV per the Applicant. Teplizumab-treated subjects had more EBV-related laboratory abnormalities than placebo, including 7 cases of EBV viremia versus none on placebo, all cases were asymptomatic and identified by scheduled/prespecified EBV viral testing the Week 28 visit. Additionally, higher rates of acute mononucleosis-like illness[6] (7.8% versus 2.7%) were seen on the Applicant's AESI analysis. On review of individual cases, no cases were considered SAEs, and the majority were asymptomatic with 2 teplizumab-treated participants with serological evidence of EBV viral reactivation who were also noted to be symptomatic; one participant noted to have EBV DNA positive at Week 28, associated with mononucleosis symptoms, one had symptoms of viral upper respiratory infection with sinusitis on Study Day 90, without symptoms of mononucleosis. TEAEs related to EBV reactivation were predominantly Grade 1 to 2, with one exception of Grade 3 EBV antibody positivity (PT :'positive EBV serology') in an asymptomatic participant.

The findings on EBV reactivations in PROTECT were largely consistent with the previous clinical program for teplizumab, where one serious adverse event of infectious mononucleosis with elevated liver function tests occurred in a 14-year-old requiring hospitalization (described previously). No serious complications such as LPD were reported in the PROTECT. These results aligned with the original BLA findings, which found that a higher rate of EBV reactivation was noted among teplizumab patients (4.5%) than controls (2.3%). Of EBV reactivations occurring in teplizumab treated patients, the majority (26/34, 76%) occurred following Course 1 and the majority 68% (23/34) occurred within 30 days of either course. Notably, subjects with acquired or congenital immunodeficiencies and autoimmune conditions (except celiac disease and autoimmune hypothyroidism) were excluded from trials, and viral PCR testing was conducted routinely.

5.4.4.5.1.2 Primary EBV Infection in Clinical Trials

Similar to the previous teplizumab clinical program, there was no imbalance in primary EBV infection events in the PROTECT trial, which occurred in two subjects: one in the placebo group and one in the teplizumab group. The placebo participant, a 16-year-old male, tested positive for EBV on Day 396 based on laboratory results and was asymptomatic. The teplizumab

[6] Applicant's search PTs for Acute Mononucleosis-like Illness AESI: Preferred Term (PT) 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, EBV Infection and CMV infection (MedDRA Version 28.0).

participant, a 15-year-old female, tested positive for EBV on Day 91; approximately one month prior (around 60 days after teplizumab administration), she experienced upper respiratory infection and sinusitis with elevated ALT (increased from 12 to 200 U/L, with recovery to 13 U/L by Week 39) but did not exhibit symptoms associated with mononucleosis. The clinical presentation is consistent with primary EBV infection developing between Weeks 8 and 12, which appears temporally related to teplizumab administration and, similar to other EBV infections, occurred following full recovery of cytopenias. Limited clinical details are available beyond the URI/sinusitis presentation, with WBC decreasing from 7.1 to 3.3 × 10^9/L between Weeks 8 and 12.

In previous clinical trials, primary EBV infection was observed in 16 teplizumab-treated subjects and 8 controls, with no overall imbalance in rates between groups. However, the timing of events in teplizumab subjects suggests potential causality given teplizumab's mechanism of action, as approximately half of the primary EBV infections in teplizumab-treated subjects occurred around or before Day 30, similar to the pattern observed with EBV reactivations. Most subjects with primary EBV infection were older adolescents and adults (63% were ≥15 years), though a few younger children were affected (one 8-year-old male and two 10-year-olds). The severity of primary EBV infection in young pediatric patients remains an area of uncertainty, as very few younger children experienced these infections during the clinical program, highlighting the need for additional safety monitoring measures for primary EBV in the confirmatory trial.

5.4.4.5.1.3 Risk Assessment and Labeling Recommendations

T cell immunity, particularly cytotoxic $CD8^+$ T cells and $CD4^+$ T helper cells, plays a critical role in controlling EBV infection. EBV establishes lifelong latency in B cells, and immune surveillance by EBV-specific T cells is essential to prevent viral reactivation and uncontrolled B cell proliferation. Published literature indicates that CD3-targeting monoclonal antibodies can impact T cell-mediated immune control, leading to an increased risk of EBV infection or reactivation.

The clinical consequences of impaired T cell immunity generally vary by patient population. In immunocompromised patients, the loss of T cell-mediated control can lead to uncontrolled viral replication and proliferation of EBV-infected B cells, manifesting as severe infectious mononucleosis with organ involvement, hemophagocytic lymphohistiocytosis, or LPD. EBV-associated LPD represents a particularly serious complication, as EBV-infected B cells can undergo malignant transformation in the absence of adequate T cell surveillance. Patients at high risk for these severe outcomes include those with congenital immunodeficiencies, those receiving chronic immunosuppressive therapy, and those with iatrogenic immunosuppression from other causes. In contrast, immunocompetent patients are expected to fully recover from EBV infection, though severe EBV complications- such as hepatitis with significant liver enzyme elevations, encephalitis, or splenic rupture- may occur. Risk factors in this population may include genetic predisposition, viral load, or strain virulence; however, severe outcomes are generally uncommon in the absence of underlying immunosuppression. Given the potential for serious EBV-related complications, particularly in at-risk populations, timely identification and

management of these cases is paramount.

Based on the safety experience with teplizumab and available literature, it is biologically plausible that teplizumab is associated with EBV infection or reactivation due to its mechanism of action. The clinical course of EBV was mostly asymptomatic or mild in the T1D population evaluated in PROTECT. However, postmarket data suggest that immunocompromised patients could be at risk of life-threatening LPD. Additionally, some (66%) of the other postmarket SAEs related to EBV reactivation experienced prolonged severe lymphopenia. Note that severe prolonged lymphopenia is already addressed in the current label, which states teplizumab be permanently discontinued if this is identified. However, this section of the labeling could be strengthened by the addition of initiation of additional monitoring for recovery in patients with persistent lymphopenia and explicit recommendations regarding the frequency of lymphocyte count monitoring during the infusion (every 2-3 days) so that persistent, severe lymphopenia is identified and monitored appropriately.

The risk of harm with viral reactivation is sufficiently serious that it could impact the prescriber's decision about whether to prescribe the drug and requires special consideration in managing the risk so that serious outcomes can be prevented or reduced through appropriate use. Additionally, increased awareness of prescribers of this potential drug-related risk is paramount for timely diagnosis and management.

Based on this assessment, FDA recommends a boxed warning to prominently display this serious risk. Additionally, the labeling should include a contraindication for use of the drug in patients who at baseline are immunocompromised and therefore at increased risk of severe consequences of EBV infection. Furthermore, while it is reassuring that no events of LPD were reported in the original ISS despite follow-up times as long as seven years, the long-term registry is designed to assess the risk of EBV-associated LPD based on evidence of EBV viremia in teplizumab-treated patients and the possible long-latency period for development of LPD.

5.4.4.6 Diabetic Ketoacidosis

Diabetic ketoacidosis is a known complication of T1D and is related to relative insulin insufficiency versus metabolic need. DKA was not observed in the PROTECT study.

In the pooled Phase 3 studies of teplizumab in patients with new-onset T1D, DKA events occurred more frequently in teplizumab-treated patients compared to controls (22/894 [2.5%] versus 2/299 [0.7%] based on FDA analysis, or 20/894 [2.2%] versus 1/299 [0.3%] per Applicant analysis). The discrepancy between analyses arose from differences in adverse event term classification, with the FDA analysis including additional cases coded as "diabetic ketosis," "ketoacidosis," or "ketosis" that clinically represented DKA.

The temporal relationship between teplizumab administration and DKA events does not support a causal association, as the mean time to DKA occurrence was 284.7 days after the last teplizumab dose, and no dose-dependent relationship was observed. Review of individual case

narratives of DKA events among patients who were teplizumab-treated (Table 10) 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. This analysis also revealed that 80% of DKA events had identifiable precipitating factors consistent with known DKA triggers in patients with T1D, including insulin insufficiency, intercurrent illness, insulin pump malfunction, or medication nonadherence. Two patients also experienced DKA between screening and study randomization.

Among the three cases without clear precipitating factors, all occurred weeks to months after teplizumab discontinuation (34 days, 681 days, and approximately 500 days post-treatment), with clinical presentations consistent with typical DKA triggers such as poor oral intake, vomiting, and physiological stress. Narratives for these three cases are as follows:

- Case 1 (16-year-old female, India): DKA occurred 34 days after last teplizumab dose (study Days 47 to 50) with precipitating factors including severe vomiting, poor oral intake, dehydration, and menstrual-associated abdominal pain, despite reported insulin compliance.
- Case 2 (14-year-old female, United States): DKA developed 681 days after discontinuation of teplizumab (which was stopped early after only 2 infusions due to Grade 3 GGT elevation) with typical DKA symptoms of emesis, confusion, and abdominal pain.
- Case 3 (19-year-old female, India): Patient with history of DKA prior to study enrollment experienced two additional DKA episodes at 311 and 530 days post-teplizumab, the first associated with gastrointestinal symptoms and the second occurring during pregnancy, leading to premature labor.

The majority (85%) of DKA events in teplizumab treated subjects were from Protégé and Encore studies and 55% of the subjects with DKA events were from India, even though only 16 to 21% of subjects in these trials were from India. There was also a notable imbalance in baseline demographics for studies included in the Applicant's primary safety pool, where participants from India made up 21.9% (196/894) of the teplizumab group and 16.7% (50/299) of the placebo group, and U.S. subjects made up a higher proportion of the control group (44.1% [132/299]) versus the teplizumab group (39.8% [356/894]).

When isolating safety analyses to U.S.-only subjects, the imbalance in DKA events was not noted (3/336 [0.89%]) teplizumab versus 1/132 control [0.76%]), and all events in the teplizumab group were distant from dosing (occurring >250 days after the last dose of teplizumab), suggesting that the initial imbalance in DKA events may have been related to baseline imbalances in enrollment of participants from India.

In general, given the lack of association with teplizumab dosing and likely preceding poor oral intake in these cases, DKA in these patients is likely most consistent with underlying T1D disease and unrelated to teplizumab treatment. The overall pattern suggests these DKA events

represent expected complications of the underlying T1D rather than drug-related adverse effects and may have been influenced by baseline demographics imbalances driven by participants from India, a country with different levels of access to care than the United States.

5.4.4.7 Serious Infection

In the PROTECT study, no SAE related to infection occurred, and infection adverse events with CTCAE severity Grade ≥3 occurred at a lower rate in teplizumab treated subjects (0.5%) compared to placebo subjects (1.8%). In the broader teplizumab clinical program, teplizumab-treated participants had a higher rate of serious infections (3.15%) than control-treated patients (2.2%), with a total of 26 SAEs related to infections were reported across both treatment courses and follow-up periods. No dose-response relationship was observed.

For this sBLA review, an exploratory analysis was conducted using the FDA safety pool (placebo-controlled Stage 3 T1D trials), accounting for duration of exposure and clinical trial size. Serious infections were defined as infection SAEs or infection adverse events with CTCAE Grade ≥3 severity. This analysis showed an exposure-adjusted incidence rate of serious infections of 2.27 (95% CI: 1.57, 3.29) per PY for the teplizumab arm and 1.81 (95% CI: 0.94, 3.48) per PY for control arms, similar to previous safety analyses showing a small imbalance in incidence rate.

Temporal analysis of individual events revealed that the majority of these infections (16 of 26 events) occurred at time intervals too remote from drug administration to establish a causal relationship with teplizumab-induced immunosuppression. These temporally distant infections, occurring 120 to 718 days postdosing, included common bacterial infections (appendicitis, pyelonephritis, cellulitis), viral illnesses (gastroenteritis, infectious mononucleosis, dengue fever), and other conditions consistent with typical infectious disease patterns in the pediatric and young adult population.

Five infections occurred within a timeframe consistent with teplizumab-related immunosuppression. Three cases had clinical features suggestive of CRS rather than true infections: viral gastroenteritis occurring 8 days postinfusion, gastritis with fever and lymphopenia on the final day of treatment, and a febrile illness with elevated inflammatory markers but negative cultures occurring during the dosing period. These presentations suggest that some reported "infections" may actually represent drug-related inflammatory responses rather than true infectious processes. One case was a PICC line infection occurring one day after the final infusion in a pediatric patient, while temporally associated, this likely represents a procedure-related complication rather than immunosuppression-mediated susceptibility. The final case was pulmonary tuberculosis in a 27-year-old Indian female occurring 151 days post-treatment, which could represent reactivation of latent tuberculosis due to teplizumab-induced immunosuppression. However, the patient's normal baseline tuberculosis screening, epidemiologic context of tuberculosis exposure risk in India, and maintenance of normal hematologic parameters throughout follow-up suggest a low likelihood of drug relatedness. Overall, while teplizumab's immunosuppressive mechanism creates theoretical risk for

opportunistic infections, the clinical data suggest that serious infectious complications directly attributable to drug-induced immunosuppression are uncommon, with most reported events either temporally unrelated to dosing or potentially representing inflammatory drug effects rather than true infectious processes. While the PROTECT study had reassuring findings regarding serious infection risk with teplizumab treatment, the labeling for teplizumab adequately describes the higher rate of serious infections and risk mitigation strategy.

Other Notable Infections

Consistent with the previous safety database for teplizumab, few opportunistic infections observed during the PROTECT study. CMV reactivation and tuberculosis infection was not observed in the PROTECT study. There was a small imbalance in herpes zoster infection occurred in 2 (0.9%) teplizumab participants, and none in placebo, consistent with the larger safety database in which varicella zoster virus infections[7] were reported in 9 teplizumab-treated patients (1.2%) and 1 control patient (0.4%). For additional discussions related to risk of viral reactivation refer to Section 5.4.4 of this review.

5.4.4.8 Cytokine Release Syndrome

The overall rate of CRS was noted to be higher in the PROTECT trial, reported in 19/217 (8.8%) of teplizumab-treated subjects in PROTECT compared to 5% of teplizumab-treated subjects in the previous safety database. This finding requires careful interpretation, as it appears to be primarily driven by an increase in Grade 1 and 2 CRS cases. As shown in Table 6 below showing a comparison of the severity of CRS events by CTCAE grade, Grade 3 CRS rates remained similar between studies at 1.4% (3/217) in PROTECT versus 0.9% (7/771) in the ISS, with no Grade 4 to 5 events reported in either dataset. There is a difference in the CTCAE version used for grading these events from Version 3.0, used in the ISS, to Version 5.0 used in the PROTECT study.[8]

[7] Reported as 'varicella', 'herpes zoster', and 'varicella zoster virus infection'

[8] CTCAE CRS Grading System (Versions 3.0 and 5.0)

CTCAE	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
CTCAE Version 5.0	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated

Source: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Versions 3.0 and 5.0
Abbreviations: CRS, cytokine release syndrome; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs, nonsteroidal anti-inflammatory drugs; IV, intravenous

Table 6. Cytokine Release Syndrome Cases by CTCAE Grading Criteria and Treatment Group, All Studies—Full ISS for BLA 761183 vs. PROTECT

Severity	ISS Teplizumab N=773 n (%)	ISS Control N=245 n (%)	PROTECT Teplizumab N=217 n (%)	PROTECT Placebo N=111 n (%)
Overall	39 (5)	2 (0.8)	19 (8.8)	1 (0.9)
1	12 (1.6)	1 (0.4)	10 (4.6)	1 (0.9)
2	20 (2.6)	1 (0.4)	8 (3.7)	0 (0)
3	7 (0.9)	0 (0)	3 (1.4)	0 (0)

Source: Modified from primary clinical review (BLA 761183); Reviewer generated using ADAE.xpt.(ISS) and PROTECT study CSR
Note: ISS includes the pooled safety population for TN-10, Protégé, Encore, Delay and AbATE studies. The ISS analysis only includes events occurring before initiation of a second treatment period, the PROTECT analysis includes events from Course 1 and 2
Abbreviations: CI, confidence interval; CTCAE, common terminology criteria for adverse events; ISS, integrated summary of safety for BLA 761183; RD, risk difference

The observed increase in lower-grade CRS events is likely attributable to methodological differences rather than a true increase in drug-related toxicity. Specifically, the PROTECT study utilized CTCAE Version 5.0 for adverse event grading, incorporating more objective and specific measurements for fever and hypotension in CRS grading, compared to Version 3.0.[8] This revision in grading methodology appears to have resulted in more sensitive detection and classification of mild to moderate CRS events, while severe CRS rates have remained consistent across the clinical development program, suggesting a similar safety signal for serious CRS events with teplizumab treatment in PROTECT compared to the overall clinical development program.

5.4.4.9 Liver Enzyme Abnormalities

Liver enzyme elevations are a key manifestation of CRS and were commonly observed in the teplizumab clinical program accompanying CRS. The label notes that CRS manifestations include increased ALT, AST, and total bilirubin, typically occurring during the first 5 days of treatment. Current safety monitoring requires discontinuation of Tzield in patients who develop ALT or AST elevations >5 times ULN or bilirubin >3 times ULN.

In pooled clinical trials, 25% of Tzield-treated patients experienced elevated aminotransferases compared to 11% of controls, with 5.1% experiencing peak ALT >3 times ULN, similar to the rate of CRS in the original BLA (5%). At the time of the original review, two cases met Hy's law criteria (bilirubin >2X ULN concurrent with ALT >3X ULN). Both cases were determined to be unrelated to drug-induced liver injury and had alternative explanations (CRS and hepatitis A infection).

Two pediatric subjects in the PROTECT study experienced hepatic enzyme elevations meeting Hy's law criteria. Subject (b) (6) (10-year-old female) developed Grade 3 ALT elevation (229 U/L, >11x ULN) on Day 4 following a constellation of CRS symptoms including myalgia, headache, nausea, increased body temperature, delirium, tachycardia, tachypnea, and rash beginning on Day 1. Subject (b) (6) (13-year-old female) experienced Grade 3 elevations in

ALT (372 U/L, >15x ULN), AST (182 U/L, >5x ULN), and bilirubin on Day 4, preceded by pyrexia, nausea, and vomiting on Day 2.

Both subjects had rapid resolution of symptoms and normalization of liver function tests after drug discontinuation and supportive care (anti-inflammatory medications and antiemetics), consistent with the expected course of CRS without persistent liver injury. The temporal relationship between teplizumab administration and hepatic enzyme elevations in the PROTECT cases, occurring within the established timeframe for CRS (first 5 days of treatment), along with the characteristic symptom constellation and rapid recovery upon discontinuation, supports that these cases are related to CRS rather than direct hepatocellular injury and are consistent with the known safety profile of teplizumab. The current safety monitoring framework appropriately identifies and manages these events.

5.4.4.10 Hypersensitivity

In the PROTECT study, there was only one teplizumab-treated subject reporting an adverse event consistent with hypersensitivity. This subject was reported to have an adverse event of 'Hypersensitivity' (CTCAE Grade 2), 16 days after receiving the last dose of a 12-day course of teplizumab and was consistent with a delayed hypersensitivity reaction with symptoms of rash and arthralgias. This subject was treated with famotidine and diphenhydramine with resolution of the event within 6 days. Unlike the previous safety database, there were no adverse events of serum sickness, angioedema or bronchospasm in the PROTECT study.

In general, the PROTECT study findings are consistent with what is known regarding teplizumab's safety regarding hypersensitivity and consistent the Tzield labeling, as hypersensitivity is listed in Warnings and Precautions, with a description of a case of delayed hypersensitivity (i.e., serum sickness) noted in TN-10 in Section 6.1 Clinical Trials Experience (Provention Bio. 2022).

Also, in the PROTECT Study, rash occurred in 30% of teplizumab-treated participants positive for anti-teplizumab-mzwv ADA and in 17% of ADA negative. As there were some trends for higher titer ADA with the new manufactured product (AGC Biologics), the Applicant also provided analyses of hypersensitivity events in the PROTECT study by ADA status and by product (AGC versus Lilly) and there was an imbalance in hypersensitivity reactions not favoring the AGC Biologics product during both Course 1 and Course 2 driven by a slightly higher rate of adverse events of rash and vomiting. Rates of cytokine release syndrome were similar by product (AGC versus Lilly) and occurred at a lower rate in AGC subjects versus Lilly subjects for Course 1 (1.5% versus 9.9%) and at a similar rate for Course 2 (3.5% versus 3.0%). Hypersensitivity AEs were notably less in Course 2 versus Course 1 for both AGC and Lilly subjects, consistent with what was observed when looking at adverse event rates by number of courses.

5.4.4.11 Hypoglycemia

In addition to being a key secondary endpoint for the PROTECT study, hypoglycemia was also evaluated as an adverse event of special interest. Similar to other clinical studies in the teplizumab development program, adverse events of hypoglycemia were recorded using investigator reporting (via electronic CRF) and were assigned a severity grade using CTCAE v5.0.

CTCAE Grade ≥3 events of hypoglycemia (defined as a blood glucose reading of <40 mg/dL) were analyzed as an AESI, including preferred terms 'Hypoglycemia', 'Hypoglycemic seizure', 'Hypoglycemic coma'; and 'Hypoglycemic unconsciousness'. However, no adverse events of hypoglycemic seizure, coma or unconsciousness were reported in the PROTECT study.

For the PROTECT study, AESI of hypoglycemia were reported in a higher proportion of placebo subjects (16.2%) versus teplizumab subjects (13.4%), consistent with the previous teplizumab clinical program. In the entire safety database for teplizumab, Grade 3 or higher events of hypoglycemia associated with altered mental and/or physical status (PTs of Hypoglycemic seizure, Hypoglycemic unconsciousness, and Hypoglycemic coma) were reported in 1.0% of participants in the teplizumab group (9/894) and 0.7% of participants in the control group (2/299).

When evaluating more severe cases, one participant (0.9%, 1/111) in the placebo group and four participants (1.8%, 4/217) in the teplizumab group had Grade 4 TEAEs of hypoglycemia (blood glucose ≤29 mg/dL), on review of the individual cases for teplizumab treated subjects, 2 subjects had events that did not appear to be temporally related (occurring at least 4 months after the last dose of teplizumab), and two had events that occurred around the timing of Course 1 or 2 of teplizumab. Of note, the one control subject with an event reported it during the IV placebo course (Day 4).

Given the lack of American Diabetes Association Level 3 hypoglycemia events (associated with symptoms), and no other notable trends in hypoglycemia events, this small imbalance was not considered to be related to teplizumab but could be related to the infusion procedure or disruption of patient's usual schedule.

5.4.4.12 Suicidal Ideation, Suicide Attempt and Depression

As there was a notable death by suicide in a teplizumab treated subject in the TN-10 Extension, Dr. Lauren Wood Heickman evaluated the Psychiatric Disorders system organ class (SOC).

Depression rates were similar in the teplizumab arm (3.2%) versus the placebo arm (3.6%) during the PROTECT study, and there was no notable imbalance in pooled adverse events in the Psychiatric Disorders SOC. There has been one death in the clinical program in a teplizumab-treated subject due to suicide and three suicide attempts in the teplizumab arm (including a PROTECT subject, a 13-year-old female, and a Delay subject, a 14-year-old male, and a 34-year-old male from Protégé) compared to none in controls. When considering the placebo-

controlled clinical trial safety pool, there is an imbalance in SAEs of suicide attempt of 3/894 (0.3%) teplizumab arm (3/894, 0.3%) versus controls (0/299). Given the approximate 3-fold difference in follow-up time between teplizumab and control arms, it is possible that this imbalance is due to differences in follow-up time. This imbalance continues to be under evaluation and will be monitored in the long-term registry and evaluated through the confirmatory trial.

5.4.4.13 Fracture

A higher incidence of adverse events consistent with fracture were identified on a custom Narrow FDA MedDRA Query, with 10/217 (4.6%) teplizumab-treated subjects and 0 placebo subjects experiencing fractures. This was not seen in the original BLA review where no imbalances in fracture were observed as SAEs (4/773 (0.5%) teplizumab and 1/245 (0.4%) controls) or on TEAE analysis, with 16/773 (2.1%) teplizumab and 5/245 (2.0%) controls experiencing fracture.

Of the subjects reporting fracture in PROTECT, 8/10 were in the age 12 to <18-year age group and the majority (7/10) of fractures affected the hand, wrist, fingers, or forearm (radius and elbow) with the other 3 involving knee, ankle, and 'chipped tooth'. The fracture events were reviewed and no events concerning for bone fragility were identified, and all fractures were consistent with common injuries occurring in older children and adolescents (typically related to sports and recreational activities). On time-to-event analyses (not pictured), there was no temporal relationship between fracture events and teplizumab treatment. While the risk difference for the narrow fracture OCMQ category shows a numerical increase (4.6% versus 0%, risk difference +4.6%), the absolute event rates remain low and likely reflect the active pediatric population rather than a drug-related effect. However, given that narratives were not captured for these events, fractures will be considered an AESI in the ongoing PMR study to allow for better characterization of this potential signal or refuting causality.

5.4.4.14 Safety Laboratory

The comprehensive laboratory safety assessment from the teplizumab clinical program demonstrated a consistent pattern of transient laboratory abnormalities that align with the drug's mechanism of action and known safety profile. The most significant findings included lymphopenia with nadir at Day 5 and recovery by Week 6, hepatic enzyme elevations (ALT, AST) with peak abnormalities occurring during the treatment cycle and resolving within 1 to 2 weeks post-treatment, and hematologic changes including decreases in hemoglobin and platelet counts with nadir between visits 5 to 8 followed by recovery before treatment completion. Additional transient abnormalities were observed for calcium and albumin levels, with calcium and albumin both decreasing during the dosing period and recovering within 1 to 2 weeks of follow-up.

The updated review of the PROTECT study laboratory findings did not reveal any new findings or trends in the known laboratory abnormalities associated with teplizumab, including hepatic enzyme elevations, lymphopenia, neutropenia, anemia, thrombocytopenia, decreased blood bicarbonate and decreased calcium, which are all transient and resolve within 1 to 4 weeks of the treatment course depending on the specific abnormality. These laboratory abnormalities are adequately described in the current teplizumab label (Provention Bio. 2022) along with appropriate laboratory monitoring and discontinuation for persistent lymphopenia or severely elevated liver transaminases or hyperbilirubinemia. There were no new trends observed that would warrant changing the labeling.

In the PROTECT study, three (1.4%) teplizumab participants reported five events of lymphopenia <500 cells/mm^3 for 7 days or more, similar to rates previously observed in teplizumab clinical trials (0.9% of teplizumab-treated patients). As described in the liver function abnormality section above, a similar rate and severity of elevations in liver function tests were observed in the PROTECT study as in the previous clinical program. Two (0.9%) participants in the teplizumab group experienced peak ALT more than 3 times the ULN, compared to 5.1% of teplizumab-treated patients and 0.8% of control-treated patients in the previous clinical program.

5.4.4.15 Vitals

At the time of the original review, small differences between teplizumab and control were observed in clinically relevant cutoffs for blood pressure, heart rate, and most notably for temperature. Review of vital signs in the PROTECT study did not identify any new or concerning trends in vital sign abnormalities. The vital sign changes observed at the time of the original BLA were expected due to teplizumab's ability to cause CRS which is often accompanied by fever, and in some cases hypotension and respiratory and heart rate changes. Based on additional analyses performed by the Applicant and reviewer at the time of the original review, teplizumab did not appear to cause meaningful blood pressure changes in most patients, but patients who experience CRS, there were more dramatic maximal drops in SBP (~25 mm Hg) noted, usually on Day 5 of teplizumab. As changes in vital signs did not appear to persist beyond the dosing period, it was determined that labeling mitigation measures such as blood pressure monitoring during infusion were sufficient to mitigate any potential risk of this vital sign abnormality limited to the days of teplizumab infusion.

5.4.4.16 Electrocardiograms and QT

Electrocardiograms

Electrocardiograms (ECGs) abnormalities are not expected for a monoclonal antibody product. At the time of the original BLA review, no clinically significant ECG findings were reported in the two studies where ECGs were specifically conducted after teplizumab dosing (Encore and TN-10). The Applicant concluded that available nonclinical and clinical data demonstrate no

evidence of any effect of teplizumab on cardiac repolarization, or other general cardiac concerns. ECG monitoring was not performed in the PROTECT study.

QT

A thorough QT study was not considered necessary, and a waiver was granted during the original BLA review cycle due to a low likelihood of direct ion channel interactions associated with large, targeted proteins and monoclonal antibodies.

5.4.4.17 Immunogenicity

The PROTECT, TN-10 and Protégé and Encore studies evaluated the immunogenicity of teplizumab through the detection and characterization of ADAs and NAbs as well as their impact on PK, PD, efficacy, and safety. These studies demonstrated that teplizumab is highly immunogenic with the overall ADA incidence ranging from 50% to 94% during the first course and up to 98% when a second course of treatment was administered. Most ADAs were noted to also be NAb, and in the PROTECT study, the proportion of ADA-positive participants with reactive NAbs was higher during Course 2 (76.7%) compared to Course 1 (54.0%), which was generally consistent with previous teplizumab trials evaluating NAbs.

No clinically significant safety observations were made in subjects with immunogenicity (ADA positive or NAbs) at the time of the original BLA review other than a potential higher rate of rash (skin reaction SOC) in ADA positive subjects compared to ADA negative subjects in Course 1 but not Course 2 of the Protégé study. 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. The PROTECT study safety immunogenicity analyses did not reveal any new immunogenicity concerns. In the PROTECT study and in the entire clinical program, Course 2 was associated with lower rates of hypersensitivity and rash adverse events in teplizumab-treated subjects regardless of immunogenicity. There were too few ADA-negative subjects in the PROTECT study to conclude safety adverse event rates by ADA. ADA positive subjects with reactive NAb in the PROTECT study had a similar rate of adverse events of rash, urticaria, hypersensitivity and cytokine release syndrome versus those with nonreactive NAb. The lack of safety events during Course 2 at the time of subsequent teplizumab exposure, when a greater number of subjects were positive for ADA, and average titers were higher, suggest there is no clinically significant association of safety events with ADA status.

Immunogenicity by Product (AGC vs. Lilly)

In a previous submission (February 2022) accompanying the PROTECT study CSR, the Applicant provided information on ADA formation in the now-marketed drug product (AGC Biologics) in comparison to the clinical trial (Lilly) drug product through a substudy which included unblinded analysis of PK/PD data and ADA titer data. The PROTECT PK/PD substudy demonstrated that the AGC product was associated with earlier appearance and higher ADA titers than the Lilly

product, but no noted difference in the incidence of ADA positivity was noted. The Applicant also provided analyses of hypersensitivity events in the PROTECT study by ADA status and by product (AGC versus Lilly) and there was an imbalance in hypersensitivity reactions not favoring the AGC Biologics product during both Course 1 and Course 2 driven by a slightly higher rate of adverse events of rash and vomiting. Rates of cytokine release syndrome were similar by product (AGC versus Lilly), and occurred at a lower rate in AGC subjects versus Lilly subjects for Course 1 (1.5% versus 9.9%) and at a similar rate for Course 2 (3.5% versus 3.0%). Hypersensitivity adverse event were notably less in Course 2 versus Course 1 for both AGC and Lilly subjects, consistent with what was observed when looking at adverse event rates by number of courses.

5.4.4.18 Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroup were performed at the time of the original BLA to evaluate whether significant adverse events (cytokine release syndrome, infections, cytopenias, hepatic enzyme elevations) differed importantly among subgroups. The incidence of AEs in the were similar by age quartiles and no treatment by age group interactions were observed. There were no differences in safety findings among subgroups of sex (male and female) and race (White, Asian, Other). However, the data were primarily from White patients, limiting conclusions.

5.4.4.19 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were noted in the PROTECT study. As discussed in the original safety review for teplizumab, the current clinical safety database for teplizumab remains insufficient to adequately evaluate malignancy risk due to short follow-up duration and the relatively young patient population, with the longest available follow-up being 7 years in the AbATE trial (n=43).

Two cases of malignancy have been previously identified in the Stage 2 and 3 T1D clinical development program.

The first case involved a 21-year-old male with Stage 3 T1D treated with teplizumab in the Protégé trial who was diagnosed with malignant melanoma of the scalp and regional lymph node metastases approximately 6 months after the last dose of teplizumab. This patient had a history of dysplastic nevi and a preexisting lesion; teplizumab causation is extremely unlikely, though a potential contribution to accelerated metastasis cannot be excluded.

The second case involved a 7-year-old female with Stage 2 T1D treated open-label with a single 14-day course of teplizumab in the PETITE-T1D trial (PRV-031-005) who was diagnosed with Grade 3 glioneuronal neoplasm of the spine approximately 1 year after treatment with teplizumab. The patient presented with upper back/posterior neck pain, was admitted to the hospital, and underwent an intramedullary spinal cord tumor resection.

The Applicant's analysis of this event and consultation with an external independent expert in pediatric neuro-oncology (b) (4) determined that tumors of this type, pediatric low-grade gliomas (LGG), almost always have a molecular driver, most commonly alterations within the MAPK pathway. Additionally, the specific mutation itself is usually the cause of tumor growth rather than host immune response, and the specific genetic mutations associated with LGG are not associated with autoimmune conditions or immune therapies and are not very active immunologically. Based on the slow growing nature of LGGs and the size of the patient's tumor, the pediatric neuro-oncologist concluded that the tumor was likely already present at the time of the participant's enrollment in the clinical trial. Given the lack of a plausible role of teplizumab in the risk of this type of neoplasm, the clinical reviewer agreed with the Applicant that this event appeared not to be causally related to teplizumab. There is an ongoing long-term PMR study designed to evaluate the potential risk of malignancy in the program.

As with the original safety review for teplizumab, there remains a theoretical malignancy concern based on teplizumab's immunosuppressive mechanism and the progenitor antibody OKT3's labeled risks for post-transplant lymphoproliferative disorders, though no lymphoproliferative disorder cases were reported in teplizumab clinical trials in the Stage 2 or 3 T1D population despite EBV reactivation events (mainly asymptomatic viremia) occurring predominantly within 30 days of treatment. However, serious EBV and CMV reactivations have been noted in postmarketing reports primarily in adults, with one particularly serious EBV reactivation with biopsy-proven lymphoproliferative disorder, specifically EBV-associated lymphoma, in an adult male patient with Down syndrome who became seropositive for EBV at the time of the infusion. Down Syndrome and past history of possible thymectomy may have predisposed this patient to a baseline immunocompromised state and increased risk of LPD.

At the time of the original approval, a 10-year registry study was recommended as a PMR for the Stage 2 T1D population in order to evaluate for long-latency events of malignancy and LPD. Nonclinical carcinogenicity and genotoxicity studies were not required given teplizumab's short treatment duration. Based on the postmarketing case of EBV-associated LPD in an immunocompromised patient and the theoretical risk of malignancy associated with teplizumab's mechanism of action, the Agency recommends the labeling of teplizumab be modified to include a boxed warning for viral reactivation and its complications, including potential LPD given the serious postmarketing event of LPD. Additionally, the Agency recommends a contraindication for use in patients with preexisting immunodeficiency.

The malignancy findings to date, including the case of EBV-associated lymphoma in an immunocompromised patient, appear consistent with teplizumab's immunosuppressive mechanism of action and at this time, the ongoing 10-year registry study will provide long-term safety data to further characterize malignancy risk, while the recommended boxed warning and contraindication for immunocompromised patients are considered appropriate risk mitigation measures to prevent serious outcomes in vulnerable populations.

Human Reproduction and Pregnancy

In the teplizumab clinical development program, 16 pregnancies were reported in teplizumab-treated women across multiple studies, despite contraceptive requirements for study participation. Pregnancy outcomes included 12 normal neonates, 2 elective terminations, 1 spontaneous abortion, and 1 case lost to follow-up.

The temporal relationship between teplizumab exposure and conception was evaluated, with 4 pregnancies occurring within 2 months of the last teplizumab dose. Among these, 3 pregnancies proceeded without complications, including 2 cases where conception occurred before treatment completion, with one resulting in elective termination and the other in normal pregnancy and delivery outcomes. The single spontaneous abortion occurred approximately 20 months after the last teplizumab dose in a patient with complicating medical conditions including Graves' disease and T1D, making a causal relationship with teplizumab unlikely given the extended time interval and confounding factors.

No congenital malformations were reported in any of the pregnancy cases, whether resulting in elective termination, spontaneous abortion, or live birth. The overall pregnancy outcome profile does not suggest a teratogenic signal, though the limited dataset and absence of published literature on teplizumab pregnancy outcomes preclude definitive safety conclusions regarding use during pregnancy. The label is consistent with the previous label regarding pregnancy and lactation and as there is an ongoing pregnancy registry PMR for this product, labeling and pregnancy safety will be updated once that study is completed.

6 Advisory Committee

No advisory committee meeting was held for this supplemental application.

7 Pediatrics

The PROTECT study was conducted in the pediatric population (ages 8 to 17 years). No pediatric-specific safety concerns were identified in the PROTECT study beyond a potential imbalance in fractures, which were not considered to be related to teplizumab. The safety of teplizumab was previously established in age 8 years and older based on a safety database featuring trial data for 773 teplizumab-treated subjects, with a high number of pediatric patients (<18 years), 477 (62%), and the majority of whom (>90%) were Stage 3 T1D patients. Subgroup analyses by age from the original safety review did not find any efficacy or safety issues specific to the pediatric population. The indication will be limited to patients 8 to 17 years, consistent with the studied population in the PROTECT study.

An impact on growth was not assessed in the safety program but is not expected for a monoclonal antibody targeting CD3. The confirmatory trial will enroll a pediatric and adult

population (age 1 to 25 years) and will be further evaluating potential impact on growth in a young pediatric population.

8 Labeling Recommendations

Labeling recommendations are discussed throughout this review; final labeling is deferred until labeling negotiations are initiated with the Applicant.

This Prescribing Information (PI) review provides a high-level summary of the rationale for major changes to the finalized PI compared with the Applicant's draft PI (Table 7). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for safe and effective use of the drug, and provides clear and concise information for healthcare practitioner. At this time, the key labeling changes and considerations below are preliminary and have not been communicated to the Applicant.

Table 7. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to the Applicant's Draft PI
BOXED WARNING	Added a boxed warning related to serious EBV infection or mononucleosis-like illness
1 INDICATIONS AND USAGE	Modified the Sponsor's proposed indication from "delay progression of Stage 3 Type 1 Diabetes" to "delay the decline in endogenous insulin production" to more accurately reflect the expected effect of teplizumab in the indicated population. Limited the indicated population to the population that the data support: age 8 to 17 years with residual beta cell function (peak C-peptide ≥0.2 pmol/mL on mixed-meal tolerance test), (b) (4) within 8 weeks of T1D diagnosis.
2 DOSAGE AND ADMINISTRATION	Changes recommended to reflect the changes to the indicated population (including confirmation of peak C-peptide ≥0.2 pmol/mL on a mixed-meal (b) (4) test) and other changes made to improve comprehension and structure of the (b) (4) section.
4 CONTRAINDICATIONS	Contraindicated Tzield in patients with preexisting immunodeficiency.
5 WARNINGS AND PRECAUTIONS	Updated to include rates of events occurring in the PROTECT study
6 ADVERSE REACTIONS	Updated to improve communication of adverse event analyses including recommending the Sponsor adjust Table (b) (4) to include the placebo-controlled pool for adverse event reporting
7 DRUG INTERACTIONS	No changes.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females	Updates to Geriatric use section to describe safety and efficacy findings in adults.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to the Applicant's Draft PI
and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	
10 OVERDOSAGE	No changes.
12 CLINICAL PHARMACOLOGY	Reverted the revised EPC proposed by the Applicant in the Highlights Section to original proposed EPC due to (b) (4).
13 NONCLINICAL TOXICOLOGY	
14 CLINICAL STUDIES	Updated to include the PROTECT study design and clinical trial findings along with many revisions to improve the presentation of information in the clinical trials, recommendations for the Sponsor to include subgroup efficacy analyses and provide more details regarding the baseline disease and demographic characteristics for the PROTECT trial.
17 PATIENT COUNSELING INFORMATION Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	No changes.

Source: Reviewer comparison of proposed labeling that is planned to be sent to the Applicant in initial labeling negotiations as of February 26, 2026
[1] Product quality sections (Sections 3, 11, and 16) are not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. Abbreviations: EPC, Established Pharmacologic Class; PI, Prescribing Information; T1D, type 1 diabetes.

9 Risk Evaluation and Mitigation Strategies

No risk evaluation and mitigation strategy is required for this indication.

10 Postmarketing Requirements and Commitment

The following PMRs and PMCs were issued at the time of the original BLA approval on November 17, 2022, for the Stage 2 T1D indication:

Table 8. Clinical Postmarketing Requirements Issued at the Time of the Original BLA Approval

PMR #	Study Type & Description	Key Milestones
4359-1	PREA Pediatric Study, PRV-031-005 (PETITE-T1D) • Safety and PK study in pediatric patients 0 to <8 years with Stage 2 T1D (12-month study +12-month extension)	• Part A Final Report: April 2026 • Part B Final Report: April 2027

PMR #	Study Type & Description	Key Milestones
4359-2	Long-Term Safety Registry, OBS18117 • 10-year observational registry (≥150 patients) to assess CRS, infections, hypersensitivity, lymphoproliferative disorders, malignancy, and pregnancy outcomes with comparator group	Annual interim reports • Final Report: September 2037
4359-3	Comparative Safety Study • Clinical study reports for PROTECT and PROTECT Extension studies comparing commercial formulation vs. clinical trial product	• PROTECT Final Report: November 2023 • Extension Final Report: May 2027

Abbreviations: CRS, cytokine release syndrome; PK, pharmacokinetics; PMR, postmarketing requirement; PREA, Pediatric Research Equity Act; T1D, type 1 diabetes

The Pediatric Research Equity Act requirement for the deferred pediatric age group (0 to <8 years) is being addressed through PMR 4359-1, a 12-month single-arm, open-label study assessing safety and pharmacokinetics in this population, followed by a 12-month open-label extension. The Part A interim analysis was submitted in April 2026, with the final Part B report scheduled for submission in April 2027.

The chemistry, manufacturing, and controls-related postmarketing commitments (PMCs 4359-4 through 4359-8) that were established at original approval have been completed or are nearing completion and do not impact the clinical assessment of this efficacy supplement. Routine pharmacovigilance measures, including adverse event reporting and the ongoing safety registry (PMR 4359-2), are considered adequate to monitor for potential safety signals in the expanded Stage 3 T1D population, and no additional postmarketing requirements or commitments specific to this supplement are needed at this time.

Additionally, the Applicant has committed to conduct a postmarketing study (EFC18241) designed to confirm the clinical benefit of teplizumab in the Stage 3 T1D population. This confirmatory study will address remaining uncertainties about the extent and durability of clinical benefit in patients with established Stage 3 disease, using primary endpoints of A1C change from baseline and total days without prandial insulin use.

11 Appendices

11.1 References

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Guidances for Industry

FDA Guidance for Industry *Accelerated Approval – Expedited Program for Serious Conditions* (December 2024)

FDA Guidance for Industry *Financial Disclosure by Clinical Investigators* (February 2013)

FDA Guidance for Industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018)

11.2 Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators.

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 543		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10		
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: 10 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 9. Listing of Clinical Trials Relevant to this sBLA

Clinical Study Phase & Dates	Study Population & Sample Size	Study Design/Type of Control	Dosing Regimen	Follow-Up Duration
Stage 3 T1D Population				
PROTECT Phase 3 April 2019 to May 2023	Age 8 to 17 years Stage 3 T1D (within 6 weeks of dx) Enrolled total: 328 (217:111)	R, DB, placebo controlled. Randomization ratio: 2:1	12-day regimen; total dose 9.0 mg/m^2 per course	Two identical courses, 26 or 52 weeks apart 78 weeks
Study 1 Phase 1/2 May 1999 to August 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[a]; Single course total dose 0.5 mg/kg 12-day regimen; total dose ~19.5 mg/m^2	2 years
Protégé Phase 2/3 February 2007 to June 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	Two courses, 26 weeks apart • **Segment 1:** Full 14-day regimen • **Segment 2:** – **Arm 1:** Full 14-day; total dose ~9.0 mg/m^2 – **Arm 2:** 1/3 dose 14-day; total dose ~3.0 mg/m^2 – **Arm 3:** 6-day; total dose ~2.4 mg/m^2 – **Arm 4:** Placebo 14-day course	2 years
Encore Phase 3 September 2009 to April 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	89.8% completed 1 year and 29.1% completed 2 years
AbATE Phase 2 September 2005 to April 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	Two courses, 1 year apart Full 14-day regimen; total dose ~9.0 mg/m^2	2 years

Clinical Study Phase & Dates	Study Population & Sample Size	Study Design/Type of Control	Dosing Regimen	Follow-Up Duration
Delay[3] Phase 2 September 2006 to August 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	Single course, Full 14-day regimen; total dose ~9.0 mg/m^2	Single course 1 year
Stage 2 T1D Population				
TN-10 (At-Risk Study) Phase 2 July 2011 to November 2018	Age ≥8 years Relatives of T1D patients at high risk with ≥2 positive autoantibodies and abnormal OGTT Enrolled total: 76 (44:32)	R, DB, PBO controlled, 2-arm, multicenter study Randomization ratio: 1:1	Single course, Full 14-day regimen; total dose ~9.0 mg/m^2	Median duration approximately 2 years[4]

Source: Reviewer adapted from ISS and ISE
A 28 participants received second course 52 weeks apart ("modified dosing regimen" due to COVID19 pandemic)
B Where listed, the Full 14-day regimen is a daily IV infusion of the following doses: 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, Total dose ~9034 µg/m2
C 18 Delay subjects initially randomized to the control arm, who were later also eligible for the open-label Course 2 administration of teplizumab, for the Applicant's analysis are counted once for each treatment arm and once in the total column of subject count, for FDA's safety analyses (fISS), these 18 subjects have not been included due to open-label treatment
D Follow-up time defined by time to protocol-specified number of T1D events observed
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; PBO, placebo; R, randomized; T1D, type 1 diabetes

11.3 Glossary

A1C	glycated hemoglobin
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
AUC	area under the curve
AWC	adequate and well-controlled
BLA	biologics license application
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CMV	cytomegalovirus
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EBV	Epstein-Barr virus
ECG	electrocardiogram
FDA	Food and Drug Administration
HLA	Human Leukocyte Antigen
IND	Investigational New Drug
ISE	integrated summary of efficacy
ISS	integrated summary of safety
IV	intravenous
LGG	low-grade gliomas
LPD	lymphoproliferative disorder
LS	least squares
LSM	least squares mean
MDS	modified dosing schedule
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MMTT	mixed-meal tolerance testing
NAb	neutralizing antibody
OCP	Office of Clinical Pharmacology
PCR	polymerase chain reaction
PD	pharmacodynamic

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient-reported outcome
PT	preferred term
PY	patient-year
RLSE	reasonably likely surrogate endpoint
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologic licensing application
SEE	substantial evidence of effectiveness
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes
TEAE	treatment-emergent adverse event
TIR	time in range
ULN	upper limit of normal
WBC	white blood cells

11.4 Appendix

Table 10. Narrative Review of Individual DKA Events in Teplizumab-Treated Patients With Stage 3 T1D

Patient Characteristics	Study	# of Courses*	Characteristics of DKA Event	Days After Last Teplizumab Dose	Insulin Dose Available?
11y male, U.S., full 14-day regimen	AbATE	2	Insulin pump malfunction	265	Yes, lowered
9y female, U.S., full 14-day regimen	Delay	2	Insulin pump malfunction, history of 2 prior pump malfunctions	296	No
14y male, U.S., 6 day curtailed	Encore	1	Noncompliance with insulin	573	No
12y female, India, 6 day curtailed	Encore	2	Noncompliance 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 second course of teplizumab, followed until 538 days after Course 2	34	No
26y male, India, ⅓ dose regimen	Encore	2	Weakness and weight loss x 1 month prior to hospitalization, no source of infection in narrative but treated with antibiotics (merepenem, amikacin, amoxicilin)	352	No
15y female, U.S., full 14-day regimen	Protégé	2	Infection, pyelonephritis	307	No
14y female, U.S., 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

Patient Characteristics	Study	# of Courses*	Characteristics of DKA Event	Days After Last Teplizumab Dose	Insulin Dose Available?
14y female, India, ⅓ 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, ⅓ dose regimen	Protégé	1	Infection: Renal abscess and sepsis	394	No
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 noncompliance 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, ⅓ 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

Patient Characteristics	Study	# of Courses*	Characteristics of DKA Event	Days After Last Teplizumab Dose	Insulin Dose Available?
10y female, India, full 14-day regimen	Protégé	1	Reportedly skipped insulin dose for the day. Note: this patient completed second 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: DKA, diabetic ketoacidosis; F, female; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; M, male; UTI, urinary tract infection

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/s/

LAUREN K WOOD HEICKMAN
03/19/2026 11:56:25 AM

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Office of Clinical Pharmacology Review

NDA/BLA Number	BLA 761183/S-010
Link to EDR	\\CDSESUB1\evsprod\BLA761183\0145
Submission Date	7/21/2025
Submission Type	Efficacy supplement, Commissioner's National Priority Voucher Pilot Program
Brand Name	Tzield
Generic Name	Teplizumab-mzwv
Dosage Form and Strength	Injection, 1 mg/mL
Route of Administration	Intravenous infusion
Proposed Indication	**Approved**: 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 **Proposed new indication**: to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D
Applicant	Provention Bio, Inc.
Associated IND	102629 and 100262
OCP Review Team	Dong Guo, Ph.D., Elyes Dahmane Ph.D., Justin Earp Ph.D., Harisudhan Thanukrishnan Ph.D., Jayabharathi Vaidyanathan Ph.D., Hao Zhu Ph.D.
OCP Final Signatory	Jayabharathi Vaidyanathan Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Teplizumab (TZIELD®) has been approved for the delay of onset of Stage 3 Type 1 Diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D. In the current efficacy supplement, the Applicant is seeking to expand the indication for delaying the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D, under accelerated approval pathway based on c-peptide as a reasonably likely surrogate marker of clinical benefit. In the single main study PROTECT (PRV-031-001) supporting this indication, the change from baseline in C-peptide area under the curve (AUC) was evaluated at Week 78 by 4-hour mixed meal tolerance test (MMTT) as the primary endpoint.

In addition to PROTECT, the Applicant submitted a meta-analysis of changes in c-peptide AUC from studies in Stage 3 T1D such as Protégé (CP-MGA031-01), Encore (CP-MGA031-03), AbATE (ISCT-MGA031-003, ITN027AI, Study 4), Delay (ISCT-MGA031-001, Study 5) and Study 1 (ISCT-MGA031-001) as supportive evidence (refer to clinical review for details).

The Applicant submitted the updated population pharmacokinetics (popPK) report after incorporating the PK and immunogenicity data from PROTECT. The clinical pharmacology review of this supplement application focused on evaluating the proposed dose in the new indication with the to-be-marketed (TBM) product, the appropriateness of the proposed dosing schedule (i.e., two courses; Course 2 was given at 6 or 12 months after Course 1) and on assessing the immunogenicity effect on exposure and efficacy.

The proposed dosing regimen to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D is ~ 9 mg/m^2 administered in two identical courses, each for 12 consecutive days with at least 30 minutes of intravenous infusion on each day as follows: Day 1: 106 mcg/m2, Day 2: 425 mcg/m2, and Day 3 through 12: 850 mcg/m2. The proposed dose regimen was the only regimen evaluated in the pivotal phase 3 study (PROTECT) and demonstrated efficacy in preserving C-peptide (refer to statistical review for detailed efficacy evaluation).

Two products were used in the pivotal phase 3 study, PROTECT: manufactured by Eli Lilly (referred as Lilly product thereafter) and by AGC Biologics (referred as AGC product thereafter). AGC product was introduced to the study later and is the TBM product. Despite the lower exposure for AGC product as compared to the Lilly product, subgroup analysis in patients administered AGC product in two courses (referred as AGC/AGC, n=57) demonstrated statistically significant preserved C-peptide relative to placebo (n=32) with a least square mean difference (95% CI) of 0.1300 (0.0625, 0.1976). A similar magnitude in C-peptide change was observed from baseline to Week 78 as those treated with two courses of the Lilly product (referred as Lilly/Lilly, n=72) relative to placebo (n = 30) with a least square mean difference (95% CI) of 0.1489 (0.0888, 0.2091). Therefore, the clinical pharmacology review team concludes that the proposed dose is appropriate for the TBM product (produced by AGC Biologics).

Due to COVID-19 pandemic restrictions, some patients who were unable to receive the second 12-day course at Month 6 were given the second course on approximately Day 364 (Week 52 visit). The

subgroup analysis showed a statistically significant difference in change in C-peptide from baseline to Week 78 compared to placebo, with the least square mean difference (95% CI) between teplizumab modified dosing regimen, i.e., second course ~ Day 364, (N=16) and placebo (N=12) being 0.1663 (0.0299, 0.3028).

Following completion of both courses, nearly all participants (98%) in study PROTECT developed anti-drug antibodies (ADAs), of whom 77% also developing neutralizing antibodies (NAbs). Both the maximum ADA titer and ADA titers at individual time points after dosing were higher after Course 2 compared to Course 1. This boost in ADA titers and NAbs after Course 2 were associated with lower observed mean pre-dose teplizumab concentrations (Days 9 and 12 post-dose) and lower predicted serum exposures for teplizumab in Course 2 than in Course 1. There were no apparent differences in the change in C-peptide AUC over time, from baseline based on the ADA titers or NAb status.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the BLA 761183 supplement 10 and recommends approval of two 12-day courses of teplizumab given 6 months apart for delaying the progress of Stage 3 T1D in pediatric patients aged 8 to 17 years of age with Stage 3 T1D based on the results from PROTECT study. The recommended dosing regimen is as follows: Daily intravenous infusions over at least 30 minutes on Day 1: 106 mcg/m2, Day 2: 425 mcg/m2, and Day 3 through 12: 850 mcg/m2.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Background and Regulatory History

Teplizumab (PRV-031) is a 150 kiloDalton (kDa) humanized immunoglobin G1 (IgG1) monoclonal antibody (mAb) that specifically recognizes the CD3ε chain of the T-cell receptor complex on human T cells. The initial drug substance (DS) was manufactured by MacroGenics from 2005-2008, which continued in partnership with Eli Lilly for another year and later, the DS was solely manufactured by Eli Lilly until 2011. After 2018, the Applicant updated manufacturing process to a new facility operated by AGC Biologics.

The initial BLA (BLA 761183) for TZIELD® (teplizumab) was submitted to FDA in November 2020 for the delay of onset of Stage 3 T1D in adults and pediatric patients aged 8 years and older with Stage 2 T1D with data from the pivotal phase 3 study in Stage 2 T1D (Study TN-10). The complete response letter issued by the FDA in July 2021 due to lack of PK comparability between the teplizumab product used in TN-10 and the planned commercial product (data from PK bridging study in healthy subjects, Study PRV-031-004). The BLA resubmission was received in February 2022 with additional PK and PD data from a sub study of the PROTECT study to evaluate the difference in exposure between the planned commercial product (AGC product) and Eli Lilly product that was used in the TN-10 study. BLA 761183 was approved on 17 November 2022 with a newly proposed dosing regimen that recommended higher doses of the AGC product in order to match the exposures resulting from the Eli Lilly product. Refer to

section 2 of the clinical pharmacology review of the re-submission in DARRTS (Reference ID: 5063936) for the detailed regulatory history of the original submission and re-submission.

2.2 Regulatory Interactions Prior to Supplementary Submission

The FDA held multiple meetings with the sponsor regarding teplizumab's development pathway for delay the progression of Stage 3 T1D from December 2018 through December 2024. In December 2018 at the Type B End of Phase 2 meeting, FDA agreed with the PROTECT study design and accepted C-peptide AUC as a reasonably likely surrogate endpoint, recommending one adequate study plus confirmatory evidence could support approval.

Following PROTECT study completion, the August and September 2023 pre-sBLA meetings revealed a critical issue: while PROTECT met its primary C-peptide endpoint, it failed to demonstrate statistical significance on key secondary clinical endpoints including insulin use, HbA1c, hypoglycemia, and time-in-range. The sponsor initially sought traditional approval (b) (4) but FDA determined this data package was insufficient.

FDA concluded that PROTECT's results do not meet traditional approval standards because the study showed superiority only on a reasonably likely surrogate endpoint (C-peptide) rather than a clinical endpoint or validated surrogate endpoint. The agency noted that C-peptide has not been validated as a surrogate endpoint for clinical benefits in this patient population.

Consequently, FDA recommended the accelerated approval pathway as the most appropriate route, which would require a post-market confirmatory study to verify clinical benefit.

2.3 General Pharmacology and Pharmacokinetics Characteristics

The general pharmacology and pharmacokinetic characteristics of teplizumab were summarized in Section 3.2 of the Clinical Pharmacology review for the original BLA (DARRTS Reference ID: 4788416). The PK parameters, immunogenicity, and half-life of teplizumab in patients with Stage 3 T1D from study PROTECT are summarized below.

- The overall mean serum concentrations at each time point except Day 4 and simulated PK parameters (i.e., AUC_{0-inf}, C_{max}, AUC_{0-13}, and C_{trough}) of teplizumab were lower in Course 2 compared with Course 1. This was likely due to the presence of ADA.
- The mean serum concentrations and simulated PK parameters (i.e., AUC_{0-inf}, C_{max}, AUC_{0-13}, and C_{trough}) of teplizumab were higher in participants who received the Eli Lilly product than those who received the AGC Biologics product at each time point.
- ADA incidence, NAb incidence, and ADA titers increased after each treatment course and decreased over time.
- The ADA titers and neutralizing antibody incidence were higher in Course 2 than Course 1.

2.3.1 General dosing

The applicant has proposed two identical 12-day courses of teplizumab administered as a daily IV infusion over 30 minutes. In each course, patients will receive doses of 106 μg/m^2 on Day 1, 425 μg/m^2 on Day 2, and 850 μg/m^2 on each of Days 3 through 12 for a total cumulative dose of 9034 μg/m^2 (~9 mg/m^2). Less than 10% of the total dose is given as a precaution to avoid adverse reactions associated with CD3-engagement. The 2nd course is recommended to be administered 6 months after the first treatment course but may be given up to 12 months after the first treatment course (Refer to Section 3.1).

2.3.2 Therapeutic individualization

No therapeutic individualization is warranted for teplizumab based on intrinsic or extrinsic factors. Teplizumab is expected to be catabolized into smaller peptides. Refer to the clinical pharmacology review of the original BLA submission (Reference ID: 4788416).

2.4 Outstanding Issues

None.

2.5 Summary of Labeling Recommendations

Section 2.2: We recommend adding the underlined words to clarify that the up to 12-month timeframe is only applicable when the preferred 6-month interval after the first course is missed: "Administer the second 12-day treatment course 6 months after the first treatment course. If the second course is delayed, administer the second course within 6 to 12 months after the first treatment course."

Section 12.2: Pharmacodynamics (CD3 receptor occupancy and lymphocyte count) were evaluated in the previously submitted PROTECT PK/PD substudy and were reviewed in the previous cycle (refer to section 4.2 of the previous clinical pharmacology review for resubmission, Reference ID: 5063936), which supports the proposed underlined addition to section 12.2: "Pharmacodynamic effects include lymphopenia in the absence of depletion of T cells with a nadir (b) (4) approximately on the 5th day of dosing, during a 14-day course (Stage 2) or 12-day course (Stage 3) of TZIELD treatment".

Section 12.6: The effect of immunogenicity on pharmacokinetics will be included, as sufficient data are available: "Following the second course, ADA titers and neutralizing activity are higher, and geometric mean teplizumab-mawv AUC (b) (4) and Ctrough after the last dose were lower by 51% and 81%, respectively, compared to those in first course."

3. CLINICAL PHARMACOLOGY REVIEW QUESTIONS

3.1 Is the proposed dose regimen for the to-be-market product (manufactured by AGC) appropriate in patients with Stage 3 T1D?

The Applicant's proposed dosing regimen to delay the progression of Stage 3 T1D in pediatric patients 8 to 17 years of age recently diagnosed with Stage 3 T1D is two identical courses of 12 consecutive days of intravenous infusion as follows: Day 1: 106 mcg/m^2, Day 2: 425 mcg/m^2, and Day 3 through 12: 850 mcg/m^2. Each course has a total cumulative teplizumab dose of 9034 μg/m^2 (~9 mg/ m^2). The second course is recommended at 6 months after the first course but may be given up to 12 months after the first treatment course.

This dose is proposed for the indication to delay the progression of Stage 3 T1D and was tested in the pivotal phase 3 study (Study PROTECT) where participants 8 through 17 years old who had been recently diagnosed with T1D (within 6 weeks of a T1D diagnosis) and who had a significant amount of β cell functional capacity (peak C-peptide ≥0.2 pmol/mL during MMTT). This dose regimen demonstrated statistically significant treatment effect relative to placebo in maintaining C-peptide levels from baseline to week 78 in the Intent to Treat (ITT) population (see Statistical and Clinical reviews for detailed efficacy evaluation).

Two products were used in the pivotal phase 3 study, PROTECT: manufactured by Eli Lilly (referred as Lilly) and by AGC biologics (referred as AGC). AGC product was introduced to the study later and is the to-be-market (TBM) product. As the TBM product was used in the pivotal phase 3 study to support treatment in Stage 3 T1D, the exposure and efficacy between these two products could be compared.

The observed mean serum concentrations of teplizumab were about 14% to 40% higher in participants who received the Eli Lilly product than those who received the AGC Biologics product at each time point in Course 1 and Course 2. This was consistent with the previous submission, where the AGC product was estimated to have about 27% lower exposure than the Lilly product after 12-days dosing based on population PK analysis using PROTECT data. The predicted PK parameters following updated popPK model with full data from study PROTECT incorporated shows similar results (Table 1). To note, for both products, the overall mean serum concentrations of teplizumab were somewhat lower in Course 2 compared with Course 1 at each time point. The ADA titer was higher after Course 2 compared to Course 1 and higher ADA titer may have led to lower observed serum teplizumab concentration in Course 2. PopPK model found that teplizumab clearance increased linearly with ln of time-varying ADA titer (Refer to Section 4.2.1).

Table 1. Summary of Predicted Exposure Parameters in Course 1 and Course 2 by Product (Study PROTECT)

exposure measure	Course 1			Course 2		
	AGC (N=65)	Lilly (N=147)	AGC vs Lilly GMR (90% CI)	AGC (N=122)	Lilly (N=66)	AGC vs Lilly GMR (90% CI)
AUCinf (ng/mL×day)	4054 (0.51)	5194 (0.59)	0.780 (0.690-0.883)	1969 (1.32)	2543 (1.44)	0.774 (0.598-1.00)
Cmax (ng/mL)	741 (0.26)	840 (0.2)	0.883 (0.833-0.937)	588 (0.33)	621 (0.38)	0.947 (0.87-1.03)
AUC0-13 (ng/mL×day)	2651 (0.61)	3183 (0.65)	0.833 (0.721-0.961)	1552 (1.09)	1994 (1.16)	0.778 (0.62-0.976)
Ctrough Day 4[a] (ng/mL)	57.4 (0.39)	73.3 (0.51)	0.783 (0.700-0.875)	70.1 (0.66)	81.3 (0.64)	0.862 (0.742-1.00)

Ctrough Day 9[a] (ng/mL)	209 (0.31)	264 (0.43)	0.789 (0.717-0.869)	105 (1.84)	147 (2.38)	0.712 (0.513-0.988)
Ctrough Day 12[a] (ng/mL)	259 (0.45)	333 (0.73)	0.777 (0.669-0.903)	62 (3.53)	103 (3.96)	0.599 (0.395-0.910)
Ctrough Last (ng/mL)	266.4 (0.47)	364.7 (0.48)	0.731 (0.654-0.816)	52.4 (4.36)	83.4 (4.92)	0.628 (0.403-0.977)

Source: reconstructed from Table 20, 21, and 22 on page 142-144 of Study PROTECT CSR.
Abbreviations: AUCinf=area under the concentration-time curve from zero to infinity, AUC0-13=AUC over the dosing interval from zero to one day after the last administered dose, Cmax=maximum concentration, Ctrough Last=concentration 24 hours after the last dose, CV=coefficient of variation, PK=pharmacokinetic, SD=standard deviation.
Note: Total AUC for 128 days from dosing start was used as AUCinf. CV computed for a lognormal distribution as sqrt(exp(var(log(data)))-1). The AGC/Lilly GMR was computed using t-test with equal variances as determined by the median-based Levene's test except AUCinf, Cmax and Ctrough last which were computed using t-test with unequal variances as determined by the median-based Levene's test.
a: For Course 1: N=145 on Day 4 and Day 12, and 143 on Day 9 for Eli Lilly product; N=63 and 62 on Days 9 and 12, respectively, for the AGC product; For Course 2: N=58 and 57 on Days 9 and 12, respectively, for Eli Lilly product; N=109 and 106, respectively for the AGC product.

Despite the lower exposure for AGC product, patients administered AGC in two courses (referred as AGC/AGC) showed benefit relative to placebo in maintaining C-peptide levels with the least square mean (LSM) different between AGC/AGC treatment and placebo of change in C-peptide ln(AUC+1) from baseline to Week 78 as 0.1300 (95% CI: 0.0625, 0.1976, P< 0.001, n=32 for placebo, n=57 for AGC/AGC) by analysis of covariance (ANCOVA) including treatment, age group at randomization and baseline C-peptide ln(AUC+1) as independent variables. In addition, the patients treated with Lilly in both courses (referred as Lilly/Lilly) also showed similar efficacy as those treated with AGC/AGC, with the similar LSM different between Lilly/Lilly treatment and placebo change in C-peptide ln(AUC+1) from baseline to Week 78: 0.1489 (95% CI: 0.0888, 0.2091, P< 0.001, n=30 for placebo, n=72 for Lilly/Lilly). Refer to Statistical and Clinical reviews for detailed information.

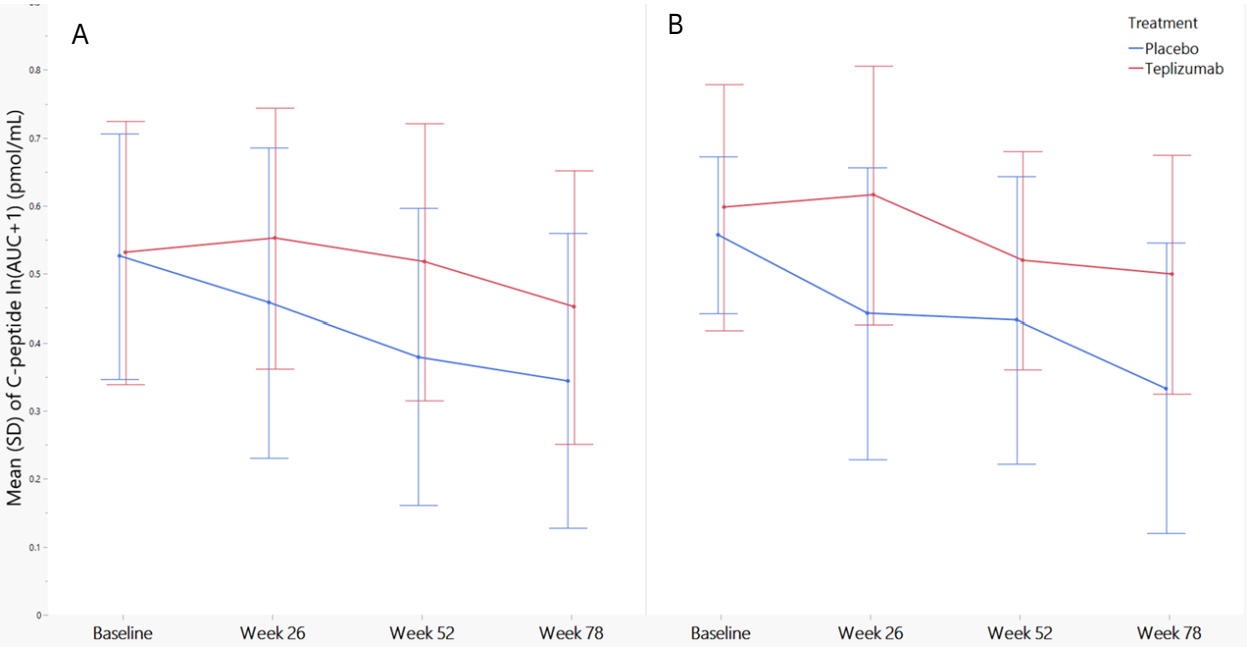
These results suggest that the dose used in the phase 3 study (study PROTECT) is appropriate for the TBM product to delay the progression of Stage 3 T1D in pediatric patients 8 -17 years of age recently diagnosed with Stage 3 T1D.

The Applicant proposed timing of the second course in the label is "Administer the second 12-day treatment course 6 months after the first treatment course (b) (4) 12 months after the first treatment course." This proposal was based on the pivotal phase 3 study (Study PROTECT) in patients with Stage 3 T1D. Initially, the 2nd course in Study PROTECT was planned to be administered at 6 months after the first treatment course which was proposed based on the safety and efficacy data from protégé study where the two teplizumab courses were separated 6 months apart.

Due to COVID-19 pandemic restrictions, some patients who were unable to receive the second 12-day course were given the second course on approximately Day 364 (Week 52 visit). There was a total of 28 (8.5% out of 328) patients who received the 2nd course at Week 52, with 12 (10.8% out of 111) and 16 (7.4% out of 217) patients randomized to placebo and teplizumab treatment groups, respectively. The primary endpoint for all patients was at Week 78 regardless of when the second course was administered. For patients who received the second course at Day 364, the C-peptide data were collected at 6 months after the second course as compared to the one year for patients who received the second course at 6 months. Subgroup analysis shown statistically significant (P = 0.019) change in C-peptide from baseline to Week 78 with the LSM difference (95% CI) between teplizumab modified dosing regimen (N=16) and placebo (N=12) as 0.1663 (0.0299, 0.3028). In addition, similar trends in

mean C-peptide ln(AUC+1) in 4h MMTT over time were observed in participants who received the second course at Day 364 and those who received the second course at 6 months (Figure 1).

Figure 1. Mean (SD) of C-peptide ln(AUC+1) (pmol/mL) Over Time by interval between courses – Study PROTECT (A: second course at 6 months, B: second course at 12 months)



Source: Reviewers' analysis from admmtt.xpt of Study PROTECT

Though the sample size of the subgroup analysis is limited, the review team considers that the available evidence could support administration of the second course up to 12 months after the first course if the patient is unable to receive the second course at 6 months. Therefore, section 2.2 of the label will specify a 6-month interval between courses, with the provision that if the dose is missed, the second course can be given 6 to 12 months after the first course: "Administer the second 12-day treatment course 6 months after the first treatment course. If the second course is delayed, administer the second treatment course within 6 to 12 months after the first treatment course."

3.2 What is the immunogenicity and its effect on the PK and efficacy of teplizumab in Study PROTECT?

Incidences of anti-drug antibodies (ADAs) and Neutralizing antibodies (Nabs)

The incidence of ADA by course in study PROTECT were summarized for patients who received second course at 6 months and had at least one dose of study drug and one evaluable ADA or PK sample (full immunology analyses dataset, FAS) in Table 2. Since only 16 patients received the second course of teplizumab at 1 year instead of 6 months (modified dosing schedule (MDS)), the ADA/NAb status was not summarized by MDS versus non-MDS groups. Instead, ADA titer was summarized by MDS status.

After treatment initiation, the incidence of participants positive for ADAs peaked at Week 2 (87.4%) and decreased to 73.1% at Week 26 (Day 182) before the start of Course 2 treatment. After the initiation of Course 2 at Week 26, the incidence of participants positive for ADAs increase to 95.4% at Week 27 and decreased to 74.3% at Week 78 (Figure 2). No apparent difference between participants who received the Lilly product and the AGC product was observed in the percentage of participants with positive ADAs.

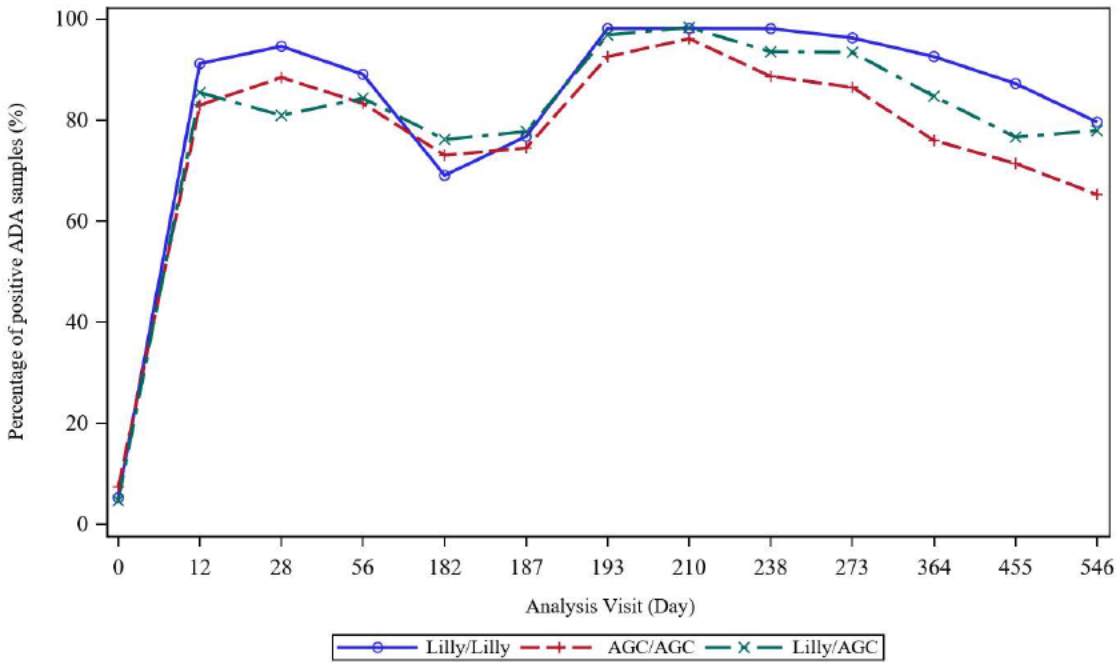
ADA titers over time for FAS (further stratified by product) and MDS were presented in Figure 3 and Figure 4, respectively. Similar to the incidence of ADA, the mean ADA titers for the FAS population appeared to increase after the start of each treatment course and decline over time after the end of treatment. In Course 1, ADA titers increased from baseline (1.84 log10) to Weeks 4-26 before the start of Course 2, when titers averaged 2.9 log10. In Course 2, mean titers peaked at Week 30 at approximately 4.01 log10. By Week 78, mean ADA titers for all participants declined to 2.74 log10. Similar trend was observed for MDS participants, mean ADA titers increased after the start of each treatment course and declined over time after the end of treatment. In Course 1, ADA titers increased from baseline (1.48 log10) to Week 26 (3.28 log10) and then declined to Week 52 (2.49 log10). In Course 2, mean titers peaked at approximately 4.32 log10. By Week 78, mean ADA titers for MDS participants declined to 3.58 log10. In general, the ADA titers are higher in Course 2 than Course 1 in both FAS (Figure 3) and MDS population (Figure 4). Among participants who received second course at 6 months, mean ADA titers at each collection time points were numerically higher in participants who received the AGC product in both courses (AGC/AGC) compared to those who received the Lilly product in both courses (Lilly/Lilly) (Figure 3). Due to the limited sample size within each product subgroup in MDS population, mean ADA titer plots were not further stratified by product.

Table 2. Summary of ADA status in Course 1 and 2 of PROTECT Study (Full Analysis Set)

Statistic	Teplizumab Lilly/Lilly	Teplizumab AGC/AGC	Teplizumab Lilly/AGC	Teplizumab All
	N=57	N=54	N=64	N=201
	n (%)	n (%)	n (%)	n (%)
Course 1				
n	57	54	64	201
Positive	56 (98.2)	50 (92.6)	62 (96.9)	189 (94.0)
Negative	1 (1.8)	4 (7.4)	2 (3.1)	12 (6.0)
Course 2				
n	57	54	64	175
Positive	56 (98.2)	53 (98.1)	63 (98.4)	172 (98.3)
Negative	1 (1.8)	1 (1.9)	1 (1.6)	3 (1.7)

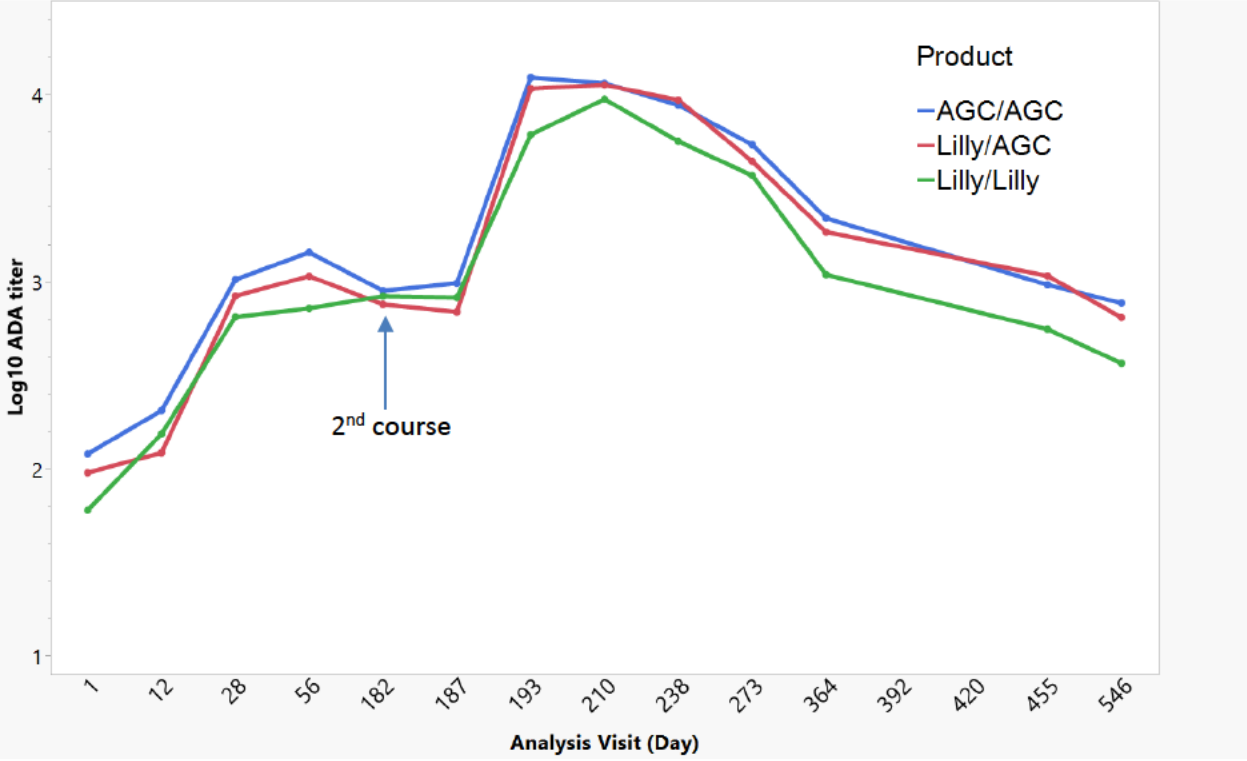
Source: Table 42 on Page 127 of integrated summary of immunogenicity-Stage3T1D

Figure 2. Proportion of participants with positive ADA samples over time - Full analysis set



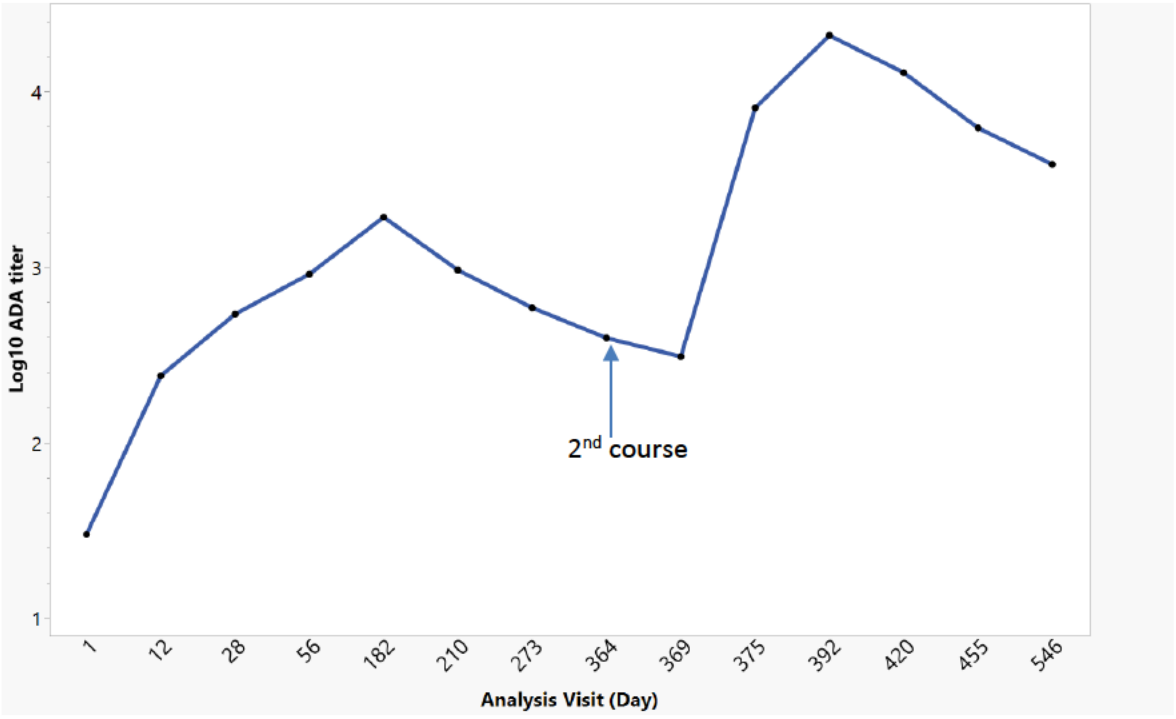
Source: Figure 37 on Page 127 of integrated summary of immunogenicity-Stage3T1D.

Figure 3. Mean ADA titers in Course 1 and 2 of PROTECT Study, by product- Full analysis set



Source: Reviewers' analysis from adis.xpt in ISI-Stage 3 T1D

Figure 4. Mean ADA titers in Course 1 and 2 of PROTECT Study- Modified Dosing Regimen Population



Source: Reviewers' analysis from adis.xpt in ISI-Stage 3 T1D

Blood samples that were positive for ADA were further tested for NAbs. NAb status by product is summarized in Table 3. A quantitative NAb assay has not been developed for teplizumab. Therefore, the summary table includes NAb results expressed as positive/negative rather than by NAb titers.

The proportion of ADA-positive participants who are NAbs positive generally increased from 3.0% at Week 2 to 59.9% at Week 8 and then decreased to 44.4% at Week 26 (Day 182). After the second course, the proportion of ADA-positive participants with NAb positivity further increased to 72.4% at Week 36 and decreased to 34.6% at the end of study at Week 78 (Figure 5). The proportion of participants who are NAbs positive was greater in Course 2 (76.7%) compared to Course 1 (54.0%) (Table 3). Participants who received the Lilly product in both courses (Lilly/Lilly) appeared to have a higher proportion of NAb positivity overall ($P < 0.01$) and after the second course ($P < 0.01$), but not after the first course, compared to those who received the AGC product in both courses (AGC/AGC) (Table 3). However, this difference in NAb incidence was not apparent when comparing Lilly/Lilly with AGC/AGC at individual time points (Figure 5).

Table 3. Summary of NAb status in Course 1 and 2 of Study PROTECT by Product (Full Analysis Set)

	Statistic	Teplizumab Lilly/Lilly N=57	Teplizumab AGC/AGC N=54	Teplizumab Lilly/AGC N=64	Teplizumab All N=201
Overall	N	57	53	63	194
	Positive	51 (89.5)	36 (67.9)	48 (76.2)	146 (75.3)
	Negative	6 (10.5)	17 (32.1)	15 (23.8)	48 (24.7)
Course 1	N	56	50	62	189
	Positive	28 (50.0)	30 (60.0)	33 (53.2)	102 (54.0)
	Negative	28 (50.0)	20 (40.0)	29 (46.8)	87 (46.0)
Course 2	N	56	53	63	172
	Positive	51 (91.1)	35 (66.0)	46 (73.0)	132 (76.7)
	Negative	5 (8.9)	18 (34.0)	17 (27.0)	40 (23.3)

Source: Table 2.1.6 on Page 32-34 of ISI-tables-jun2024.

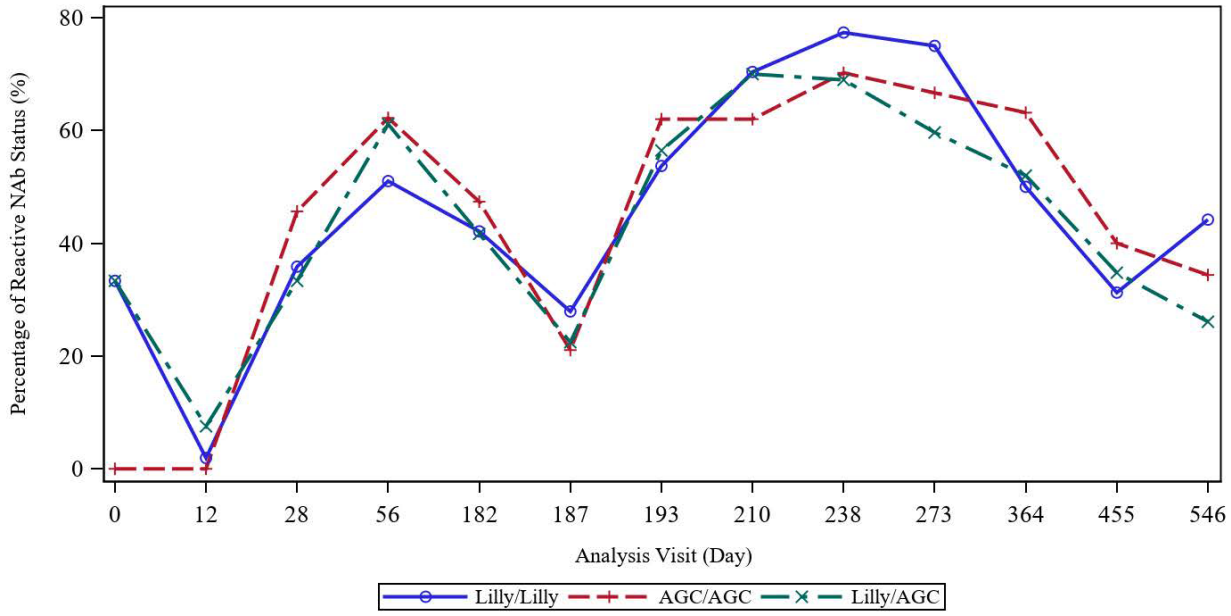
Note: NAb = Neutralizing Antibody

Note: Positive NAb status is defined as at least one positive sample at any timepoint in each course. Negative NAb status is defined as no positive samples and at least one negative sample at any time point in each course.

Note: Percentages are based on the number of non-missing observations in each treatment group.

Note: Subjects who only received Course 1 of teplizumab are included in the Teplizumab All group.

Figure 5. Proportion of participant with positive NAb samples over time (Full analysis set)



Source: Figure 53 on Page 148 of integrated summary of immunogenicity-Stage3T1D

Effect of immunogenicity on PK:

The following data supports that immunogenicity decreases teplizumab exposure in Course 2: a. comparison of observed concentrations between Course 1 and Course 2, b. observed concentrations

among different ADA titer groups, and NAb status, c. predicted exposure comparison between Course 1 and 2 using population pharmacokinetic analysis.

a. Observed concentrations comparison between Course 1 and Course 2

Regardless of the products used, compared to Course 1, Course 2 showed lower teplizumab concentrations on Days 9 (pre-dose), 12 (pre-dose) and 28 (Table 4), where ADA titers were generally higher than corresponding time points in Course 1 (Figure 4).

Table 4. Summary of Observed Teplizumab Serum Concentrations (ng/mL, PK population in study PROTECT)

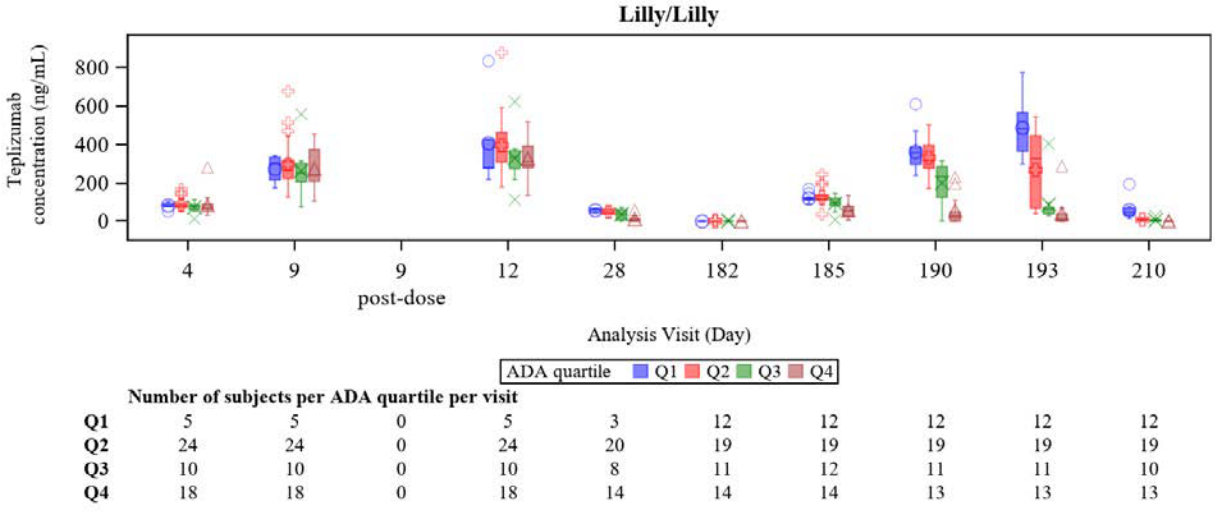
Time	Stat	Course 1			Course 2		
		Teplizumab All (N=217)	Teplizumab Lilly (N=151)	Teplizumab AGC (N=66)	Teplizumab All (N=123)	Teplizumab Lilly (N=66)	Teplizumab AGC (N=57)
Day 1	n	216	150	66	121	65	56
	Mean (SD)	0.22 (1.39)	0.26 (1.50)	0.14 (1.12)	0.33 (1.73)	0.53 (2.29)	0.10 (0.55)
Day 4	n	210	145	65	123	66	57
	Mean (SD)	78.54 (39.88)	86.75 (43.91)	60.23 (19.00)	96.45 (48.54)	105.60 (52.49)	85.85 (41.51)
Day 9	n	206	143	63	119	64	55
	Mean (SD)	276.67 (123.61)	296.32 (125.51)	232.08 (107.38)	199.70 (151.25)	236.88 (152.73)	156.43 (138.66)
Day 9 post-dose	n	59	14	45	N/A	N/A	N/A
	Mean (SD)	668.41 (221.72)	647.00 (129.81)	675.07 (244.20)	N/A	N/A	N/A
Day 12	n	208	145	63	121	64	57
	Mean (SD)	349.36 (164.37)	371.55 (162.70)	298.29 (157.86)	185.17 (199.57)	213.02 (211.08)	153.89 (182.58)
Day 28	n	186	126	60	118	63	55
	Mean (SD)	28.83 (23.05)	33.96 (24.22)	18.04 (15.76)	12.81 (23.24)	16.13 (29.47)	9.01 (12.06)

Source: reconstructed from Table 14.4.1.1 on page 1015-1021 of study PROTECT tables.pdf.
Abbreviations: CV = Coefficient of Variation (SD/Mean), GM = Geometric Mean, PK = Pharmacokinetic, SD = Standard Deviation
Note: For Course 1, subjects are classified under the product received in Course 1. For Course 2, subjects who were dosed in Courses 1 and 2 only with the Lilly product are classified under Lilly. Subjects who were dosed in Courses 1 and 2 only with the AGC product are classified under AGC. Subjects who dosed with both products are excluded from the Course 2 summary.
Note: The Pharmacokinetic (PK) population includes all randomized participants who received at least one dose of teplizumab with at least one valid pharmacokinetic sample.
Note: PK samples were collected prior to dosing except for Day 9 in Course 1. An additional PK sample was collected 45 minutes after infusion on Day 9 in Course 1.
Note: Concentration values below Lower Limit of Quantification (2.50 ng/mL) are set to zero for summary statistics.
Note: Course 2 day numbers were set relative to the first day of dosing, regardless of normal or modified dosing schedule.

b. Observed concentrations compared among ADA titer quantiles and Nab status

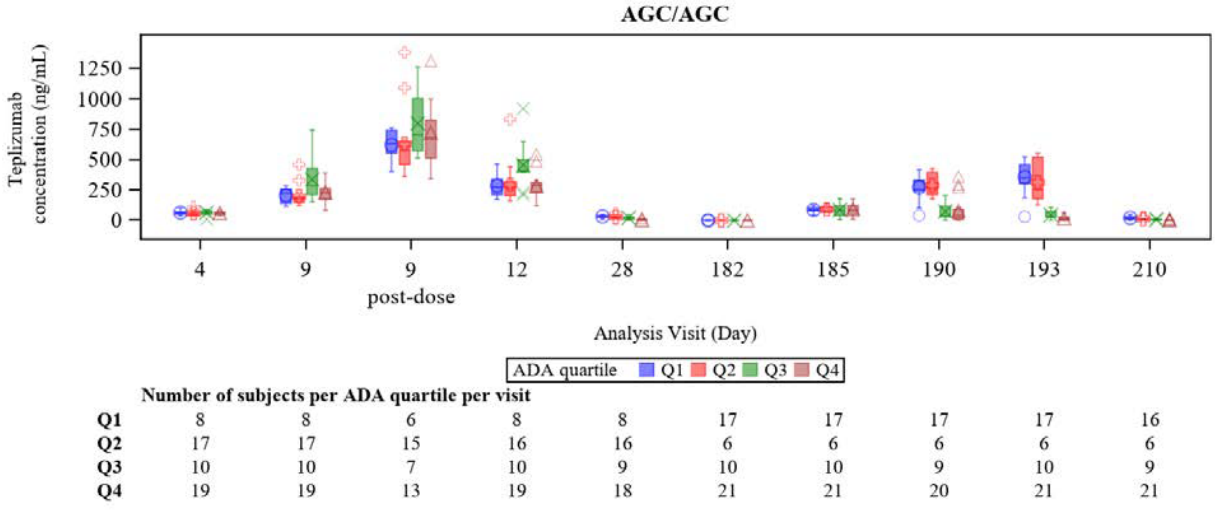
Since the majority of subjects were ADA positive after treatment, the effect of immunogenicity on PK and efficacy cannot be definitively concluded from ADA status alone. Therefore, the effect of immunogenicity on PK and efficacy was further evaluated by ADA titer. The ADA titer quantiles were defined based on the maximum ADA titer value for each subject by course in the PROTECT study. The effect of ADA titer on teplizumab concentration at Days 190 and 193 in Course 2 was demonstrated with higher ADA titers (Q3 and Q4) appearing to have a greater impact on reducing teplizumab concentrations for both Lilly and AGC products (Figure 6). For AGC/AGC, mean pre-dose teplizumab concentrations in participants with Q3 and Q4 ADA titers were ~30% of Q1 ADA participants at Day 190 [Q3: 73.0 ng/mL (n=9), Q4: 77.0 ng/mL (n=20) vs Q1: 272.0 ng/mL (n=17)] and 12% and 5%, respectively, at Day 193 [Q3: 43.3 ng/mL (n=10), Q4: 16.3 ng/mL (n=21) vs Q1: 357.0 ng/mL (n=17)].

Figure 6. Box plots of PK concentrations (ng/mL) over time by maximum ADA titer quartile and by product (Full Analysis Set)



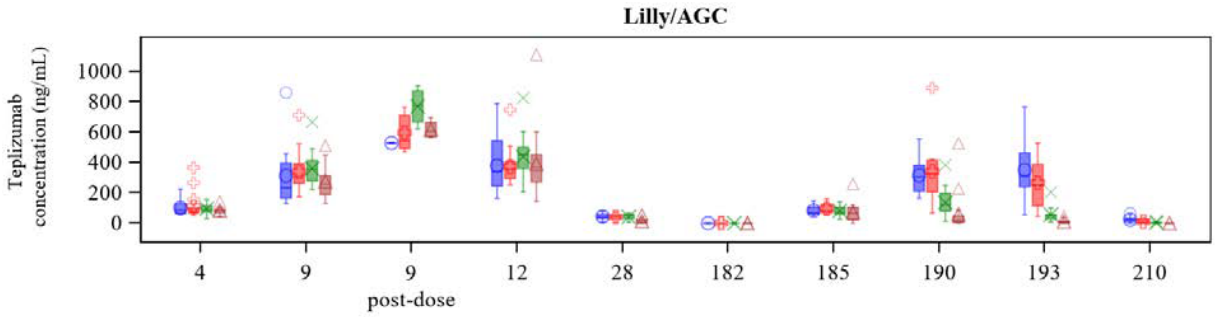
Number of subjects per ADA quartile per visit

Q1	5	5	0	5	3	12	12	12	12	12
Q2	24	24	0	24	20	19	19	19	19	19
Q3	10	10	0	10	8	11	12	11	11	10
Q4	18	18	0	18	14	14	14	13	13	13



Number of subjects per ADA quartile per visit

Q1	8	8	6	8	8	17	17	17	17	16
Q2	17	17	15	16	16	6	6	6	6	6
Q3	10	10	7	10	9	10	10	9	10	9
Q4	19	19	13	19	18	21	21	20	21	21



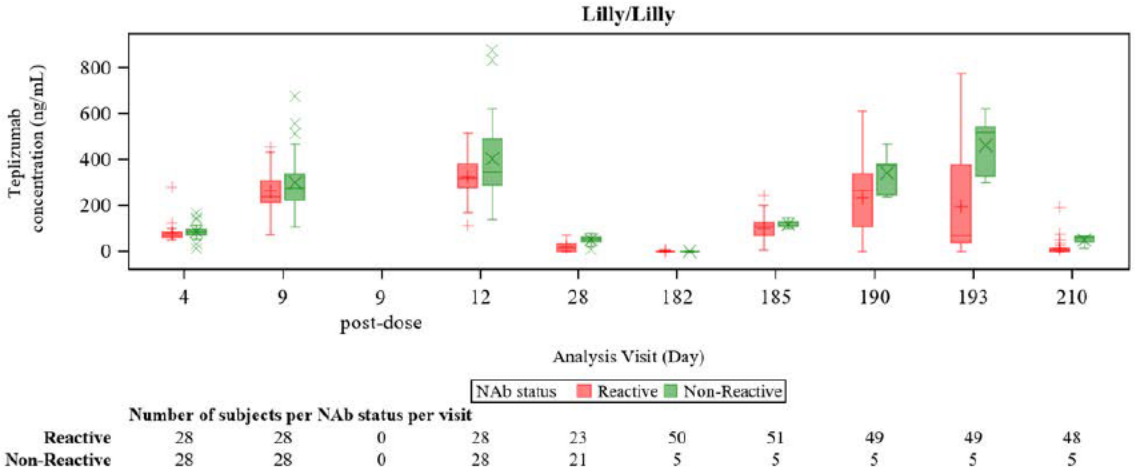
Number of subjects per ADA quartile per visit

Q1	11	11	1	11	10	16	16	14	16	15
Q2	17	17	5	16	16	12	12	11	12	11
Q3	15	16	4	16	15	15	15	15	15	14
Q4	20	19	4	20	20	21	21	21	21	21

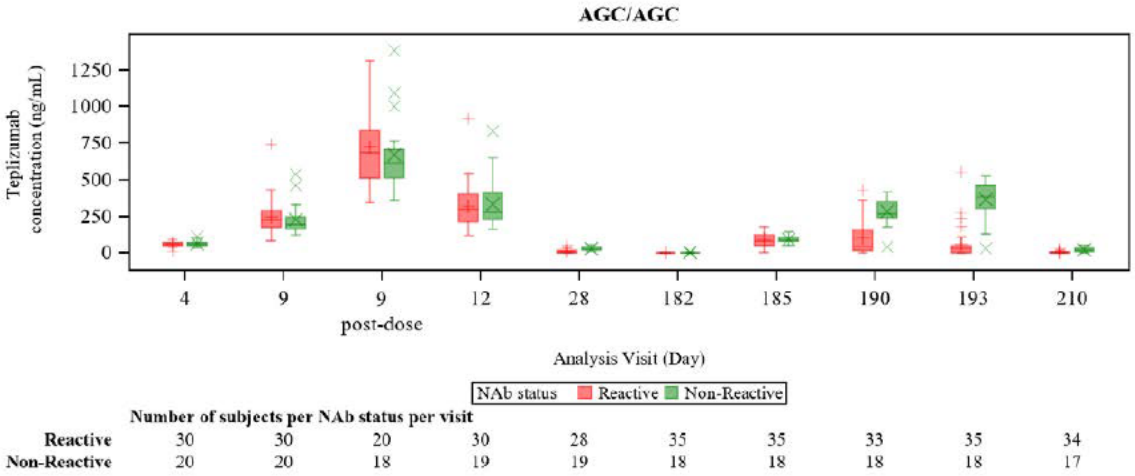
Source: Figure 3.1.3 on Page 12 of ISI-figures-12jun2024.
Note: Concentration values below Lower Limit of Quantitation (2.50 ng/mL) are set to zero for summary statistics.
Note: PK samples were collected prior to dosing. An additional PK sample was collected 45 minutes after infusion on Day 9 in Course 1. Pre-dose PK samples on Day 1 are not displayed.
Note: Quartiles of the ADA titer are based on the maximum ADA titer values (log 10 scale) of subjects within each course.
Note: Course 1 – Q1 < 2.08, Q2 [2.08, 2.98), Q3 [2.98, 3.58), Q4 >= 3.58. Course 2 – Q1 < 3.28, Q2 [3.28, 4.49), Q3 [4.49, 5.09), Q4 >= 5.09.

Similar to the observed effect of ADA titers on PK in Course 2, participants with NAbs had lower average teplizumab concentrations compared to participants without NAbs at Days 190 and 193 in Course 2 (Figure 7). However, since the teplizumab concentration assay employed an anti-idiotype antibody for detection, the Applicant stated that lower teplizumab concentrations could be caused by assay interference from NAbs in the teplizumab PK assay. A consultation request was sent to OCP Therapeutic Biological Program (TBP) team. The TBP team concluded that NAbs are expected to interfere with the bioanalytical method using an anti-idiotype antibody for detection. However, this interference only indicates that the bioanalytical method is detecting the active moiety, which consists of antibody drugs that are not bound to NAb. Therefore, it can be concluded that NAb positive subjects have lower active teplizumab concentration at Course 2. For AGC/AGC, mean pre-dose teplizumab concentrations in NAb-positive participants were 35% (101.8 ng/mL, n=33) and 16% (57.5 ng/mL, n=35) of NAb-negative participants (283.0 ng/mL, n=18; 362.8 ng/mL, n=17) at Days 190 and 193, respectively.

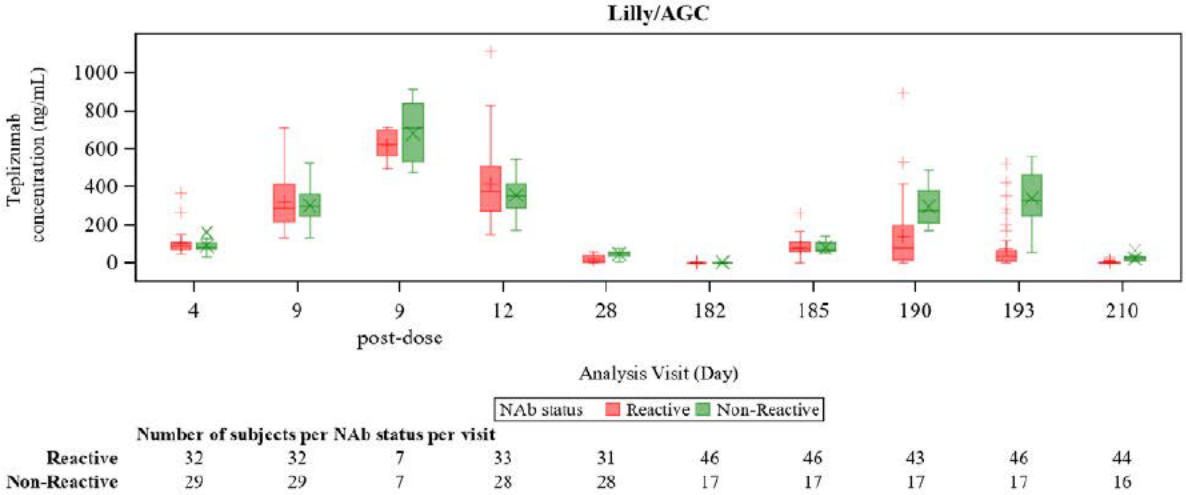
Figure 7. Box plots of PK concentrations (ng/mL) over time by NAb status and by product, full analysis set



Number of subjects per NAb status per visit										
Reactive	28	28	0	28	23	50	51	49	49	48
Non-Reactive	28	28	0	28	21	5	5	5	5	5



Number of subjects per NAb status per visit										
Reactive	30	30	20	30	28	35	35	33	35	34
Non-Reactive	20	20	18	19	19	18	18	18	18	17



Number of subjects per NAb status per visit										
Reactive	32	32	7	33	31	46	46	43	46	44
Non-Reactive	29	29	7	28	28	17	17	17	17	16

Source: Figure 3.1.2 on page 9-11 of isi-figures-12jun2024
Note: Concentration values below Lower Limit of Quantitation (2.50 ng/mL) are set to zero for summary statistics.
Note: PK samples were collected prior to dosing. An additional PK sample was collected 45 minutes after infusion on Day 9 in Course 1. Pre-dose PK samples on Day 1 are not displayed.
Note: Reactive NAb status is defined as at least one positive sample at any timepoint in each course. Non-Reactive NAb status is defined as no positive samples and at least one negative sample at any time point in each course.

c. Population pharmacokinetics model analysis

In the current updated population PK model, time-varying ADA titer (natural log - Ln - transformed) was a significant covariate on teplizumab clearance of both Lilly and AGC products and for both courses of Study PROTECT, with an estimated slope of relative increase in clearance with increasing Ln(ADA titers) of 0.68, for Ln(ADA titer) above an estimated threshold of 6.55 (i.e., titer of 700, log10 titer of 2.845). Below this threshold the effect of ADA titers on drug's clearance was considered absent.

As a result of the earlier incidence of higher ADA titers during the 12-day treatment in Course 2 (Figure 3), the PK exposure metrics were lower in Course 2 than in Course 1 (Table 1). To describe the lower exposure during Course 2, an additional time-dependent ADA effect affecting teplizumab bioavailability (assuming the immediate binding of the drug to the ADA upon dosing) was estimated in the PK model. See section 4.2 for additional details.

In general, it was observed that participant with lower exposure in Course 2 compared to Course 1 of treatment (Figure 12) had higher ADA titers (Table 17 and Table 18), further indicating the impact of immunogenicity on PK. However, the difference in exposure did not seem to affect teplizumab treatment effect on C-peptide. Refer to section 4.2.2 for detailed evaluation indicating the lack of significant differences in C-peptide results in patients with lower exposure.

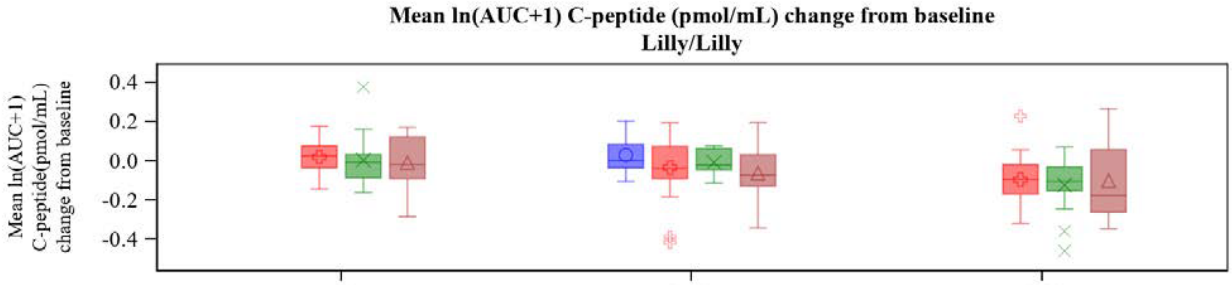
Overall, based on the above observations for the observed concentrations and predicted exposures of teplizumab versus the ADA titers and NAb status, we recommend including the effect of immunogenicity on teplizumab pharmacokinetics in the labeling.

Effect of immunogenicity on C-peptide AUC:

In teplizumab-treated participants, the change in C-peptide AUC was -0.0887 in ADA-positive participants (N=157) versus 0.0313 in ADA-negative participants (N=3) at Week 78. Due to the small number of ADA-negative participants, no conclusive evaluation can be performed.

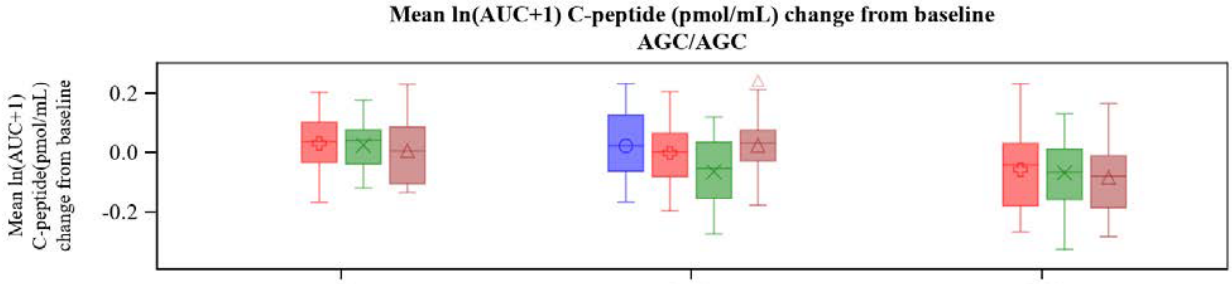
The Applicant performed longitudinal comparisons of C-peptide change from baseline at each time point (Weeks 26, 52, and 78) by visit-specific ADA titer quartiles, maximum ADA titer quartiles for each course, and by products. These analyses did not reveal any clear trend (Figure 8).

Figure 8. Box plots of change from baseline in C-peptide ln(AUC+1) values over time by visit-specific ADA titer quartile and by product, full analysis set (teplizumab group only)



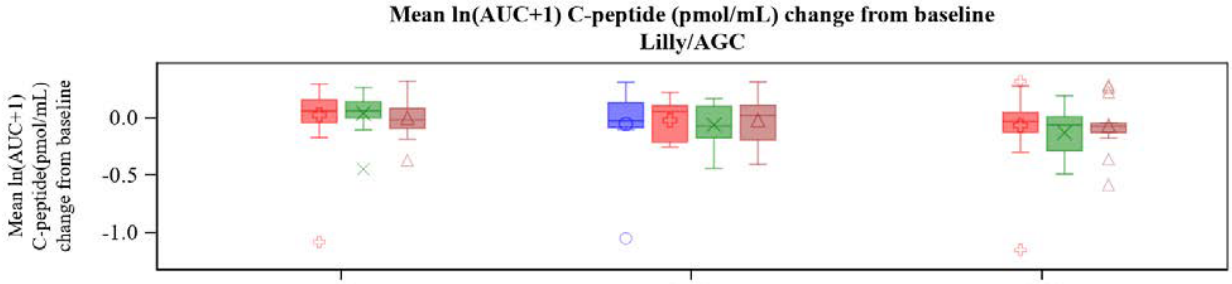
Number of subjects per visit-specific ADA quartile

Q1	0	5	0
Q2	27	24	28
Q3	14	5	16
Q4	14	19	10



Number of subjects per visit-specific ADA quartile

Q1	0	13	0
Q2	24	10	24
Q3	12	7	15
Q4	16	20	10



Number of subjects per visit-specific ADA quartile

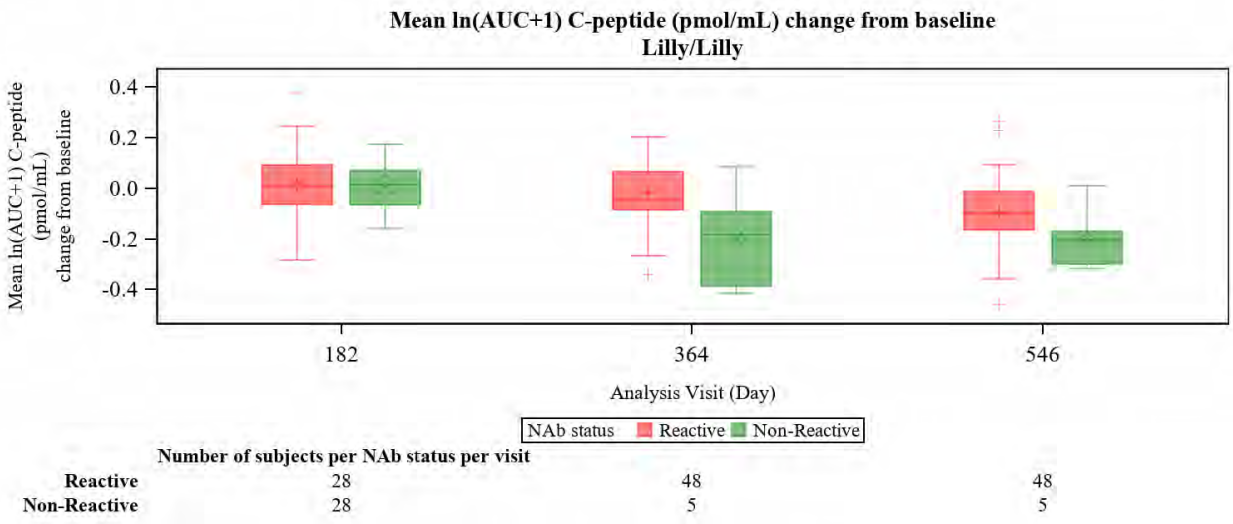
Q1	0	11	0
Q2	30	12	24
Q3	15	15	16
Q4	17	20	14

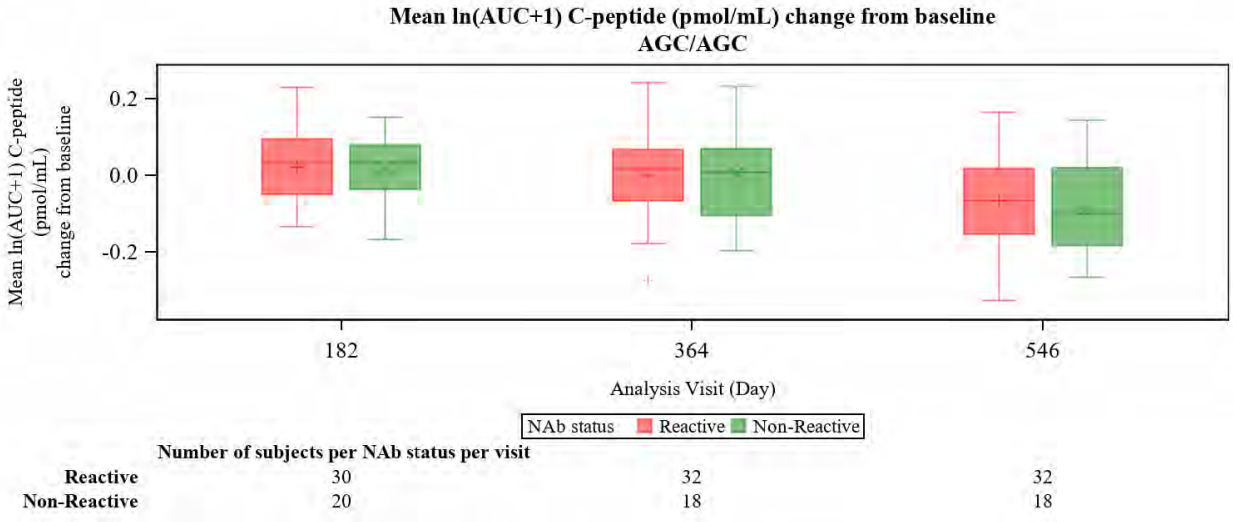
Source: Figure 4.1.4 on page 27-29 of ISI Figures 12Jun2024.

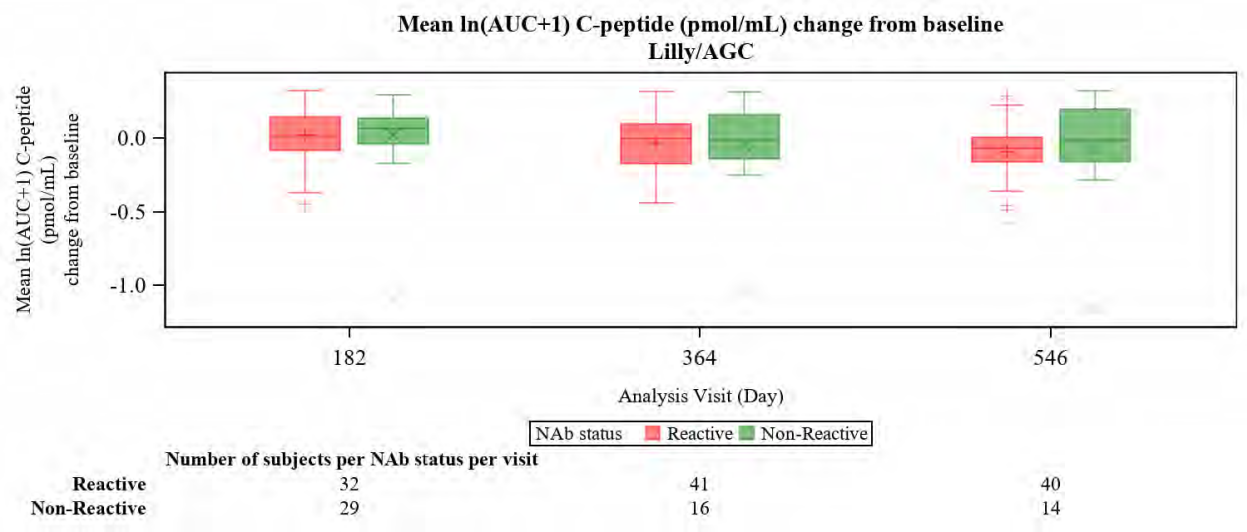
Note: Quartiles of the ADA titer are based on the ADA titer values (log 10 scale) at each study visit. Note: Week 26 (Day 182) – Q1 < 0, Q2 [0, 2.38), Q3 [2.38, 3.28), Q4 >= 3.28. Week 52 (Day 364) – Q1 < 1.78, Q2 [1.78, 2.83), Q3 [2.83, 3.58), Q4 >= 3.58. Week 78 (Day 546) – Q1 < 0, Q2 [0, 2.38), Q3 [2.38, 3.28), Q4 >= 3.28.

At each time point (Weeks 26, 52, and 78), there does not appear to be a difference in C-peptide AUC change when comparing participants with and without Nabs.

Figure 9. Box plots of change from baseline in C-peptide ln(AUC+1) values over time by NAb status and by product, Full Analysis Set (teplizumab group only)







Source: Figure 4.1.2 on page 21-23 of ISI Figures 12Jun2024.Note: Reactive NAb status is defined as at least one positive sample at any timepoint in each course. Non-Reactive NAb status is defined as no positive samples and at least one negative sample at any time point in each course.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The PROTECT study samples were analyzed using method ICD-788 version 1.02 ("An MSD-ECL Method for the Quantitation of PRV-031 in Human Serum"). The analyte stability in frozen matrix was updated from the original method validation report (up to 365 days at -25°C and -80°C) to extended timeframes in addendum 3 of the method validation report (up to 734 days at -25°C and up to 1,178 days at -80°C). Method ICD-788 was previously evaluated in the clinical pharmacology review of the original BLA submission and was considered adequate (Reference ID: 4788416).

4.2 Population PK Analyses

The updated population pharmacokinetic (PK) model, with new data following completion of the PROTECT study, was considered appropriate for describing the observed teplizumab concentrations from 2 courses of teplizumab treatment (with either the Lilly product or AGC product). Therefore, the PK model was considered appropriate for estimating teplizumab exposure metrics and for performing PK simulations and predictions. More specifically, the population PK model was utilized to support the current submission as outlined below:

Table 5. Utility of the Population PK Modeling

Utility of the final model	Reviewer's Comments
• The prior PK model, based on data from 4 studies following a single course (Course 1) of teplizumab treatment, was refined with additional data following completion of the PROTECT study, in children and adolescents (8 to 17 years old) recently diagnosed with T1D, who received 2 courses of teplizumab treatment. The refined PK model used the same structural PK model as the prior PK model and describes teplizumab PK from 2 courses of treatment. The updated PK model was used to refine the characterization of the ADA effects on teplizumab clearance (CL) for the Lilly and AGC product • In Course 1 of treatment, the effect of ADA titers on CL was estimated separately for TN-10 study and for PROTECT study. In PROTECT study, the effect of ADA titers on CL (using time-varying ADA titer) was estimated be similar for Lilly and AGC products, consistent with the reviewer's prior findings. • In the newly modeled PK from Course 2 treatment, the same ADA effects on CL from Course 1 was applied to Course 2. Due to earlier incidence of high ADA titers during the 12-day treatment in Course 2, an additional ADA effect on teplizumab bioavailability (F) was estimated to account for the lower exposure observed compared to Course 1, with some patients showing very low concentrations or BLQ values during the 12-day treatment. • The PK model was used to derive teplizumab exposure metrics (Cmax, Ctrough and AUC) from the PROTECT study to compare PK exposure between teplizumab products (Lilly and AGC product) and between treatment courses. • Exposures were lower in Course 2 compared to Course 1, regardless of drug's product (Lilly and AGC), due to higher prevalence of ADAs and higher ADA	• The Applicant's refined PK model was considered reasonable for describing teplizumab concentrations and their variability from 2 courses of teplizumab treatment in PROTECT study, for both the Lilly and AGC products. • PK parameters from the refined PK model for Course 1 treatment were close to the corresponding parameters estimated in the prior model. • Although, the AGC product showed lower exposure compared to the Lilly product consistent with the previous PK comparability sub-study findings, no dose adjustment for the AGC product was deemed warranted for the intended indication in patients with stage 3 T1D, as the evaluation of the clinical data from PROTECT study did not find a difference in treatment effect between products, with patients treated exclusively with either the Lilly or AGC product during both courses showing a significant treatment effect compared to placebo, in terms of change from baseline in C-peptide AUC after 4-hour MMTT at Week 78 (primary endpoint). • Apart from the effect of teplizumab product on treatment effect in PROTECT study, the review team evaluated the difference in treatment effect in patients with lower exposure in Course 2 compared Course 1 of

titers early during the 12-day Course 2 treatment and after Course 2. Consistent with the Lilly product, the AGC product, geometric mean AUCinf and AUC_{0-13} (AUC from 0 to Day 13), Ctrough (Day 13), and Cmax were 51%, 41%, 81%, and 20% lower in Course 2 compared to Course 1. • Consistent with the PK comparability between products during Course 1 from the prior PK model, the updated PK model found that the exposure to teplizumab in both treatment courses was higher in participants treated with the Lilly product compared to the AGC product. AUCinf, AUC_{0-13}, Ctrough (Day 13), and Cmax, for AGC product were estimated to be 22%, 17%, 27%, and 12% lower than the Lilly product in Course 1, and 23%, 22%, 37%, and 5% lower than the Lilly product in Course 2.	treatment (regardless of drug product). Patients with lower exposure in Course 2 were defined as having an AUC_{0-28} (AUC from 0 to Day 28) below 2000 ng*Day/mL. The AUC_{0-28} threshold of 2000 ng*Day/mL corresponds to the minimum AUC_{0-28} estimated in subjects who received all 12 doses of teplizumab during Course 1. According to the statistical review team assessment, no statistically significant difference in treatment effect was observed for patients with low exposure and patients with $AUC_{0-28} \geq 2000$.

4.2.1 Applicant's Pharmacokinetic Modeling

In a previous submission (for the indication of delaying the onset of Stage 3 T1D in subjects with Stage 2 T1D, aged 8 years and older) a population PK model for teplizumab was developed based on data from 4 studies following a single course (Course 1) of treatment: Protégé study (Course 1 treatment only used), TN-10 study (only 1 Course studied), PRV-031-004 study (single dose PK comparability study in healthy volunteers), and a PROTECT sub-study (Course 1 treatment only for PK comparability assessment between Lilly and AGC products; with data cut-off of 06-Aug-2021).

In the current submission, the prior PK model was updated with additional data following completion of the PROTECT study, in children and adolescents recently diagnosed with T1D, who received 2 courses of teplizumab treatment separated by 6 months. Few patients (n=14) received their 2nd course 12 months after the start of treatment (9 patients (13.6%) and 6 patients (4.9%) for the Lilly and AGC product, respectively). Each 12-day course of teplizumab consisted of IV infusions of 106 μg/m^2 on study Day 1, 425 μg/m^2 on Day2, and 850 μg/m^2 on each of study Days 3 to 12 (for a cumulative dose of approximately 9.0 mg/m2 per course).

In the main PROTECT study, pre-dose serum samples for PK analysis were collected at baseline (Day 1), Day 4, Day 9, Day 12 and Day 28 in both courses of study drug treatment. In the PROTECT sub-study, an additional PK sample was drawn 45 minutes after the end of infusion on Day 9 of the first course. Anti-drug antibody (ADA) samples were collected at baseline (Day 1), Day 12, Day 28, Day 56 and Day 182 in both courses. An additional ADA sample was collected on Day 6 in the second course.

The PK dataset included a total of 779 subjects with a total of 4908 quantifiable PK samples. PK samples below the limit of quantification (BLQ) were excluded from the analysis dataset during PK model development for Course 2 of treatment. In the prior PK model, it was shown that accounting for BLQ

values using the M3 method was not necessary for Course 1. As there were more BLQ observations in Course 2 of PROTECT study (3% BLQ observations in Course 1 vs. 16% in Course 2), a sensitivity analysis was performed by including these observations and testing the final model using the M3 method. Table 6 summarizes the numbers of quantifiable and BLQ samples by treatment course and drug product in PROTECT study. No difference in the frequency of BLQ samples was observed between drug products (Lilly and AGC) in PROTECT study.

Table 7 summarizes the demographic characteristics of subjects in PROTECT study. ADA occurrences and titers for subjects with ADAs are summarized in Table 8 and Table 9.

During the 2nd course of treatment (Course 2), patients experienced a higher ADA titers resulting in lower exposures and higher BLQ observations compared to Course 1 of treatment. Table 10 and Table 11 summarize the natural logarithm (Ln) of ADA titers and quantiles of Ln ADA titers, during the 2nd course of treatment, in patients who received all 12 teplizumab doses, stratified by the occurrence or not any BLQ observation during the 12-day treatment period. In contrast, during the 1st course of treatment, no patient (who received all 12 teplizumab doses) had a BLQ observation during the 12-day treatment period.

Table 6. Number of Subjects and PK Samples from PROTECT Study Included in the PK analysis

Product	Course 1			Course 2		
	Number of Subjects	Number of Quantifiable Concentrations	Number of Post-Dose BQL samples	Number of Subjects	Number of Quantifiable Concentrations	Number of Post-Dose BQL samples
AGC	65[a]	282	11	122[b]	403	80
Eli Lilly	147	561	16	66	221	39
Total	212[c]	843	27	188	624	119

[a] One additional subject (ID=(b) (6)) who received only 1 dose had only BQL concentrations and was excluded from the PK analysis.
[b] Three additional subjects had only BQL concentrations and were excluded from the PK analysis.
[c] Three additional subjects had only one pre-Course 1 BLQ measurement and 1 subject had only pre-Course 1 and End of study/ET BLQ measurements. They were excluded from the PK analysis.
Source: Applicant's Population PK Modeling Report (07 November 2023), Table 2, page 31.

Table 7. Summary of Demographic Characteristics by Course and Product in PROTECT Study

	Course 1		Course 2	
	Lilly (N=147)	AGC (N=65)	Lilly (N=66)	AGC (N=122)
Age (years)				
Mean (SD)	12.0 (2.50)	12.0 (2.55)	11.9 (2.31)	12.3 (2.60)
Median [Min, Max]	12.0 [8.00, 17.0]	12.0 [8.00, 17.0]	12.0 [8.00, 17.0]	12.5 [8.00, 17.0]
Body weight (kg)				
Mean (SD)	47.2 (15.6)	45.8 (13.4)	49.8 (16.0)	51.6 (15.9)
Median [Min, Max]	45.0 [23.1, 104]	47.9 [21.6, 73.8]	46.2 [28.4, 111]	52.2 [14.1, 106]
BSA (m2)				
Mean (SD)	1.43 (0.288)	1.41 (0.283)	1.46 (0.282)	1.51 (0.286)
Median [Min, Max]	1.42 [0.930, 2.31]	1.46 [0.860, 1.96]	1.44 [1.03, 2.43]	1.54 [0.940, 2.38]
Sex				
Male	80 (54.4%)	38 (58.5%)	33 (50.0%)	76 (62.3%)
Female	67 (45.6%)	27 (41.5%)	33 (50.0%)	46 (37.7%)
Ethnicity				
Not Hispanic or Latino	133 (90.5%)	56 (86.2%)	59 (89.4%)	109 (89.3%)
Hispanic or Latino	10 (6.8%)	4 (6.2%)	5 (7.6%)	7 (5.7%)
Missing	4 (2.7%)	5 (7.7%)	2 (3.0%)	6 (4.9%)
Race				
White	132 (89.8%)	55 (84.6%)	59 (89.4%)	107 (87.7%)
Black/African American	4 (2.7%)	1 (1.5%)	3 (4.5%)	2 (1.6%)
Asian	2 (1.4%)	1 (1.5%)	0 (0%)	3 (2.5%)
Amer.Ind./Alas.Nat.	1 (0.7%)	0 (0%)	1 (1.5%)	0 (0%)
Other	6 (4.1%)	3 (4.6%)	3 (4.5%)	4 (3.3%)
Missing	2 (1.4%)	5 (7.7%)	0 (0%)	6 (4.9%)

Source: FDA reviewer.

Table 8. Frequency of ADA in Courses 1 and 2 of PROTECT Study, Overall and by Product

Timepoint	ADA Positive?	Course 1			Course 2		
		Total	Lilly	AGC	Total	Lilly	AGC
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any time	No	14 (6.6%)	8 (5.4%)	6 (9.2%)	3 (1.6%)	1 (1.5%)	2 (1.6%)
	Yes	198 (93.4%)	139 (94.6%)	59 (90.8%)	185 (98.4%)	65 (98.5%)	120 (98.4%)
Day 1	Missing	-	-	-	5 (2.7%)	2 (3%)	3 (2.5%)
	No	199 (93.9%)	140 (95.2%)	59 (90.8%)	60 (31.9%)	24 (36.4%)	36 (29.5%)
	Yes	13 (6.1%)	7 (4.8%)	6 (9.2%)	123 (65.4%)	40 (60.6%)	83 (68%)
Day 6	Missing	-	-	-	7 (3.7%)	2 (3%)	5 (4.1%)
	No	-	-	-	49 (26.1%)	17 (25.8%)	32 (26.2%)
	Yes	-	-	-	132 (70.2%)	47 (71.2%)	85 (69.7%)
Day 12	Missing	6 (2.8%)	4 (2.7%)	2 (3.1%)	2 (1.1%)	2 (3%)	-
	No	31 (14.6%)	21 (14.3%)	10 (15.4%)	8 (4.3%)	2 (3%)	6 (4.9%)
	Yes	175 (82.5%)	122 (83%)	53 (81.5%)	178 (94.7%)	62 (93.9%)	116 (95.1%)
Day28	Missing	12 (5.7%)	6 (4.1%)	6 (9.2%)	7 (3.7%)	2 (3%)	5 (4.1%)
	No	29 (13.7%)	21 (14.3%)	8 (12.3%)	5 (2.7%)	2 (3%)	3 (2.5%)
	Yes	171 (80.7%)	120 (81.6%)	51 (78.5%)	176 (93.6%)	62 (93.9%)	114 (93.4%)
Day 56	Missing	7 (3.3%)	4 (2.7%)	3 (4.6%)	7 (3.7%)	4 (6.1%)	3 (2.5%)
	No	34 (16%)	25 (17%)	9 (13.8%)	13 (6.9%)	2 (3%)	11 (9%)
	Yes	171 (80.7%)	118 (80.3%)	53 (81.5%)	168 (89.4%)	60 (90.9%)	108 (88.5%)

Note: Day 1 represents samples at baseline, before start of treatment.

Source: Applicant's Population PK Modeling Report (07 November 2023), Table 5, page 34.

Table 9. Summary of ADA titers in Course 1 and 2 in PROTECT Study, Overall and by Product

	Course 1		Course 2	
	Lilly (N=147)	AGC (N=65)	Lilly (N=66)	AGC (N=122)
Highest Ln ADA Titer (Day 1 to 56)				
Mean (SD)	7.04 (2.09)	7.35 (2.22)	9.71 (2.49)	9.61 (3.08)
Median [Min, Max]	6.87 [3.40, 11.7]	6.87 [3.40, 11.7]	9.64 [4.79, 14.5]	10.3 [3.40, 14.5]
Geo. mean (Geo. CV%)	6.73 (31.3%)	7.01 (31.9%)	9.37 (28.8%)	9.03 (38.5%)
Ln ADA Titer (Day 1)				
Mean (SD)	4.19 (1.29)	4.33 (0.841)	6.52 (1.89)	6.60 (1.82)
Median [Min, Max]	3.40 [3.40, 6.87]	4.44 [3.40, 5.48]	6.17 [3.40, 11.0]	6.17 [3.40, 10.3]
Geo. mean (Geo. CV%)	4.05 (27.3%)	4.26 (19.9%)	6.26 (29.9%)	6.34 (29.4%)
Ln ADA Titer (Day 6)				
Mean (SD)	NA (NA)	NA (NA)	6.53 (2.38)	6.53 (1.85)
Median [Min, Max]	NA [NA, NA]	NA [NA, NA]	6.17 [3.40, 13.8]	6.17 [3.40, 11.0]
Geo. mean (Geo. CV%)	NA (NA%)	NA (NA%)	6.14 (35.9%)	6.28 (29.0%)
Ln ADA Titer (Day 12)				
Mean (SD)	5.11 (1.25)	5.31 (1.28)	8.82 (2.78)	9.22 (3.17)
Median [Min, Max]	4.79 [3.40, 9.64]	5.48 [3.40, 8.25]	8.95 [3.40, 14.5]	10.3 [3.40, 14.5]
Geo. mean (Geo. CV%)	4.96 (24.7%)	5.16 (24.5%)	8.35 (35.6%)	8.59 (41.3%)
Ln ADA Titer (Day 28)				
Mean (SD)	6.61 (1.91)	6.85 (2.23)	9.34 (2.53)	9.21 (2.99)
Median [Min, Max]	6.17 [3.40, 11.7]	6.17 [3.40, 11.7]	9.64 [4.79, 14.5]	10.3 [3.40, 14.5]
Geo. mean (Geo. CV%)	6.35 (29.5%)	6.48 (35.3%)	8.97 (30.2%)	8.64 (39.8%)
Ln ADA Titer (Day 56)				
Mean (SD)	6.83 (2.30)	7.18 (2.24)	8.77 (2.51)	9.02 (2.76)
Median [Min, Max]	6.87 [3.40, 11.7]	6.87 [3.40, 11.7]	8.95 [4.09, 14.5]	9.64 [3.40, 13.8]
Geo. mean (Geo. CV%)	6.43 (36.5%)	6.83 (33.5%)	8.37 (33.0%)	8.53 (36.8%)

Note: Day 1 represents samples at baseline, before start of treatment. Patients with ADA negative status (ADA titer equal 0) were omitted from the summary. Ln ADA titer of 3.4 represents the natural logarithm of the minimal required dilution (MDR)/lower limit of quantification of the ADA assay (i.e., an ADA titer of 30).
Source: FDA reviewer.

Table 10. Summary of ADA titers in Course 2 of PROTECT Study in Fully Adherent Patients (All 12 Doses) With and Without Concentrations Below Limit of Quantification, Stratified by Product

	Lilly in Course 2		AGC in Course 2	
	no BLQ during treatment (N=57)	BLQ during treatment (N=7)	no BLQ during treatment (N=102)	BLQ during treatment (N=13)
Highest Ln ADA Titer (Day 1 to 56)				
Mean (SD)	9.03 (2.55)	13.3 (0.659)	8.94 (3.22)	12.9 (1.07)
Median [Min, Max]	9.64 [0, 14.5]	13.1 [12.4, 14.5]	9.64 [0, 14.5]	13.1 [10.3, 14.5]
Ln ADA Titer (Day 1)				
Mean (SD)	3.48 (3.26)	8.26 (2.19)	3.98 (3.20)	8.89 (1.04)
Median [Min, Max]	4.09 [0, 8.95]	8.60 [4.79, 11.0]	4.79 [0, 9.64]	8.95 [6.17, 10.3]
Missing	1 (1.8%)	1 (14.3%)	2 (2.0%)	0 (0%)
Ln ADA Titer (Day 6)				
Mean (SD)	3.96 (3.00)	10.0 (2.33)	4.11 (3.03)	9.11 (1.07)
Median [Min, Max]	4.79 [0, 10.3]	9.64 [6.17, 13.8]	4.79 [0, 8.95]	8.95 [6.87, 11.0]
Missing	2 (3.5%)	0 (0%)	3 (2.9%)	0 (0%)
Ln ADA Titer (Day 12)				
Mean (SD)	7.98 (2.83)	13.2 (0.741)	8.18 (3.59)	12.6 (0.957)
Median [Min, Max]	8.25 [0, 12.4]	13.1 [12.4, 14.5]	8.25 [0, 14.5]	13.1 [10.3, 13.8]
Ln ADA Titer (Day 28)				
Mean (SD)	8.56 (2.79)	13.1 (0.440)	8.48 (3.28)	12.1 (1.00)
Median [Min, Max]	8.95 [0, 14.5]	13.1 [12.4, 13.8]	8.95 [0, 13.8]	12.4 [10.3, 14.5]
Missing	0 (0%)	1 (14.3%)	5 (4.9%)	0 (0%)
Ln ADA Titer (Day 56)				
Mean (SD)	7.99 (2.79)	12.1 (0.378)	7.61 (3.71)	11.9 (0.987)
Median [Min, Max]	8.25 [0, 14.5]	12.1 [11.7, 12.4]	8.25 [0, 13.8]	11.7 [10.3, 13.8]
Missing	3 (5.3%)	1 (14.3%)	3 (2.9%)	0 (0%)

BLQ: Concentrations Below Limit of Quantification.

Note: During Course 1 of treatment, no patient who received all 12 teplizumab doses had a BLQ observation during the 12-day treatment period.

Source: FDA reviewer.

Table 11. Summary of ADA titers Quantiles in Course 2 of PROTECT Study in Fully Adherent Patients (All 12 Doses) With and Without Concentrations Below Limit of Quantification

	Lilly in Course 2		AGC in Course 2	
	no BLQ during treatment (N=57)	BLQ during treatment (N=7)	no BLQ during treatment (N=102)	BLQ during treatment (N=13)
Highest Ln ADA Titer (Day 1 to 56)				
Q1: Lilly [0 - <7.56] / AGC [0 - <6.17]	13 (22.8%)	0 (0%)	22 (21.6%)	0 (0%)
Q2: Lilly [7.56 - <9.64] / AGC [6.17 - <8.25]	12 (21.1%)	0 (0%)	17 (16.7%)	0 (0%)
Q3: Lilly [9.64 - <10.33] / AGC [8.25 - <11.03]	10 (17.5%)	0 (0%)	21 (20.6%)	1 (7.7%)
Q4: Lilly [10.33 - <11.72] / AGC [11.03 - <12.41]	13 (22.8%)	0 (0%)	25 (24.5%)	1 (7.7%)
Q5: Lilly [11.72 - 14.49] / AGC [12.41 - 14.49]	9 (15.8%)	7 (100%)	17 (16.7%)	11 (84.6%)
Ln ADA Titer (Day 1)				
Q2: Lilly [0 - <4.09] / AGC [0 - <4.79]	25 (43.9%)	0 (0%)	45 (44.1%)	0 (0%)
Q3: Lilly [4.09 - <5.48] / AGC [4.79 - <6.17]	8 (14.0%)	1 (14.3%)	19 (18.6%)	0 (0%)
Q4: Lilly [5.48 - <7.56] / AGC [6.17 - <7.56]	14 (24.6%)	1 (14.3%)	18 (17.6%)	1 (7.7%)
Q5: Lilly [7.56 - 11.03] / AGC [7.56 - 10.33]	9 (15.8%)	4 (57.1%)	18 (17.6%)	12 (92.3%)
Missing	1 (1.8%)	1 (14.3%)	2 (2.0%)	0 (0%)
Ln ADA Titer (Day 6)				
Q2: Lilly [0 - <4.79] / AGC [0 - <4.79]	24 (42.1%)	0 (0%)	41 (40.2%)	0 (0%)
Q3: Lilly [4.79 - <5.48] / AGC [4.79 - <6.17]	9 (15.8%)	0 (0%)	26 (25.5%)	0 (0%)
Q4: Lilly [5.48 - <7.836] / AGC [6.17 - <7.56]	17 (29.8%)	1 (14.3%)	17 (16.7%)	1 (7.7%)
Q5: Lilly [7.836 - 13.8] / AGC [7.56 - 11.03]	5 (8.8%)	6 (85.7%)	15 (14.7%)	12 (92.3%)
Missing	2 (3.5%)	0 (0%)	3 (2.9%)	0 (0%)
Ln ADA Titer (Day 12)				
Q1: Lilly [0 - <6.17] / AGC [0 - <4.79]	12 (21.1%)	0 (0%)	14 (13.7%)	0 (0%)
Q2: Lilly [6.17 - <7.56] / AGC [4.79 - <7.56]	11 (19.3%)	0 (0%)	28 (27.5%)	0 (0%)
Q3: Lilly [7.56 - <9.64] / AGC [7.56 - <11.03]	12 (21.1%)	0 (0%)	24 (23.5%)	1 (7.7%)
Q4: Lilly [9.64 - <11.03] / AGC [11.03 - <11.72]	11 (19.3%)	0 (0%)	16 (15.7%)	0 (0%)
Q5: Lilly [11.03 - 14.49] / AGC [11.72 - 14.49]	11 (19.3%)	7 (100%)	20 (19.6%)	12 (92.3%)
Ln ADA Titer (Day 28)				
Q1: Lilly [0 - <6.17] / AGC [0 - <5.48]	10 (17.5%)	0 (0%)	19 (18.6%)	0 (0%)
Q2: Lilly [6.17 - <8.25] / AGC [5.48 - <8.25]	10 (17.5%)	0 (0%)	22 (21.6%)	0 (0%)
Q3: Lilly [8.25 - <10.33] / AGC [8.25 - <10.75]	17 (29.8%)	0 (0%)	25 (24.5%)	1 (7.7%)
Q4: Lilly [10.33 - <11.306] / AGC [10.75 - <11.72]	14 (24.6%)	0 (0%)	12 (11.8%)	2 (15.4%)
Q5: Lilly [11.306 - 14.49] / AGC [11.72 - 14.49]	6 (10.5%)	6 (85.7%)	19 (18.6%)	10 (76.9%)
Missing	0 (0%)	1 (14.3%)	5 (4.9%)	0 (0%)
Ln ADA Titer (Day 56)				
Q1: Lilly [0 - <5.618] / AGC [0 - <4.79]	13 (22.8%)	0 (0%)	18 (17.6%)	0 (0%)
Q2: Lilly [5.618 - <8.25] / AGC [4.79 - <7.56]	9 (15.8%)	0 (0%)	22 (21.6%)	0 (0%)
Q3: Lilly [8.25 - <9.64] / AGC [7.56 - <10.33]	12 (21.1%)	0 (0%)	23 (22.5%)	0 (0%)
Q4: Lilly [9.64 - <11.03] / AGC [10.33 - <11.306]	14 (24.6%)	0 (0%)	24 (23.5%)	3 (23.1%)
Q5: Lilly [11.03 - 14.49] / AGC [11.306 - 13.8]	6 (10.5%)	6 (85.7%)	12 (11.8%)	10 (76.9%)
Missing	3 (5.3%)	1 (14.3%)	3 (2.9%)	0 (0%)

Source: FDA reviewer.

Final Population PK model

The current updated PK model was developed in 2 steps. In the first step, the prior PK model (which describes teplizumab PK from only a single course [Course 1] of treatment from 4 studies) was refined with additional PK and ADA data from Course 1 of treatment of the PROTECT study. In a second step, the refined Course 1-PK model was further updated to describe the PK data from a 2nd course (Course 2) of treatment of the PROTECT study (the only study contributing with a 2nd course of treatment in the PK analysis). All model parameters from Course 1-PK model were fixed and any additional influence of ADA (during Course 2) on PK parameters and other modifications were tested and implemented.

The updated PK model used the same structural model as the prior PK model following teplizumab IV infusion (of at least 30 minutes) and consisted of a 3-compartment model, with linear non-specific elimination from the central compartment, target-mediated drug disposition (TMDD) in all 3 compartments (central compartment, 1st peripheral compartment, and a 2nd fast/rapidly-equilibrating peripheral compartment), as well as an additional binding and TMDD through a non-renewable pool of target from the 1st peripheral compartment during Course 1 of treatment only. The quasi-steady-state (QSS) approximation of the TMDD was used in the PK model.

The 3-compartment QSS TMDD model was parameterized in terms of CL, central and 2 peripheral volumes of distribution (Vc, Vp, Vp2), inter-compartmental clearances (Q and Qp2), concentration of target at baseline (BASE), the quasi-steady-state constant (KSS), an internalization rate constant (Kint) for all products except for the AGC product, target degradation rate constant (Kdeg), the concentration of non-renewable pool of target at baseline (RMAX) and an elimination/association rate constant to the non-renewable pool of target (Kb).

As with the prior PK model, the inter-individual variability (IIV) was estimated for teplizumab CL, Vc, Vp, Q, Qp2, Kb, Kss and on the residual error. The IIV on Vc and Qp2 was included only for subjects with dense sampling (i.e., study PRV-031-004 and segment 1 of the Protégé study). The residual variability was best described by a proportional error model, with a lower residual variability for study PRV-031-004.

Update for Course 1-PK model:

In the updated PK model, with Course 1 of PROTECT study, the effect of ADA titers on CL was estimated separately for TN-10 study and for PROTECT study. The parameter estimates from the final Course 1-PK model are listed in Table 12. All parameters (except those related to ADA) were close to the corresponding parameters of the prior model.

- The relative effect of ADA titers on CL in TN-10 study (i.e., $CL_{MLTITR4}$ = slope of fractional increase of CL with natural-logarithm [Ln] of highest ADA titer measurement) was estimated to be close to zero and was therefore fixed to zero in the updated PK model. In TN-10 study, the ADA assessment was performed only at month 3 or 4 after start of the single course treatment. Therefore, ADA titer could not be used as a time-varying covariate.

- In PROTECT study, the relative effect of ADA titers on CL was tested using time-variant ADA (LTITRV = Ln of time-varying ADA titer). The effect of time-varying ADA on CL ($CL_{LTITRV78}$ = slope of fractional increase of CL with LTITRV) was similar for Lilly and AGC products.

  For the Lilly product LTITRV alone did not fully account for influence of ADA on CL, and an additional fractional increase in CL for the Lilly product ($CL_{MLTITR7}$) with an increase in MLTITR (Ln of highest ADA titer measurement up to Day 56) was estimated to be statistically significant.

  Of note, in PROTECT study, the effect of ADA titers on CL was considered absent if the ADA titer did not reach an estimated Ln(titer) threshold ($Thresh_{LTITRV}$) of 6.55 (i.e., titer of 700), for either the time-varying ADA titer (LTITRV) or the highest measured ADA titer up to Day 56 (MLTITR).

Update for Course 2-PK and final model:

The additional estimated covariate effect (ADA effect) and inter-individual variability of PK parameters for Course 2 are listed in Table 13.

- The BASE parameter at Course 2 (i.e., the concentration of target at baseline) was estimated to only partially recover following Course 1 and was estimated to be 64.4% (BASE2=64.4%) of that in Course 1 (BASE = 157 ng/mL, Table 12). RMAX (concentration of a non-renewable pool of target in 1st peripheral compartment) was set to zero during Course2.
- The same ADA effects on CL, as estimated for Course 1, related to the time-variant ADA titers (LTITRV) and the maximum ADA titer (MLTITR2 for Course 2), was applied to Course 2.

  However, teplizumab exposures were lower in Course 2 compared to Course 1 due to higher ADAs and some patients showed very low concentrations or BLQ values during the 12-day treatment, despite their adherence to treatment. To describe this additional ADA effect on exposure, not observed in Course 1, the Course 2-PK model included a time-dependent effect of the highest ADA titers on teplizumab's bioavailability (see Emax relationship in Table 13 footnote), with the ADA's maximum effect (Emax= EFFMAX) on bioavailability (F) depending on the maximum ADA titer in Course 2 (MLTITR2).
  The inclusion of the additional ADA effect on bioavailability instead on CL provided a better model fit. According to the Applicant, in the context of IV dosing, a decrease of F may be interpreted as an immediate binding of the drug to the ADA upon dosing (assuming that this complex is not detected by the assay).
- The final model introduced a separate IIV for CL in Course 2 ($\omega^2 CL_2$) that was correlated with the IIV for CL in Course 1 (ω^2 CL). An IIV was also estimated for the time of half maximum effect (T_{50}). All other IIVs on PK parameters were fixed to those estimated in Course 1-PK model.

Table 12. Parameter Estimates from the Refined Final PK Model for Course 1

Parameter		Estimate	RSE (%)	95%CI
CL (L/day)	θ1	1.64	4.23	1.51 ; 1.78
V_c (L)	θ2	2.27	3.07	2.13 ; 2.4
Q (L/day)	θ3	8.55	5.26	7.67 ; 9.43
V_p (L)	θ4	6.00	3.44	5.6 ; 6.41
BASE (ng/mL)	θ6	157	5.13	141 ; 173
K_{SS} (ng/mL)	θ7	18.9	6.16	16.6 ; 21.2
Vc_{WT}, Vp_{WT}	θ8	0.710	5.6	0.632 ; 0.788
CL_{WT}	θ9	0.524	12	0.4 ; 0.647
CL_{HAHA2}	θ10	0.138	13.4	0.102 ; 0.174
Kint (1/day)	θ12	0.025	8.76	0.0207 ; 0.0293
Kdeg (1/day)	θ13	0.101	12.8	0.0754 ; 0.126
Qp_2 (L/day)	θ14	52.8	6.56	46 ; 59.6
Vp_2 (L)	θ15	0.962	4.18	0.883 ; 1.04
Kb * 1000 (1/day/(ng/mL))	θ16	0.247	12.6	0.186 ; 0.308
R_{MAX}	θ17	1490	13.3	1110 ; 1880
$CL_{MLTITR4}$	θ18	0 FIX	-	-
Kss_{Lilly}	θ20	1.74	7.98	1.47 ; 2.02
CL_{TRT6}	θ21	3.12	7.91	2.64 ; 3.61
$Kint_{AGC}$	θ22	0 FIX	-	-
CL_{TRT8}	θ23	1.57	6.69	1.36 ; 1.78
$Thresh_{LTITRV}$	θ24	6.55	2.3	6.26 ; 6.85
$CL_{LTITRV78}$	θ25	0.86	13.4	0.634 ; 1.09
$CL_{MLTITR7}$	θ26	0.0964	41.7	0.0176 ; 0.175

SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate; 95% CI: 95% confidence interval. CL: clearance; Vc, Vp, and Vp2: volumes of central and 2 peripheral compartments; Q and Qp_2: inter-compartmental clearance of the peripheral compartments; BASE: concentration of target (in drug units) at baseline; K_{SS}: quasi-steady-state constant; Kint: internalization rate constant; K_{deg}: target degradation rate constant; K_b: association rate constant for non-renewable target; R_{MAX}: concentration of non-renewable target (in drug units) at baseline; CL_{WT}, Vc_{WT}, Vp_{WT}: power coefficients for dependence of CL, Vc, and Vp on body weight; CL_{HAHA2}, $CL_{MLTITR4}$, $CL_{LTITRV78}$, $CL_{MLTITR7}$: slope of fractional increase of CL with HAHA2 in Protégé, with MLTITR in TN-10, with LTITRV in PROTECT, and with MLTITR in Lilly PROTECT respectively; $Thresh_{LTITRV}$: threshold for LTITRV; Kss_{Lilly}: multiplicative effect of Lilly product on Kss; CL_{TRT6} and CL_{TRT8}: multiplicative effect of AGC in Study 004 and AGC in PROTECT respectively on CL; $Kint_{AGC}$: Kint for AGC.

Source: Applicant's Population PK Modeling Report (07 November 2023), Table 11, page 40.

(Table 12 continued)

Parameter		Estimate	RSE (%)	95%CI	CV (%)	Shrinkage (%)
ω^2_{CL}	Ω(1,1)	0.123	8.27	0.103 ; 0.143	35.1	18.4
ω^2_{Kss}	Ω(2,2)	0.178	12.7	0.134 ; 0.223	42.2	44.6
ω^2_{Q}	Ω(3,3)	0.271	10.2	0.217 ; 0.325	52.0	40.8
ω^2_{Vp}	Ω(4,4)	0.088	12.3	0.0667 ; 0.109	29.7	31.0
ω^2_{σ}	Ω(5,5)	0.036	10.7	0.0284 ; 0.0435	19.0	37.9
ω^2_{Qp2}	Ω(6,6)	0.180	29.3	0.0765 ; 0.283	42.4	30.0
ω^2_{Vc}	Ω(7,7)	0.028	15.8	0.0194 ; 0.0367	16.7	11.5
ω^2_{Kb}	Ω(8,8)	0.350	38.4	0.0865 ; 0.613	59.1	72.3
σ_{prop}	θ5	0.289	2.31	0.276 ; 0.303	28.9	15.0
EPS_{ST4}	θ11	0.274	4.04	0.252 ; 0.296	-	-

SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate;. 95% CI: 95% confidence interval. CV: coefficient of variation; ω^2_{CL}, ω^2_{Kss}, ω^2_{Vp}, ω^2_{Q}, ω^2_{Kb}, ω^2_{σ}: variances of inter-individual random effects for CL, Kss, Vp, Q, Kb, and residual error; ω^2_{Qp2}, ω^2_{Vc}: variances of inter-individual random effects for Qp_2 and Vc for subjects with dense sampling; EPS_{ST4}: fraction of standard deviation for the residual error in healthy subjects (study PRV-031-004).

Source: Applicant's Population PK Modeling Report (07 November 2023), Table 12, page 41.

Table 13. Additional Parameter Estimates from the Refined Final PK Model for Course 2

Parameter		Estimate	RSE (%)	95%CI
BASE2	θ27	0.644	4.24	0.591 ; 0.698
F_{MTITR2}	θ28	1.61	10.6	1.28 ; 1.95
T_{50} (day)	θ29	7.47	13.1	5.56 ; 9.39
γ	θ30	4.36	13.8	3.18 ; 5.54

SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate; 95% CI: 95% confidence interval. BASE2: fraction of BASE at the start of Course 2; F_{MTITR2}, T_{50} and γ: parameters that describe time-dependent bioavailability in course 2 as follows

$$EFFmax = [F_{MTITR2} * (MTITR2 - Thresh_{LTITRV})/3.8]^{\gamma}$$

$$F = 1/(1 + EFFmax * TIME^5/(T_{50}^5 + TIME^5)).$$

Source: Applicant's Population PK Modeling Report (07 November 2023), Table 13, page 42.

(Table 13 continued)

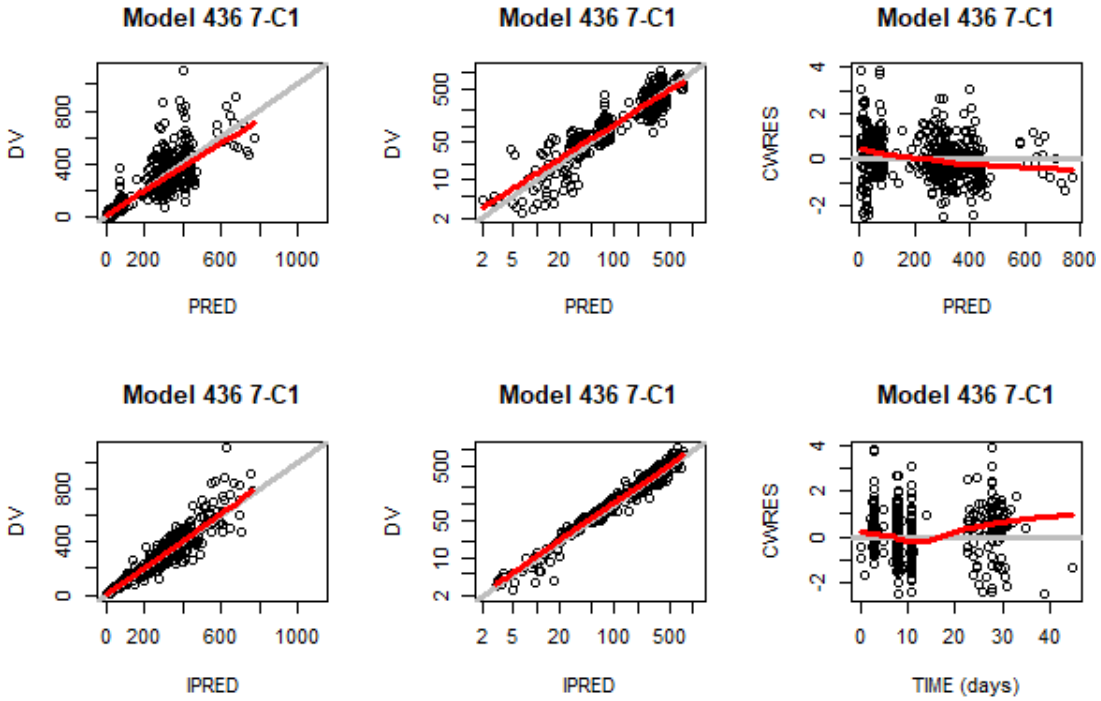
Parameter		Estimate	RSE (%)	95%CI	CV (%)	Shrinkage (%)
ω^2_{CL}	Ω(1,1)	0.0872	12.0	0.0667 ; 0.108	29.5	12.6
$\omega_{CL,CL2}$	Ω(2,1)	0.0624	24.9	0.032 ; 0.0929	R=0.439	-
ω^2_{CL2}	Ω(2,2)	0.232	12.0	0.178 ; 0.287	48.2	15.2
ω^2_{T50}	Ω(10,10)	0.139	26.4	0.0668 ; 0.21	0.372	35.4

Note: ω^2_{CL}, ω^2_{CL2}, ω^2_{T50}: variances of inter-individual random effects for CL in courses 1 and 2 respectively, and for T50 ; $\omega_{CL,CL2}$: and R: covariance and correlation between CL and CL2.
Source: Applicant's Population PK Modeling Report (07 November 2023), Table 14, page 43.

The final PK model was evaluated using goodness of fit (GOF) plots and prediction-correction visual predict checks (pcVPC) plots. Figure 10 and Figure 11 show the GOF plots and pcVPC plots for the PROTECT study.

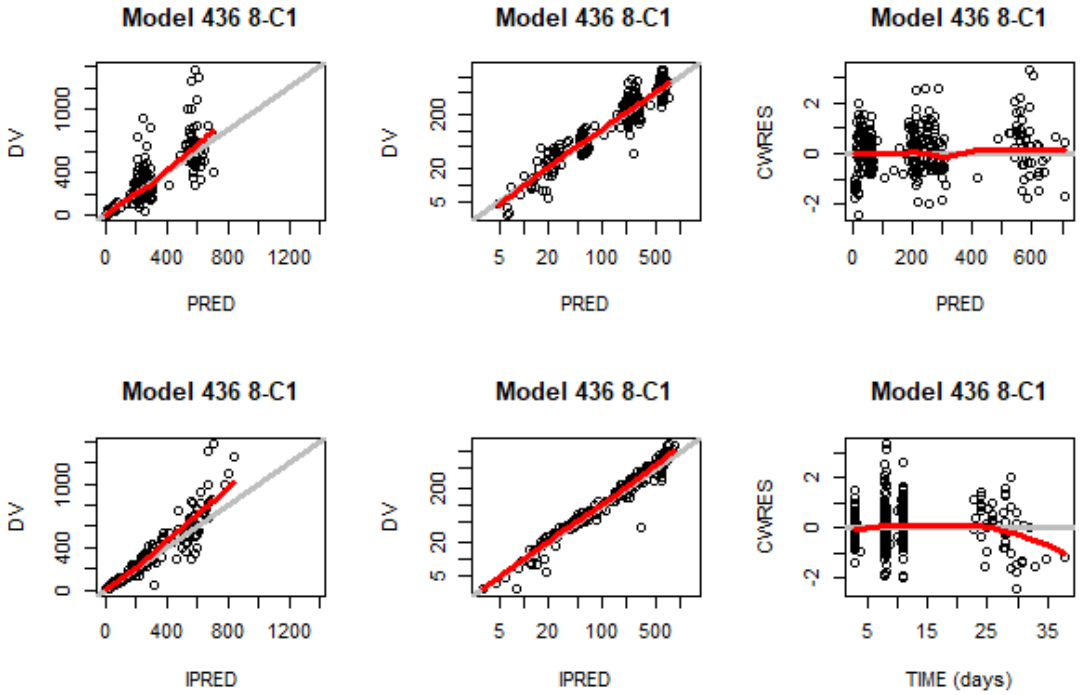
Figure 10. Goodness of Fit Plot from Final PK Model for PROTECT Study, by Course and Product

Course 1: Lilly product



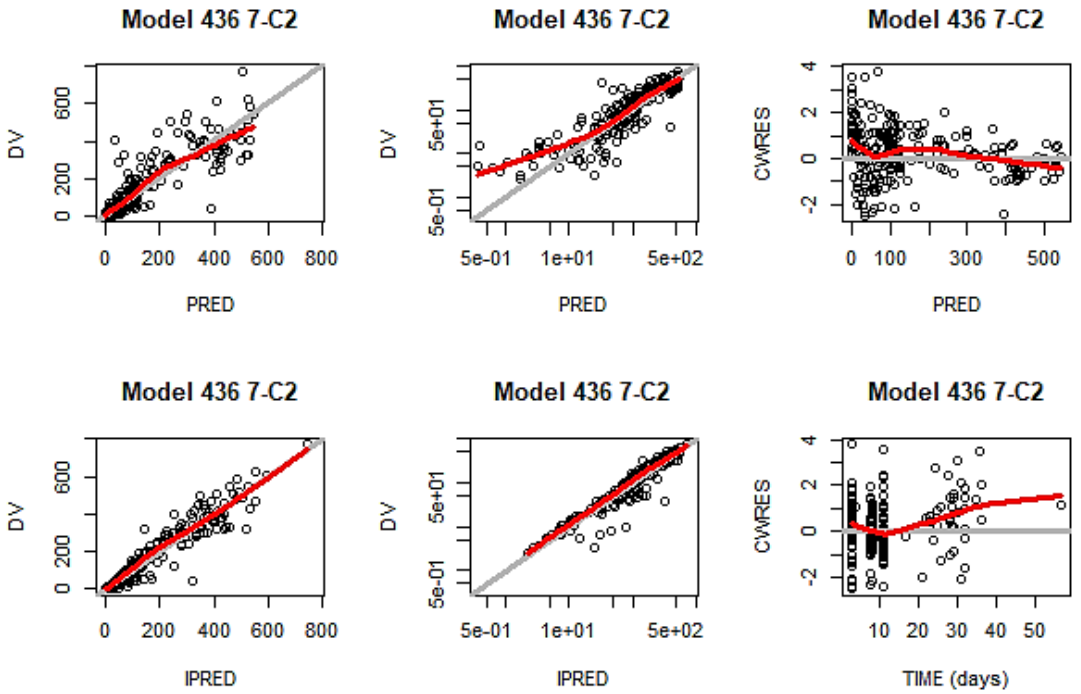
Note: "7-C1" in the plot titles denote TRT=7 (Lilly) in Course 1.

Course 1: AGC product



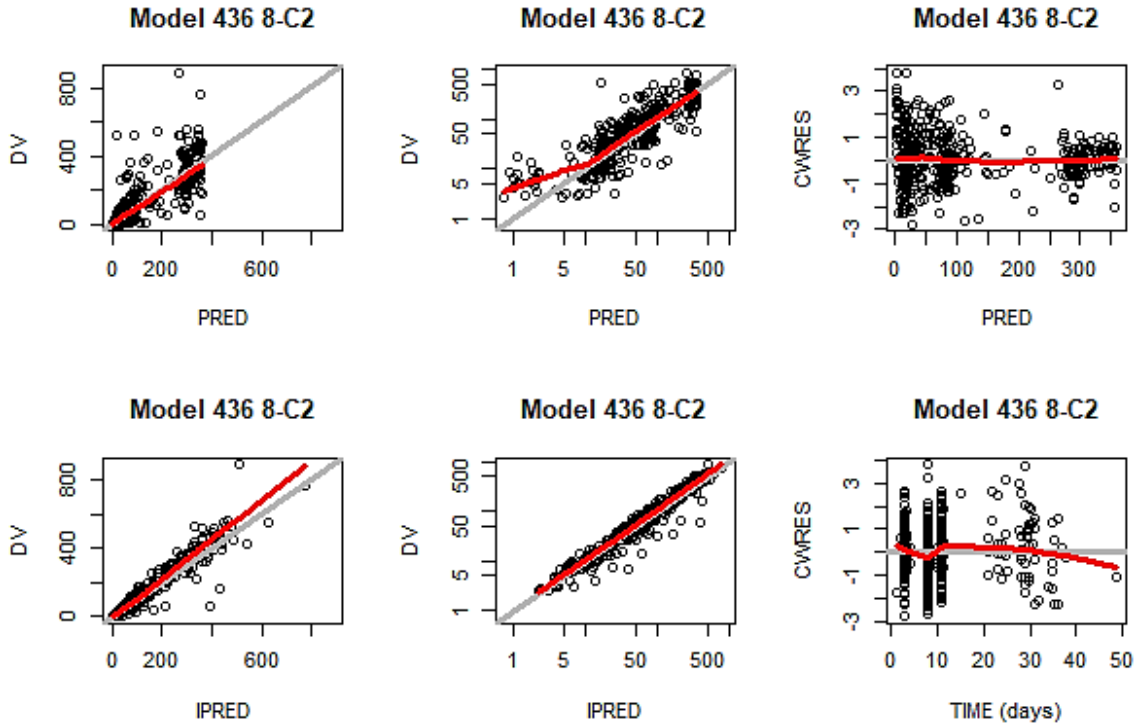
Note: "8-C1" in the plot titles denote TRT=8 (AGC) in Course 1.

Course 2: Lilly product



Note: "7-C2" in the plot titles denote TRT=7 (Lilly) in Course 2.

Course 2: AGC product



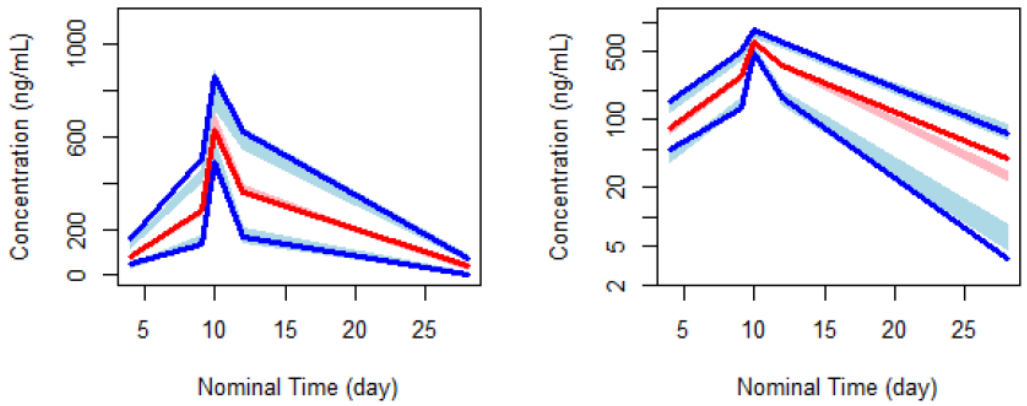
Note: "8-C2" in the plot titles denote TRT=8 (AGC) in Course 2.

DV: Observed concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; TIME: time from start of the first infusion; IWRES: individual weighted residuals. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the loess (local regression smoother) trend lines. All plots are using arithmetic scales except for the plots in the middle column that are using log scales.

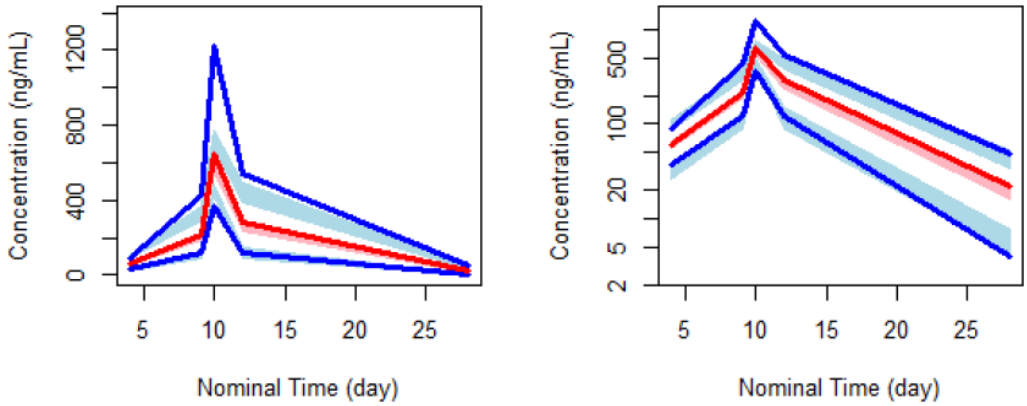
Source: Applicant's Population PK Modeling Report (07 November 2023), Figures 16 - 19, pages 62 - 65.

Figure 11. Visual Predictive Check plots from Final PK Model for PROTECT Study, by Course and Product

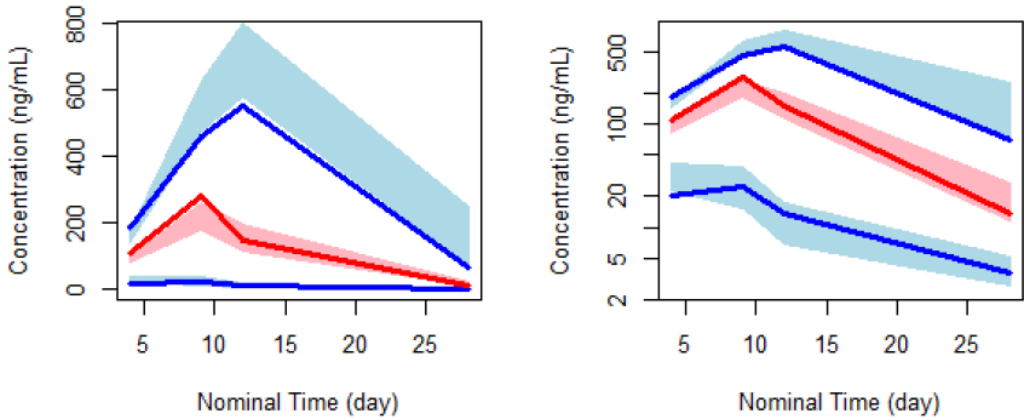
Course 1: Lilly product



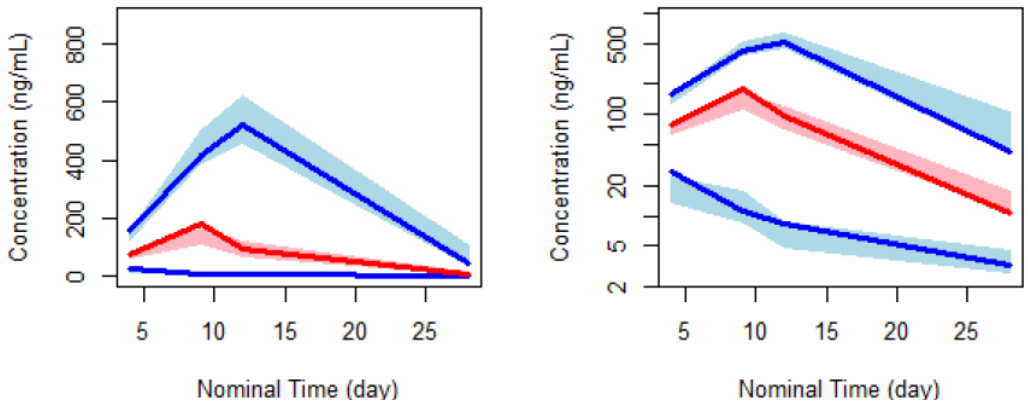
Course 1: AGC product



Course 2: Lilly product



Course 2: AGC product



The left figures are on arithmetic scales and the right figures are on semi-log scales. The solid lines are median (red), and 5th and 95th percentiles (blue) of observed concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations from the final model. The simulated values were computed from 500 simulated trials with dosing, sampling, and covariate values in the dataset. Nominal Time for data on Day 9 was slightly modified to separate troughs and peaks on the plots.
Source: Applicant's Population PK Modeling Report (07 November 2023), Figures 26 - 29, pages 72 - 75.

Reviewer's Comments:

Overall, the Applicant's refined PK model adequately describes the individual observed concentrations of teplizumab and their variability in patients from all studies (including the completed PROTECT study), dosing regimens and products.

- PK parameters for the refined Course 1-PK model (with additional data from PROTECT study) were close to the corresponding parameters estimated in the prior model
- The PK parameters (fixed-effects parameters) from the final PK model (describing Course 1 and Course 2 PK data) were estimated with good precision (RSE<14%), except for the additional effect of maximum ADA titer (MLTITR) on CL of the Lilly product in PROTECT study (RSE=41.7%).
- The estimated inter-individual random effect (eta) shrinkages were low for the parameters with estimated meaningful covariate effects, particularly CL (<20%). Shrinkage for the residual (intra-individual) error was low (21 % for final model with Course 2 PK data) indicating the informativeness of the GOF plots to diagnose structural and residual error model misspecifications.
- The GOF plots and the pcVPC plots show that the Applicant's PK model reasonably describes the median and variability (5th and 95th percentile) of the observed teplizumab concentrations of the Lilly and AGC products during both courses of treatment in PROTECT study.
- The PK model was considered acceptable for estimating teplizumab exposure metrics and predicting the ADA effect on exposure for the Lilly and AGC product in both treatment courses of PROTECT study.

4.2.2 Applicant's Prediction and Comparison of Exposures between Courses and Products

The final PK model was used to predict individual concentrations and estimate individual exposure metrics (AUC_{inf}, Cmax, AUC_{0-13}, and $Ctrough_{Last}$ 24 hours after the last dose) in both treatment courses of the PROTECT study, using actual dosing and covariates of each subject. All timepoints of the analysis dataset (including BLQ observations) supplemented by points at the end of each infusion, Ctrough at Day 4, 9, 12 and 13 (one day after the last planned 12th dose in each course), and at 128 days after start of each course. AUC_{inf} was estimated as AUC for 128 days from the start of each course. AUC_{0-13} represents AUC over a 12-day period (from zero to 24 hours after the planned 12th dose).

Exposures were lower in Course 2 compared to Course 1, Regardless of drug's product (Lilly and AGC), due to higher prevalence of ADAs and higher ADA titers early during and after Course 2.

- For the Lilly product, geometric mean AUCinf, AUC_{0-13}, $Ctrough_{Last}$, and Cmax were 51%, 37%, 77%, and 26% lower in Course 2 compared to Course 1 (Table 14 and Table 15).
- For the AGC product, geometric mean AUCinf, AUC_{0-13}, $Ctrough_{Last}$, and Cmax were 51%, 41%, 81%, and 20% lower in Course 2 compared to Course 1 (Table 14 and Table 15).

Exposure to teplizumab in both treatment courses was higher in participants treated with the Lilly product compared to the AGC product (Table 16). AUCinf, $AUC_{0\text{-}13}$, $Ctrough_{Last}$, and Cmax, for AGC product were estimated to be:

- 22%, 17%, 27%, and 12% lower than the Lilly product in Course 1,
- 23%, 22%, 37%, and 5% lower than the Lilly product in Course 2.

Table 14. Estimated Exposure Metrics in Course 1 of PROTECT study, Stratified by Product

Exposure Measure	Statistic	Product	
		AGC Biologics (N=65)	Lilly (N=147)
AUC_{inf} (ng/mL*day)	Mean (SD)	4384 (1525)	5745 (2052)
	Median (Range)	4145 (209-9434)	5817 (357-12408)
	GeoMean (CV[b])	4054 (0.51)	5194 (0.59)
C_{max} (ng/mL)	Mean (SD)	758 (122)	855 (148)
	Median (Range)	748 (124-1071)	865 (303-1257)
	GeoMean (CV[b])	741 (0.26)	840 (0.2)
$AUC_{0\text{-}13}$ (ng/mL*day)	Mean (SD)	2864 (783)	3490 (967)
	Median (Range)	2825 (51-5193)	3533 (127-6644)
	GeoMean (CV[b])	2651 (0.61)	3183 (0.65)
C_{trough} Day 4[a] (ng/mL)	Mean (SD)	60.8 (18.9)	79.3 (28.8)
	Median (Range)	60 (12-112.2)	74.8 (3.4-244.3)
	GeoMean (CV[b])	57.4 (0.39)	73.3 (0.51)
C_{trough} Day 9[a] (ng/mL)	Mean (SD)	219 (71.6)	281 (84.5)
	Median (Range)	204 (109-478)	279 (19-570)
	GeoMean (CV[b])	209 (0.31)	264 (0.43)
C_{trough} Day 12[a] (ng/mL)	Mean (SD)	279 (104)	374 (129)
	Median (Range)	266 (50-621)	374 (10-762)
	GeoMean (CV[b])	259 (0.45)	333 (0.73)
$C_{troughLast}$ (ng/mL)	Mean (SD)	287.2 (104.1)	395.2 (135.6)
	Median (Range)	269.3 (20.6-650.2)	398 (59.6-816.7)
	GeoMean (CV[b])	266.4 (0.47)	364.7 (0.48)

Abbreviations: AUC_{inf}=AUC from zero to infinity; C_{max}=maximum concentration; $AUC_{0\text{-}13}$=AUC over the dosing interval, from zero to 24 hours after the last administered dose; $C_{troughLast}$=concentration one day after the last administered dose; CV=coefficient of variation; SD=standard error. Total AUC for 128 days from dosing start was used as AUC_{inf}.

Individual exposure parameters were computed using the final model, individual model parameters, and actual individual dosing history.

a N=145 on Day 4 and Day 12, and 143 on Day 9 for Eli Lilly product; N=63 and 62 on Days 9 and 12, respectively, for the AGC Biologics product.

b CV computed for a lognormal distribution as sqrt(exp(var(log(data)))-1).

Source: Applicant's Summary of Clinical Pharmacology studies, Table 6, page 28.

Table 15. Estimated Exposure Metrics in Course 2 of PROTECT study, stratified by product

Exposure Measure	Statistic	Teplizumab Product	
		AGC Biologics (N=122)	Lilly (N=66)
AUC_{inf} (ng/mL×day)	Mean (SD)	2961 (2378)	3760 (2697)
	Median (Range)	2146 (140-11724)	3217 (120-10886)
	GeoMean (CV[b])	1969 (1.32)	2543 (1.44)
C_{max} (ng/mL)	Mean (SD)	619 (201)	661 (230)
	Median (Range)	572 (323-1276)	593 (175-1246)
	GeoMean (CV[b])	588 (0.33)	621 (0.38)
AUC_{0-13} (ng/mL×day)	Mean (SD)	2123 (1444)	2665 (1565)
	Median (Range)	1726 (135-6496)	2636 (119-6301)
	GeoMean (CV[b])	1552 (1.09)	1994 (1.16)
C_{trough} Day 4 (ng/mL)	Mean (SD)	80 (35.7)	91.2 (33.7)
	Median (Range)	74.6 (3.8-214.7)	96 (7.3-191)
	GeoMean (CV[b])	70.1 (0.66)	81.3 (0.64)
C_{trough} Day 9[a] (ng/mL)	Mean (SD)	173 (137.4)	239 (151.5)
	Median (Range)	143 (3-626)	244 (1-596)
	GeoMean (CV[b])	105 (1.84)	147 (2.38)
C_{trough} Day 12[a] (ng/mL)	Mean (SD)	153 (163)	221 (194)
	Median (Range)	64 (1-771)	154 (0-744)
	GeoMean (CV[b])	62 (3.53)	103 (3.96)
C_{trough} Last (ng/mL)	Mean (SD)	148 (165.4)	206.8 (201.3)
	Median (Range)	46.4 (0.9-797.1)	120.4 (0.4-774.7)
	GeoMean (CV[b])	52.4 (4.36)	83.4 (4.92)

Abbreviations: AUC_{inf}=AUC from zero to infinity; C_{max}=maximum concentration; AUC_{0-13}=AUC over the dosing interval, from zero to 24 hours after the last administered dose; $C_{troughLast}$=concentration one day after the last administered dose; CV=coefficient of variation; SD=standard error.

a N=64 on Days 9 and 12 for Eli Lilly product; N=117 on Day 9 for the AGC product.

b CV computed for a lognormal distribution as sqrt(exp(var(log(data)))-1)

Source: Applicant's Summary of Clinical Pharmacology studies, Table 7, page 29.

Table 16. Comparison of Estimated Exposure Metrics between Products in PROTECT Study

Exposure Measure	GMR (90% CI)[a]	
	Course 1	Course 2
AUC_{inf}	0.780 (0.690-0.883)[b]	0.774 (0.598-1.00)
C_{max}	0.883 (0.833-0.937)[b]	0.947 (0.87-1.03)
AUC_{0-13}	0.833 (0.721-0.961)	0.778 (0.62-0.976)
C_{trough} Day 4	0.783 (0.700-0.875)	0.862 (0.742-1.00)
C_{trough} Day 9	0.789 (0.717-0.869)	0.712 (0.513-0.988)
C_{trough} Day 12	0.777 (0.669-0.903)	0.599 (0.395-0.910)
C_{trough} Last	0.731 (0.654-0.816)[b]	0.628 (0.403-0.977)

Abbreviations: AUC_{inf}=area under the concentration-time curve from zero to infinity; AUC_{0-13}=AUC over the dosing interval from zero to one day after the last administered dose; CI=confidence interval; C_{max}=maximum concentration; C_{trough} Last=concentration 24 hours after the last dose, GMR=geometric mean ratio.

a Unless noted, the AGC/Lilly GMR was computed using t-test with equal variances as determined by the median-based Levene's test.

b The GMR was computed using t-test with unequal variances as determined by the median-based Levene's test.

Source: Applicant's Summary of Clinical Pharmacology studies, Table 8, page 30.

Reviewer's Comments:

- The reviewer agrees with the Applicant's assessment regarding the estimated difference exposure metrics between the Lilly product and the AGC product in PROTECT study, taking into account actual dosing and covariates (differences in ADA titers effect) of each subject.
- Although, the AGC product showed lower exposure compared to the Lilly product consistent with the previous PK sub-study findings, no dose adjustment for the AGC product was deemed warranted for the intended indication in patients with stage 3 T1D, as the evaluation of the clinical data from PROTECT study did not find a difference in treatment effect between products, with patients treated exclusively with either the Lilly or AGC product during both courses showing a significant treatment effect of teplizumab compared to placebo, in terms of change from baseline in C-peptide AUC after 4-hour MMTT at Week 78 (primary endpoint).
- Apart from the effect of teplizumab product on treatment effect, the review team evaluated the difference in treatment effect in patients with lower exposure in Course 2 compared Course 1 of treatment (regardless of drug product).

  Patients with lower exposure in Course 2 were defined as having an AUC_{0-28} (AUC to time zero up to Day 28) below 2000 ng*Day/mL. The AUC_{0-28} threshold was defined based on the range of exposure during Course 1 (regardless of product) and corresponded to the minimum AUC_{0-28} estimated in subjects who received all 12 doses of teplizumab during Course 1 (Figure 12). As little to no drug accumulation is expected beyond Day 28 (estimated half-life of approximately 3 days) and the last PK samples were collected in almost all patient around the planned visit on Day 28 and, AUC_{0-28} was selected as the exposure metric.

Anong patients who received all 12 teplizumab doses in Course 2, 55 of 115 patients (48%) had an $AUC_{0\text{-}28}$ < 2000 in Course 2, in AGC arm. In Lilly arm, 20 of 64 patients (31%) had an $AUC_{0\text{-}28}$ < 2000 in Course 2.

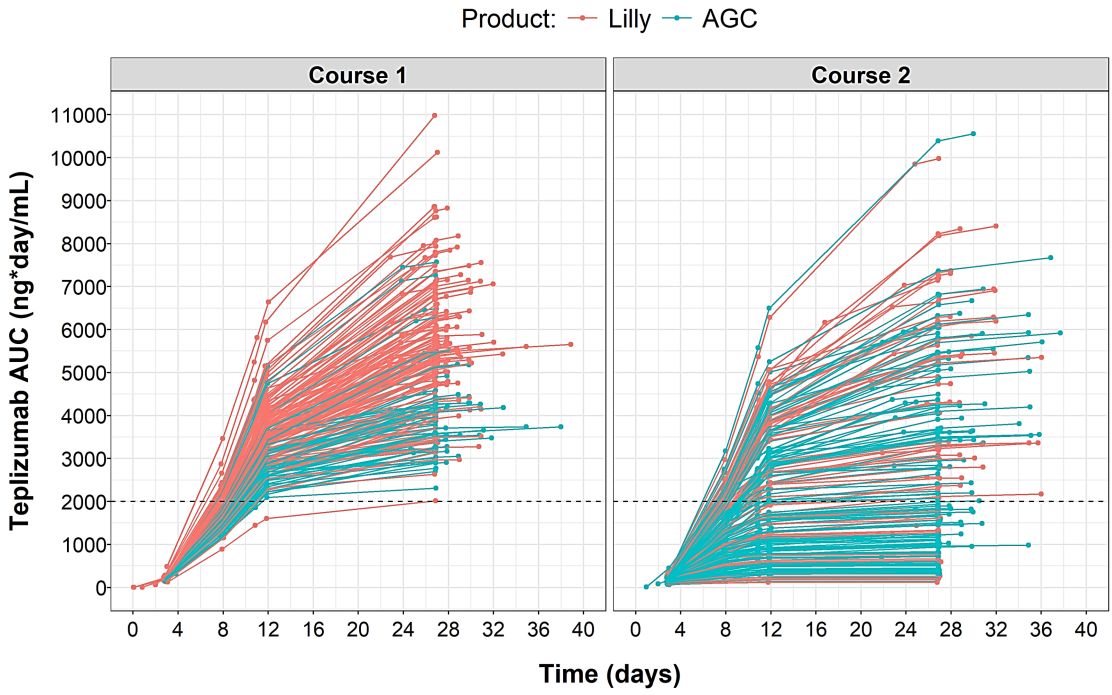
Patients with lower exposure have higher median ADA titers on days 1 to 56 (Table 17). Few of these patients, have no measurable or low ADA titer between Day 1 to 12.

In terms of ADA titer quantiles (Table 18), 84% of patients in AGC arm with low exposure, had a Ln(highest ADA) titer ≥ 11.03. However, 13% of patients with Ln(highest ADA) titer ≥ 11.03 had $AUC_{0\text{-}28}$ ≥ 2000. On Day 1, 74.5% of patients in AGC arm with low exposure had a Ln(ADA) titer on Day1 ≥ 6.17. However, 13% of patients with Ln(ADA) titer on Day 1 ≥ 6.17 had an $AUC_{0\text{-}28}$ ≥ 2000.

The statistical review team assessment of the difference in treatment effect in patients with lower exposure (TZP-lo: $AUC_{0\text{-}28}$ < 2000, n=83) versus higher exposure (TZP-hi: $AUC_{0\text{-}28}$ ≥ 2000, n=105) in Course 2 did not find a statistically significant difference between the 2 groups, with a least square mean (LS-mean) difference and standard error (95%CI) of 0.03 (-0.01, 0.08) corresponding to a 2-sided p-value = 0.16.

In addition, both exposure groups were superior to placebo (LS-mean difference (TZP-hi vs. placebo): 0.15 (0.11, 0.20), 2-sided p-value < 0.0001, and LS-mean difference (TZP-lo vs. placebo): 0.12 (0.07, 0.17), 2-sided p-value < 0.0001).

Figure 12. Cumulative AUC in Patients Who Received All 12 Doses of Teplizumab in Course 1 and All Patients in Course 2



Source: FDA reviewer.

Table 17. Summary of ADA titers in Course 2 of PROTECT Study in Fully Adherent Patients (All 12 Doses), Stratified by Product and $AUC_{0\text{-}28}$ Threshold of 2000 ng*Day/mL

	Lilly in Course 2		AGC in Course 2	
	AUC[0-Day28] ≥ 2000 (N=44)	AUC[0-Day28] < 2000 (N=20)	AUC[0-Day28] ≥ 2000 (N=60)	AUC[0-Day28] < 2000 (N=55)
Highest Ln ADA Titer (Day 1 to 56)				
Mean (SD)	8.22 (2.28)	12.3 (1.17)	7.05 (2.83)	11.9 (1.25)
Median [Min, Max]	8.95 [0, 11.7]	12.4 [10.3, 14.5]	6.87 [0, 14.5]	11.7 [9.64, 14.5]
Ln ADA Titer (Day 1)				
Mean (SD)	2.52 (3.00)	7.16 (1.99)	2.26 (2.71)	7.05 (2.10)
Median [Min, Max]	0 [0, 8.95]	8.25 [4.09, 11.0]	0 [0, 8.25]	7.56 [0, 10.3]
Missing	1 (2.3%)	1 (5.0%)	1 (1.7%)	1 (1.8%)
Ln ADA Titer (Day 6)				
Mean (SD)	3.06 (2.64)	8.25 (2.35)	2.55 (2.76)	6.98 (2.04)
Median [Min, Max]	4.09 [0, 7.56]	8.25 [4.79, 13.8]	0 [0, 7.56]	6.87 [0, 11.0]
Missing	1 (2.3%)	1 (5.0%)	2 (3.3%)	1 (1.8%)
Ln ADA Titer (Day 12)				
Mean (SD)	7.26 (2.30)	11.4 (2.91)	5.95 (2.94)	11.7 (1.29)
Median [Min, Max]	7.22 [0, 11.0]	11.7 [0, 14.5]	6.17 [0, 14.5]	11.7 [8.25, 13.8]
Ln ADA Titer (Day 28)				
Mean (SD)	7.69 (2.52)	12.0 (1.21)	6.68 (3.04)	11.3 (1.32)
Median [Min, Max]	8.25 [0, 11.0]	11.7 [9.64, 14.5]	6.87 [0, 13.1]	11.0 [6.87, 14.5]
Missing	0 (0%)	1 (5.0%)	3 (5.0%)	2 (3.6%)
Ln ADA Titer (Day 56)				
Mean (SD)	7.20 (2.60)	11.2 (1.23)	5.56 (3.41)	10.9 (1.31)
Median [Min, Max]	7.56 [0, 11.7]	11.0 [9.64, 14.5]	6.17 [0, 12.4]	11.0 [7.56, 13.8]
Missing	2 (4.5%)	2 (10.0%)	1 (1.7%)	2 (3.6%)
Age (years)				
Mean (SD)	12.1 (2.24)	11.6 (2.56)	12.6 (2.51)	12.1 (2.66)
Median [Min, Max]	12.0 [8.00, 17.0]	12.0 [8.00, 17.0]	13.0 [8.00, 17.0]	12.0 [8.00, 17.0]
Body weight (kg)				
Mean (SD)	51.7 (16.9)	45.5 (13.9)	54.4 (16.1)	49.3 (15.7)
Median [Min, Max]	50.0 [29.0, 111]	41.4 [28.4, 80.0]	53.6 [14.1, 106]	49.7 [23.1, 85.1]
BSA (m2)				
Mean (SD)	1.50 (0.294)	1.39 (0.250)	1.57 (0.267)	1.46 (0.301)
Median [Min, Max]	1.45 [1.03, 2.43]	1.35 [1.04, 1.99]	1.55 [1.06, 2.38]	1.51 [0.940, 2.11]
Sex				
Male	22 (50.0%)	10 (50.0%)	33 (55.0%)	39 (70.9%)
Female	22 (50.0%)	10 (50.0%)	27 (45.0%)	16 (29.1%)

Source: FDA reviewer.

Table 18. Summary of ADA titers Quantiles in Course 2 of PROTECT Study in Fully Adherent Patients (All 12 Doses), Stratified by Product and AUC_{0-28} Threshold of 2000 ng*Day/mL

	Lilly in Course 2		AGC in Course 2	
	AUC[0-Day28] ≥ 2000 (N=44)	AUC[0-Day28] < 2000 (N=20)	AUC[0-Day28] ≥ 2000 (N=60)	AUC[0-Day28] < 2000 (N=55)
Highest Ln ADA Titer (Day 1 to 56)				
Q1: Lilly [0 - <7.56] / AGC [0 - <6.17]	13 (29.5%)	0 (0%)	22 (36.7%)	0 (0%)
Q2: Lilly [7.56 - <9.64] / AGC [6.17 - <8.25]	12 (27.3%)	0 (0%)	17 (28.3%)	0 (0%)
Q3: Lilly [9.64 - <10.33] / AGC [8.25 - <11.03]	10 (22.7%)	0 (0%)	13 (21.7%)	9 (16.4%)
Q4: Lilly [10.33 - <11.72] / AGC [11.03 - <12.41]	8 (18.2%)	5 (25.0%)	5 (8.3%)	21 (38.2%)
Q5: Lilly [11.72 - 14.49] / AGC [12.41 - 14.49]	1 (2.3%)	15 (75.0%)	3 (5.0%)	25 (45.5%)
Ln ADA Titer (Day 1)				
Q2: Lilly [0 - <4.09] / AGC [0 - <4.79]	25 (56.8%)	0 (0%)	42 (70.0%)	3 (5.5%)
Q3: Lilly [4.09 - <5.48] / AGC [4.79 - <6.17]	5 (11.4%)	4 (20.0%)	9 (15.0%)	10 (18.2%)
Q4: Lilly [5.48 - <7.56] / AGC [6.17 - <7.56]	11 (25.0%)	4 (20.0%)	6 (10.0%)	13 (23.6%)
Q5: Lilly [7.56 - 11.03] / AGC [7.56 - 10.33]	2 (4.5%)	11 (55.0%)	2 (3.3%)	28 (50.9%)
Missing	1 (2.3%)	1 (5.0%)	1 (1.7%)	1 (1.8%)
Ln ADA Titer (Day 6)				
Q2: Lilly [0 - <4.79] / AGC [0 - <4.79]	24 (54.5%)	0 (0%)	36 (60.0%)	5 (9.1%)
Q3: Lilly [4.79 - <5.48] / AGC [4.79 - <6.17]	7 (15.9%)	2 (10.0%)	15 (25.0%)	11 (20.0%)
Q4: Lilly [5.48 - <7.836] / AGC [6.17 - <7.56]	12 (27.3%)	6 (30.0%)	5 (8.3%)	13 (23.6%)
Q5: Lilly [7.836 - 13.8] / AGC [7.56 - 11.03]	0 (0%)	11 (55.0%)	2 (3.3%)	25 (45.5%)
Missing	1 (2.3%)	1 (5.0%)	2 (3.3%)	1 (1.8%)
Ln ADA Titer (Day 12)				
Q1: Lilly [0 - <6.17] / AGC [0 - <4.79]	11 (25.0%)	1 (5.0%)	14 (23.3%)	0 (0%)
Q2: Lilly [6.17 - <7.56] / AGC [4.79 - <7.56]	11 (25.0%)	0 (0%)	28 (46.7%)	0 (0%)
Q3: Lilly [7.56 - <9.64] / AGC [7.56 - <11.03]	12 (27.3%)	0 (0%)	15 (25.0%)	10 (18.2%)
Q4: Lilly [9.64 - <11.03] / AGC [11.03 - <11.72]	9 (20.5%)	2 (10.0%)	1 (1.7%)	15 (27.3%)
Q5: Lilly [11.03 - 14.49] / AGC [11.72 - 14.49]	1 (2.3%)	17 (85.0%)	2 (3.3%)	30 (54.5%)
Ln ADA Titer (Day 28)				
Q1: Lilly [0 - <6.17] / AGC [0 - <5.48]	10 (22.7%)	0 (0%)	19 (31.7%)	0 (0%)
Q2: Lilly [6.17 - <8.25] / AGC [5.48 - <8.25]	10 (22.7%)	0 (0%)	21 (35.0%)	1 (1.8%)
Q3: Lilly [8.25 - <10.33] / AGC [8.25 - <10.75]	16 (36.4%)	1 (5.0%)	10 (16.7%)	16 (29.1%)
Q4: Lilly [10.33 - <11.306] / AGC [10.75 - <11.72]	8 (18.2%)	6 (30.0%)	2 (3.3%)	12 (21.8%)
Q5: Lilly [11.306 - 14.49] / AGC [11.72 - 14.49]	0 (0%)	12 (60.0%)	5 (8.3%)	24 (43.6%)
Missing	0 (0%)	1 (5.0%)	3 (5.0%)	2 (3.6%)
Ln ADA Titer (Day 56)				
Q1: Lilly [0 - <5.618] / AGC [0 - <4.79]	13 (29.5%)	0 (0%)	18 (30.0%)	0 (0%)
Q2: Lilly [5.618 - <8.25] / AGC [4.79 - <7.56]	9 (20.5%)	0 (0%)	22 (36.7%)	0 (0%)
Q3: Lilly [8.25 - <9.64] / AGC [7.56 - <10.33]	12 (27.3%)	0 (0%)	12 (20.0%)	11 (20.0%)
Q4: Lilly [9.64 - <11.03] / AGC [10.33 - <11.306]	6 (13.6%)	8 (40.0%)	6 (10.0%)	21 (38.2%)
Q5: Lilly [11.03 - 14.49] / AGC [11.306 - 13.8]	2 (4.5%)	10 (50.0%)	1 (1.7%)	21 (38.2%)
Missing	2 (4.5%)	2 (10.0%)	1 (1.7%)	2 (3.6%)

Source: FDA reviewer.

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JAYABHARATHI VAIDYANATHAN
03/09/2026 10:00:59 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW MEMO

CLINICAL STUDIES

NDA/BLA #:	BLA 761183
Supplement #:	S-010
Drug Name:	TZIELD (teplizumab-mzwv), by intravenous infusion once daily for 12 days
Indication(s):	Delay the progression of Stage 3 Type 1 diabetes (T1D) in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D
Applicant:	Provention Bio a Sanofi Company
Date(s):	Stamp Date: July 21, 2025
	Goal Date (4-Month Goal Date): November 21, 2025
Review Priority:	Commissioner's National Priority Voucher (CNPV) Pilot Program
Biometrics Division:	DB II
Statistical Reviewer:	Wenda Tu (Statistical Reviewer)
Statistical Analysts:	Emily Nguyen, Xiaofeng Wang/ Liping Sun (Supervisor)
Concurring Reviewers:	Yoonhee Kim (Team Lead)
Medical Division:	DDLO
Clinical Team:	Lauren WoodHeickman/Mahtab Niyyati (TL)
Project Manager:	Supendeep Dosanjh

Keywords:

Type 1 diabetes (T1D), Commissioner's National Priority Voucher (CNPV) Pilot Program, Surrogacy analysis, Accelerated approval, Reasonably likely surrogate endpoint (RLSE)

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1 STATISTICAL EVALUATION

1.1 Evaluation of Efficacy

1.1.1 Statistical Methodologies

Information in this section is summarized based on SAP for Study PROTECT, Version 5.0, dated March 17, 2023. The study PROTECT initiated on April 5, 2019, and completed on May 1, 2023.

Sample Size Determination

The sample size for PROTECT was determined based on the following assumptions:

1. The mean C-peptide log (AUC + 1) for the placebo group = 0.25
2. A difference of at least 40% in C-peptide response between teplizumab and placebo
3. Standard deviation for C-peptide log (AUC + 1) = 0.19

Specifically, based on Assumption 1, the mean C-peptide AUC for the placebo group = exp(0.25) – 1 = 0.28. Together with Assumption 2, the mean C-peptide AUC for the teplizumab group = 0.28 * (1 + 40%) = 0.392. Hence, the assumed treatment difference (teplizumab vs. placebo) with respect to C-peptide log (AUC + 1) = log (0.392 + 1) – 0.25 = 0.08. Consequently, approximately 300 subjects, randomized in a 2:1 ratio to teplizumab and placebo arms, would provide 90% power, assuming a 2-sided 0.05 level and 10% dropout rate.
In practice, a total of 328 subjects were randomized in the study, with 217 subjects to the teplizumab arm, and 111 subjects to the placebo arm. The standard deviation for change from baseline in C-peptide log (AUC + 1) based on observed data from PROTECT is 0.19.

Primary Efficacy Analysis

Analysis Set

ITT Population defined as all randomized participants.

Intercurrent Events

Intercurrent events (ICEs) included use of medications disallowed according to the protocol, modified dosing schedule (MDS) due to COVID-19, premature discontinuation of study treatment, and non-adherence to the planned treatment regimen. All ICEs were handled with the treatment policy strategy.

Statistical Model

The primary endpoint was analyzed with an ANCOVA model adjusting for:

- Treatment
- Age strata (8 to 12 years [inclusive] vs. > 12 to 17 years)
- Baseline C-peptide ln (AUC + 1)

Missing primary endpoint measurements were handled with a pattern mixture multiple imputation method. Specifically, subjects with missing Week 78 measurements were classified into 2 groups based on their treatment completion status. Group 1 consisted of subjects who discontinued treatment prematurely and did not have Week 78 measurements collected, whereas

Group 2 comprised subjects who completed study treatment, but missed the Week 78 measurements. Imputation for Group 1 was performed based on data from retrieved dropouts (RDs), i.e., subjects who discontinued treatment before Week 78, but still have the Week 78 measurements collected. Imputation for Group 2 was performed based on data from treatment completers, that is, subjects who completed treatment and have the Week 78 measurements collected. For both Groups 1 and 2, the imputation model was a linear regression model with covariate adjustment: treatment, age at randomization, sex, C-peptide log (AUC + 1) at previous time points and baseline C-peptide log (AUC +1). Results from 100 multiply imputed datasets were combined via Rubin's Rule.

Reviewer's Note: The above primary analysis model does not adjust for the randomization stratification factor: screening peak C-peptide category. This is not in alignment with the current recommended practice that a covariate adjustment model should generally include strata variables.[1] *The Applicant re-analyzed the primary endpoint based on a model with proper adjustment of all strata variables in the response to the Information Request (IR) dated September 12, 2025.*

Sensitivity Analyses

To examine the robustness of the primary efficacy result to missing data, the following sensitivity analyses were performed.

- Placebo-washout imputation: This imputation method assumes that subjects from the active treatment group who discontinue treatment early have similar performance to placebo-treated subjects after treatment discontinuation. For a simple implementation, missing endpoints in the teplizumab group, regardless of missing patterns, were multiply imputed based on observed placebo data via a linear regression model adjusted for age, sex, and baseline C-peptide log (AUC + 1) values. Missing endpoints in the placebo arm were multiply imputed based on observed placebo data, using a linear regression model adjusted for age, sex, baseline and intermediate C-peptide log (AUC+ 1) values.
- Two-way tipping point analysis: Following the primary imputation procedure, each multiply imputed dataset undergoes adjustment using a pair of shift parameters (Δ_t, Δ_p), applied to the imputed values for the teplizumab arm and placebo arm, respectively. The treatment effect was subsequentially estimated from these adjusted datasets. A range of (Δ_t, Δ_p) were applied to the imputed data to fine-tune the tipping point(s), i.e., the critical threshold condition(s) where the estimated treatment effect would no longer achieve statistical significance (i.e., one-sided p-value ≥ 0.025). An assessment of whether these tipping points represent clinically plausible scenarios would provide insight regarding the robustness of the primary efficacy findings.

Assessment of Key Secondary Endpoints

Multiplicity adjustment

[1] https://www.fda.gov/media/148910/download

To control the family-wise Type 1 error, inference on the key secondary efficacy endpoints would be drawn only if the hypothesis testing on the primary endpoint achieved statistical significance. In this case, the Hochberg procedure[2] for multiplicity adjustment would be used to test the following efficacy endpoints:

- Average daily use of exogenous insulin (U/kg/day) at Week 78
- Change from baseline in A1C (%) at Week 78
- Glucose time-in-range (%) (percent of time with blood glucose between 70 and 180 mg/dL, inclusive), as assessed by continuous glucose monitoring (CGM) at Week 78
- Level 2 and Level 3 hypoglycemic event rate assessed throughout the study

Derivation of Average Daily Insulin Use Data

Participants' daily insulin use was self-reported in an eDiary for 7 days prior to randomization, and at pre-specified time points throughout the study. The average daily insulin use (U/kg/day) at each time point was derived from the eDiary data and body weight measured at each time point. The mean body weight at the closet prior and post time points were used for a timepoint with missing body weight. Participants needed to have insulin data for at least 3 days at each time point in order to calculate the average daily use. For participants who had more than 7 days of insulin use data for a given visit, the data from the 7 days that were closest to the target day were used in the calculation of average daily insulin use.

Derivation of Time-in-Range from Raw CGM data

To assess glycemic control, CGM device was provided to participants at pre-specified study visits and would stay on for the following 2 weeks. Time in range (TIR) for blood glucose was defined as the daily average percentage of time a participant's blood glucose is $\geq$ 70 mg/dL and $\leq$ 180 mg/dL. The derivation of TIR from raw CGM data is described as follows.

1. For each subject, compute the daily TIR as number of CGM readings in range divided by the total number of CGM entries for a given day. For participants with less than 8 hours of CGM entries for a given day, their daily TIR for that day was considered missing in the TIR analysis.
2. For each subject, take the average of daily TIR across the total number of available days. For participants who have less than 3 days of daily TIR data for a given visit, the average TIR for that visit was considered missing in the TIR analysis. For participants with more than 14 days of daily TIR data for a given visit, the daily TIR data from the 14 days closest to the target day were used in the calculation of the average TIR.

Statistical Modeling

Continuous key secondary endpoints (i.e., average daily insulin use at Week 78, change from baseline in A1C at Week 78, and time-in-range at Week 78) were analyzed with an ANCOVA that adjusted for treatment groups, and the 2 stratification factors. The ANCOVA for the endpoint "A1C change from baseline at Week 78" also adjusted for baseline A1C.

The rate (number of events/ study follow-up time) of Level 2 and Level 3 hypoglycemic events through Week 78 was analyzed with a negative binomial model with covariate adjustment:

[2] Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika. 1988 Dec 1;75(4):800-2.

treatment group, the 2 stratification factors. The treatment difference was summarized as a rate ratio (teplizumab vs. placebo), with its 95% confidence interval and p-value.
For continuous endpoints, missing data were handled with multiple imputation based on the primary pattern mixture model. No missing data imputation was performed for the hypoglycemic event data.

Reviewer's Note: The ANCOVA models for both the endpoints "average daily insulin intake" and "TIR" did not account for baseline values of the response variables. For both endpoints, post-hoc analyses with baseline adjustment[3] were performed.

1.1.2 Patient Disposition

Patient disposition was generally balanced between the two treatment arms. While the placebo arm had a higher completion rate for the full (12 days) Course 1 compared to the teplizumab arm (94.6% vs. 87.1%), the completion rate for Course 1&2 was the same for the two treatment arms (i.e., 79.3%). For both treatment arms, treatment discontinuation and study discontinuation were around 14% and 10%, respectively. Among subjects who discontinued treatment, more than half of them (24/45) were followed up till end of the study. Compared to the placebo arm, however, more subjects from the teplizumab arm discontinued treatment (2.7% vs. 6.9%) and discontinued study (0% vs. 2.3%) due to adverse events. Also, it is worth noting that 28 (8.5%) participants received the study drug according to the modified dosing schedule (MDS), i.e., the second course was initiated at Week 52 due to the impact of COVID-19.

Table 1: Patient Disposition

	Teplizumab (N = 217)	**Placebo (N = 111)**	**Total (N = 328)**
Received any study drug			
Course 1	217 (100)	111 (100)	328 (100)
Course 2	191 (88.0)	99 (89.2)	290 (88.4)
Received full course			
Course 1	189 (87.1)	105 (94.6)	294 (89.6)
Course 2	182 (83.9)	91 (82.0)	273 (83.2)
Course 1 & 2	172 (79.3)	88 (79.3)	260 (79.3)
Normal dosing schedule	**175 (80.6)**	**87 (78.4)**	**262 (79.9)**
Modified dosing schedule	**16 (7.4)**	**12 (10.8)**	**28 (8.5)**
Discontinued study drug, n (%)	**30 (13.8)**	**15 (13.5)**	**45 (13.7)**
Adverse event	15 (6.9)	3 (2.7)	18 (5.5)
Patient decision	12 (5.5)	11 (9.9)	23 (7.0)
Other	3 (1.4)	1 (0.9)	4 (1.2)
Discontinued study*, n (%)	**22 (10.1)**	**10 (9.0)**	**32 (9.8)**
Adverse event	5 (2.3)	0	5 (1.5)
Withdrawal of consent	11 (5.1)	8 (7.2)	19 (5.8)
Lost to follow-up	5 (2.3)	0	5 (1.5)

[3] The TIR data were not collected until 2 weeks after the treatment started. Instead, TIR at Week 2 served as the "pseudo-baseline" value in the post-hoc analysis.

Other	1 (0.5)	2 (1.8)	1 (0.9)
Discontinued study drug but completed study, n (%)	**18 (8.3)**	**6 (5.4)**	24 (7.4)

Abbreviations: N = number of randomized participants, n (%) = number (percent) of participants with the event
* 10 subjects from teplizumab arm and 1 subject from placebo arm discontinued the study, but completed treatment Course 1 & 2.

Source: Reviewer's analysis based on ADSL.XPT, with software SAS 9.4.

1.1.3 Efficacy Results

1.1.3.1 Data and Analysis Quality

The current sBLA submission includes data from Study PROTECT. The clinical study report (CSR), together with the final statistical analysis plan (SAP, Version 5.0), and protocol amendment (Version 4.0) for Study PROTECT were submitted earlier (eCTD No. 111) upon completion of Study PROTECT. The study datasets are sufficiently documented, and of sufficient quality with no significant data integrity issues. However, the high missing data rate, in particular, with respect to the key secondary endpoints "average daily insulin intake" (55% missing at Week 78) and "TIR" (38% missing at Week 78), has introduced considerable uncertainties to the statistical analyses and could lead to biased results, thereby creating uncertainties in determining the drug's benefit profile.

1.1.3.2 Primary Efficacy Result

The result of the primary analysis of the change from baseline in C-peptide log (AUC + 1) at Week 78 is demonstrated in
Table 2. At Week 78, missing rate for C-peptide AUC was 13.3% for the teplizumab arm and 20.7% for the placebo arm. On average, subjects from the teplizumab arm exhibited a 0.13 pmol/mL (or 59%) less reduction from baseline in C-peptide log(AUC + 1), compared to subjects from the placebo arm. Transforming back to the original scale, the mean C-peptide AUC at Week 78 was 0.56 pmol/mL (SE =0.02) for the teplizumab arm, against 0.37 pmol/mL (SE = 0.02) for the placebo arm[4], resulting in a 50% improvement from the placebo arm. It is also worth noting that the least square mean (LS mean) estimate for the treatment difference in C-peptide log (AUC + 1) is highly significant with two-sided p-value $< 10^{-5}$. This magnitude of statistical significance provides sufficient assurance required when clinical benefit is inferred through a reasonably likely surrogate endpoint (i.e., C-peptide AUC) rather than directly measured via a validated clinical endpoint.

[4] This result were derived from an ANCOVA model with response variable: C-peptide log (AUC + 1) at Week 78, and the same covariate adjustment as the primary analysis model. The LSMean estimates were transformed back to the original scale, with SE approximated via delta method.

Table 2: Primary Analysis of Change from Baseline in C-peptide log (AUC + 1) (pmol/mL) at Week 78, ITT population

	Teplizumab N=217	**Placebo N=111**
Baseline		
Missing Data (n)	0	0
Mean (SD)	0.54 (0.20)	0.53 (0.17)
Week 78		
Missing data, n (%)	29 (13.3)	23 (20.7)
Retrieved Dropouts†, n (%)	6 (5.4)	16 (7.4)
CFB, LSMean* (SE)	-0.09 (0.01)	-0.22 (0.02)
Difference from Placebo, LSMean* (CI)	0.13 (0.08, 0.17)	
Two-sided p-value	$< 10^{-5}$	

Abbreviations: CFB = change from baseline, CI = 95% confidence interval, LS = least square, N = number of randomized participants, SD = standard deviation, SE = standard error

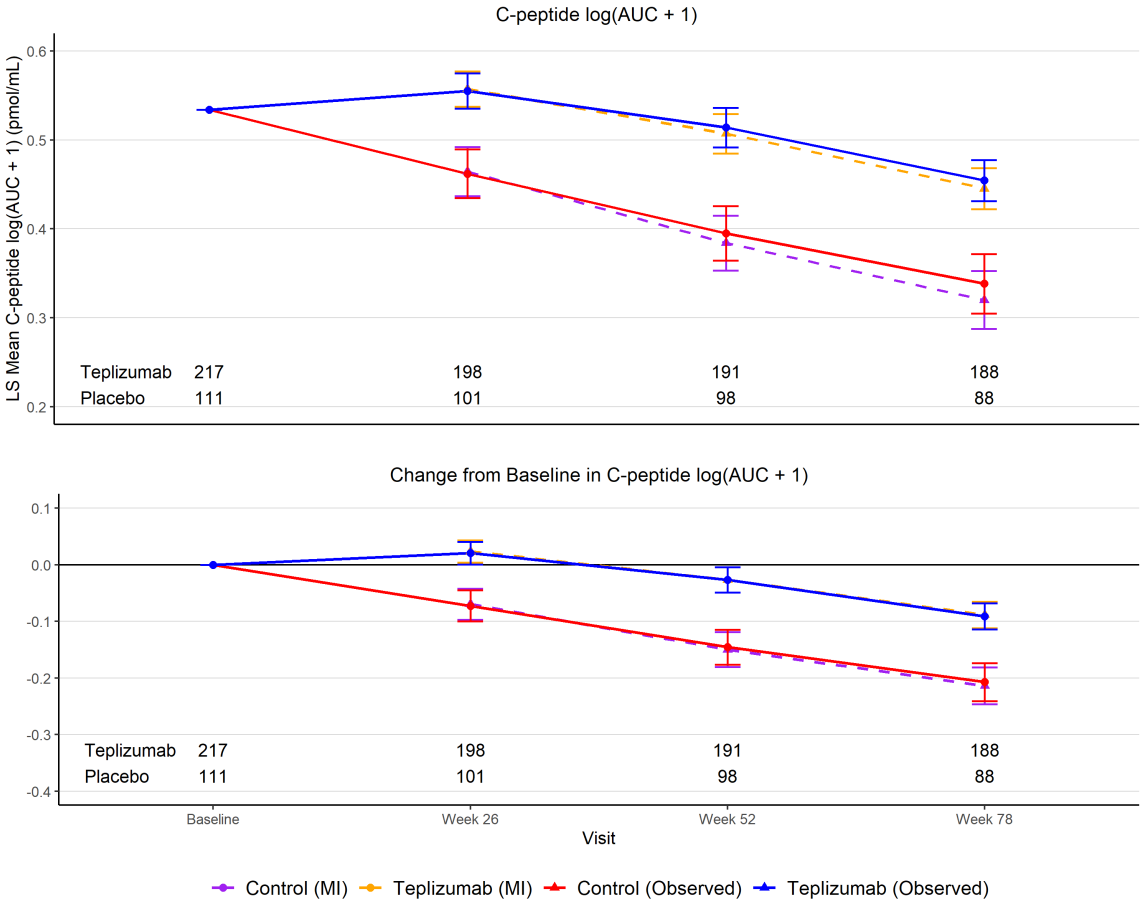
† Retrieved dropouts are defined as subjects who prematurely discontinued treatment, but have Week 78 C-peptide AUC measurements collected

* The LSMean estimates were derived from an ANCOVA model with response variable CFB in C-peptide log (AUC +1) at Week 78, and covariate adjustment for treatment, baseline C-peptide log (AUC + 1), age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). Missing data were multiply imputed based on the primary pattern-mixture model, with a 0 lower bound.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4.

Figure 1 displays the LS means of C-peptide log (AUC + 1) and LS means of "change from baseline in C-peptide log (AUC + 1)" over time by treatment arms. The estimates based on observed data (solid line) and imputed data (dashed line) were similar. While the placebo arm demonstrated a steady, continuous decline, the teplizumab arm displayed a slight upward trend until Week 26, followed by a decline that almost paralleled the rate observed in the placebo arm, though its mean C-peptide AUC values remained consistently higher than placebo at all post-baseline visits.

Figure 1: LS means for C-peptide log (AUC + 1) and LS means for "change from baseline in C-peptide log (AUC + 1)" over time, based on observed and imputed data



Abbreviations: MI = Multiple Imputation
Note: The table on the bottom of each plot displays the number of observed data at each timepoint for Teplizumab arm and placebo arm. Multiple imputation was performed at each visit based on the primary pattern mixture model.

Source: Statistical Analysts' analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4.

1.1.3.3 Sensitivity Analyses

Multiple Imputation based on Placebo Washout

To investigate the impact of missing data, the placebo-washout multiple imputation method was performed. As the placebo-washout multiple imputation assumes subjects from the teplizumab arm had similar performance to the placebo arm after dropping out from the study, it generally leads to a more conservative estimate than the pattern mixture multiple imputation used for the primary analysis. As shown in Table 3, the placebo-adjusted treatment effect estimate (95% CI) based on placebo-washout multiple imputation was 0.12 (0.08, 0.16), consistent with the primary analysis finding.

Table 3: Sensitivity Analysis of the primary endpoint based on Placebo washout multiple imputation, ITT population

	Teplizumab N=217	**Placebo N=111**
Change from baseline at Week 78, LSMean (SE)	-0.10 (0.01)	-0.22 (0.02)
Difference from Placebo, LSMean (CI)	0.12 (0.08, 0.16)	
Two-sided nominal p-value	$< 10^{-5}$	

Abbreviations: CI = 95% confidence interval, LS = least square, N = number of randomized participants, SD = standard deviation, SE = standard error

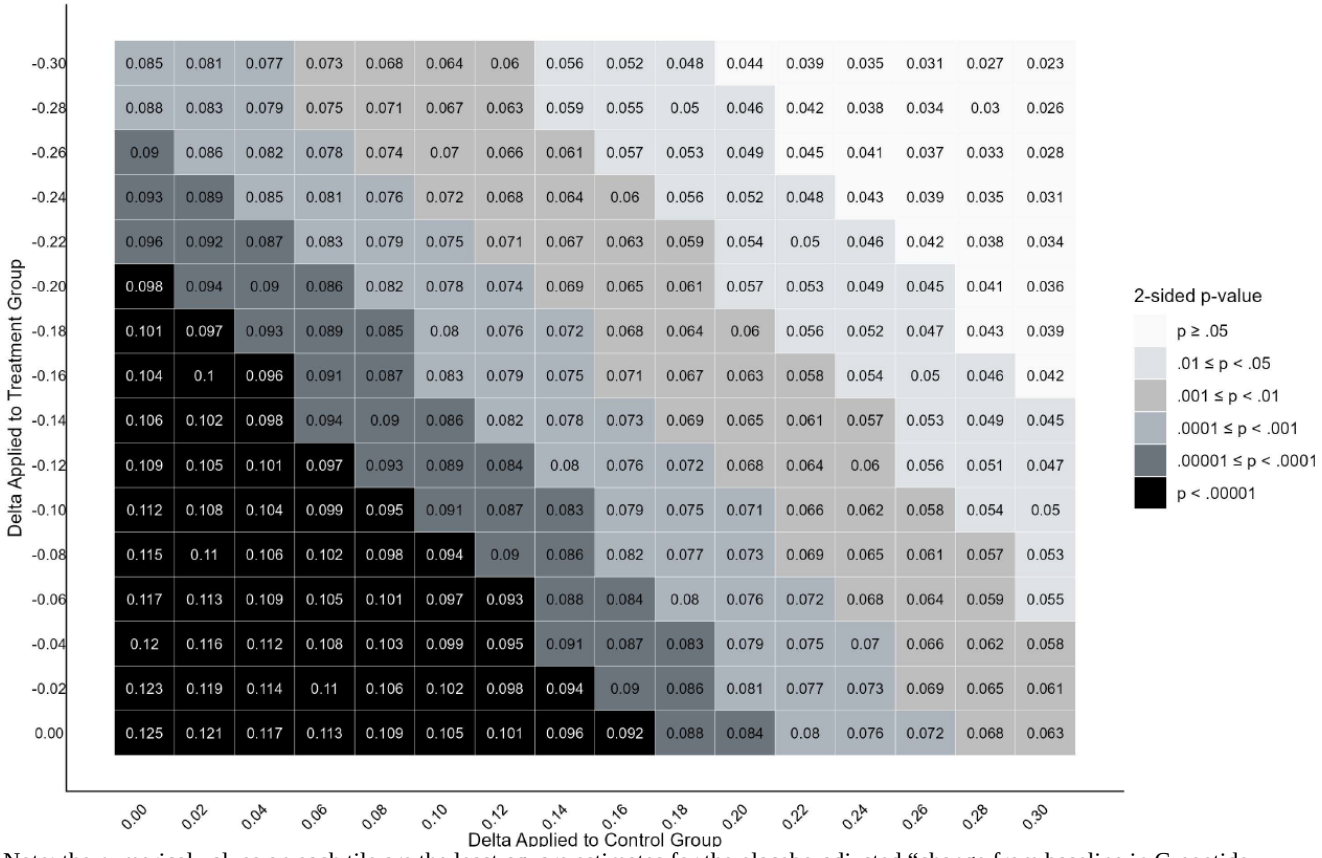
Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, baseline C-peptide log (AUC + 1), age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). Missing data were multiply imputed based on placebo-washout, with a 0 lower bound.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4.

Two-Way Tipping Point Analysis

Delta adjustment was applied to the imputed primary endpoint values, using increments of -0.02 for the teplizumab arm, and 0.02 for the placebo arm. As displayed in Figure 2, the boundary of highly significant results with 2-sided p-value $< 10^{-5}$ was traced out by cases that are clinically implausible. For example, the case located on the boundary's top corner involves a 0.26 pmol/mL C-peptide log (AUC + 1) reduction from all imputed values of the teplizumab arm—a magnitude of change that is highly unlikely as suggested by clinical experience. The conditions to overturn the pre-specified statistical significance (i.e., 2-sided p-value < 0.05) are even more extreme (e.g., a 0.30 reduction from all imputed values in teplizumab arm, combined with a 0.20 addition to all imputed values in placebo arm). Hence, the tipping point analysis confirmed robustness of the primary efficacy finding.

Figure 2: Two-Way Tipping Point Analysis for the Primary Efficacy Finding



Note: the numerical values on each tile are the least-square estimates for the placebo-adjusted "change from baseline in C-peptide log (AUC + 1) at Week 78" under various delta adjustments.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4, and R (Version 4.4.1).

Multiple Imputation Based on Retrieved Dropouts

As shown in Table 4, 10 subjects on teplizumab and 1 subject on placebo completed treatment but discontinued the study. Their missing primary endpoint measurements were imputed with the primary pattern mixture model based on observed data from treatment completers. The validity of this strategy relies on the assumption that subjects who dropped out prematurely after Course 2 would have similar performance to those who completed both treatment and study follow-up. However, given the substantial time gap between Course 2 completion (Week 27) and study conclusion (Week 78), subjects could discontinue study due to ICEs (e.g., lack of efficacy or adverse events) after receiving Course 2. Hence, a retrieved dropout multiple imputation was applied to these missing data, while the imputation strategy for the other missing patterns remains the same as the primary approach. Results based on this new pattern mixture model was demonstrated in Table 5. The placebo-adjusted treatment effect was 0.13, with a 95% CI (0.08, 0.17), which is highly similar to the primary efficacy result. This again demonstrated the robustness of the primary efficacy finding.

Table 4: Treatment & Study Completion Status Among Subjects with Missing Primary Endpoints, ITT Population

	Teplizumab	Placebo	Total

	N = 217	N = 111	N = 328
Missing Week 78 data, n (%)	**29 (13.4)**	**23 (20.7)**	**52 (15.9)**
Completed Treatment	**15 (6.9)**	**14 (12.6)**	**29 (8.8)**
Completed study	5 (2.3)	13 (11.7)	18 (5.5)
Discontinued study	10 (4.6)	1 (0.9)	11 (3.4)
Discontinued Treatment	**14 (6.5)**	**9 (8.1)**	**23 (7.0)**
Completed study	2 (0.9)	1 (0.9)	3 (0.9)
Discontinued study	12 (5.5)	8 (7.2)	20 (6.1)

Abbreviations: N = number of randomized participants, n (%) = number (percent) of subjects with the event

Source: Reviewer's analysis based on ADSL.XPT, with R (Version 4.4.1).

Table 5: Sensitivity analysis of the primary endpoint based on retrieved dropout multiple imputation, ITT population

	Teplizumab N=217	Placebo N=111
Change from baseline at Week 78, LSMean (SE)	-0.10 (0.01)	-0.22 (0.02)
Difference from Placebo, LSMean (CI)		0.13 (0.08, 0.17)
Two-sided nominal p-value		$<10^{-5}$

Abbreviations: CI = 95% confidence interval, LS = least square, N = number of randomized participants, SD = standard deviation, SE = standard error

Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, baseline C-peptide log (AUC + 1), age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). For subjects who discontinued either treatment or study prematurely, missing endpoint measurements were multiply imputed based on retrieved dropouts. For subjects who completed both treatment and study, missing endpoint measurements were multiply imputed based on observed measurements from treatment completers.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4, and R (Version 4.4.1).

1.1.3.4 Key Secondary Efficacy Results

The results for key secondary endpoints: average daily insulin use at Week 78, A1C change from baseline at Week 78, TIR at Week 78, and Level 2 & 3 hypoglycemic event rate are presented in Table 6, Table *7*, Table *8*, and Table *9*, respectively. Although teplizumab showed numerical improvement with respect to insulin use, A1C reduction and TIR, none of the key secondary endpoint achieved the pre-specified statistical significance. Further, missing data at Week 78 were alarmingly high for the average daily insulin use (55%) and TIR (38%). Besides, more than 40% subjects had missing insulin endpoint at baseline. Hence, the estimated results should be interpreted with caution, given the great uncertainties introduced by the substantial missing data.

Table 6: Average Daily Insulin Use (u/kg/day) at Week 78, ITT population

	Teplizumab N=217	Placebo N=111
Baseline		
Missing data at baseline, n (%)	91 (41.9)	48 (43.2)
Mean (SD)	0.45 (0.31)	0.38 (0.25)
Week 78		
Missing data at Week 78, n (%)	119 (54.8)	61 (55.0)

LSMean (SE)	0.46 (0.05)	0.59 (0.06)
Difference from Placebo, LSMean (CI)		-0.13 (-0.28, 0.02)

Abbreviations: CI = 95% confidence interval, LS = least square, N = number of randomized participants, n (%) = number (percent) of subjects with the event, SD = standard deviation, SE = standard error
Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, baseline value , age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). Missing data were handled via the primary pattern mixture model.

Source: Table: 14, page 115, CSR.

Table 7: A1C (%) change from baseline at Week 78, ITT population

	Teplizumab N=217	**Placebo N=111**
Baseline		
Missing data, n (%)	0	1 (0.9)
Mean (SD)	8.90 (1.73)	9.18 (1.92)
Week 78		
Missing data, n (%)	25 (11.5)	12 (10.8)
Change from baseline LSMean (SE)	-1.98 (0.10)	-1.89 (0.14)
Difference from Placebo, LSMean (CI)		-0.09 (-0.42, 0.24)

Abbreviations: CI = 95% confidence interval, LS = least square, N = number of randomized participants, n (%) = number (percent) of subjects with the event, SD = standard deviation, SE = standard error
Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, baseline A1C , age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). Missing data were handled via the primary pattern mixture model.

Source: Table: 14, page 117, CSR.

Table 8: Glucose Time in Range (%) (from 70mg/dL to 180mg/dL, inclusive) at Week 78, ITT Population

	Teplizumab N=217	**Placebo N=111**
Week 78		
Missing data, n (%)	77 (35.4)	48 (43.2)
LSMean (SE)	67.4 (1.9)	62.7 (2.7)
Difference from Placebo, LSMean (CI)		4.7 (-1.7, 11.2)

Abbreviations: CI = 95% confidence interval, LS = least square, N = number of randomized participants, n (%) = number (percent) of subjects with the event, SD = standard deviation, SE = standard error
Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). Missing data were handled via the primary pattern mixture model.

Source: Table: 16, page 121, CSR.

Table 9: Level 2 & 3 Hypoglycemic event rate through Week 78, ITT Population

	Teplizumab N=217	**Placebo N=111**
Incidence (%) of Level 2 Event	141 (65.0)	72 (64.9)
Number of Level 2 Event	1497	729
Estimated event rate (CI)	4.68 (3.70, 5.91)	4.24 (3.06, 5.89)

Estimated rate ratio (CI)	1.10 (0.74, 1.64)

Abbreviations: CI = 95% confidence interval, LS = least square, SD = standard deviation, SE = standard error
Note: Event rate for each participant as the number of events / total study follow-up time. The total study follow-up time is calculated as (the date of last study contact – the first dose date + 1)/365.25. Estimates rates are obtained from a negative binomial model using event rate as dependent variable, and adjusting for treatment, age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), and screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL). Event rate ratio = teplizumab/placebo.

Source: Table: 17, page 124, CSR.

For insulin endpoint and TIR endpoint, post-hoc analyses adjusted for baseline values were performed. As shown in
Table **10** and Table 11, the results for both endpoints with baseline adjustment are similar to the results without baseline adjustment. Both results remained numerically favorable to the teplizumab arm without statistical significance despite narrower confidence intervals.

Table 10: Post-Hoc Analysis of Average Daily Insulin Use (U/kg/day) at Wek 78, adjusted for baseline, ITT Population

	Teplizumab N=217	**Placebo N=111**
Week 78		
LSMean (SE)	0.46 (0.05)	0.60 (0.06)
Difference from Placebo, LSMean (CI)		-0.15 (-0.29, 0.00)

Abbreviations: CI = 95% confidence interval, LS = least square, SD = standard deviation, SE = standard error
Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, baseline value , age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL) and baseline values. Missing data were handled via the primary pattern mixture model.

Source: Table: 14.2.2.6a, page 1291, CSR.

Table 11: Post-Hoc Analysis of Glucose Time in Range (%) at Week 78, adjusted for baseline, ITT Population

	Teplizumab N=217	**Placebo N=111**
Week 78		
LSMean (SE)	67.0 (1.8)	63.4 (2.5)
Difference from Placebo, LSMean (CI)		3.6 (-2.5, 9.7)

Abbreviations: CI = 95% confidence interval, LS = least square, SD = standard deviation, SE = standard error
Note: The LSMean estimates were derived from an ANCOVA model that adjusted for treatment, age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL, and TIR at Week 2 (as “pseudo-baseline” values). Missing data were handled via the primary pattern mixture model.

Source: Table: 14.2.4.4a, page 1298, CSR.

1.1.3.5 Surrogacy Analysis

Given that C-peptide AUC, the primary endpoint for Study PROTECT, was designated as a reasonably likely surrogate endpoint (RLSE), we conducted additional analyses to evaluate its surrogacy relationship with two clinical efficacy endpoints: A1C (a validated surrogate endpoint for glycemic control) and average daily insulin use. The surrogacy analysis aimed to characterize the relationship between the RLSE and these clinical efficacy endpoints to inform the accelerated

approval decision-making process, which necessitates a confirmatory study incorporating these endpoints for full approval. The Sponsor provided supportive studies for teplizumab that included these efficacy endpoints. Consequently, we conducted meta-analytic surrogacy analyses using data from the PROTECT study along with the supportive studies: AbATE, Delay, Encore, Protégé, and Study1. We explored the correlation of treatment effects as measured by the RLSE (i.e., change from baseline in C-peptide AUC at year 1) and "change from baseline in A1C at year 1", and "change from baseline in average daily insulin use at year 1". The 1 year timepoint was selected because it represented the longest timepoint with substantial data availability across all studies (See Table 12: Missing Data at Baseline and Year 1, for Study PROTECT and the 5 supportive studies for missing rate of each study). A two-stage bivariate fixed-effect model[5] (in place of the full bivariate mixed-effect model) was adopted to assess the strength of surrogacy, due to limited number of studies available and adjust for the heterogeneity of the studies.

Table 12: Missing Data at Baseline and Year 1, for Study PROTECT and the 5 supportive studies

	C-peptide AUC		**A1C**		**Insulin**	
	Teplizumab	Control	Teplizumab	Control	Teplizumab	Control
AbATE, N	**52**	**25**	**52**	**25**	**52**	**25**
Baseline, n (%)	0	0	0	1 (4.0)	3 (5.8)	1 (4.0)
Month 12, n (%)	2 (3.9)	3 (12.0)	1 (1.9)	4 (16.0)	2 (3.9)	3 (12.0)
Delay, N	**32**	**28**	**32**	**28**	**32**	**28**
Baseline, n (%)	0	0	0	0	0	0
Month 12, n (%)	2 (6.3)	0	2 (6.3)	0	3 (9.4)	0
Encore, N	**63**	**62**	**63**	**62**	**63**	**62**
Baseline, n (%)	0	0	0	1 (1.6)	3 (4.8)	1 (1.6)
Month 12, n (%)	46 (73.0)	45 (72.6)	8 (12.7)	5 (8.1)	12 (19.0)	7 (11.3)
PROTECT, N	**217**	**111**	**217**	**111**	**217**	**111**
Baseline, n (%)	0	0	0	1 (0.9)	91 (41.9)	48 (43.2)
Month 12, n (%)	26 (12.0)	13 (11.7)	23 (10.6)	11 (9.9)	116 (53.5)	64 (57.7)
Protégé, N	**207**	**98**	**207**	**98**	**207**	**98**
Baseline, n (%)	2 (1.0)	0	0	0	5 (2.4)	3 (3.1)
Month 12, n (%)	15 (7.3)	7 (7.1)	12 (5.8)	4 (4.1)	12 (5.8)	5 (5.1)
Study 1, N	**21**	**21**	**21**	**21**	**21**	**21**
Baseline, n (%)	0	0	0	1 (4.8)	1 (4.8)	1 (4.8)
Month 12, n (%)	0	0	0	1 (4.8)	0	1 (4.8)

Abbreviations: N = number of randomized participants, n (%) = number (percent) of subjects with missing endpoint measurement

[5] The R package "Surrogate" was used for modeling.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, ADIN.XPT, and ADHB.XPT with R (Version 4.4.1).

Details for the bivariate fixed effect model is deferred to Appendix XX. As implicated by the model structure, estimate of the trial-level surrogacy R^2_{trial} captures the association between treatment effects measured by the surrogate and the clinical efficacy endpoint across different trials, whereas and estimate of the individual-level surrogacy R^2_{indiv} measures the correlation between the surrogate and the clinical efficacy endpoint within patients after accounting for the drug effect. For an endpoint with strong surrogacy, both R^2_{indiv} and R^2_{trial} should be close to 1. As shown in
Table 13: Surrogacy of C-peptide AUC (pmol/mL) for A1C (%), and for average daily insulin use (U/kg/day),
Table 13, for both A1C and average daily insulin use, the surrogacy of C-peptide AUC is strong at a trial level (i.e., R^2_{trial} = 0.83 for A1C and 0.80 for insulin), but weak at an individual level (i.e., R^2_{indiv} = 0.21 for A1C and 0.10 for insulin). This pattern of higher trial-level surrogacy coupled with lower individual-level surrogacy is also reflected in **Error! Reference source not found.**, Figure 4, Figure 5, and Figure 6. These surrogacy analyses suggest that C-peptide AUC may reliably predict the treatment benefits related to A1C and insulin use reduction at the study level, but could have limited utility for predicting these treatment benefits at an individual level. The underlying mechanism or potential confounders contributing to this weak individual-level surrogacy merits further investigation. Also, the result should be interpreted with caution, given the limited number of studies in the analysis.

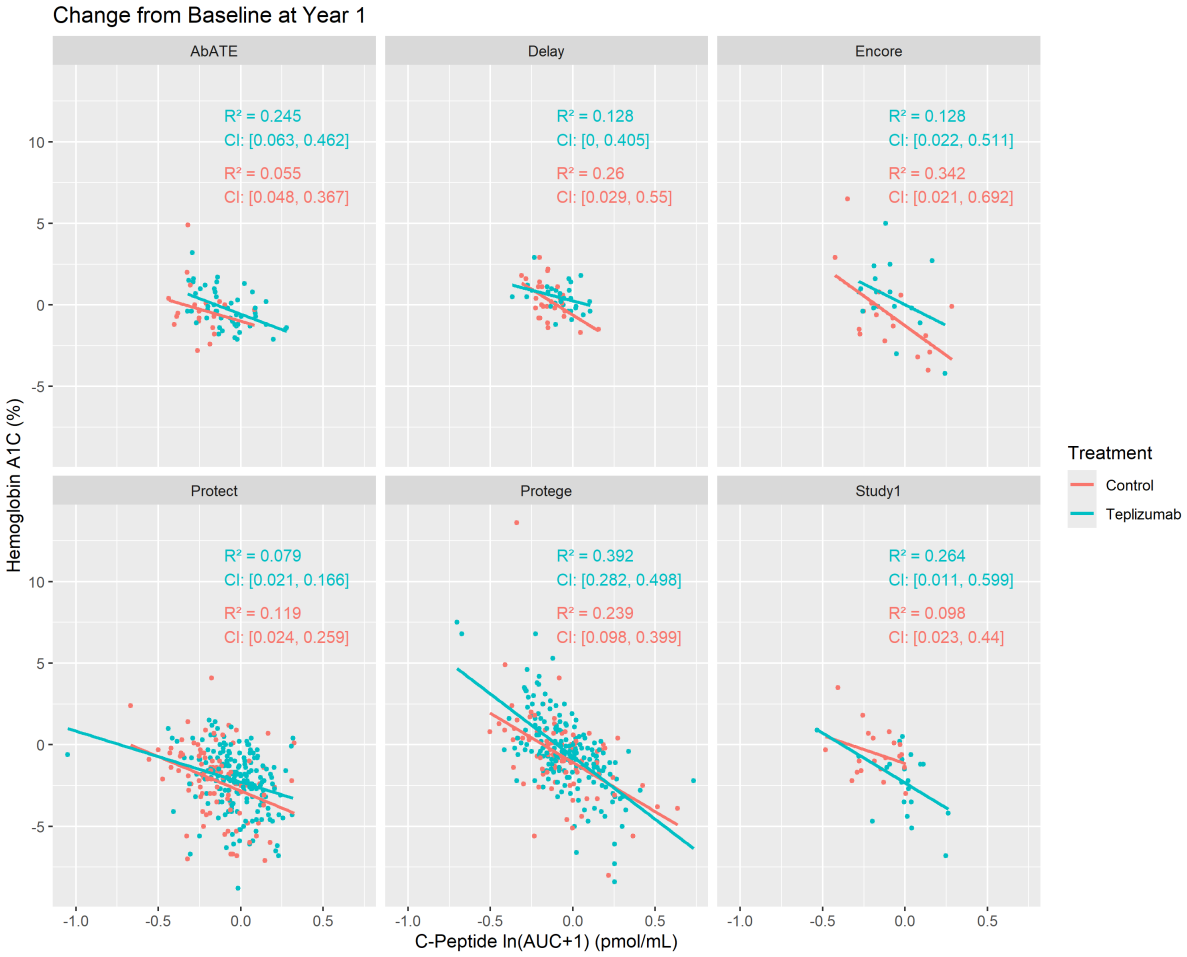
Table 13: Surrogacy of C-peptide AUC (pmol/mL) for A1C (%), and for average daily insulin use (U/kg/day)

	R^2_{trial}	R^2_{indiv}
CFB in A1C	0.83 (0.48, 1)	0.21 (0.15, 0.26)
CFB in average daily insulin use	0.80 (0.40, 1)	0.10 (0.05, 0.15)

Abbreviations: CFB = change from baseline
Note: The two surrogacy analyses were conducted based on the endpoints: "CFB in C-peptide log (AUC + 1) at year 1" and "CFB in A1C at year 1", and "CFB in C-peptide log (AUC+1) at year 1" and "CFB in average daily insulin use at year 1". Each analysis was performed based on a two-stage bivariate fixed-effect model, with observed data from 6 studies: AbATE, Delay, Encore, Protect, Protégé, and Study1.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, ADIN.XPT, and ADHB.XPT with R (Version 4.4.1).

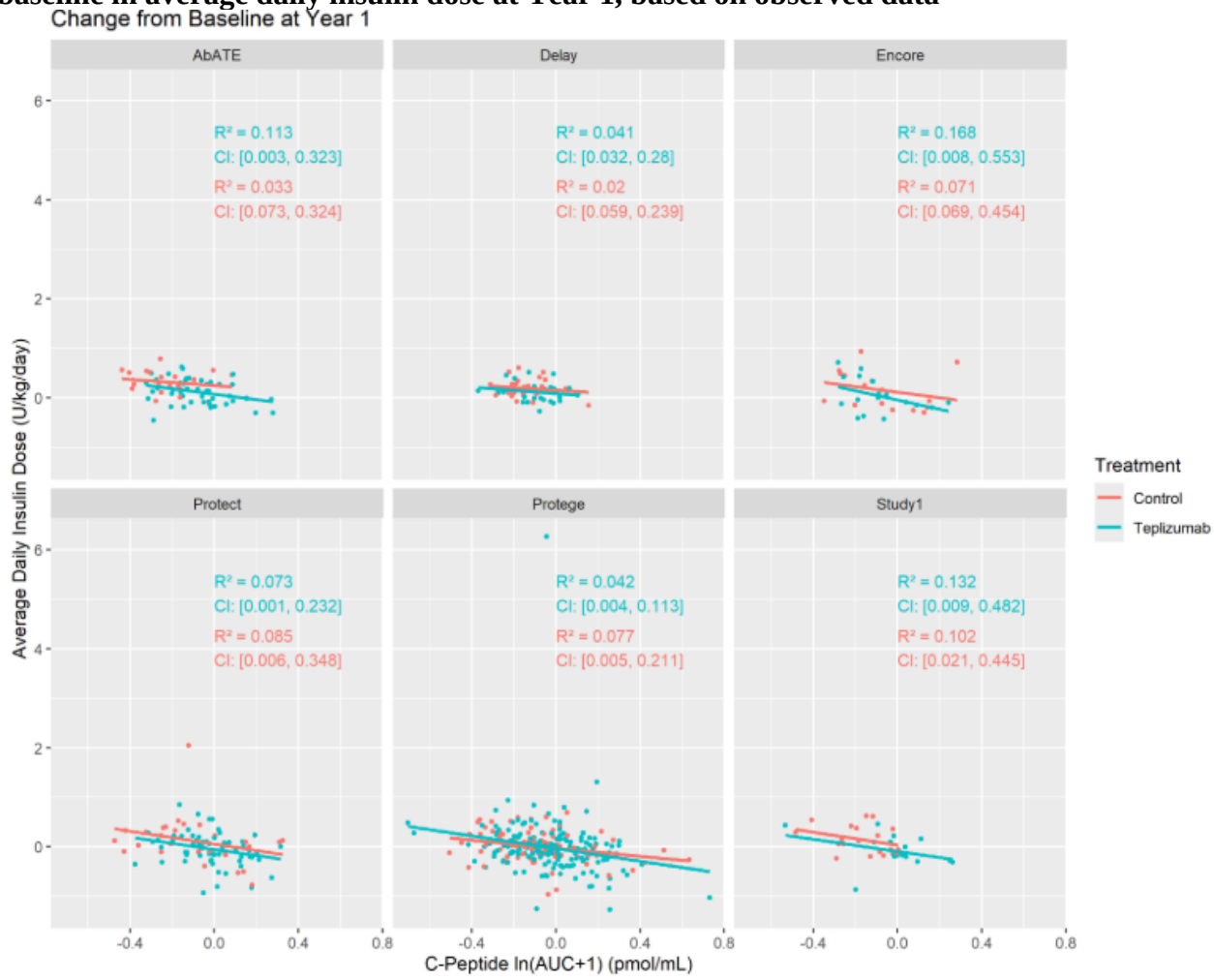
Figure 3: Change from baseline in C-peptide log (AUC + 1) (pmol/mL) vs change from baseline in A1C (%) at Year 1, based on observed data



Abbreviation: CI = 95% confidence interval, R^2= coefficient of determination between "change from baseline in C-peptide ln (AUC+1) at Year 1" and "change from baseline in A1C at Year 1" at individual level for each study

Source: Statistical analysts' analyses based on based on ADSL.XPT and ADMMTT.XPT, ADIN.XPT, and ADHB.XPT

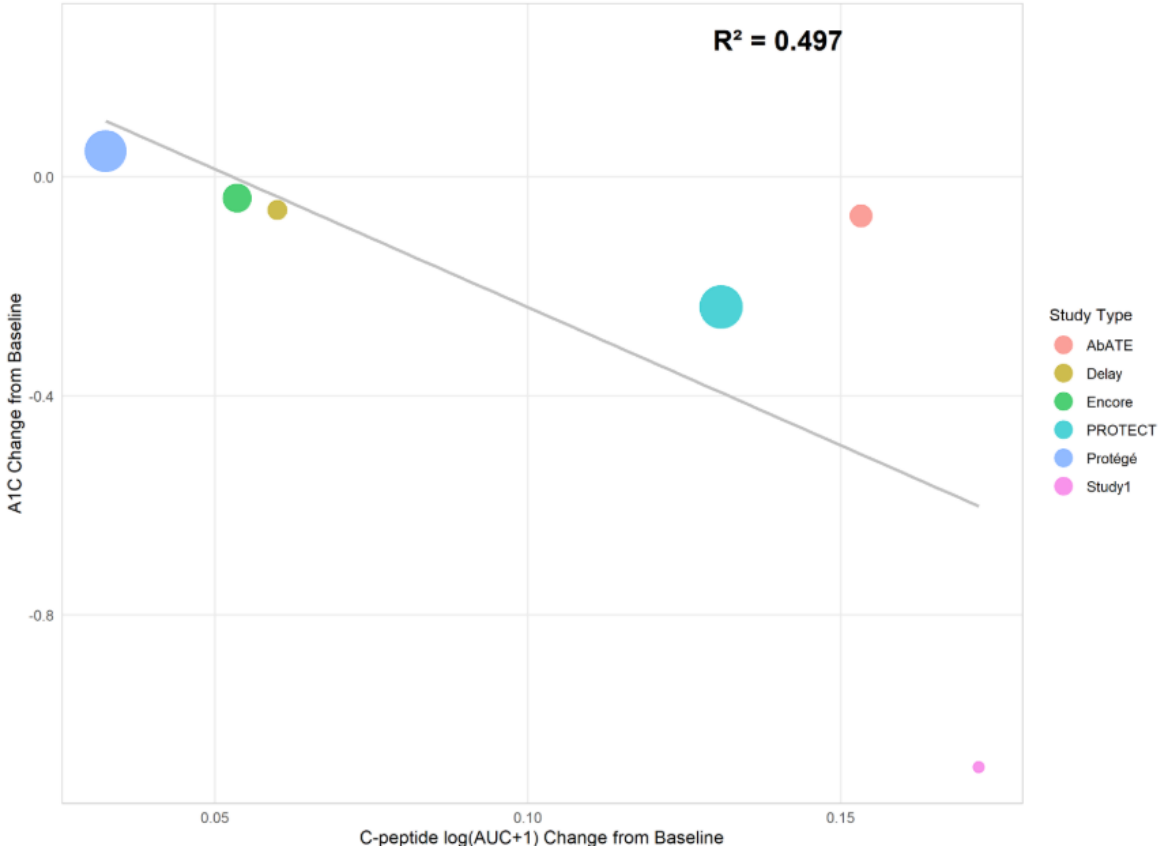
Figure 4: Change from baseline in C-peptide log (AUC + 1) (pmol/mL) vs change from baseline in average daily insulin dose at Year 1, based on observed data



Note: R^2 (CI) = coefficient of determination (95% confidence interval) between "change from baseline in C-peptide ln (AUC+1) at Year 1" and "change from baseline in average daily insulin dose at Year 1" using individual level data

Source: Statistical analysts' analyses based on based on ADSL.XPT and ADMMTT.XPT, ADIN.XPT, and ADHB.XPT

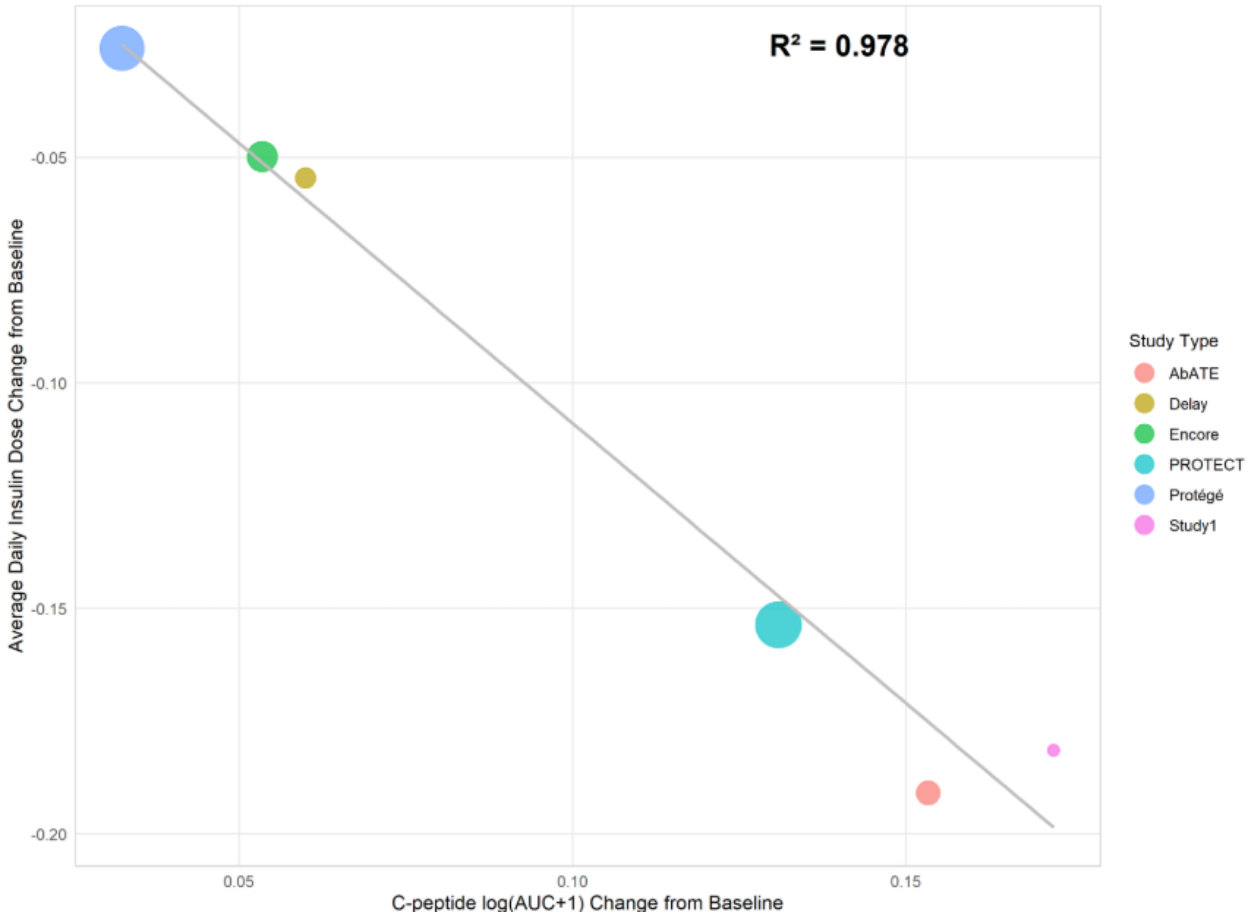
Figure 5: Placebo-Adjusted Treatment Effect at Year 1: change from baseline in C-peptide log (AUC + 1) (pmol/mL) vs. change from baseline in A1C (%)



Note: The x-axis represents the LS Means for treatment difference (teplizumab vs. placebo) for C-peptide log (AUC + 1) (pmol/mL) change from baseline at Year 1. The y-axis represents the LS Means for treatment difference (teplizumab vs. placebo) for A1c (%) change from baseline at Year 1. For both endpoints, the LS Mean estimates were derived from ANCOVA adjusted for treatment, baseline age and baseline value of the response variable. Missing data were multiply imputed based on the primary pattern mixture model.
Note: R^2= coefficient of determination between "C-peptide log (AUC + 1) change from baseline at Year 1" and "A1C change from baseline at Year 1" using study-level least square mean estimates.
Note: The dot size reflects the relative sample size for each study, with larger dots associated with studies of larger sample sizes.

Source: Statistical analysts' analyses based on based on ADSL.XPT and ADMMTT.XPT, ADIN.XPT, and ADHB.XPT

Figure 6: Placebo-adjusted treatment effect at Year 1: change from baseline in C-peptide log (AUC + 1) (pmol/mL) vs. change from baseline in average daily insulin use (U/kg/day)



Note: The x-axis represents the LS Means for treatment difference (teplizumab vs. placebo) for C-peptide log (AUC + 1) (pmol/mL) change from baseline at Year 1. The y-axis represents the LS Means for treatment difference (teplizumab vs. placebo) for average daily insulin dose change from baseline at Year 1. For both endpoints, the LS Mean estimates were derived from ANCOVA adjusted for treatment, baseline age and baseline value of the response variable. Missing data were multiply imputed based on the primary pattern mixture model.
Note: R^2= coefficient of determination between "C-peptide log (AUC + 1) change from baseline at Year 1" and "average daily insulin dose change from baseline at Year 1", using study-level least square mean estimates.
Note: The dot size reflects the relative sample size for each study, with larger dots associated with studies of larger sample sizes.

Source: Statistical analysts' analyses based on based on ADSL.XPT and ADMMTT.XPT, ADIN.XPT, and ADHB.XPT

2 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

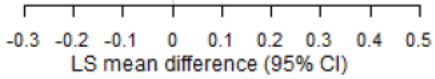
2.1 Race, Age, and Geographic Region

As shown in Figure 7, analyses of the primary endpoint were conducted in subgroups based on age, race, region, and sex. For the subgroup analysis based on race, the "other" category consists of 1 American Indian/Alaska Native on teplizumab, 1 Native Hawaiian/Other Pacific Islander on placebo, and 5 subjects self-reported as the "other" racial category (1 from placebo arm and 4 from teplizumab arm). Except for the "Asian" subgroup category, all the other subgroup levels

have a point estimate above 0, indicating a consistent treatment effect regarding C-peptide AUC preservation with the overall population, and across all subgroups. The negative point estimate for the Asian category is likely due to chance as a result of small sample size and high variability. In addition, none of the interaction test suggests a significant treatment-by-subgroup interaction.

Figure 7: Subgroup analysis of the primary endpoint based on age, sex, race, and region

Subgroup	Placebo (N)	Teplizumab (N)	Estimate (95% CI)	P-value for Interaction
Overall	111	217	0.13 (0.08, 0.17)	—
Age category				
≤11	49	97	0.12 (0.07, 0.18)	0.77
12-17	62	120	0.13 (0.07, 0.19)	
Sex				
M	42	98	0.13 (0.06, 0.19)	0.79
F	69	119	0.12 (0.07, 0.18)	
Race				
Asian	3	4	-0.09 (-0.35, 0.16)	0.45
Black	6	5	0.15 (-0.06, 0.36)	
White	94	189	0.19 (0.01, 0.38)	
Other	2	11	0.14 (-0.13, 0.41)	
Not Reported	6	8	0.12 (0.08, 0.17)	
Region				
North America	48	78	0.14 (0.07, 0.20)	0.59
Europe	63	139	0.12 (0.07, 0.17)	



Abbreviations: CI = 95% confidence interval, N = number of subjects
Note: each subgroup estimates were derived from an ANCOVA model that adjusted for treatment, age group at randomization (≥ 8 to 12 years vs. > 12 to ≤ 17 years), screening peak C-peptide category (≥ 0.2 to ≤ 0.7 pmol/mL vs. > 0.7 pmol/mL), baseline C-peptide log (AUC +1), subgroup levels, and treatment-by-subgroup interaction. Missing data were handled via the primary pattern mixture model.

Source: Reviewer's analysis based on ADSL.XPT and ADMMTT.XPT, with software SAS 9.4, and R (Version 4.4.1).

2.2 Other Special/Subgroup Populations

The proposed indication encompasses patients 8 years of age and older with no upper age restriction. (b) (4)

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As demonstrated displayed in Figure 8, the treatment effect appears generally consistent among the pediatric (< 18 years) subgroup; specifically, both the 1-stage and 2-stage meta-analyses yielded a nominally significant placebo-adjusted treatment effect of 0.09 pmol/mL, while individual studies consistently favored teplizumab, with effects ranging from 0.07 to 0.14 pmol/ml. (b) (4)

(b) (4)

Given these limitations in the adult data, extrapolation from pediatric findings to adult populations presents great challenges and uncertainties.

Figure 8: Subgroup analysis for change from baseline in C-peptide log (AUC + 1) at 1 Year, by age category, ITT population

Age Category	Study	Total N	Teplizumab N	Control N	Effect Estimate (95% CI)	P-value
< 18 years	Overall (2-stage)	396	242	154	0.09 (0.04, 0.14)	0.006
	Overall (1-stage)	396	242	154	0.09 (0.05, 0.14)	<0.001
	AbATE	72	48	24	0.14 (0.06, 0.23)	0.001
	Delay	55	29	26	0.07 (-0.02, 0.16)	0.116
	Encore	73	37	36	0.07 (-0.05, 0.19)	0.235
	Protege	165	112	53	0.08 (0.02, 0.14)	0.008
	Study 1	31	16	15	0.10 (-0.02, 0.22)	0.109

(b) (4)

Abbreviations: CI = confidence interval, Effect Estimate = least square mean estimate for treatment effect (teplizumab vs placebo), N = number of randomized participants, P-value = 2-sided p-value for treatment effect

(b) (4)

Source: Reviewer's summary based on IR Response dated September 25, 2025

3 SUMMARY AND CONCLUSIONS

3.1 Overview of Efficacy Findings

In support of the proposed indication, the Applicant conducted the study PROTECT, a multicenter, randomized, double-blind, placebo-controlled, phase 3 study among pediatric patients aged 7 to 17 years old. The study met its primary endpoint: change from baseline in C-

peptide log (AUC + 1) at Week 78. Specifically, the placebo-adjusted primary treatment effect was 0.13, with a 95% confidence interval (0.08, 0.16) and 2-sided p-value < 10^{-5}. The primary efficacy result was found robust to missing data, which comprised 16% of the study population. Subgroup analyses based on age (≤11 and 12-17 years old), sex, race, and region were largely consistent with the primary efficacy findings. Post-hoc surrogacy analyses based on Study PROTECT and 5 supportive studies found a strong correlation between C-peptide AUC changes and both A1C and insulin reduction outcomes at a trial level, but the correlation was weak at an individual level. As subgroup analyses in adult patients (≥ 18 years old) relied on limited data from supportive studies with great inter-trial heterogeneity, extrapolating pediatric results to broader adult patient populations remains challenging.

Key secondary endpoints under multiplicity control included average daily insulin use (U/kg/day) at Week 78, change from baseline in A1C (%) at Week 78, time in range (%) defined as blood glucose between 70 and 180 mg/dL measured by CGM, and Level 2 and 3 hypoglycemic event rate throughout 78 weeks. The trial did not win on any of the key secondary endpoints. Numerically favorable results were demonstrated for the endpoints: average daily insulin use, change from baseline in A1C, and TIR. However, the high missing data rate, in particular, with respect to insulin data (55% missing at Week 78) and TIR data (38% missing at Week 78), considerably compromised the reliability and interpretability to these efficacy findings. It is noted that the study PROTECT was powered to solely demonstrate superiority to placebo regarding C-peptide AUC, without accounting for marginal powers for any key secondary endpoints. A confirmatory trial with a co-primary endpoint of “A1C change from baseline” and “number of days without prandial insulin”, has been planned to further investigate the treatment benefit of teplizumab among patients with newly diagnosed T1D.

3.2 Conclusions

The statistical findings have demonstrated robust and superior effectiveness of teplizumab in preserving C-peptide AUC compared to placebo among pediatric patients 8 to 17 years old, inclusive. Post-hoc surrogacy analysis based on the pivotal PROTECT trial and 5 supportive studies suggested a strong correlation between C-peptide AUC changes and both A1C and insulin reduction outcomes at a trial level. However, the paucity of adult patient data limits confidence in age extrapolation to adult populations.

APPENDICES

Two-Stage Bivariate Fixed Effect Model:

- Stage 1: fit the following models:

$$S_{ij} = \mu_{Si} + \alpha_i Z_{ij} + \epsilon_{Sij}$$
$$T_{ij} = \mu_{Ti} + \beta_i Z_{ij} + \epsilon_{Tij}$$

  where *i* and *j* are the trial and subject indicators, S_{ij} and T_{ij} are the surrogate (i.e., change from baseline in C-peptide log (AUC + 1)) and true endpoint (i.e., change from baseline in A1C) values of subject *j* in trial *i*, Z_{ij} is the treatment indicator for subject *j* in trial *i*, μ_{Si} and μ_{Ti} are the trial-specific intercepts for S and T, and α_i and β_i are the trial-specific treatment effects for S and T, respectively. The error terms ϵ_{Sij} and ϵ_{Tij} are assumed to be mean-zero normally distributed with the variance covariance matrix Σ:

$$\Sigma = \begin{pmatrix} \sigma_{SS} & \sigma_{ST} \\ \sigma_{ST} & \sigma_{\mathrm{TT}} \end{pmatrix}$$

  The individual-level surrogacy: $R^2_{indiv} = corr\left(\epsilon_{Sij}, \epsilon_{Tij}\right)^2 = \frac{\sigma^2_{ST}}{\sigma_{SS}\sigma_{TT}}$ can be estimated from the Stage 1 model.

- Stage 2: fit the following model:

$$\hat{\beta}_i = \lambda_0 + \lambda_1 \hat{\mu}_{Si} + \lambda_2 \hat{\alpha}_i + \epsilon_i$$

  where the parameter estimates for β_i, μ_{Si}, and α_i are based on the models that were fitted in Stage 1. The trial-level surrogacy R^2_{trial} is computed as the classical coefficient of determination of the Stage 2 model.

APPEARS THIS WAY ON ORIGINAL

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/s/

WENDA TU
03/05/2026 12:48:20 PM

YOONHEE KIM
03/05/2026 12:55:59 PM
I concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA #:	761183 / S-010
Drug Name:	Tzield (teplizumab-mzwv)
Indication(s):	Delay of progression of stage 3 Type I diabetes (T1D) in adult and pediatric patients 8 years of age or older recently diagnosed with stage 3 T1D
Applicant:	Provention BIO a Sanofi Company
Date(s):	Stamp date: 7/21/2025 Completion date: 10/20/2025 PDUFA date: 11/21/2025
Safety Endpoints:	Diabetic ketoacidosis, serious infection
Review Priority:	Priority (Commissioner's National Priority Voucher Program)
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Joo-Yeon Lee, PhD
Concurring Reviewer:	Clara Kim, PhD, Team Leader
Consulting Division:	Division of Diabetics, Lipid Disorders and Obesity
Consulting Team:	Lauren WoodHeickman, MD Mahtab Niyyati, MD, Team Leader
Project Manager:	Supendeep Dosanjh

Keywords: diabetic ketoacidosis, serious infection, incidence rates, incidence rate difference, Mantel-Haenszel estimate

1 INTRODUCTION

Teplizumab was first approved in November 2022 for the delay of onset of stage 3 Type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with stage 2 T1D. On July 21, 2025, the Applicant (Provention Bio a Sanofi Company) submitted an efficacy BLA supplement for accelerated approval for a new indication — delay of progression of stage 3 T1D in adult and pediatric patients 8 years of age or older recently diagnosed with stage 3 T1D. This efficacy supplement was selected for the Commissioner's National Priority Voucher pilot program. Therefore, the review time clock was reduced to 4 months.

The Division of Diabetes, Lipid Disorders and Obesity (DDLO) requested the Division of Biometrics VII (DB VII) to assess potential safety signals for diabetic ketoacidosis (DKA) and serious infection.

This review includes the summary of the analysis methods and the results from the safety analyses. For the full safety review of teplizumab, refer to the clinical review by DDLO.

2 SUMMARY OF SAFETY ANALYSES

2.1 STUDIES

The safety analyses were based on four randomized, double-blinded, placebo-controlled clinical trials—DELAY, ENCORE, PROTECT, and PROTÉGÉ and one extension study (Table 1). Note that the open-label part of PROTÉGÉ (Segment 1) was not included in the safety assessment. The primary safety population included all subjects who were randomized and received at least one dose of teplizumab or placebo.

Table 1: Summary of Study Design and Population in Five Clinical Trials.

Clinical Study Study Phase Status	Primary endpoint	Study Population[a]	Total Planned/ Randomized/ Completed	Study Design Type of Control[b] Follow-up Duration	Route of Administration Dosage Regimen
PROTECT PRV-031-001 **Phase 3** Completed	AUC of C-peptide after 4-hour MMTT at Week 78	Age ≥8 to ≤17 years Participants recently diagnosed with Stage 3 T1D (≤6 weeks) At least 1 T1D-associated autoantibody according to American Diabetes Association criteria Peak stimulated C-peptide ≥0.2 pmol/mL at screening	300/328/296	Randomized, double-blind, 2-arm, multinational, study Placebo Follow-up duration: 18 months	IV infusion 12-day regimen 2 identical courses: Baseline, 6 months or 12 months[c] Total dose per course ~ 9031 µg/m²
Protégé CP-MGA031-01 **Phase 2/3** Completed	Proportion of participants with both total daily insulin dose <0.5 U/kg/day and HbA1c <6.5% at Week 52	Age ≥8 to ≤35 years Participants recently diagnosed with Stage 3 T1D (≤12 weeks)	Segment 1: 10/38/35 Segment 2: 500/516/462	Randomized, double-blind, 2-arm, multicenter study Placebo Segment 1: Open label Segment 2: Randomized, double-blind, placebo-controlled, multicenter, multinational, 4-arm, dose-ranging study Follow-up duration: 24 months	IV infusion Segment 1: 14-day regimen 1 single course Total dose ~9034 µg/m² Segment 2: 2 identical courses: Baseline, 6 months Arm 1: Full 14-day regimen Total dose ~9034 µg/m² Arm 2: 1/3 14-day regimen Total dose ~2985 µg/m² Arm 3: Full 6-day regimen Total dose ~2426 µg/m² Arm 4: Placebo 14-day course
Protégé Extension CP-MGA031-02 **Phase 2/3** Completed Early terminated by the Sponsor		Age ≥8 to ≤35 years Participants recently diagnosed with Stage 3 T1D (≤12 weeks) who completed Day 728 in the Protégé study	219/90/0 (study terminated early)	3-year extension of study of Protégé, a double-blind, multicenter, multinational, placebo-controlled study. Follow-up: 3 years	No study drug administered
Encore CP-MGA031-03 **Phase 3** Completed Early terminated by the Sponsor	Proportion of participants with composite endpoint of HbA1c <7.0% and Insulin <0.25 U/kg/day at Week 52	Age ≥8 to ≤35 years Participants recently diagnosed with Stage 3 T1D (≤12 weeks) At least 1+ - islet-cell autoantibodies (ICA512/IA-2) - anti-GAD65+, or -insulin autoantibodies (if present during first 2 weeks, but not beyond 2 weeks of insulin treatment) Detectable C-peptide levels	400/254/74 (study terminated early)	Randomized, double-blind, multinational, 4-arm, dose-ranging study Placebo Follow-up duration: planned for 24 months; study modified when Protégé primary endpoint not met; 89.8% completed 12 months and 29.1% completed 24 months	IV infusion 2 identical courses: Baseline, 6 months Arm 1: 14-day regimen Total dose per course ~ 9034 µg/m² Arm 2: 1/3 14-day regimen Total dose ~2985 µg/m² Arm 3: Full 6-day regimen; Total dose ~2426 µg/m² Arm 4: Placebo 14-day course
Delay ISCT-MGA031-001 (Study 5) **Phase 2** Completed	C-peptide AUC during the MMTT at the Month 12.	Age ≥8 to ≤30 years Diagnosed with T1D between 4-12 months	60/63/57	Randomized, double-blind, multicenter study Placebo Follow-up duration: 12 months	IV infusion 14-day regimen 1 single course: Baseline Total dose ~9034 µg/m²

Source: Applicant's report, clinical overview, pages 15-17.

2.2 SATISTICAL METHOD

Safety Outcome of Interest

The adverse events (AEs) of interest were DKA and serious infection. These two AEs were defined by Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. Specifically, DKA included the preferred terms (PTs) of diabetic ketoacidosis, diabetic ketosis, ketoacidosis, and ketosis. Serious infection was defined based on the system organ class (SOC) of infections and infestations with ≥ grade 3 category or events flagged as 'Y' in the serious adverse event variable.

Analysis Method

Four randomized clinical trials and one extension study were pooled for the analyses. The proportion of subjects with at least one AE and incidence rate (IR), defined as the number of subjects with at least one AE divided by the person-years (PYs) at risk, were calculated by treatment arm. The PYs at risk was the time from the first dose to either the first AE of interest or the last follow-up time for those without an event. To compare the teplizumab and placebo arms, the incidence rate difference (IRD) with its 95% confidence interval (CI) were calculated. To account for study variability, the inverse variance method and the Mantel-Haenszel method were used to estimate the IR and IRD, respectively. The 95% CI of the IRD was estimated using the Greenland and Robins method[1]. In addition, cumulative incidence rates based on Kaplan-Meier estimates were examined. For PROTÉGÉ and PROTECT where multiple dosing regimens (full 14-day regimen, full 6-day regimen, and one-third dosing for the full 14-day regimen) were used, the IR and IRD were calculated by different dosing regimens to determine whether the risk was dose-dependent.

In addition, the reviewer plotted individual profiles of subjects who experienced DKAs to assess the time of occurrence of DKA with respect to that of dosing.

3 RESULTS

Diabetic Ketoacidosis

Table 2 presents the results from the analyses of DKA. Twenty-one subjects (2.5%) in the teplizumab arm and three subjects (1.0%) in the placebo arm experienced DKA. The IRs that accounted for study variability were 1.24 per 100 PY and 0.54 per 100 PY in the teplizumab and placebo arms, respectively, which led to 0.7 additional DKA events per 100 PY in the teplizumab arm compared to the placebo arm (95% CI: -0.12, 1.52).

Figure 1 presents individual profiles of the timing of DKA event occurence. The reviewer examined the 21 subjects in the teplizumab arm who experienced DKA events individually to assess the time of DKA events since the last dosing cycle. Most DKA events occurred more than

[1] Greenland, Sander, and James M. Robins. "Estimation of a common effect parameter from sparse follow-up data." Biometrics (1985): 55-68.

200 days after the last dose, with a median time to event of 312 days. Three subjects experienced their first DKA event during the extension period of PROTÉGÉ. Excluding those three subjects, the incidence rate was reduced to 1.12 per 100 PY in the teplizumab arm. Also, only 3 subjects in the teplizumab arm and 2 subjects in the placebo arm in the U.S. region had DKA events (data not shown). The cumulative incidence rates (Figure 2) also showed similar results, with DKA incidence rising sharply later in the study period.

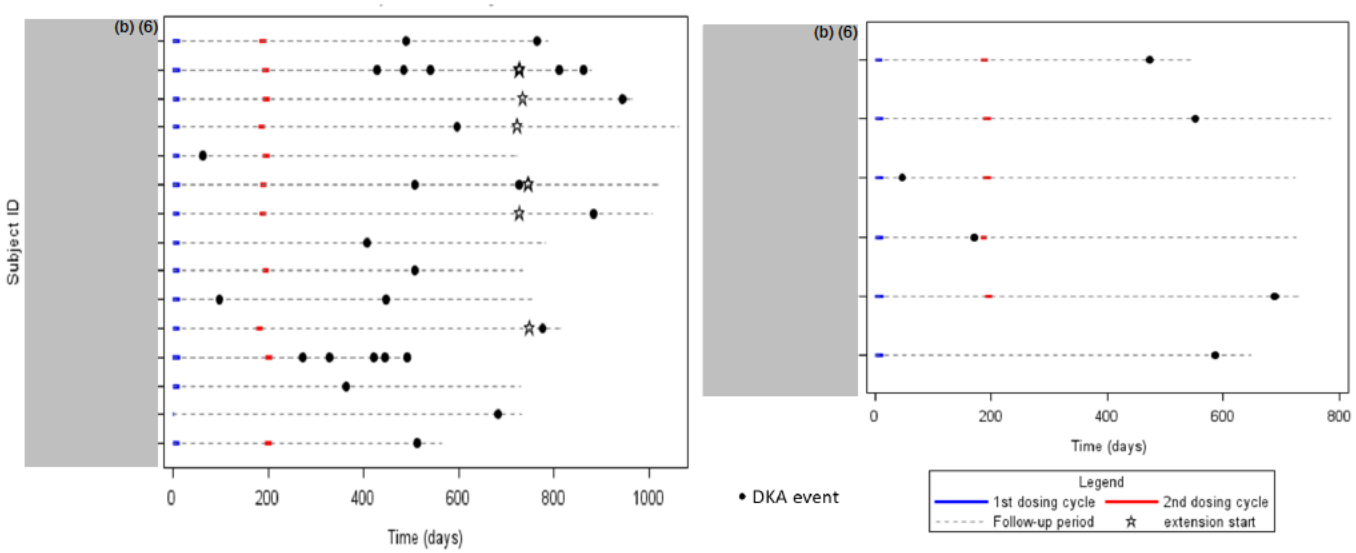
Table 3 shows incidence rates and incidence rate differences by dosing regimen. The incidence rates were 0.48, 1.37, 2.36, and 2.06 per 100 PY in placebo, full 14-day regimen, full 6-day regimen, and one-third dosing for the 14-day regimen, respectively. No clear dose-dependent increase in DKA risk was observed.

Table 2: Incidence Rate and Incidence Rate Difference of DKA.

	Teplizumab N=856	Placebo N=299
Number of subjects (%) Person-Time at Risk (year)	21 (2.5%) 1495.8	3 (1.0%) 513.1
Incidence Rate (100 PY)	1.24	0.54
Incidence Rate Difference (100 PY) (95% CI)	0.70 (-0.12, 1.52)	

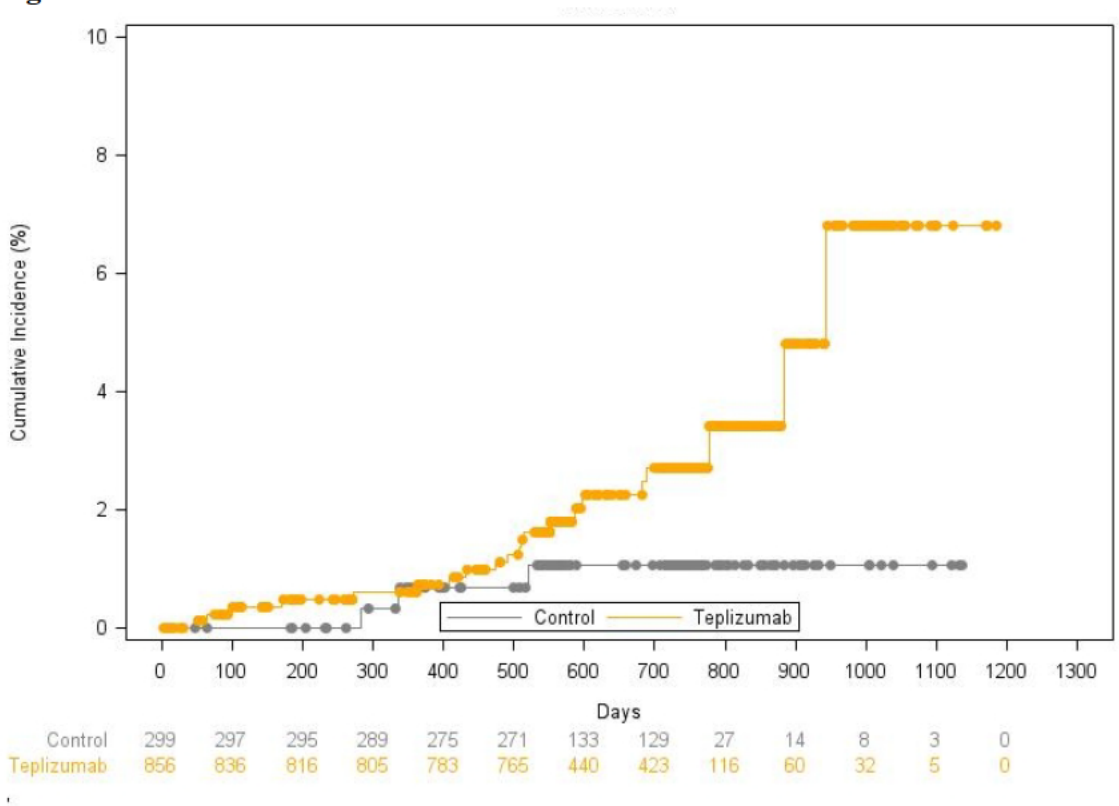
Source: reviewer's analysis using adsl.xpt and adae.xpt

Figure 1: Individual Profile of Timing DKA and Dosing by Subject (Teplizumab Arm)



Source: reviewer's analysis using adsl.xpt and adae.xpt

Figure 2: Cumulative Incidence Rate of DKA.



Source: reviewer's analysis using adsl.xpt and adae.xpt
Control indicates placebo arm.

Table 3: Incidence Rate and Incidence Rate Difference of DKA by Dosing Regimen.

	Teplizumab			
	Full 14-day Regimen (Harold Regimen) N=270	Full 6-day Regimen (Curtailed Herold Regimen) N=169	1/3 14-day Regimen (1/3 Herold Regimen) N=168	Placebo N=160
Number of subjects (%) Person-Time at Risk (year)	7 (2.59 %) 514.2	7 (4.14 %) 309.4	6 (3.57 %) 311.1	1 (0.63 %) 307.5
Incidence Rate (100PY)	1.37	2.36	2.06	0.48
Incidence Rate Difference (100 PY), 95% CI	0.98 (-0.25, 2.21)	1.95 (0.14, 3.77)	1.60 (-0.07, 3.28)	

Source: reviewer's analysis using adsl.xpt and adae.xpt

Serious Infection

Table 4 shows that 28 subjects (3.3%) in the teplizumab arm and 9 subjects (3.0%) in the placebo arm experienced serious infection in the pooled data from four clinical trials. The incidence rates after adjusting study variability were 1.63 and 1.76 per 100 PY in the teplizumab arm and the placebo arm, respectively. Mantel-Haenszel estimate of the incidence rate difference (95% CI) was -0.14 (-1.45, 1.17). Figure 3 shows the cumulative incidence rate over time. There was no clear separation of incidence rates between two arms.

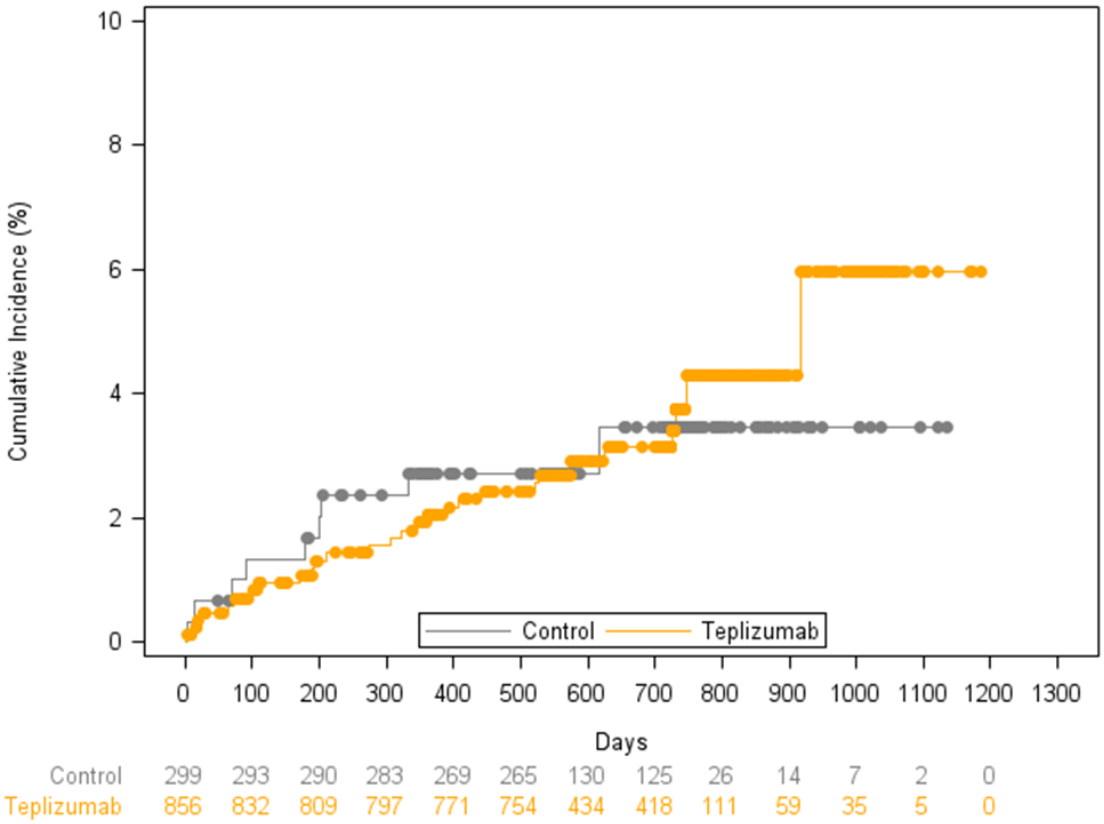
The reviewer also analyzed serious infection by dosing regimen (Table 5). The incidence rates were 1.62, 1.97, 3.69 and 2.88 per 100 PY in placebo, full 14-day regimen, full 6-day regimen and one-third dosing for 14-day regimen, respectively, which does not show a clear dose-dependent relationship.

Table 4: Incidence Rate and Incidence Rate Difference of Serious Infection.

	Teplizumab N=856	Placebo N=299
Number of subjects (%) Person-Time at Risk (year)	28 (3.3%) 1479.6	9 (3.0%) 502.7
Incidence Rate (100PY)	1.63	1.76
Incidence Rate Difference (100 PY) 95% CI	-0.14 (-1.45, 1.17)	

Source: reviewer's analysis using adsl.xpt and adae.xpt

Figure 3: Cumulative Incidence Rate of Serious Infection



Source: reviewer's analysis using adsl.xpt and adae.xpt
Control indicates placebo arm.

Table 5: Incidence Rate and Incidence Rate Difference of Serious Infection by Dosing Regimen.

	Teplizumab			Placebo N=160
	Full 14-day Regimen (Harold Regimen) N=270	Full 6-day Regimen (Curtailed Herold Regimen)	1/3 14-day Regimen (1/3 Herold Regimen) N=168	
Number of subjects (%) Person-Time at Risk (year)	10 (3.70 %) 509.41	11 (6.51 %) 298.40	6 (3.57 %) 310.94	5 (3.13 %) 300.4
Incidence Rate (100PY)	1.97	3.69	2.88	1.62
Incidence Rate Difference (100 PY), 95% CI	0.36 (-1.55, 2.27)	2.02 (-0.59, 4.64)	0.27 (-1.86, 2.40)	

Source: reviewer's analysis using adsl.xpt and adae.xpt

4 CONCLUSION

The reviewer analyzed data from four randomized, placebo-controlled clinical trials and one extension study to assess the safety profile of DKA and serious infections, as requested by the DDLO.

For DKA, more subjects in the teplizumab arm experienced events compared with the placebo arm (IRD: 0.70, 95% CI: -0.12, 1.52). Nevertheless, these events generally occurred a long time after the last dose (median time to DKA: 312 days), and no clear dose-response relationship was observed. Moreover, only three subjects in the teplizumab arm and two subjects in the placebo arm experienced DKA events in the United States.

A numerically higher proportion of subjects with serious infection was observed in the teplizumab arm compared with the placebo arm (3.3% vs. 3.0%). However, after accounting for study variability, the incidence rate difference (95% CI) was estimated at -0.14 (-1.45, 1.17). Taken together, these findings suggest that the occurrence of DKA or serious infections is unlikely to be related to teplizumab. We defer to DDLO for the clinical assessment of DKA and serious infection.

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/s/

JOO YEON LEE
10/20/2025 09:43:29 AM

CLARA KIM
10/20/2025 09:45:32 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s010

PRODUCT QUALITY REVIEW(S)

Submission Tracking Number (STN):	BLA 761183 SUPPL-10 (eCTD 0145)
Subject:	Efficacy supplement to add a new indication to delay the progression of recently diagnosed Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older recently diagnosed with stage 3 type 1 diabetes.
Stamp Date:	7/21/2025
Review/Revision Date:	10/6/2025
Primary Reviewer:	Kun Dong, Ph.D., OPQAIII/DPQAXIII
Secondary Reviewer:	Chringma Sherpa, Ph.D., OPQAIII/DPQAXIII
RBPM:	Andrew Shiber
Consults:	None
Applicant:	Provention Bio
Product:	Tzield (teplizumab-mzwv)
Indication:	Delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 Type 1 diabetes
Action Due Date:	11/21/2025

Summary Basis of Recommendation:

a. **Recommendation:** I recommend approval of this supplement.

b. **Justification:** Provention Bio has submitted an efficacy supplement to add a new indication to delay the progression of recently diagnosed Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older recently diagnosed with stage 3 type 1 diabetes. The clinical data from the efficacy study PROTECT (PRV-031-001) was submitted to support approval of the new indication. The supplement does not include any CMC changes with respect to teplizumab, in Module 3 of BLA761183. Provention Bio requested categorical exclusion from an environmental assessment (EA), which is acceptable. While there are changes in the doses and dosing regimen (one course versus two course treatments), the maximum dose in the new population still remains within the approved dose range requiring no additional safety assessment of process-related impurities. Immunogenicity data was provided as part of the clinical data, but no new assay validation was performed. Anti-drug antibody (ADA) assay and neutralizing antibody (NAb) assay used for immunogenicity evaluations of teplizumab in PROTECT clinical study is same as that approved in original BLA for TN-10 clinical study (stage 2 T1D). The use of the approved assays to generate immunogenicity data to support the new indication is acceptable because the patient population (i.e., stage 3 T1D) in PROTECT study is very similar to that in TN-10 (i.e., stage 2 T1D), there is no impact of serum teplizumab concentration on the immunogenicity assays outcome, and a very high treatment induced ADA incidence rate of 94%-98.3% was reported in the new population using the approved assays. Therefore, the previously validated ADA assay and NAb are sufficient to support the immunogenicity assessment in the current clinical trials. Overall, this supplement is acceptable from a product quality perspective.

Assessment:

5.3.5.3 Integrated Summary of Immunogenicity

The Applicant provided a complete clinical study (PROTECT, PRV-031-001) in this submission, to add a new indication to delay the progression of recently diagnosed Stage 3 type 1 diabetes (T1D) in adults and pediatric patients 8 years of age and older recently diagnosed with stage 3 type 1 diabetes. The applicant stated (Table 4) that the anti-drug antibody (ADA) assay (Method 3) and neutralizing antibody (NAb) assay (Method 2A) used for immunogenicity evaluations of teplizumab in PROTECT clinical study is same as that approved in original BLA for TN-10 clinical study (stage 2 T1D). The ADA incidence rate for all treatment (Lilly/Lilly, AGC/AGC, and Lilly/AGC) are 94% and 98.3% for course 1 and 2, respectively (Table 42).

Assessor Comments: *The patient populations in stage 2 and stage 3 T1D clinical trials are very similar and are within the same continuum of disease (100% of patients with Stage 2 T1D will develop Stage 3 T1D) and the only difference between Stage 2 and 3 T1D is meeting the diagnostic thresholds for hyperglycemia consistent with clinical diabetes. In addition, the treatment induced ADA incidence rate reported for the PROTECT study is very high (94%-98.3%), the ability of the assay to identify ADA positive samples by using proved ADA assay in TN-10 study is supported.*

Compared to the dosing regimen of TN-10 study that is used to support original BLA approval (single 14-day course), the dosing regimen of PROTECT study is 12 days per course with two courses (Table 10) as below:

Study	Phase and Blinding Status	Drug Product Batches	Number of Doses	Dose Regimen	Number of subjects with ADA results	Number of subjects with NAb results
TN-10 At-Risk ISCT-MGA031-005	A Phase 2, 2-arm, multi-center, randomized, double-masked, placebo-controlled clinical trial	FIN-0695 (DS lot 060706001), 1-FIN-1643 (DS lot A573777), 1-FIN-2543 (DS lot A742373)	14-day infusion of either teplizumab or placebo	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 Total dose ~9034 µg/m²	Teplizumab: 44 Placebo: 32	29 samples - Screen: 1 placebo, 2 teplizumab - 3 months: 2 placebo, 24 teplizumab
PROTECT PRV-031-001	A Phase 3, randomized, double-blind, placebo-controlled study	1-FIN-2543, 3-FIN-3689	12-day infusion administered of either teplizumab or placebo in two treatment courses	Day 1: 106 µg/m² Day 2: 425 µg/m² Day 3-12: 850 µg/m² Total per course: 9031 µg/m²	201	201

Assessor Comments: *There are changes in dose and dosing regimen between the two efficacy trials but the maximum dose in the new population still falls within the approved dose range. Therefore, no additional safety assessment of process-related impurities such as endotoxin and host cell DNA exposure is needed. Further, although the serum teplizumab concentration (Figure 39) significantly exceeds the drug tolerance (12.5 ug/ml for 10 ng/ml ADA, 50 ug for 111ng/ml and 1000ng/ml ADA, Table 7) established by the validated ADA assay, no significant impact of serum teplizumab concentration on ADA and NAb assays outcome was observed.*

Environmental Assessment

Provention Bio requested a categorical exclusion from the requirements to prepare an EA under 21 CFR 25.31(c). A justification for exclusion was provided in Section 1.12.14.

Reviewer comment: *The claim of categorial exclusion from an EA is acceptable.*

Assessment Conclusion:

I. **Recommendation:** Approval
II. **Sections deferred to other reviewers:** None
III. **Post-marketing commitments:** None
IV. **Future Inspection Items:** None

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/s/

KUN DONG
03/09/2026 10:39:15 AM

CHRINGMA SHERPA
03/09/2026 10:45:03 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s010

OTHER REVIEW(S)

Memo to the File

From:	Michael Davis, MD, PhD Acting Director Center for Drug Evaluation and Research (CDER)
To:	Biologics License Application (BLA) 761183-Supplement 010
Applicant's original proposed Indication:	(b) (4) indicated to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D.
Revised indication following discussions with the FDA review team:	To delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D. This indication is approved under accelerated approval based on evidence of reduced C-peptide decline *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
Subject:	Documentation of concurrence with Division recommendation

The purpose of this memo is to document my concurrence with the Division of Diabetes, Lipid Disorders and Obesity's (DDLO) recommendation that CDER approve BLA 761183, Supplement 010 without holding a public discussion before an advisory committee.

Background

BLA 761183 for Tzield (teplizumab-mzwv) injection was approved on November 17, 2022, under traditional approval for the delay of onset of Stage 3 Type 1 diabetes (T1D) in adults and pediatric patients 8 years of age and older with Stage 2 T1D.[1] On July 21, 2025, the Applicant submitted a supplemental BLA (sBLA) requesting approval under accelerated approval for the proposed indication:

[1] This indication was expanded with the approval of an sBLA on April 20, 2026, to delay the onset of Stage 3 T1D in pediatric patients between 1 to 8 years of age with Stage 2 T1D

(b) (4)

indicated to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D.

The Applicant requested a priority review designation for the sBLA. The application was designated as a priority review application and filed on July 21, 2025, with a user fee goal date of January 21, 2026. The goal date was extended to April 21, 2026, after receipt of a major amendment.

By letter dated October 24, 2025, FDA communicated to the Applicant that the sBLA was selected for the FDA Commissioner's National Priority Voucher (CNPV) pilot program[2], on the basis that the Tzield injection for recently diagnosed Stage 3 T1D sBLA met pilot program criteria based on its alignment with critical U.S. national health priorities.

Before May 2026, following a presentation and a preliminary recommendation by the primary review team, applications reviewed under the CNPV were discussed internally before a select group (the CNPV Review Council) within FDA who voted on the application review issues brought before them, such as the benefits/risks of the drug product covered by the application. This supplement was discussed before the CNPV Review Council three times: on October 28, 2025, April 1, 2026, and April 8, 2026. Each of those meetings concluded with a vote from the CNPV Review Council. A separate non-voting briefing was also held on February 2, 2026; this meeting included only a small group from the application review team, former FDA Commissioner Dr. Marty Makary, former acting CDER Director Dr. Tracy Beth Hoeg, and former CBER Director Dr. Vinay Prasad.

During each of these meetings, the review team presented its position that the pivotal study (PROTECT) showed a statistically significant effect of teplizumab-mzwv on C-peptide, a surrogate endpoint considered reasonably likely to predict clinical benefit to support accelerated approval.[3] The review team also presented safety data related to risks of diabetic ketoacidosis (DKA), Epstein-Barr Virus (EBV) reactivation, infections, and cancer, and their conclusion was that these risks were unlikely related to

[2] On June 17, 2025, FDA announced the Commissioner's National Priority Voucher (CNPV) pilot program intended to shorten review time "from approximately 10-12 months to 1-2 months following an applicant's final drug application submission." On October 16, 2025, FDA announced that this sBLA was among nine recipients of a CNPV. Neither the Applicant nor the review division requested that this application be reviewed under the CNPV pilot program.

[3] Section 506(c) of the FD&C Act codified the accelerated approval program which provides a pathway for approval of drugs for serious conditions that fill an unmet medical need based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

teplizumab-mzwv; or if related, the risks did not outweigh the benefits of teplizumab-mzwv if used as directed in labeling, including with a narrowed indication and recommendations to mitigate risks. In addition, the review team stated that the Applicant's agreed-to confirmatory trial to verify clinical benefit was already underway and would continue as a post-marketing requirement (PMR).[4] A PMR to conduct an observational registry study to assess long-term safety of teplizumab-mzwv to evaluate cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders (LPD) and malignancy is ongoing. Long-term safety data are also being collected as a PMR for an additional 42 months in participants who complete the PROTECT study.[5]

At each CNPV Review Council meeting, Dr. Hoeg voiced objection to approval of this application. She disagreed with the review team's view that the product's benefits outweighed its risks, including the risks of DKA, EBV reactivation, or cancer. She met with the Division review team, the Office Deputy Director, and the Office of New Drugs (OND) Director on April 9, 2026, stating that she could not approve the application. On April 21, 2026, the Applicant was informed that the Agency was going to miss the PDUFA goal date for the application in order to hold a public advisory committee meeting to discuss the benefits and risks of this product for its proposed indication.

Materials Reviewed

As the current acting Center Director, I reviewed the many documents provided by the multi-disciplinary review team to understand the benefits and risks of this product for this specific indication. These documents included:

1. Statistical Review, finalized October 20, 2025
2. Statistical Review, finalized March 5, 2026
3. Office of Oncology Drugs, Division of Hematologic Malignancies 2 consult dated January 9, 2026
4. Office of Infectious Diseases, Division of Antivirals consult dated January 9, 2026
5. Office of Infectious Diseases, Division of Antivirals consult dated March 30, 2026
6. Clinical Review from the Division of Diabetes, Lipids and Obesity (DDLO) and the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN), finalized March 19, 2026
7. Office of Surveillance and Epidemiology (OSE) consult dated April 14, 2026
8. OSE DPV review dated April 30, 2026

[4] Section 506(c) of the FD&C Act, as amended by the Consolidated Appropriations Act, 2023, gives FDA authority to require, as appropriate, that a confirmatory trial be underway prior to accelerated approval or within a specified time period after the data of accelerated approval.

[5] As per the applicant's Annual Status Report received on January 15, 2026, and reviewed by FDA on March 31, 2026, both of these PMRs are ongoing.

Dr. Hoeg is no longer at the FDA; however, it is important to consider the safety concerns that she voiced on each of the occasions discussed above before determining whether the course of action previously directed by her should be followed. Dr. Hoeg did not provide any written review in the administrative record discussing her analyses of the safety findings, her consideration of the Division's recommendation, including labeling changes, or her consideration of the multiple consults provided to the Division; thus, there is no discussion of a counter-perspective of her concerns in this document. However, upon my independent review, I believe the multiple reviews and consult reviews, including one requested by Dr. Hoeg, provide evidence of a very thorough review performed by career FDA scientists with expertise in endocrinology, infectious disease, oncology/hematology, biostatistics, and epidemiology. Below, I summarize the conclusions from these reviews:

- The clinical and statistical reviews concluded that the applicant was able to demonstrate robust and superior effectiveness of teplizumab-mzwv in preserving C-peptide area under the curve (AUC) compared to placebo among pediatric patients 8 to 17 years of age.
- The clinical and statistical reviews provided very detailed reviews and analyses of DKA and serious infections, concluding that the totality of evidence, including individual review of cases, suggests that the occurrence of DKA or serious infections in the PROTECT study is unlikely to be related to teplizumab-mzwv.
- Two consult reviews from the Division of Antivirals and one consult from the Division of Hematologic Malignancies 2 on the cases of EBV reactivation, including risk of LPDs, acknowledged the biologic plausibility of EBV reactivation which is similar to other immune modulator drugs and recommended labeling to strengthen the warnings for this risk, including the addition of a Boxed Warning.
- The OSE consult, conducted at the request of Dr. Hoeg, to evaluate the risks for neoplasms, including EBV-associated LPD, provided a thorough review of five cases of neoplasm and a summary of a literature review performed by OSE. The consult review concluded that, based on available information, it is not possible to implicate teplizumab-mzwv as having a direct effect on the development of reported neoplasms. The consult recommended labeling changes regarding viral reactivation, continued pharmacovigilance, and fulfillment of PMRs.
- Another OSE review of all U.S. serious cases submitted to the FDA's Adverse Event Reporting System (FAERS) in pediatric patients under 18 years of age from November 17, 2022, to March 9, 2026, identified no new safety signals, no increased severity of any labeled adverse events, and no deaths directly associated with teplizumab-mzwv. This review concluded that no new pediatric

safety concerns for teplizumab-mzwv were identified at this time and that routine pharmacovigilance monitoring should continue.

All of these reviews led to consistent conclusions that the Applicant demonstrated a significant effect on an accepted endpoint to support accelerated approval, and that the risks identified did not outweigh this efficacy and could be further mitigated through labeling, required post-marketing studies, and postmarket pharmacovigilance to ensure the benefit-risk profile of this product for this indication remains favorable. None of these reviews stated that an advisory committee meeting would be useful for the regulatory decision.

Conclusion

Delegation of signatory authority for marketing applications is assigned to the OND Clinical Office Director (or deputy) for new molecular entity (NME) new drug applications (NDAs) or BLAs and the OND Division Director (or deputy) for non-NME NDAs or BLAs and supplemental applications to an approved NDA or BLA. The signatory authority for BLA 761183-Supplement 010 rests with the Director (or Deputy) of DDLO.

After reading the finalized reviews and consults and meeting with the review team, I believe the multi-disciplinary review team has carefully considered the available efficacy and safety data and reached reasonable, scientifically justified conclusions about the benefit/risk profile of this drug product for its proposed indication (with appropriate labeling and PMRs). I support their unanimous recommendation to approve teplizumab-mzwv under the accelerated approval pathway to delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years, recently diagnosed with Stage 3 T1D.

I also agree with the review team that an advisory committee meeting to discuss the pending application, as requested by former acting Center Director Dr. Hoeg, is not warranted here. Except in limited circumstances that are not applicable to this application, FDA is not required to convene an advisory committee meeting to discuss a pending drug application before taking action on the application. Although advisory committee meetings can be helpful in providing independent expert advice to FDA on FDA-regulated products, taking a pending drug application to an advisory committee for discussion and recommendations can add significant time to the drug review process and can require significantly more Agency and sponsor resources. Thus, FDA typically does not convene an advisory committee meeting to discuss a pending drug application unless the relevant Center determines that obtaining the advisory committee's non-binding advice on one or more scientific topics may be important to inform the Center's review and final decision on the application. For the reasons explained above, that is not the case here. Thus, CDER will not convene an advisory committee meeting to

discuss the application; instead, the review team will proceed to approve the application under accelerated approval with appropriate labeling and PMRs.

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MICHAEL C DAVIS
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Office of Medical Policy (OMP)
Division of Medical Policy Programs (DMPP)
Center for Drug Evaluation and Research (CDER)

PATIENT LABELING REVIEW

Date: June 10, 2026

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

From: **DMPP Patient Labeling Reviewer**: Sharon Williams, MSN, BSN, RN
DMPP Team Leader: Marcia Williams, PhD
OPDP Reviewer: Ankur Kalola, PharmD

Subject: **Review of Patient Labeling**: Medication Guide (MG) for TZIELD (teplizumab-mzwv), BLA 761183, S-010

On July 21, 2025, Provention Bio, Inc. submitted for the Agency's review as part of the Commissioner's National Priority Voucher (CNPV) program a Part 2 submission for an Efficacy Supplemental New Drug Application NDA 761183, S-010 TZIELD (teplizumab-mzwv) injection, for intravenous use. On November 24, 2025, a major amendment was submitted to this application resulting in a review extension. An additional Part 2 submission was made on March 10, 2025. The purpose of the supplement is to seek approval for the following proposed indication: delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D.

This collaborative review is written by DMPP and OPDP in response to a request by DDLO on July 21, 2025, for DMPP and OPDP to review the Applicant's proposed MG for TZIELD injection, for intravenous infusion. DMPP and OPDP reviewed the MG received by the Agency on May 4, 2026, revised throughout the review cycle, and received by DMPP and OPDP on June 6, 2026.

Our review of the MG targets a 6th to 8th grade reading level with a reading ease score of at least 60% to enhance patient comprehension.

In our collaborative review of the MG we:

- Evaluated the MG for consistency with the Prescribing Information (PI) received by DMPP and OPDP on June 6, 2026.
- Simplified wording, clarified concepts, and removed unnecessary or redundant information.
- Removed promotional language where possible.
- Ensured the MG meets the Regulations as specified in 21 CFR 208.20
- Evaluated the MG per the criteria in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

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MARCIA B WILLIAMS
06/10/2026 11:24:48 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 10, 2026

To: Supendeep Dosanjh, Regulatory Project Manager, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Melinda Wilson, Associate Director for Labeling, DDLO

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TZIELD® (teplizumab-mzwv) injection, for intravenous use

BLA: 761183, S-10

Background:
In response to DDLO's consult request dated July 31, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 10 for Tzield. This supplement proposes a new indication to delay the progression of Stage 3 T1D.

PI & Medication Guide:
OPDP's review of the proposed PI and Medication Guide is based on the draft labeling emailed to OPDP on June 6, 2026, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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ANKUR S KALOLA
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Memorandum

Date:	April 13, 2026
To:	Tracy Beth Høeg, MD, PhD Acting Director Center for Drug Evaluation and Research (CDER)
From:	Graça M. Dores, MD, MPH Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER
Through:	S. Christopher Jones, PharmD, MS, MPH Director, DPV II OSE, CDER Gerald J. Dal Pan, MD, MHS Director, OSE CDER
Product Name(s):	TZIELD (teplizumab)
Application Number:	761183/S-010
Subject:	Neoplasms following teplizumab

Background

Teplizumab is a humanized anti-CD3ε monoclonal antibody that is approved in the United States 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. The recommended dosage for the currently approved indication for Stage 2 T1D is once daily for 14 consecutive days based on body surface area. Presently, review of a supplement is being finalized in the Center for Drug Evaluation and Research (CDER) with a recommendation by the Division of Diabetes, Lipid Disorders and Obesity to limit the indication to treatment of patients 8 to 17 years of age with residual beta cell function, ideally within 6 weeks of T1D diagnosis, but no later than within 8 weeks of T1D diagnosis.

Teplizumab targets CD3, a component of the T-cell receptor complex required for T-cell activation and signal transduction that plays a key role in the destruction of pancreatic β cells.[1] It is an immunomodulatory agent that induces partial CD8+ T-cell exhaustion and increased regulatory T-cells rather than causing broad immune suppression.[1,2] Teplizumab induces transient lymphopenia that generally resolves within 6 weeks.[1]

The current labeling for teplizumab (April 2025) includes serious infections and lymphopenia as a Warning and Precaution:

> **5.2 Serious Infections**
>
> Bacterial and viral infections have occurred in TZIELD-treated patients. In clinical trials, TZIELD-treated patients had a higher rate of serious infections (3.5%) than control-treated patients (2%), including gastroenteritis, cellulitis, pneumonia, abscess, sepsis *[see Adverse Reactions (6.1)]*. Use of TZIELD is not recommended in patients with active serious infection or chronic infection other than localized skin infections. Monitor patients for signs and symptoms of infection during and after TZIELD treatment. If serious infection develops, treat appropriately, and discontinue TZIELD.
>
> **5.3 Lymphopenia**
>
> In clinical trials, 78% of TZIELD-treated patients developed lymphopenia compared to 11% of control-treated patients. For most TZIELD-treated patients who experienced lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pre-treatment values within two weeks after treatment completion and without dose interruption. Severe lymphopenia (<500 cells per mcL) lasting 1 week or longer occurred in 0.9% of TZIELD-treated patients, and 0.5% of TZIELD-treated patients permanently discontinued TZIELD because of lymphopenia *[see Adverse Reactions (6.1)]*. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD.

At the time of initial approval of teplizumab on 11/17/2022, a Postmarketing Requirement was put in place:

"Conduct an observational registry study to assess the long-term safety of teplizumab-mzwv in patients with Stage 2 type 1 diabetes. The study should evaluate cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders and malignancy. […] The study design should include a comparator group and monitor patients for at least 10 years after their first course of treatment. The study should enroll at least 150 subjects exposed to teplizumab-mzwv and collect sufficient clinical information to assess for sources of confounding for the target outcomes."

Case Review

On April 3, 2026, DPV II was asked to comment on cases of neoplasms reported with teplizumab. The five cases are summarized below:

1) A 22-year-old male with T1D in the Protégé study developed **malignant melanoma (pigmented epithelioid melanocytoma) with lymph node metastases** in (b) (6) approximately 6 months after receiving 4 of 14 daily infusions of teplizumab. The patient was reported to have a history of dysplastic nevi syndrome ("since (b) (6)") and a pre-existing lesion at the site of diagnosis of the melanoma that was not diagnosed until after entering study. Teplizumab was discontinued due to bilirubin elevation. The melanoma was resected and there was no evidence of recurrence 2 years after excision.

   Reviewer comment:
   The total number of nevi, dysplastic nevi, and atypical moles are risk factors for development of melanoma.[3] Although information on number of nevi and atypical or dysplastic nevi are not provided, the reporting that the patient had been diagnosed with dysplastic nevi syndrome 10 years prior (at an estimated age of 12 years) supports a prior history of dysplastic nevi. Also, the young age at diagnosis of dysplastic nevi syndrome raises the possibility of an underlying heritable melanoma syndrome. Sun exposure is also an established risk for melanoma; however, based on this patient's age, it is difficult to attribute melanoma risk to UV exposure, although the report does not provide information on duration and intensity of the patient's sun exposure history. Information on other risk factors for melanoma (e.g., skin type, family history) was not provided. It is well-established that the immune system has an important role in the progression and regression of melanoma, and that immunosuppression (e.g., hematopoietic or solid organ transplant) is associated with an increased risk of melanoma. This patient has a documented risk factor for melanoma (dysplastic nevi syndrome), and notably, the time to onset of melanoma following start of teplizumab (estimated 7 months) is relatively short for latency intervals typically associated with malignant neoplasms (years). However, given the immunomodulating effect of teplizumab and the temporal pattern of melanoma occurring following

exposure, a contributory role of teplizumab in development of melanoma cannot be entirely excluded.

2) A 37-year-old female renal transplant recipient with T1D and asthma was enrolled in Study 8223 (Phase 1 study for treatment of renal allograft rejection) developed Grade 2 **squamous cell carcinoma** (SCC) in (b) (6), approximately 5 months after receiving 10 of 14 daily teplizumab infusions. The patient was also receiving concomitant mycophenolate mofetil and prednisone therapy for prevention of renal transplant rejection.

   Reviewer comment: The SCC is presumed to be cutaneous SCC (site is not specified in the report). This patient is at high risk of developing cutaneous SCC related to her organ transplant status and the ongoing immunosuppression regimen to prevent organ rejection. Solid organ transplant recipients have much higher risks of developing cutaneous SCC than the general population (i.e., 30-fold higher risk).[4] Notably, the time to onset of SCC following start of teplizumab (estimated 6 months) is unusually short for latency period typically associated with malignant neoplasms (years). However, given the temporal association of teplizumab and SCC and the drug's mechanism of action, a contributory role of teplizumab cannot be entirely excluded.

3) A 7-year-old female with stage 2 T1D, seasonal allergies, and asthma enrolled in the PETITE study (open-label study to assess the safety and pharmacokinetics of a 14-day daily regimen of teplizumab in pediatric Stage 2 T1D developed a **low-grade glioneuronal neoplasm** in (b) (6), approximately 11.5 months after receiving 14-days of teplizumab. The patient presented with severe upper back and posterior neck pain. Computerized tomography (CT) scan showed a small focal calcification in the posterior floor of the mouth not suggested to be the cause of her symptoms. Because of progressive symptoms, the patient subsequently underwent a magnetic resonance imaging (MRI) of the cervical (C) spine, which identified a heterogeneous, expansile intramedullary mass involving the cervical spinal cord and extending into the thoracic (T) cord down to the level of T7. MRI of the brain was negative. No pre-enrollment MRI of the spine had been performed. The patient underwent C3-C6 laminoplasty and intramedullary spinal cord tumor resection. Pathology revealed a biphasic tumor composed of neuronal and glial components. The neuronal component showed dysplastic neurons, and the glial component showed morphology consistent with astrocytic differentiation. No high-grade features were identified. Tumor cells were positive for GFAP and olig2 (in the glial component), markers used to identify glial cells. ATXR was retained (wild type), and IGH1-R132H was negative, with these findings supporting a diagnosis of true low grade glioneuronal neoplasm (i.e., as opposed to suggesting a

diffuse infiltrating glioma or astrocytoma). A low-grade neoplasm was further supported by a low Ki67 labeling index (estimated at 2%) indicating a low proliferative index. Extensive testing was performed on the tumor specimen related to tumor classification, prognostication, and treatment options. However, no genetic testing was planned to exclude inherited conditions known to predispose to pediatric central nervous system tumors (e.g., neurofibromatosis type 1 and 2).

The investigator considered the glioneuronal tumor possibly related to teplizumab given the temporal association and no information on whether the spinal lesion was present prior to start of therapy. An external pediatric neuro-oncologist consulted by the Applicant indicated that "in her experience, there has been no association with immune-mediated conditions (including T1D) or immunotherapies for this type of pediatric tumor. She emphasized that low grade gliomas (LGG) occur sporadically, and spinal cord LGG or low-grade glioneuronal tumor (LGGN) are extremely rare. […] the size of the tumor and typical slow rate of growth, suggests that this tumor was likely already present at the time of the enrollment in the clinical trial. Apart from the genetic alterations, no factor is known to increase the rate of the tumor growth." In the consultant's opinion, the low-grade glioneuronal neoplasm was not related to the study drug.

> Reviewer comment: Glioneuronal tumors are rare and other than the association with genetic predisposition syndromes (i.e., neurofibromatosis types 1 and 2), their etiology is unknown.[5] Although an underlying heritable syndrome cannot be entirely excluded, it is plausible to consider that the tumor was present prior to the start of teplizumab based on the indolent nature of low grade glioneuronal tumors. The time to onset (approximately one year) from start of teplizumab is atypically short for tumorigenesis. However, based on the temporal association of the low grade glioneuronal neoplasm occurring after exposure to teplizumab and the absence of baseline imaging of the cervical spine, a contributory role of teplizumab in tumor development cannot be definitively excluded.

4) A case of "**lymphoproliferative syndrome**" described as lymphadenopathy, Epstein-Barr virus (EBV) infection, and sore throat was reported in an islet cell transplant recipient (no age or sex provided) in an investigator-initiated study. The patient was treated with "3 additional immunosuppressive agents" in addition to hOK3Ƴ1(Ala-Ala) (muromonab-CD3, the mouse anti-CD3 monoclonal antibody precursor to teplizumab). The patient's symptoms resolved after discontinuation of immunosuppression and treatment with antiviral therapy. The Applicant stated that this case was not considered in their analysis as it was a "non-malignant disease, associated with acute EBV infection."

Reviewer comment: Lymphoproliferative disorders (LPD) are classified as intermediate between benign (lymphoid hyperplasia) and malignant lesions (lymphoma), but they can evolve to malignant entities. LPDs may be associated with EBV, an oncogenic virus,[6] or may be unrelated. This patient had risks for lymphoproliferation or LPD that included EBV reactivation and a history of islet cell transplant requiring immunosuppressive therapy (drug names not specified). This case includes limited clinical details; however, the resolution of symptoms with antiviral therapy and decrease and discontinuation of immunosuppression supports a virally mediated, reversible process. Despite established risk factors for LPD, based on the temporality of LPD following exposure to the teplizumab precursor and its immunomodulatory effects, a contributory role of teplizumab in LPD development cannot be entirely excluded.

5) This report (#26088435), originating from a physician in Germany, was submitted to the FDA Adverse Event Monitoring System (AEMS), formerly known as the FDA Adverse Event Reporting System (FAERS). A 44-year-old male with Down syndrome and history of repair of Tetralogy of Fallot, hypothyroidism, and stage 2 T1D started daily teplizumab on (b) (6) and on (b) (6) developed lymphopenia. Teplizumab was continued with increasing dose; on (b) (6) and (b) (6), teplizumab was paused due to lymphopenia. Teplizumab was then resumed at the previously administered dose between (b) (6) and (b) (6) at which time the course of teplizumab was completed. Of note, the lymphocyte count was <0.5/nl on (b) (6), and on (b) (6) "for first time," the total white blood cell (WBC) count was low (before the last dose of teplizumab). At the end of (b) (6), the patient developed cervical lymphadenopathy, was not doing well, and was hospitalized at an outside facility (other than the treating physician's facility) on (b) (6). He developed a high-grade fever and a rapidly progressive sepsis-like illness with multiorgan dysfunction. He was diagnosed with EBV reactivation and during his hospitalization he required care in the intensive care unit for approximately 12 days for respiratory failure, renal failure, shock, and liver failure.

During his hospital course abdominal CT scan showed mesenteric lymphadenopathy in addition to the cervical adenopathy he had upon admission. Biopsy of a cervical lymph node was done under general anesthesia, and the tentative diagnosis was "EBV reactivation with lymphadenopathy." He then received weekly rituximab for **EBV reactivation and suspected LPD or lymphoma**. He had a good response to rituximab with EBV viral load decreasing from >2 million IU/ml to 853 IU/ml. Lymph node pathology on (b) (6): Evidence of a highly proliferative, mixed, and at least partially EBV-associated lymphoproliferation. The histological picture showed a mixed-cell infiltrate. The B-cell infiltrate contained within the mixed infiltrate was immunohistochemically CD79a+ and CD38-positive and CD20-negative. The

"professor" (Professor (b) (6) referenced in the report) commented that "despite alarming histological appearance, the clinical context and certain histological elements suggested a lymphoma-limiting EBV-associated lymphoproliferation." He believed this represented either a primary EBV infection or an EBV reactivation in the context of an immunocompromised state; given the patient's age, he assumed the latter more likely. There were no translocations involving the c-MYC, BCL2, or BCL6 genes (translocations that can be seen in B-cell lymphomas). Molecular analyses demonstrated a "clonal immunoglobulin heavy chain gene rearrangement and T-Cell Receptor Gamma (TCRG) clonality analysis showed several peaks meeting the manufacturer's criteria for clonality, but results did not correspond to a clonal TCRG gene rearrangement. Despite detection of B-cell clonality, Professor (b) (6) would not diagnose a B-cell lymphoma and continued to assume an EBV reactivation." No evidence of clonality for T-cells was found. The professor's final assessment was that findings were best interpreted as EBV reactivation despite the detection of clonality of B-cells, although this would need to be confirmed by the patient's clinical course; however, this case does not provide any information beyond the acute illness. The patient recovered after a 3-week hospitalization.

> Reviewer comment: Individuals with Down syndrome have an immunophenotype of combined immunodeficiency and dysregulation of the innate and adaptive immune system. This patient had evidence of lymphoproliferation that was histologically difficult to classify in the setting of his acute illness; however, the presence of clonality is highly suspect of a B-cell neoplasm that in the context of his clinical course likely represented an EBV-driven process. The patient's EBV viral load decreased markedly in response to rituximab (an anti-CD20 monoclonal antibody), and it is noted that a CD20-positive B-cell lymphoma would also likely respond to this treatment, at least temporarily. The patient's innate immunodeficiency from Down Syndrome along with exposure to teplizumab (with continued administration despite lymphopenia) likely contributed to the EBV reactivation and associated LPD or lymphoma.

Literature review

A search of "cancer" and "teplizumab" in the PubMed database (without filters applied) yielded 17 publications, none of which described cancer occurring after teplizumab exposure. One article reported that in a murine xenograft model, teplizumab demonstrated anti-leukemic properties in CD3+ T-cell acute lymphoblastic leukemia (T-ALL).[7]

A search for "lymphoma" and "teplizumab" in the PubMed database (without filters applied) identified two publications. One article[7] was identified in the "cancer and teplizumab" search noted above,[7] and the second article described use of a second mitochondrial-derived activator of

caspases (SMAC) mimetic (birinapant) in combination with teplizumab in patient-derived T-ALL xenografts to enhance antileukemic properties of teplizumab.[8]

A search for "neoplasm" and "teplizumab" in the PubMed database (without filters applied) yielded five publications, of which two are referenced in the searches noted above.[7,8] The remaining three publications did not describe neoplasms occurring following teplizumab exposure.

General Comments

Lymphoproliferative disorders (based on reference[9])

Immune deficiency and dysregulation (IDD)–associated LPDs are clinicopathologically and etiologically heterogeneous. It is increasingly recognized that individuals treated with chemotherapy regimens for previous solid cancers or hematological malignancies experience significant immune dysregulation leading to IDD-LPDs. Notably, the spectrum of therapy-related IDD-LPDs is expanding, with increasing reports of IDD-LPDs occurring following:

- Novel immunotherapies (e.g., anti-CD20, anti-CD38, chimeric antigen receptor T-cell therapy, BTK inhibitors)
- Immunomodulatory treatments (e.g., as induction strategies for immune tolerance in solid-organ transplantation),
- Novel immunosuppression in autoimmune and inflammatory diseases (e.g. asthma)
- More effective antiretroviral treatment strategies in patients with HIV

The World Health Organization classifies lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation into the following categories:[9]

- Hyperplasias arising in immune deficiency/dysregulation
- Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation
- EBV-positive mucocutaneous ulcer
- Lymphomas arising in immune deficiency/dysregulation
- Inborn error of immunity-associated lymphoid proliferations and lymphomas

However, lymphoproliferative disorders and lymphomas can arise in the setting of autoimmune disease and/or exposure to immunosuppressive/immunomodulatory medications and in the setting of latent infection with EBV (an oncogenic virus):

- Hyperplasias
    - Follicular hyperplasia (EBV+ or EBV-)
    - Infectious mononucleosis-like hyperplasia (EBV+ or EBV-)
    - Plasmacytic hyperplasia (EBV+ or EBV-)
    - Other hyperplasias (EBV+ or EBV-)

- LPDs of varied malignant potential
    - Polymorphic lymphoproliferative disorder (EBV+ or EBV-)
      [Note: In the post-transplant setting, LPDs may be referred to as post-transplant lymphoproliferative disorders (PTLD)]
    - EBV-positive mucocutaneous ulcer (EBV+ only)
- Lymphomas
    - Small cell, B-cell lymphoma (EBV+ or EBV-)
    - Diffuse large B-cell lymphoma (EBV+ or EBV-)
    - Classic Hodgkin lymphoma (EBV+ or EBV-)
    - Plasmablastic lymphoma (EBV+ or EBV-)
    - Plasma cell neoplasms (EBV+ or EBV-)
    - T-cell and NK-cell lymphomas (EBV+ or EBV-)

Hyperplasias are reactive and non-malignant proliferations whereas lymphomas are malignant entities. Polymorphic LPDs are classified between reactive hyperplasia and overt malignancy. However, LPDs can evolve into frankly malignant entities. Their classification and biologic behavior depend heavily on the clinical context of immunodeficiency. A critical feature is that polymorphic LPDs have variable clonality (polyclonal, oligoclonal, or monoclonal), and this variability is what makes their biologic behavior unpredictable. Monoclonal polymorphic LPDs are often driven by EBV and immunosuppression, and their progression appears to correlate with acquisition of additional genetic alterations (e.g., BCL6 somatic hypermutations, TP53 mutations, MYC rearrangements).

Down Syndrome

Down syndrome has an immunophenotype of combined immunodeficiency and dysregulation of the innate and adaptive immune system. This manifests with an increased susceptibility to autoimmune disease (including T1D) and more severe infections than the general population.[10,11] Infections, in particular respiratory infections, are the most common cause of death in childhood and adulthood, in part related to immunodeficiencies.[12] Pneumonia accounts for up to 40% of deaths in Down Syndrome.[10] Many groups have documented the greater severity of viral infections in Down syndrome for various viruses.[10] Genome-wide association studies have shown that the genetic makeup of individuals with Down syndrome can influence disease outcome.[10] This may help to explain the clinical heterogeneity seen across individuals with trisomy 21, including the immune system.[10]

Individuals with Down syndrome also have an increased risk of transient abnormal myelopoiesis which affects approximately 10% of affected neonates (generally before age 5 years).[12] Transient abnormal myelopoiesis usually resolves spontaneously but risk of myeloid leukemia is increased 20-30% in these patients.[12] Furthermore, compared to the general population, patients with

Down syndrome, even those without transient abnormal myelopoiesis, have a 20-fold increased risk of developing acute myeloid leukemia (greater than 480-fold risk before age 5 years), and an overall 18-fold risk of ALL, with the highest risk observed prior to age 20 and an approximately 4-fold increased risk after age 20 years.[13] However, despite case reports of lymphoma in individuals with Down syndrome, the risk of lymphoma has not been found to differ significantly from that of the general population.[13]

Cutaneous SCC

Cutaneous squamous-cell carcinoma (cSCC), a non-melanoma skin cancer, accounts for 20% of all skin cancers.[14] The incidence increases markedly with increasing age, with individuals older than 75 years having 5- to 10-fold higher risk than those younger than 55 years of age.[14,15] In addition to age, the most important risk factors for cSCC are cumulative exposure to ultraviolet radiation and systemic immunosuppression.[14] Immunosuppression – whether innate, acquired, or therapy-related – can increase the risk of cSCC. Among solid organ transplant recipients, the risk of cSCC has been estimated to range from 5- to 113-fold higher than that of immunocompetent individuals.[14] Compared to the general population, solid organ transplant recipients have a 30-fold higher risk of cSCC.[4]

Solid organ transplantation (including islet cell transplantation)

A well-recognized adverse outcome of solid organ transplantation is development of post-transplant malignancy, where immunosuppression required for prevention of organ rejection is an established risk factor.[4,16] Allogenic islet cell transplantation is variably regulated such that it is considered cell therapy in the United States and a solid organ transplant in other parts of the world.[17] Irrespective of how the product is regulated, individuals receiving an islet cell transplant require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction.[17] Solid organ transplant recipients have approximately a 2- to 4-fold increased risk of cancer compared to the general population with notable risk variation by cancer site.[4,16] Two-fold overall cancer risks have been reported for both infection-related cancers (i.e., EBV and other persistent viral infections) and infection-unrelated cancers.[16] Specifically, the risk for EBV-related non-Hodgkin lymphoma has been reported to be 7.5-fold higher than that in the general population representing an estimated absolute excess risk of 168.3 cases per 100,000 person-years.[16] Notably, non-Hodgkin lymphoma and lymphoproliferative disorders have been reported to be the most common malignancy in U.S. transplant recipients.[16]

Summary

Carcinogenesis involves a multi-step and multigene process that occurs over time, during which there are genetic and epigenetic changes that occur in a normal cell that eventually results in the development of malignancy. Much information on time to cancer onset has been derived from studies of long-term cancer survivors exposed to chemo/immunotherapy and/or radiation who develop subsequent neoplasms outside of the transplant setting.[18-27] In the transplant setting, time to onset of malignancies in adults ranges from early-onset (1-2 years) to intermediate-onset (3-7 years) to late-onset (>5-10 years).[28] Post-transplant lymphoproliferative disorders in adults occurs in a bimodal pattern with an early peak in the first year (largely affecting EBV-positive transplant recipients and driven by intense immunosuppression) and a later peak at 5-15 years (often in EBV-negative transplant recipients).[28] Notably, risk of subsequent neoplasms is affected not only by treatment-related factors (e.g., type of treatment, treatment dose, cumulative exposure, duration of exposure); type of transplant (solid organ or hematopoietic stem cell transplant), if applicable; and host immune status but also by factors relevant to the general population, including patient characteristics (e.g., age, sex); hormonal, environmental and lifestyle factors; and genetic susceptibility. In brief, patients who develop post-treatment malignancies often have multiple risk factors and disentangling individual risks often requires large studies with appropriate controls to determine if neoplasms are occurring at a higher rate than expected.

Case reports describing cancer as an adverse event may provide insights into cancers occurring after specific exposures, such as drugs, but assessing causality for individual cases has limitations due to concurrent confounding exposures, inherent individual susceptibility, the latency period associated with neoplastic processes, and missing information in most case reports. However, case reports may provide insights into patterns of malignancy, and that information that can be assessed subsequently in inferential studies to assess a drug-event association and degree of risk, if any.

In this focused case review of neoplasms occurring following teplizumab exposure (or, in one case, the teplizumab precursor) over a 29-year period (1997-2025), four of five cases reported risk factors for development of a subsequent neoplasm. Glioneuronal neoplasms are rare pediatric tumors (outside the setting of neurofibromatosis syndromes) of unknown etiology. This isolated case of glioneuronal neoplasm reported with teplizumab does not describe the pattern of risks exhibited by the remaining four cases. In light of this single instance of a rare glioneuronal tumor that may have been present prior to start of therapy with teplizumab, continued pharmacovigilance is recommended. The remaining four case reports describe risk factors for each of the neoplasms that included solid organ (including islet cell) transplantation, concurrent use of immunosuppressive agents, presence of innate immunodeficiency and dysregulation, inherent patient susceptibility with potential precursor lesions (i.e., dysplastic nevus) and/or medical conditions, and latent EBV infection with reactivation.

Teplizumab is an immunomodulating agent that causes time-limited lymphopenia that generally resolves within 6 weeks. The drug is associated with viral reactivation (e.g., CMV, EBV), and

severe, life-threatening cases of viral reactivation have been reported with its use (as also described in a case in this review). EBV-related lymphoproliferative neoplasms can range from benign to malignant lesions. Notably, the increased risk of viral reactivation observed in clinical trials of teplizumab has resulted in the most recent proposed labeling including a Boxed Warning for viral reactivation.

In summary, of the five cases of neoplasms diagnosed following exposure to teplizumab (or, in one case, its precursor), most describe additional risk factors for development of these neoplasms, and all describe a short time to onset (i.e., within approximately one year) since teplizumab exposure, a time frame that is shorter than typically seen with drug-related neoplasms outside of the transplant setting but that is plausible for virally mediated lymphoproliferative disorders. To this end, it is noted that tepizumab trials have generally followed patients for 1 to 2 years. Although it is not possible to ascribe a direct causal relationship of teplizumab to these lymphoproliferative lesions, one cannot exclude an indirect or contributory effect of teplizumab from drug-related immunomodulation and drug-related risk of viral reactivation. The review division's proposal to add a Boxed Warning to teplizumab labeling for viral reactivation (with specific mention of immunocompromised individuals being at increased risk) is a prudent undertaking that addresses the concerns raised by some of cases reviewed above. With a single case having a potential inherent cancer predisposition to develop malignant melanoma, a single case describing a rare glioneuronal tumor, and both of these cases raising suspicion that lesions may have present prior to teplizumab exposure, continued pharmacovigilance is warranted. Given the multiple confounding risks identified in patients who developed neoplasms, the long-term (10-year) registry-based study included as a postmarketing requirement at the time of initial approval of teplizumab is a responsible and cautious approach that is being undertaken to help provide further insights into whether there is a potential relationship between teplizumab and subsequent neoplasms.

At the present time, based on the available information, it is not possible to implicate teplizumab as having a direct effect on the development of the reported neoplasms. However, the additional planned labeling regarding viral reactivation, with specific mention of immunocompromised patients being at increased risk, continued pharmacovigilance, and the fulfillment of the postmarketing requirement will allow for close monitoring of patients treated with teplizumab.

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/s/

GRACA M DORES
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U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS

MEMORANDUM

Date: March 30, 2026

From: Susan Wollersheim, MD
Physician
CDER/OND/OID/DAV

Through: Virginia Sheikh, MD
Clinical Team Leader
CDER/OND/OID/DAV

To: Lauren K. Wood Heickman, MD
CDER/OCHEN/DDLO

Subject: Teplizumab-mzwv (TZIELD) sBLA 761183/S-010 and S-013

GENERAL INFORMATION

BLA	761183
Applicant	Provention Bio/A Sanofi Company
Drug Name	Teplizumab-mzwv (TZIELD)
Indication	Delay the onset of Stage 3 type 1 diabetes (T1D)
Mechanism of action	Teplizumab-mzwv binds is a CD3-directed monoclonal antibody (humanized IgG1 kappa); the mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.
Date of consult request	March 27, 2026
Consult due date	April 3, 2026
Consult requested by	Lauren K. Wood Heickman Division of Diabetes, Lipid Disorders and Obesity (DDLO)

EXECUTIVE SUMMARY

The review was conducted at the request of the Division of Diabetes, Lipid Disorders and Obesity (DDLO) as a follow-up to our original consult dated January 13, 2026, regarding a potential safety signal for EBV reactivation with teplizumab, for our expert opinion on current labeling and our feedback on the autopsy report that was pending for our original consult.

CONSULT REQUEST (VERBATIM)

As follow up to your original consult dated January 13, 2026, regarding a potential safety signal for Epstein-Barr Virus (EBV) reactivation with teplizumab, we are asking for your follow up and expert opinion on the following questions:

Question 1: We're currently reviewing a PREA study to expand teplizumab use in the approved indication (Stage 2 T1D) down to age 1 year. We're incorporating a black box warning for viral reactivations and would like to include your previous recommendations regarding labeling of viral reactivations from your consult. The first round of labeling for this pediatric supplement is due to the Applicant by the end of this week (3/27/26). Given that it's been some time since your initial consultation, would you be able to review the current labeling in SharePoint and provide feedback on whether you agree with the proposed approach?

DAV Response: We have the following suggestions for the current labeling:

Boxed Warning:
Consider the following edits:

- **Patients who are immunocompromised are at increased risk for life-threatening viral reactivation (5.1).**
- **TZIELD is not recommended in patients with laboratory or clinical evidence of active EBV or CMV infection. Test patients for active EBV and CMV infection prior to starting treatment (5.1). Seek expert consultation, as clinically indicated.**

Section 2.2 Laboratory and Infection Evaluation, and Vaccination Prior to Initiation:
Consider adding a sub-bullet under viral testing, as follows:

- Use of TZIELD is also not recommended in patients with *[see Warnings and Precautions (5.1, 5.2)]*:
  - Laboratory or clinical evidence of active infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
    - Consider expert consultation for appropriate laboratory and clinical evaluation to assess for active EBV or CMV infection.
  - Active serious infection or chronic active infection other than localized skin infections

Section 5.1 Viral Reactivation:
Please consider the following suggested edits:

Monitor patients for signs and symptoms of viral reactivation during TZIELD treatment and for at least 2 months following the last infusion. Adhere to lymphocyte count monitoring requirements and discontinuation recommendations (2, 5.4). If viral reactivation is suspected, discontinue TZIELD *[see Dosage and Administration (2.X)]*. Consult an expert for management of severe viral reactivation, (b) (4)

Serious cases of viral reactivation, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV), have been reported with TZIELD. Life-threatening cases, including EBV-associated lymphoproliferative disease and organ failure, have occurred in patients who are

immunocompromised. Primary infection or reactivation of EBV or CMV may present with increased severity during treatment with TZIELD. The majority of serious viral reactivation cases occurred in patients who continued TZIELD despite persistent, severe lymphopenia *[see Warnings and Precautions 5.4]*.

Test patients for active EBV and CMV infection prior to starting treatment with TZIELD. TZIELD is not recommended in patients with laboratory or clinical evidence of active EBV or CMV infection *[see Dosage and Administration (2.X)]*.

Section 5.4 Lymphopenia:
Consider putting the recommendation paragraph first regarding laboratory monitoring and discontinuation of the product, as follows:

Obtain a CBC prior to starting TZIELD and monitor white blood cell counts during TZIELD treatment. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD.

In clinical trials, (b) (4)% of TZIELD-treated patients developed lymphopenia compared to 11(b)(4)% of control-treated patients. For most TZIELD-treated patients who experienced lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pre-treatment values within two weeks after treatment completion and without dose interruption. Severe lymphopenia (<500 cells per mcL) lasting 1 week or longer occurred in(b)(4).9% of TZIELD-treated patients, and(b) (4)% of TZIELD-treated patients permanently discontinued TZIELD because of lymphopenia [*see Adverse Reactions (6.1)*].

Question 2: Please provide your feedback on the autopsy report for the 30 year old male with autoimmune hypothyroidism, hypogonadism, prior cavernous malformation surgery, and recently diagnosed Stage 3 T1D who was treated off-label with teplizumab. DDLO's interpretation of this autopsy is as follows:

A fatal case involved a 30-year-old male with autoimmune hypothyroidism, hypogonadism, prior cavernous malformation surgery, and recently diagnosed Stage 3 T1D who was treated off-label with teplizumab. Baseline laboratory results were suggestive of past exposure to EBV and CMV without active infection. The patient presented approximately 2 weeks after completing teplizumab treatment with progressive tonsillar hypertrophy, extensive cervical lymphadenopathy, and breathing difficulties. Laboratory evaluation revealed thrombocytopenia (platelets 95,000/µL), elevated liver enzymes (ALT 140 U/L, aspartate aminotransferase [AST] 65 U/L), and elevated lactate (3.3 mmol/L), initially attributed to a viral syndrome and treated with antibiotics, antifungals, and steroids. The patient visited the emergency room on Days 27 to 28 post-treatment initiation with worsening symptoms, and experienced sudden death on Day 32 post-treatment initiation while normoglycemic. Although the clinical presentation—including the 10-day delay from treatment completion, fever, arthralgia, lymphadenopathy, hepatitis, and thrombocytopenia—was suggestive of a viral syndrome (e.g., EBV reactivation) viral testing was limited to respiratory panels and monospot (both negative), along with blood cultures. EBV or CMV reactivation was not confirmed by PCR testing. An autopsy report submitted on February

10, 2026, to the FDA, determined that the final pathologic diagnoses were undetermined natural causes, hypertensive cardiovascular disease, reactive splenomegaly, and elevated creatinine. While the autopsy results remain inconclusive and the ultimate cause of death is unclear, the clinical presentation of the patient is suggestive of a viral syndrome (e.g., EBV reactivation), and a contribution of teplizumab to the death cannot be ruled out. No clear evidence of an underlying immunodeficiency was identified.

DAV Response: We agree with your interpretation of the autopsy report. The patient's reported clinical findings were consistent with a viral reactivation, with progressive tonsillar hypertrophy, extensive cervical lymphadenopathy and breathing difficulties, in addition to thrombocytopenia and elevated liver enzymes and reactive splenomegaly observed on the autopsy.

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/s/

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VIRGINIA M SHEIKH
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U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS

MEMORANDUM

Date: January 9, 2026

From: Susan Wollersheim, MD
Physician
CDER/OND/OID/DAV

Through: Virginia Sheikh, MD
Clinical Team Leader
CDER/OND/OID/DAV

To: Lauren K. Wood Heickman, MD
CDER/OCHEN/DDLO

Subject: Teplizumab-mzwv (TZIELD) sBLA 761183/S-010

GENERAL INFORMATION

BLA	761183
Applicant	Provention Bio/A Sanofi Company
Drug Name	Teplizumab-mzwv (TZIELD)
Indication	Delay the onset of Stage 3 type 1 diabetes (T1D)
Mechanism of action	Teplizumab-mzwv binds is a CD3-directed monoclonal antibody (humanized IgG1 kappa); the mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.
Date of consult request	December 18, 2025
Consult due date	January 10, 2026
Consult requested by	Lauren K. Wood Heickman Division of Diabetes, Lipid Disorders and Obesity (DDLO)

EXECUTIVE SUMMARY

The review was conducted at the request of the Division of Diabetes, Lipid Disorders and Obesity (DDLO) to evaluate a potential safety signal for Epstein-Barr virus (EBV) reactivation and possible lymphoproliferative disease associated with teplizumab-mzwv. DAV agrees with DDLO that the two identified serious cases are concerning for EBV-associated disease, warranting further evaluation and consideration for labeling changes. DAV provides preliminary responses to DDLO's consult questions with this memo and offers DDLO continued infectious disease support as additional information becomes available and specific labeling changes and risk mitigation strategies are considered.

CONSULT REQUEST (VERBATIM)
We are requesting consultation from DAV regarding a potential safety signal for Epstein-Barr Virus (EBV) reactivation and possible lymphoproliferative disease associated with teplizumab therapy. Please note that this consult has also been submitted to Oncology (DHM2) and DRTM. DRTM instructed us to consult DAV.

Two serious adverse events have occurred in the post-marketing setting that are concerning for a potential serious safety signal and we are requesting assistance in interpretation of the two safety events in context of the broader clinical program and advice based on your expertise with other immunomodulators to inform risk assessment and mitigation strategies.

On October 27, 2025, the Agency received a fatal case safety report via FAERS (Mfr Report # 2025SA283830) involving a 30-year-old male patient who died 18 days after completing a 14-day course of teplizumab-mzwv. The patient experienced a progressive infection vs. inflammatory syndrome beginning 10 days post-completion of treatment, characterized by tonsillitis and pharyngitis, lymphadenopathy, dyspnea, tachycardia, hepatitis, thrombocytopenia, with a witnessed cardiorespiratory arrest proceeded by dizziness and confusion on (b) (6) (b) (6) (exposure day 32) with possible seizure-like head movements at the time of event. Following this report, the review division asked the Sponsor to identify similar safety reports for patients experiencing serious events consistent with opportunistic infections, with a focus on EBV or CMV viral infections within 1 month of drug administration. Following this IR, the Sponsor submitted a recent serious case of severe EBV reactivation in a 44 year old male with Down syndrome treated with teplizumab who required ICU care, intubation/ventilator support and dialysis within 1 month of a single 14-day course of teplizumab, along with a summary of other serious EBV infections.

Regulatory Context:

The case of severe EBV infection and the fatality represents a novel safety signal not observed in clinical trials (>900 patients with type 1 diabetes (T1D) treated with teplizumab in similar dose and regimen during the clinical development program). Per the most recent DSUR and 120-day safety update, >900 patients have also been exposed to teplizumab postmarketing. DDLO is currently reviewing BLA 761183/S-010 for expansion of the currently indicated population (age 8 years and older with Stage 2 T1D, at risk of developing clinical T1D, not yet meeting diabetes diagnostic criteria or requiring insulin) to a much larger population of patients recently diagnosed with Stage 3 T1D (clinically diagnosed with diabetes, requiring insulin) under the CNPV program, via the accelerated approval pathway. If approved for this indication under the accelerated approval pathway, the clinical benefit of teplizumab in Stage 3 T1D would be verified through the conduct of a large confirmatory trial evaluating teplizumab in 723 patients age 1-25 years with new-onset Stage 3 type 1 diabetes.

Case Summaries:

Case 1: Fatal Event in 30-Year-Old Patient in the U.S. (FAERS Case ID 25854795)

- **Patient Profile:** 30-year-old male with history of autoimmune hypothyroidism, hypogonadism, cavernous malformation requiring surgery in (b) (6), and recently diagnosed type 1 diabetes (T1D)
- **Clinical Presentation:** Initial presentation with lymphadenopathy and tonsillitis progressing to extensive reactive lymphadenopathy throughout neck, elevated liver

enzymes (ALT 140, AST 65), thrombocytopenia, and elevated lactate (3.3). Symptoms began ~2 weeks post-treatment completion with progressive deterioration

Timeline:

· Days 1-14: Expected treatment-related effects (lymphopenia, GI symptoms)

· Day 19: Localized rash (resolved with antihistamines)

· Day 24: Onset of tonsillar hypertrophy, lymphadenopathy, breathing challenges

· Days 27-28: Emergency presentations with elevated liver enzymes (ALT 140, AST 65), thrombocytopenia (95K)

· Day 32: Fatal cardiac arrest and seizure?, in the context of normoglycemia

· Workup: Infectious evaluation negative (blood cultures, viral panels, imaging)

The temporal relationship (10-day delay), clinical triad (fever, arthralgia, lymphadenopathy), and laboratory pattern was considered by the team to be consistent with an acute viral infection with a mononucleosis-like presentation, however the viral testing performed in the emergency room visit evaluation was limited to respiratory viral panel (COVID, Flu testing negative), monospot (negative), blood cultures (negative). The team confirmed that EBV viral DNA titers were not performed during this patient's evaluation and to-date, an infectious source was not identified in this case (i.e. it is unknown if the fatality occurred in context of acute EBV infection).

· **Pending Investigations:** Autopsy has been performed and results are awaited in 3-4 weeks [redacted (b) (6)])

Case 2: Severe EBV Reactivation with Multi-Organ Failure (Case 2025SA159679)

· **Patient Profile:** 44-year-old male with Down syndrome, history of Tetralogy of Fallot with surgical repair (potential thymectomy), hypothyroidism

· **Clinical Presentation:** EBV reactivation (viral load 2,184,797 IU/mL) progressing to pneumonia, respiratory failure, hepatorenal syndrome, suspected lymphoproliferative disorder, and multiorgan failure requiring ICU care, intubation, and dialysis

· **Outcome:** Severe, life-threatening event with gradual recovery following rituximab therapy

· **Risk Factors:** Down syndrome with associated immunocompromise, potential thymic disruption from cardiac surgery

Historical Safety Profile Context is provided in the attached word document summary (summarized from original BLA review 2020 with updated safety data from the 2025 sBLA-10, including the PROTECT study, and the Sponsor's response to the IR). In summary, the clinical program demonstrated a consistent pattern of increased EBV reactivation risk (EBV reactivation among teplizumab patients (4.5%) than controls (2.3%), without a noted increase in primary EBV infection, teplizumab (2.5%) vs. controls (3.3%), EBV viral DNA levels did increase post-dosing in studies where this was evaluated with declining viral titers noted in all subjects within 3 months of dosing, and EBV infection events in immunocompetent patients were typically asymptomatic or mild. We now have evidence from postmarketing reports of severe infection occurring within 30 days of dosing in 2 adults (age 30 and 44 years).

Questions for DAV consultant:

Given the severity of these events, ongoing clinical trials, and potential impact on the approved indication, we request a consultation due January 10, 2026, to inform risk assessment decisions and potential regulatory actions.

We request advice on the following topics and have the following questions for the consultant:

1) **Clinical Assessment:** Provide an expert opinion on the mechanism and causality assessment for both cases

   DAV Response: *Given teplizumab-mzwv's mechanism of action, we agree that it is biologically plausible that teplizumab-mzwv's may impair immune mechanisms that suppress EBV, such as EBV-specific cytotoxic T cells, potentially resulting in EBV-associated disease. Given the seriousness of the 2 post-marketing cases reported, we also agree with DDLO that labeling changes should be considered and that additional information is needed to inform the benefit/assessment of teplizumab-mzwv for the proposed expanded patient population.*

   For Case 1, we agree that the clinical presentation is suspicious for EBV reactivation; we await further information from the autopsy results which will likely help with more definitive adjudication. The EBV serology drawn 15 days prior to initiation of the teplizumab course were indicative of past EBV infection and the clinical symptoms of rash, pharyngitis, tonsillar hypertrophy, lymphadenopathy with laboratory findings of thrombocytopenia and elevated liver enzymes were consistent with EBV reactivation.

   For Case 2, we agree that the clinical presentation is consistent with a severe case of EBV reactivation/possible lymphoproliferative disease in the context of a patient with autoimmune thyroiditis, Down syndrome and potential immunocompromise.

2) **Risk Stratification**: Recommendations for identifying high-risk or at-risk patients who should be excluded or require enhanced monitoring.
   a. What patient-specific risk factors may have predisposed these patients to severe outcomes that were not adequately identified or represented in clinical trial populations (i.e. prior thymectomy from cardiac surgery, down syndrome, multiple autoimmune conditions)? Can we effectively mitigate the risk?

   DAV Response: *Given the limited nature of the data available for these isolated post-marketing cases, DAV is not able to recommend specific risk mitigation strategies at this time. However, we will be happy to work with the review team to further evaluate the potential EBV reactivation risk and to develop appropriate risk mitigation strategies as more information becomes available.*

   We observe that both cases occurred in individuals with other autoimmune conditions in addition to Type 1 diabetes. Although there is a body of scientific literature supporting an association between EBV infection and autoimmune disease, the prevailing hypotheses position EBV as a trigger for autoimmunity rather than autoimmune disease as a risk factor for EBV reactivation (Robinson et al. Nature Reviews Oct 2024). We are also aware that

individuals with autoimmune conditions are at higher risk of developing additional autoimmune conditions, and that hypothyroidism as a result of Hashimoto's thyroiditis is a relatively common condition.

We acknowledge your observation that the 44-year-old male (Case 2) underwent tetralogy of Fallot repair as an infant, which may have included thymectomy. It is possible that thymectomy resulted in unrecognized T cell deficit or functional impairment, contributing to the patient severe outcome following EBV reactivation.

b. We notice that the postmarketing cases of severe EBV and the death are adults (age 30, 44 and 58 years) whereas the majority of our clinical database for teplizumab was pediatric (only 296/1008, 29% were adults ≥18 years). Would you suspect age to impact severity of EBV reactivation based on experience with other immunomodulators?

DAV Response: *Based on our review of the cases and the literature, we do not consider age to be a primary indicator for the severity of EBV-associated disease following reactivation.*

3) **Monitoring Protocol:** We request specific guidance on the current EBV and lymphoproliferative disease surveillance in clinical trials.
   a. What additional safety monitoring should be implemented in our ongoing confirmatory trial (723 patients, ages 1-25 years, Stage 3 T1D, attached protocol)?
   b. What are optimal methods, timing, and frequency for EBV surveillance following anti-CD3 therapy? Can high-risk patients be prospectively identified?

DAV Response: *In light of teplizumab-mzwv's mechanism of action and the two reported serious post-marketing cases, we are concerned about both EBV reactivation and primary EBV infection.*

We note that the ongoing confirmatory study is allowing enrollment of pediatric patients as young as 1 year of age, who are more likely to be EBV-naïve than the populations previously evaluated. We consider potential risks of acute EBV infection following teplizumab-mzwv treatment to be an important data gap, which may be addressed, at least in part, in the ongoing study (Trial EFC18241). We recommend revising the protocol to more clearly define EBV exposure status at baseline. To identify participants at risk for primary EBV infection, we recommend requiring baseline testing for EBV capsid antigen IgG/IgM and EBV nuclear antigen IgG, in addition to EBV PCR testing and providing clinicians with guidance on how to interpret results (b) (4) *We also recommend that serology testing be repeated prior to subsequent treatment courses of teplizumab-mzwv for participants who were determined to be EBV naïve prior to the initial course, as EBV exposure status may change over the 6-month interval between courses in pediatric populations.*

To better inform the impact of teplizumab-mzwv on host immune responses to EBV and to increase the likelihood of promptly and definitively identifying cases of EBV-associated disease, we recommend that you consider more frequent EBV PCR testing in the immediate

period following each course of teplizumab-mzwv treatment. If feasible, we would suggest weekly or every-other-week EBV PCR testing over the first month or two following treatment initiation. We also recommend that the protocol be amended to provide clinicians with specific guidance for EBV-related testing for any acute illness clinic visits with fever or EBV-like illness (fever, fatigue, malaise, cervical lymphadenopathy and pharyngitis) that occur within the immediate period following teplizumab treatment.

Of note, although this consult is specific to EBV reactivation, CMV is similar to EBV in that it is very common chronic, herpes viral infection for which immune suppression is mediated by similar immune mechanisms to that of EBV, and manifests in diseases similar to that of EBV. Therefore, baseline assessment of CMV exposure status and inclusion of CMV PCR testing with EBV PCR testing for acute illness/EBV-like illness should also be considered.

4) **Regulatory Recommendations:** Advice on labeling modifications to currently approved label if approved
    a. Based on your assessment of these events and experience with similar immunosuppressive therapies, what specific risk mitigation strategies should be implemented in labeling? Provide advice regarding specific labeling modifications needed to the current approved indication (Stage 2 T1DM prevention), including enhanced warnings about EBV reactivation risk in immunocompromised patients, contraindications for specific populations, or mandatory baseline and follow-up EBV monitoring.

DAV Response: *We agree with the primary team's current plan to revise the product labeling to include specific risks of EBV reactivation and are happy to assist with these revisions as additional information becomes available. In the meantime, you may consider the following as preliminary suggestions:*

- *Updating Section 2.2 of the label (Laboratory and Infection Evaluation, and Vaccination Prior to Initiation) to provide more specific recommendations as to the laboratory tests that can be used to evaluate for acute EBV or CMV infection in Section 2.2.*
- *Modifying Section 5.2 (Warnings and Precautions, Serious Infections) to include a paragraph focused on EBV reactivation and to provide prescribers with recommendations for promptly identifying and managing patients who develop EBV-like illness during or following treatment with teplizumab-mzwv.*

    b. Should baseline EBV serology/viral load be required? What clinical signs should trigger immediate EBV evaluation, and what viral load thresholds warrant antiviral intervention?

DAV Response: *DAV continues to deliberate whether requiring baseline EBV serology and/or EBV PCR levels are likely to mitigate risks related to EBV reactivation (or acute EBV infection), beyond the Section 2.2 recommendations. At this time, we are not aware of specific EBV PCR copy number thresholds that can reliably distinguish teplizumab-mzwv recipients at risk of severe EBV-associated disease from teplizumab-mzwv recipients who experience transient asymptomatic elevations in EBV PCR levels. We also note that a variety of EBV PCR assays are likely to be in used in the commercial setting and EBV PCR*

copy number may vary by assay. Our preliminary advice would be to consider EBV testing for any patients who develop fever, fatigue, malaise, cervical lymphadenopathy or pharyngitis in the immediate period following teplizumab-mzwv administration. Although antiviral drugs approved for other herpes viruses are used off-label in some settings, no antiviral drugs are approved for the treatment of acute EBV infection or EBV reactivation. DAV defers recommendations regarding B-cell targeting therapies for EBV-associated proliferative disease to FDA experts in malignant hematology.

Attachments:

- Complete safety reports for both cases and Sponsor's response to Agency Information Request requesting a summary of EBV reactivation cases
    - Sponsor's October 31, 2025 Response to Agency IR requesting full FAERS case for fatality (Appendix 3), hospital/ER summaries (Appendix 1), summary from treating physician (Appendix 6).
    - Sponsor's November 3, 2025 Response to Agency IR including the following in the Appendix:
        - A serious EBV case in a 44 year old male with Down Syndrome (Appendix 5, Report #2025SA159679, page 21-46)
        - The Sponsor's assessment of serious EBV cases (Appendix 10, page 62-102)
- Historical EBV data from clinical program (attached, word document summary)
- Most Recent Protocol for Confirmatory Trial (BetaPreserve)
- Current draft Tzield labeling

2. LINK(S) (*EDR Link to Submission, SharePoint link to response document*)

See links above

3. RELEVANT DATES

PDUFA Goal date for this efficacy supplement is January 21, 2026. However, it is likely we will issue a major amendment and can extend the review clock for this consultation, to provide more time for a more thorough and complete review.

DIVISION OF ANTIVIRALS REVIEW
Materials Reviewed

- Sponsor's October 31, 2025 Response to Agency IR requesting full FAERS case for fatality (Appendix 3), hospital/ER summaries (Appendix 1), summary from treating physician (Appendix 6).
- Sponsor's November 3, 2025 Response to Agency IR including the following in the Appendix:
    - A serious EBV case in a 44 year old male with Down Syndrome (Appendix 5, Report #2025SA159679, page 21-46)
    - The Sponsor's assessment of serious EBV cases (Appendix 10, page 62-102)
- Historical EBV data from clinical program
- TZIELD full prescribing information

- Current draft Tzield labeling
- Clinical Reviews of BLA 761183

Background / Regulatory History
In 2022, FDA approved TZIELD (Teplizumab-mzwv), a first-in-class humanized anti-CD3 monoclonal antibody, to 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 (T1D). The initial BLA was submitted in 2020 and received a Complete Response (CR) for non-clinical reasons, based on deficiencies identified from the Office of Clinical Pharmacology and the Office of Pharmaceutical Quality. The CR submission included new and updated clinical safety information.

In July 2025, the sponsor submitted BLA 761183/S-010 for expansion of the currently indicated population (age 8 years and older with Stage 2 T1D, at risk of developing clinical T1D, not yet meeting diabetes diagnostic criteria or requiring insulin) to a much larger population of patients recently diagnosed with Stage 3 T1D (clinically diagnosed with diabetes, requiring insulin) under the CNPV program, via the accelerated approval pathway. If approved for this indication under the accelerated approval pathway, the clinical benefit of teplizumab in Stage 3 T1D would be verified through the conduct of a large confirmatory trial evaluating teplizumab in 723 patients 1-25 years of age with new-onset Stage 3 type 1 diabetes.

Epstein-Barr virus background
Epstein-Barr virus (EBV) is one of the most ubiquitous of human viruses, infecting at least 90% of people worldwide. The epidemiology is shifting with a later age of primary EBV infection in developing countries, potentially due to improved hygiene with higher socioeconomic status, higher household income and education levels. There appears to be a complex relationship between age of acquisition of primary EBV, severity of acute illness and subsequent risk of EBV-associated cancers or autoimmune diseases. The younger age at primary EBV infection during infancy may be associated with increased risk of endemic Burkitt lymphoma, nasopharyngeal carcinoma and multiple sclerosis (MS) in childhood. Later acquisition of primary EBV infection in adolescence or early adulthood typically results in infectious mononucleosis (IM) more often than in children, as many young children seroconvert asymptomatically. IM symptoms include fever, tender lymphadenopathy, sore throat, hepatosplenomegaly, and skin rash, which is indicative of primary EBV infection in 80% of cases but also occur with reactivation at lower frequencies. EBV reactivation can occur following impairment of the cellular immune response caused by psychological stress of various types, ranging from student examination stress to intensive care admission or immunosuppression. Reactivation of EBV has been observed in patients who have received teplizumab, as well as other immunotherapies that affect T-cell function.

Teplizumab-mzwv mechanism of action and potential impact on immune control of EBV

From the DAV perspective, it is biologically plausible that teplizumab-mzwv may impair immune mechanisms that suppress EBV, such as EBV-specific cytotoxic T cells, potentially resulting in EBV-associated disease.

Teplizumab-mzwv is a CD3-directed humanized monoclonal antibody that binds to CD3 epsilon molecules within the T cell receptor (TCR) complex on T lymphocytes, likely preventing cytolytic T cell interactions with target cells through allosteric hindrance of TCR-peptide-MHC interactions. In the context of Stage 2 Type 1 diabetes, this likely results in partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes, leading to increased regulatory T cells and exhausted CD8+ T cells in peripheral blood.

The mechanism that makes teplizumab effective against autoimmune diabetes may simultaneously negatively impact host immune control of EBV. CD8+ T cell exhaustion, a key therapeutic effect of teplizumab-mzwv, likely undermines a key immune mechanism controlling EBV, cytotoxic T cells.

DAV Assessment of the clinical cases with severe/fatal outcomes following teplizumab
Case 1: The case report of a fatality 18 days after completion of a teplizumab course in a 30-year-old male patient with autoimmune hypothyroidism on thyroid hormone replacement, obesity, infertility associated with hypogonadism, recurrent tonsillitis, history of cavernous malformation s/p surgery in (b) (6) who was diagnosed with T1D in (b) (6) was reviewed. It appears that teplizumab was given off-label as the patient was diagnosed with T1D and treated with insulin one year prior to the teplizumab course in (b) (6). EBV serology drawn 15 days prior to the teplizumab course were indicative of past EBV infection (positive EBV Capsid IgG and EBV nuclear antigen IgG; negative EBV Capsid IgM and EBV early antigen IgG). His clinical presentation is suggestive of an EBV reactivation with rash, pharyngitis, neck lymphadenopathy, with thrombocytopenia and transaminitis. His underlying autoimmune thyroiditis, in addition to the T1D diagnosis may have contributed to the severity of this outcome following teplizumab. The autopsy results will hopefully be helpful to evaluate for viral or other causes for this fatal outcome following teplizumab.

Case 2: The case report details from a MedWatch report form describe the severe EBV reactivation with suspected lymphoproliferative disease, requiring ICU admission for multiorgan failure following a teplizumab course in a 44-year-old male patient with Down syndrome s/p Tetralogy of Fallot repair/potential thymectomy, Hashimoto's thyroiditis/hypothyroidism were also reviewed. EBV IgM was negative and obtained approximately 4 months prior to the treatment course and no other EBV testing was repeated prior to initiation of teplizumab. He began to have symptoms of vomiting, dyspnea and abdominal pain within 1 week of completion of teplizumab, which progressed to general lymphadenopathy and hospitalization with hepatosplenomegaly, transaminitis, pneumonia, and eventually respiratory failure and multiorgan failure. During the ICU stay, the patient had positive EBNA IgG indicating past EBV infection, with elevated EBV DNA PCR measurements up to 2.1 million IU/mL, indicating EBV reactivation. He was treated with rituxumab for suspected lymphoproliferative disease and lymph node biopsy results were pending. He improved clinically and was discharged home after an approximately 1-month hospitalization.

If Case 1 is confirmed to be EBV related, these 2 cases would be the first post-marketing severe case reports of EBV reactivation following teplizumab administration. Given the mechanism of action and previously published evidence of EBV viremia with anti-CD3 monoclonal antibody products, we would have expected more EBV cases. The protocol study populations generally excluded participants with other autoimmune diseases, other comorbid diseases, active or chronic infections and participants with immunosuppression, which may have selected for a

population that is less likely to progress to severe EBV reactivation. One medical similarity between these 2 cases is the presence of hypothyroidism, which indicates that additional autoimmunity is a potential risk factor for severe EBV disease (if Case 1 is confirmed to be related to EBV).

The current pooled clinical trial experience showing an increased risk of EBV reactivation, but with mild or asymptomatic cases appears to support that the per protocol study populations limit the risk of severe EBV disease. One limitation is that a majority of study participants had evidence of EBV disease at screening and there were very few cases of primary EBV infection captured in the trial data, so the effect of teplizumab on primary EBV infection is unclear. The currently ongoing confirmatory trial in participants 1-25 years of age is an opportunity to evaluate the EBV primary infection risks, as well as better document the effect of teplizumab on EBV infection, viremia and disease.

Limitations to the DAV Review

Our review is limited by the following:

- Lack of a concurrent control group in the post-marketing period.
- Lack of full information for the reported fatal case, as the autopsy results are pending.

REFERENCES

1. Dunmire SK, Verghese PS, Balfour HH Jr. Primary Epstein-Barr virus infection. J Clin Virol. 2018 May;102:84-92. doi: 10.1016/j.jcv.2018.03.001. Epub 2018 Mar 5. PMID: 29525635. https://pubmed.ncbi.nlm.nih.gov/29525635/
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VIRGINIA M SHEIKH
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CDER Clinical Consult Review
Division of Hematological Malignancies 2

Referenced Application:	**sBLA 761183/S-010**
Applicant:	**Provention Bio, Inc.**
Drug(s):	**Teplizumab (PRV-031)**
Consult Requested:	**12/14/2025**
Desired Completion Date:	**1/10/2026**
Primary Reviewer:	Emily Jen, MD, PhD (DHMI)
Deputy Division Director:	Bindu Kanapuru, MD (DHMII)

Product Information:
Teplizumab, a humanized anti-CD3ε monoclonal antibody, is approved to delay the onset of Stage 3 type 1diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D and is currently under review by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) for the treatment of patients with Stage 3 T1D. For the approved indication, treatment consists of a single 14-day course teplizumab. For the proposed indication, treatment consists of two 12-day courses of teplizumab 6 months apart.

Reason for Consultation (from the DDLO consult request):
We are requesting consultation from the Oncology Division regarding a potential safety signal for Epstein-Barr Virus (EBV) reactivation and possible lymphoproliferative disease associated with teplizumab therapy. Two serious adverse events have occurred in the post-marketing setting that are concerning for a potential serious safety signal and we are requesting assistance in interpretation of the two safety events in context of the broader clinical program and advice based on your expertise with other immunomodulators to inform immediate risk assessment and mitigation strategies.

Given the severity of these events, ongoing clinical trials, and potential impact on the approved indication, we request expedited consultation due January 10, 2026, to inform immediate risk assessment decisions and potential regulatory actions.

We request advice on the following topics and have the following questions for the oncology consultant:

1. **Clinical Assessment**: Provide an expert opinion on the mechanism and causality assessment for both cases.

   <u>OOD Response</u>:
   As noted in the prior DHM1 consult review[1] dated 4/28/21:

   - Patients who are immunocompromised for any reason are at increased risk for development of lymphoproliferative disorders (LPD) compared to the general

[1] CDER Clinical Consult Review (DHM1) for BLA 761183 dated 4/28/21.

population. At-risk patients include those with congenital or acquired immunodeficiencies as well as those on immunosuppressive drugs for treatment of autoimmune disorders or after organ transplantation.[2]

- The risk appears to wane with time when immunosuppressive therapy is reduced or removed and T cell function recovers.[3]
- Based on DHM1's consult review of the original BLA clinical database (i.e., treatment with a single 14-day course of teplizumab)[1]:
    - EBV reactivation is more common among patients treated with teplizumab than controls and is a clear risk of treatment with this drug.
    - T-cell immunosuppression occurred following treatment with teplizumab:
        - Circulating CD3 lymphocytes were almost entirely depleted on day 1 post dose with initial recovery beginning 14 days post-dose and return to baseline by 43 days post-dose.
        - Absolute CD4 count followed a similar profile, but rare patients had prolonged and profound depletion of CD4 cells lasting as late as 3-6 months post-treatment with teplizumab.

Regarding the narratives included in this consult:

- Case 1 describes a patient with a medical history that includes autoimmune hypothyroidism and T1D who had symptoms consistent with "acute viral infection with a mononucleosis-like presentation" starting 10 days after completion of a 14-day course of teplizumab. Symptoms included tonsillitis, pharyngeal swelling, and lymphadenopathy. In subsequent days the patient presented with elevated ALT and AST and thrombocytopenia. An improvement in tonsil size and symptoms was reported following initiation of steroids. Eight days after the onset of symptoms, the patient suffered a possible seizure and had fatal cardiac arrest. No EBV titers were done during the course of these events, and no other infectious etiology was identified. Autopsy results are pending.
    - Prior to start of treatment with teplizumab, the patient's serology testing was positive for CMV IgG, EBV Capsid Antigen IgG, and EBV Nuclear Antigen IgG. EBV IgM was negative.
    - The timing of the start of the event (10 days post treatment/23 days since start of treatment according to the safety report in Appendix 3) falls within the window of EBV reactivation observed in DHM1's original consult review[1]. Median time to reactivation was 28 days (range: 14 – 722) and the time was > 30 days after last dose for 12 patients.

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[2] Kamel OW, et al. (1995) Immunosuppression- Associated Lymphoproliferative Disorders in Rheumatic Patients. Leuk Lymph 16: 363-368; Basgoz N and Preiksaitis JK. (1995) Post-transplant lymphoproliferative disorder. Inf Dis Clinic NA 9:901 - 923; Lam GY, et al. (2015) Lymphoproliferative disorders in inflammatory bowel disease patients on immunosuppression: Lessons from other inflammatory disorders. World J Gas Patholphys 6:181-192.

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- The description of "possible seizure" prior to fatal cardiac arrest is vague but LPD can cause neurologic symptoms including seizures.
- This patient has a history of multiple autoimmune disorders. It is possible that these or other background autoimmune issues not previously diagnosed increased this patient's risk for developing LPD.
- Contribution of teplizumab to the events described in the narrative cannot be ruled out.

- Case 2 describes a patient with Down Syndrome and a history of possible thymectomy, hypothyroidism, and T1D who developed vomiting and generalized lymphadenopathy 5 days after completion of teplizumab/20 days after start of therapy. EBNA and EBV IgG were reported to be positive on Day 24. Subsequently, EBV reactivation was confirmed with a verbal report of "75,000 copies" (date unknown). The highest measured viral load was 2,184,797 IU/mL 36 days after start of teplizumab. The narrative mentions a lymph node biopsy, but no results were included in the safety report. The clinical presentation is described as "suspected lymphoproliferative disorder" and the outcome is "gradual recovery following rituximab therapy" with decreasing viral load.
  - The clinical picture is consistent with EBV reactivation and LPD.
  - Down Syndrome and past history of thymectomy may predispose this patient to a baseline immunocompromised state.
  - Contribution of teplizumab to the events described in the narrative cannot be ruled out.

2. **Risk Stratification**: Recommendations for identifying high-risk or at-risk patients who should be excluded or require enhanced monitoring.

   a. What patient-specific risk factors may have predisposed these patients to severe outcomes that were not adequately identified or represented in clinical trial populations (i.e. prior thymectomy from cardiac surgery, down syndrome, multiple autoimmune conditions)? Can we effectively mitigate the risk?

      OOD Response: See response to Question 1 regarding patients at risk for developing LPD. We agree that the patient-specific factors identified in your question could put patients at risk for LPD. We defer to the DDLO review team regarding whether excluding a subset of at-risk patients is warranted in the T1D disease setting under study.

   b. We notice that the postmarketing cases of severe EBV and the death are adults (age 30, 44 and 58 years) whereas the majority of our clinical database for teplizumab was pediatric (only 296/1008, 29% were adults ≥18 years). Would you suspect age to impact severity of EBV reactivation based on experience with other immunomodulators?

OOD Response: We are not aware of any data to suggest that the severity of EBV reactivation is related to age. However, the cumulative risk of EBV infection increases over time and may account for the observation of cases of EBV reactivation in adults in the postmarketing setting that were not observed in the predominantly pediatric population in the original teplizumab review.

3. **Monitoring Protocol**: We request specific guidance on the current EBV and lymphoproliferative disease surveillance in clinical trials.

    a. What additional safety monitoring should be implemented in our ongoing confirmatory trial (723 patients, ages 1-25 years, Stage 3 T1D, attached protocol)?

    OOD Response:
    The protocol appears to include EBV and CMV assessments at screening and (b) (4). There are no standard instructions for monitoring for EBV reactivation and LPD. The risk is present for the duration of treatment and until T cell recovery occurs. Serial monitoring during the period of risk is warranted but this period is product- and regimen-dependent. We defer to the DDLO review team regarding the period of risk for the teplizumab regimen administered in clinical trials.

    b. What are optimal methods, timing, and frequency for EBV surveillance following anti-CD3 therapy? Can high-risk patients be prospectively identified?

    OOD Response:
    Monitoring of EBV is considered practice of medicine. Most transplant centers have incorporated EBV monitoring into routine evaluation and baseline assessment prior to transplantation is standard of care. However, the optimal method, timing, and frequency of EBV surveillance have not been established. Patients with evidence of EBV reactivation are at risk for worsening clinical course without intervention.

    OOD Additional Comment:
    We note that in the protocol, Section 2.3.1 Risk Assessment states (b) (4) ". We recommend removing language that downplays the risk and ensuring that providers have a low index of suspicion for testing in the event of symptoms consistent with a viral infection.

4. **Regulatory Recommendations**: Advice on labeling modifications to currently approved label if approved

    a. Based on your assessment of these events and experience with similar immunosuppressive therapies, what specific risk mitigation strategies should be implemented in labeling? Provide advice regarding specific labeling

modifications needed to the current approved indication (Stage 2 T1DM prevention), including enhanced warnings about EBV reactivation risk in immunocompromised patients, contraindications for specific populations, or mandatory baseline and follow-up EBV monitoring.

OOD Response:

- Given the severity of the cases described in this consult request, we recommend expanding the warnings to describe the risk of EBV reactivation to inform providers of the serious risks involved with treatment with teplizumab. However, as previously noted, monitoring and management of infections or viral reactivation in patients on immunosuppressive therapy is considered practice of medicine, so we have no specific advice on frequency of monitoring. See response to Question 4.b.
- Contraindications in labeling are included based on an assessment of risk:benefit for the intended population. For patients in the post-transplant setting, the benefits of immunosuppressive therapy outweigh the risks, and labeling for these drugs do not include a contraindication related to the risk of EBV reactivation or LPD. Whether these risks are outweighed by the evidence of benefit for teplizumab in support of the current and potential future indicated populations is outside the clinical expertise of the consult review team. We defer to the DDLO review team regarding this issue.

b. Should baseline EBV serology/viral load be required? What clinical signs should trigger immediate EBV evaluation, and what viral load thresholds warrant antiviral intervention?

OOD Response:

See response to Question 3b regarding monitoring. There are no standard guidelines for when intervention is necessary, and such decisions are population specific. For the immunocompromised population of patients receiving transplantation, standard of care includes pre-transplantation assessment of viral status, serial monitoring post-transplantation, and preemptive treatment of patients at the time of viral reactivation. Whether this is an appropriate course of action for the population with TID in your application treated with teplizumab is unknown. You may consider consulting with reviewers in the Office of Infectious Diseases for additional advice on this matter.

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LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 4, 2025
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761183/S-010
Product Name, Dosage Form, and Strength:	Tzield (teplizumab-mzwv) injection, 2 mg/ml (1 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Provention Bio, Inc.
FDA Received Date:	July 21, 2025
TTT ID #:	2025-15624
DMEPA 1 Safety Evaluator:	Susan Shermock, PharmD, CPPS
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP

1 INTRODUCTION

Provention Bio, Inc. submitted an Efficacy Supplement for Tzield (teplizumab-mzwv) injection proposing a new indication, to delay the progression of recently diagnosed Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older recently diagnosed with stage 3 type 1 diabetes.

Subsequently, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Tzield Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Tzield (teplizumab-mzwv) was approved under BLA 761183 on November 17, 2022 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.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review

Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
FDA Adverse Event Reporting System (FAERS)	D

3 CONCLUSION

The proposed Tzield Prescribing Information (PI) and Medication Guide (MG) may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) in Section 4.

4 RECOMMENDATIONS FOR THE DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

A. Prescribing Information

1. Highlights of Prescribing Information

a. Recommendations to increase the readability of important product information for Highlights of Prescribing Information are noted in track changes below:

(b) (4)

2. Section 2 Dosage and Administration

   a. Recommendations to increase the readability of important product information for Section 2.3 are noted in track changes below:

(b) (4)

   b. Recommendations to increase the readability of important product information for Section 2.4 are noted in track changes below:

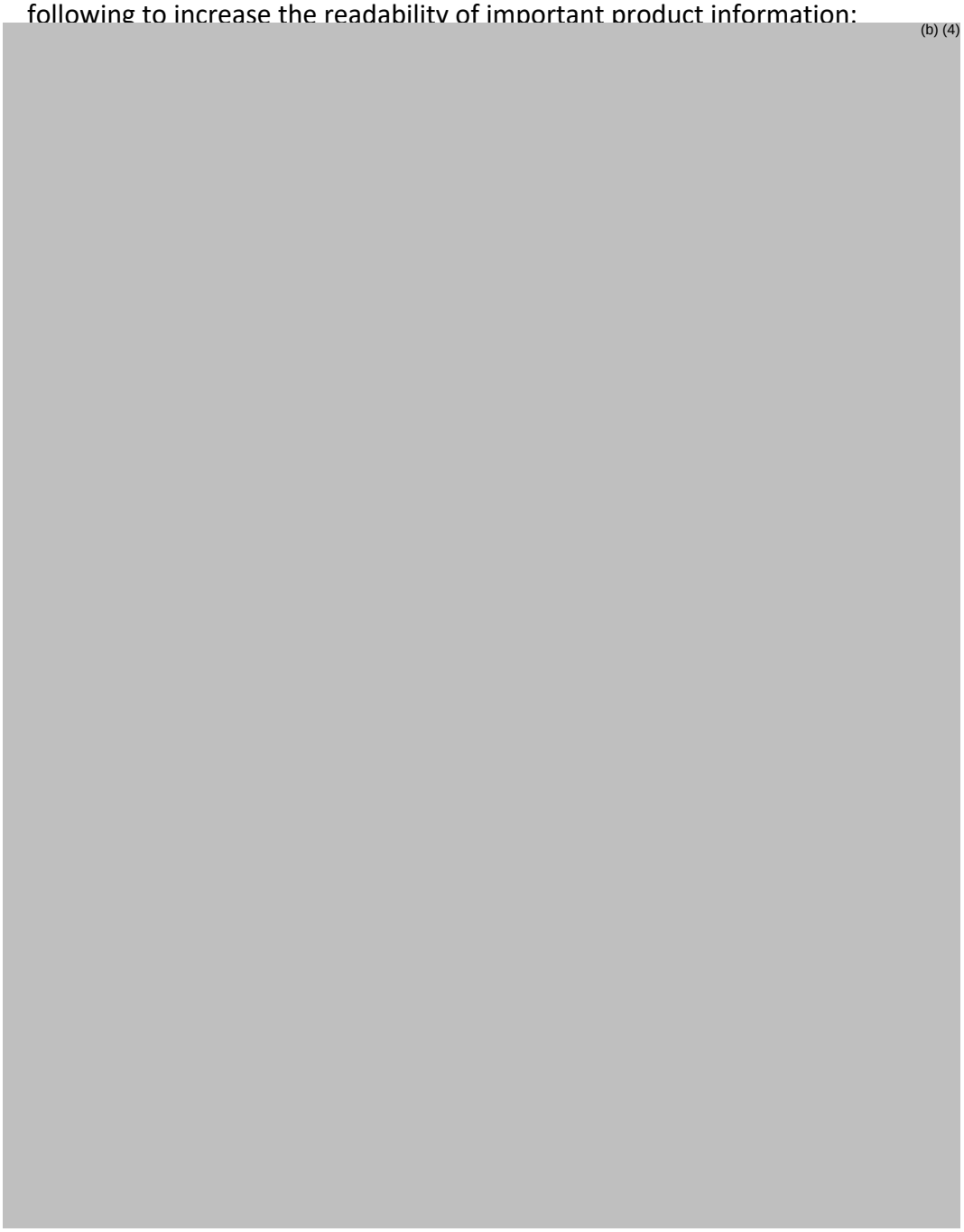
(b) (4)

   c. Recommendations to increase the readability of important product information for Section 2.5 are noted in track changes below:

(b) (4)

Recommendation to replace the remaining text in Section 2.5 with the following to increase the readability of important product information:

(b) (4)



3. Section 3 Dosage Forms and Strengths
    a. Recommendations to increase the readability of important product information for Section 3 are noted in track changes below:

(b) (4)

4. Section 16 How Supplied/Storage and Handling

a. Recommendations to increase the readability of important product information for Section 16 are noted in track changes below:

(b) (4)

B. Medication Guide (MG)

1. Recommendations to increase the readability of important product information for the MG are noted in track changes below:

(b) (4)

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Tzield received on July 21, 2025 from Provention Bio, Inc.

Table 2. Relevant Product Information for Tzield	
Initial Approval Date	November 17, 2022
Nonproprietary Name	teplizumab-mzwv
Indication	• 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 (1). • to delay the progression of Stage 3 T1D in adults and pediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D (Proposed)
Dosage Form	injection
Strength	2 mg/ml (1 mg/mL)
Route of Administration	Intravenous infusion
Dose and Frequency	<u>Patients with Stage 2 T1D</u> Administer TZIELD by intravenous infusion (over a minimum of 30 minutes), using a body surface area (BSA)-based dosing, once daily for 14 consecutive days as follows: • Day 1: 65 mcg/m^2 • Day 2: 125 mcg/m^2 • Day 3: 250 mcg/m^2 • Day 4: 500 mcg/m^2 • Days 5 through 14: 1,030 mcg/m^2 <u>Patients recently diagnosed with Stage 3 T1D (Proposed)</u> Administer TZIELD by intravenous infusion (over a minimum of 30 minutes), using a BSA-based dosing, once daily for 12 consecutive days for each of the 2 treatment courses as follows: • Day 1: 106 mcg/m2 • Day 2: 425 mcg/m2 • Days 3 through 12: 850 mcg/m2 A second treatment course is recommended to be administered 6 months after the first treatment course but may be given up to 12 months after the first treatment course.

Table 2. Relevant Product Information for Tzield	
How Supplied	TZIELD (teplizumab-mzwv) injection is a clear and colorless solution (2 mg/2 mL (1 mg/mL)) supplied in a single-dose vials in cartons with quantities as follows: • 1 single dose vial • 10 single dose vials • 14 single dose vials
Storage	Refrigerate TZIELD vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Store upright. Do not freeze or shake the vials. If not used immediately, store the diluted solution at room temperature [15°C to 30°C (59°F to 86°F)] and complete infusion within 4 hours of the start of preparation. Discard the diluted solution if not administered within 4 hours of preparation.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tzield labels and labeling submitted by Provention Bio, Inc.

- Prescribing Information received on July 21, 2025, available from \\CDSESUB1\EVSPROD\bla761183\0145\m1\us\proposed-pi.docx
- Medication Guide received on July 21, 2025, available from \\CDSESUB1\EVSPROD\bla761183\0145\m1\us\proposed-mg.docx

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 21, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, Tzield. Our search identified 5 previous review(s)[b,c,d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Conrad, A. Label and Labeling Review for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 26. OSE RCM No.: 2020-2286.

[c] Conrad, A. Review of Revised Label and Labeling for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 24. OSE RCM No.: 2020-2286-1.

[d] Conrad, A. Review of Revised Label and Labeling for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAY 04. OSE RCM No.: 2020-2286-2.

[e] Conrad, A. Review of Revised Label and Labeling for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 OCT 14. OSE RCM No.: 2020-2286-3.

[f] Conrad, A.. Review of Revised Label and Labeling for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 NOV 16. OSE RCM No.: 2020-2286-4.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

On August 25, 2025, we searched FAERS using the criteria in the table below and identified 248 cases. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with the label and labeling and dosage. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[g] We excluded 234 cases because they did not appear to describe an error associated with the label and labeling and dosage.

Table 3. Criteria Used to Search FAERS	
Initial FDA Receive Dates:	January 1, 2022 – December 31, 2024
Product Name:	Tzield
Product Active Ingredient (PAI):	teplizumab-mzwv
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

D.2 Results

Our search identified 248 cases, of which 10 described errors relevant for this review. Table 4 is a list of the FAERS case number, manufacturer control numbers, initial FDA received date, and brief summary for the cases relevant for this review.

Table 4. Tzield wrong dosage error reports (received last 3 years)			
FAERS Case Numbers	Manufacturer Control Number	Initial FDA Received Date	Summary of Error Narrative
22623903	US-PROVENTION BIO, INC.-US-PRAG-23-00030	6/21/2023	This case describes an infusion nurse who consulted a pharmacist during preparation/mixing of product but got confused and mixed too much into the bag when she loaded the infusion. The infusion nurse stopped the infusion when the medication error was recognized and notified the physician of error. The patient received a dose comparable to the dosage for infusion Day 5 rather than Day 1.

[g] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

22623905	US-PROVENTION BIO, INC.-US-PRAG-23-00035	6/21/2023	This case describes a patient who received the first infusion of Tzield at a dose of 250 mcg/sqm instead of 65 mcg/sqm. It was reported that this patient 'received day 3 injection instead of day 1'.
22623907	US-PROVENTION BIO, INC.-US-PRAG-23-00033	6/21/2023	This case describes a patient who ‘was infused with Day 3 dose in error for Day 1 infusion.’ It was reported that there was an issue with information given to mix the medication and the nurse did not realize the bags were labeled by date.
23320352	US-PROVENTION BIO, INC.-US-PRAG-23-00085	12/20/2023	This case describes a patient who experienced adverse events. The doctor claimed that there were concerns about the possibility that there was a medication error since the infusion nurse called, stating that she wasn't clear on how to administer Tzield. They concluded that it was possible that the wrong dose was given. No additional specifics were provided on the dose patient received.
23320359	US-PROVENTION BIO, INC.-US-PRAG-23-00098	12/20/2023	This case describes a patient who received Tzield at the hospital outpatient center for 5 days, and the rest of the treatment was administered by a nurse at the patient’s home. However, the infusion nurse thought that all 14 infusion days were at home, thus she ‘dosed day 6 as day 1’ and then the following infusion days 7-13 as the initial five days. “It was noted that the dispensing label from SP indicated that the home infusion doses were supposed to start within infusion day 6, and doses were dispensed from the pharmacy and labeled for days 6-14. It was also reported that the nurse had been

			trained to follow the pharmacy's labeling instructions and was specifically informed that home infusions should begin on infusion 6." The patient completed treatment over the course of 17 days, after receiving three additional doses, due to the previously mentioned underdose.
24138156	US-SA-2024SA213383	7/25/2024	This case describes a patient who 'took' an extra dose of Tzeild. No additional specifics were provided on how patient received an extra dose.
24198208	US-SA-2024SA227179	8/12/2024	This case describes a patient who 'received the day 3 dose on day 2.'
24316907	US-SA-2024SA263055	9/13/2024	This case describes a nurse who 'stated he mixed it correctly like he always did and was wondering if it was possible that the rest of the diluted Tzield was lining the inside of the bag / in the corners to where it wasn't able to be drawn up." The nurse was only able to draw up 18.6 mL total from the mixing bag (dose was 19.5 mL).
24633217	US-SA-2024SA326198	11/18/2024	This case describes a 'nurse doing incorrect dose for patient.'
24633235	US-SA-2024SA323794	11/18/2024	This case describes a 'nurse dosed the patient wrong that she used 2 vials instead of 1 vial for day 2 infusion.'

D.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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/

SUSAN B SHERMOCK
09/04/2025 11:01:31 AM

DAMON A BIRKEMEIER
09/04/2025 04:08:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 100262

MEETING MINUTES

Provention Bio, Inc.
Attention: Mayuresh Gadre, MS
Director, Regulatory Affairs
55 Broad Street, 2nd floor
Red Bank, NJ 07701

Dear Mayuresh Gadre:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PRV-031.

We also refer to the video conference between representatives of your firm and the FDA on August 29, 2023. The purpose of the meeting was to discuss the content and format of the sponsor's planned efficacy supplemental biologics license application (sBLA) for the treatment of newly diagnosed Stage 3 type 1 diabetes (TID).

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Supendeep Dosanjh, Regulatory Project Manager, at Supendeep.Dosanjh@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	Tuesday, August 29, 2023; 11:00 AM – 12:00 PM
Meeting Location:	ZoomGov link to be provided by the FDA regulatory project manager (RPM).
Application Number:	100262
Product Name:	PRV-031 (teplizumab)
Indication:	treatment of recent-onset T1D
Sponsor Name:	Provention Bio, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	John Sharretts M.D.
Meeting Recorder:	Supendeep Dosanjh Pharm.D.

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN),

Lisa B. Yanoff, M.D.	Deputy Director

Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

John Sharretts, M.D.	Director
Michael Nguyen, M.D.	Clinical Team Lead
Kristen Pluchino, Ph.D., M.P.H.	Clinical Team Lead
Lauren Wood Heickman, M.D.	Clinical Reviewer

Office of Regulatory Operations

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

Callie Cappel-Lynch. Pharm.D., RAC	Chief, Project Management Staff
Supendeep Dosanjh, Pharm.D.	Regulatory Project Manager

Office of Translational Sciences (OTS), Office of Clinical Pharmacology

Division of Cardiometabolic and Endocrine Pharmacology

Edwin Chow, Ph.D.	Clinical Pharmacology Team Lead
Xiaomeng Xu, Ph.D.	Clinical Pharmacology Reviewer

Division of Pharmacometrics

Elyes Dahmane, Ph.D.	Pharmacometrics Reviewer

OTS, Office of Biostatistics

Division of Biometrics II

Yoonhee Kim, Ph.D.	Statistical Team Lead
Sung Hee Kim, Ph.D.	Statistical Reviewer

SPONSOR ATTENDEES

Attendees for Provention Bio, A Sanofi Company

Eleanor Ramos, MD	Chief Medical Officer
Laura Knecht, MD	Vice President, Clinical Development
Wei Tian, PhD	Vice President, Head of Biometrics
(b) (4)	PK/PD Modeling Consultant ((b) (4)
Ann Andre	Senior Vice President, Clinical Operations and Project Management
Francisco Leon, MD, PhD	Chief Scientific Officer
Sharon Rowland, PhD, RAC	Senior Vice President, Regulatory Affairs
Shobha Gopalakrishnan, PhD, ELS	Vice President, Regulatory Affairs
Mayuresh Gadre, MS	Director, Regulatory Affairs

Attendees for Sanofi

Elisabeth Niemoeller, MD	DVC Deputy; Senior Global Project Head Teplizumab, Insulin & GLP-1 R&D, DCV Development
Elisabeth Souhami, MD, Msci	Clinical Lead, Senior Clinical Research Director
Oscar Gonzalez, MD	Director, Global Safety Officer
Hannelore Halfer-Wirkus, MD	Diabetes TA Lead Pharmacovigilance, QPPV & General Medicines PV
Pierre Mancini	Global Biostatistics Head, Medical Affairs, Diabetes and Cardiovascular
Wolfgang Schmider, PhD	Head of Clinical Pharmacokinetics and Pharmacodynamics, Frankfurt
Caroline Dubey, PhD	Global Regulatory Affairs, Diabetes Head
Audrey Mouthiers	Global Regulatory Lead
Anton Berezhko, PharmD	Regulatory Strategist
Evelyn Dombrecht, PhD	Global Project Manager, I&I GPPM

1.0 BACKGROUND

BLA 761183 was submitted on October 31, 2020, for PRV-031, also known as teplizumab, for the proposed indication of the delay of T1D in at-risk individuals. Prior to the submission of the BLA, teplizumab was being developed for the delay of T1D under IND 102629 and for the treatment of recent-onset T1D under IND 100262.

IND 100262 was originally filed on July 25, 2006, by MacroGenics and orphan-drug designation was granted by the FDA for teplizumab for the treatment of recent-onset T1D. In May 2018, teplizumab was acquired by Provention Bio. An end of phase 2 (EOP2) type B meeting was held on December 13, 2018, to discuss the phase 3 development program for teplizumab. At that meeting, FDA agreed with the overall

study design and dosing regimen for the PROTECT study and accepted the primary endpoint of C-peptide AUC measured at Week 78 by 4-hour mixed meal tolerance test as an endpoint that was reasonably likely to predict clinical benefit. The FDA agreed that the combination of safety data from the PROTECT and PROTÉGÉ study (conducted by MacroGenics) in subjects with recent-onset T1D could provide an adequate safety database, provided there were no unexpected safety issues during development, but recommended that the sponsor also collect robust long-term efficacy and safety data through at least 4-5 years. The long-term safety data could be provided in a long-term safety extension study after drug approval (i.e., as a post-market requirement (PMR)), but the source for the long-term efficacy data had not yet been determined.

FDA agreed that one potential pathway to approval could consist of one adequate and well-controlled study (PROTECT) plus confirmatory evidence from other phase 2/3 clinical trials but recommended further discussion about data requirements for a BLA and/or the appropriate regulatory pathway once the results from PROTECT were available. The FDA communicated to the Sponsor that whether the PROTECT study provides convincing evidence of clinical benefit would ultimately be a review issue.

BLA 761183 was approved on November 17, 2022, for the indication to delay the onset of Stage 3 T1D in adults and pediatric patients aged 8 years and older with Stage 2 T1D (previously under IND 102629).

On July 3, 2023, the sponsor formally submitted a pre-sBLA type B meeting request. On July 17, 2023, the type B meeting was granted to take place on August 29, 2023, from 11:00am-12:00pm EST. The purpose of this meeting is to discuss the content and format of the sponsor's planned efficacy supplement (sBLA) for the treatment of newly diagnosed Stage 3 TID.

FDA sent Preliminary Comments to Provention Bio on August 25, 2023.

2.0 DISCUSSION

The Sponsor's questions are repeated below in regular text and the FDA's preliminary response to each question is **bolded**. Following that is the Sponsor's response provided by email on August 28, 2023, in *italics* followed by the meeting discussion which is underlined. Any post meetings comments are shown in **bold and underline**.

2.1. Specific Questions

General FDA Comments:

The purpose of this meeting is to discuss the components needed to file an efficacy supplement for a new indication for the treatment of stage 3 T1D in patients within 6 weeks of diagnosis. The proposed efficacy data consists of a

new clinical trial PROTECT (PRV-031-001) and (b) (4) previously completed efficacy trials (PROTÉGÉ, (b) (4) Encore, AbATE, Delay, Study 1 (b) (4) PROTECT is a phase 3, randomized, double-blind, placebo-controlled, multi-national study in 328 patients aged 8 through 17 years of age with peak stimulated C-peptide levels of ≥0.2 pmol/mL who were randomized to receive either two 12-day courses of teplizumab given 6-12 months apart or placebo. The trial met its primary endpoint showing a statistically significant difference in the change from baseline AUC C-peptide after a 4-hour mixed meal tolerance test at Week 78 (0.125 (95% CI: 0.085, 0.165). Results from the key secondary endpoints, incorporated to quantify the clinical meaningfulness of preservation of C-peptide, were not statistically significant at Week 78 (exogenous insulin use, HbA1c, clinically significant hypoglycemic episodes, and time in range (TIR)), nor were there any notable trends on the validated surrogate endpoint HbA1c and clinically significant hypoglycemia. (b) (4)

(b) (4)

However, C-peptide is considered a surrogate endpoint reasonably likely to predict a clinical benefit (EOP2 Meeting Minutes, December 13, 2018). Given that PROTECT did not demonstrate any statistically positive results (or favorable trends) in the secondary endpoints designed to quantify the clinical meaningfulness of C-peptide preservation, it is not clear how you plan to demonstrate substantial evidence of effectiveness per the guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*[1], which describes both the quality and quantity of evidence needed. We have the following comments:

a. **Traditional approval involves at least one adequate and well-controlled clinical investigation in which the methods of assessment of subjects' response (i.e., efficacy endpoints) are well-defined and reliable. An efficacy endpoint in an adequate and well-controlled trial could be either a clinical endpoint (a characteristic or variable that directly measures how a patient feels, functions, or survives; e.g., reduction in Level 2 or Level 3 hypoglycemia rates or assessment of clinical outcomes from fit-for-**

[1] We update guidances periodically. For the most recent version of a guidance, chck the FDA Guidance Documents Database

purpose clinical outcome assessment measures) or a validated surrogate endpoint (an endpoint that is known to predict clinical benefit; e.g., change from baseline HbA1c). In either case, the effect demonstrated must be, in FDA's judgment, clinically meaningful. It does not appear that the data from PROTECT could meet the standard for traditional approval, (b) (4) .

b. Accelerated approval involves at least one clinical investigation using a surrogate endpoint reasonably likely to predict clinical benefit and requires a post-approval trial to verify the predicted clinical benefit. It is not clear whether you plan to use the PROTECT study, coupled with a post-approval trial for this pathway. If so, you have not yet attained FDA agreement on the design and conduct (including appropriate endpoints) of a trial to verify the predicted clinical benefit of C-peptide preservation. If you intend to pursue an accelerated approval, we recommend further discussion with FDA on this topic prior to an sBLA submission.

c. FDA agreed that one potential pathway to approval could consist of one adequate and well-controlled study (PROTECT) plus confirmatory evidence from other phase 2/3 clinical trials, but you did not provide information on how you plan to demonstrate substantial evidence of effectiveness. Please clarify the specific confirmatory evidence upon which you intend to rely.

It is unclear that the improvement in C-peptide AUC demonstrated in the PROTECT study is clinically meaningful. You state that (b) (4) the PROTECT study failed to demonstrate improved glycemic control (that might reasonably be anticipated to lead to microvascular benefit) or decreased risk of hypoglycemia as a result of improved C-peptide AUC at Week 78 and was not designed to evaluate the other outcomes (risk reduction in diabetic ketoacidosis or microvascular complications). (b) (4) We acknowledge that it is also possible that the PROTECT study may have been underpowered to detect a small treatment effect on clinically meaningful

endpoints.

Furthermore, it is not clear that a longer period of observation in PROTECT Extension would detect treatment differences in any of the secondary endpoints intended to quantify clinical meaningfulness. We recommend you provide evidence for why you anticipate that continued observation of the PROTECT trial subjects would uncover a treatment effect on clinically meaningful outcomes including glycemic control and/or hypoglycemia that was not observed in the parent trial. We also ask that you address the differences in baseline C-peptide level, TIR, HbA1c, and insulin dose, and account for these differences in your interpretation of analyses of these variables. If you elect to pursue an accelerated approval pathway, you would need to provide additional data, such as interim analyses of the PROTECT Extension, to justify the design of the confirmatory trial(s).

Given the concerns detailed above, the need for clarity on your intended regulatory pathway, and the quantity of evidence required for approval, we strongly recommend that you request further discussion with the FDA, e.g., in the form of a type C guidance meeting.

Sponsor's Response (received by email on August 28, 2023) to General FDA Comments:

We thank the Agency for the preliminary comments to our briefing package and would like to clarify as follows:

The scope of the integrated analysis of efficacy is to evaluate participant improvements in efficacy parameters of C-peptide AUC levels, a measure of beta cell preservation, as well as metabolic markers of diabetes management, including insulin use and hemoglobin A1c (HbA1c) across multiple studies in subjects with recently diagnosed T1D (i.e., Stage 3).

The C-peptide data from the PROTECT study will be provided along with the previous C-peptide meta-analysis in Stage 3 T1D patients. New integrated analyses for HbA1c, hypoglycemic event rates, and insulin use will also be included in the sBLA.
We would like to clarify that the totality of evidence intended to support the efficacy supplement will consist of the studies listed below:

- *Pivotal Study*
  - *PRV-031-001 (PROTECT)*

- *Supportive Studies (randomized controlled studies)*
  - *Study 1*
  - *Protégé*
  - *Encore*
  - *AbATE*

- *Delay*

We propose to exclude (b) (4) *from the pooled efficacy analysis* (b) (4)

Similarly, we propose to exclude (b) (4) *from the pooled efficacy analysis* (b) (4)

Additionally, we will address the differences in baseline C-peptide level, TIR, HbA1c, and insulin dose between the teplizumab and placebo groups, and account for these differences in our interpretation of analyses of these variables.

In our view, the pivotal PROTECT study data, including additional hypoglycemia data to be presented to the Agency during the meeting, and confirmatory evidence from the previous Stage 3 T1D studies provide substantial evidence of effectiveness for approval in the intended indication. We would like to discuss this further at the meeting.

Meeting Discussion on General FDA Comments:
In response to FDA's preliminary meeting comments, the Sponsor presented slides to clarify their intended regulatory approval pathway and the quantity of evidence to meet substantial evidence of effectiveness (see attached). The Sponsor stated that they were seeking to submit an efficacy supplement to the original teplizumab BLA for traditional approval (b) (4)

(b) (4)

(b) (4)

PROTECT showed a statistically significant effect on a reasonably likely surrogate endpoint (C-peptide), and thus is most suitable for use as the single adequate and well controlled trial in an accelerated approval pathway (and accompanied by confirmatory evidence), where the benefit on a clinical endpoint must be verified in a postmarket study.

(b) (4)

FDA recommended a type C meeting to further discuss both the sBLA submission package for accelerated approval and the design and conduct of the postmarketing trial that would verify the clinical benefit.

(b) (4)

FDA also stated that one potential approach to developing a data package that would support traditional approval would for the Sponsor to validate C-peptide as a surrogate endpoint for clinical benefits related to beta cell preservation (as was elaborated upon at the C-path workshop; see post-meeting comment below as well).

In summary, FDA stated that the accelerated approval pathway appears to be the most reasonable pathway for filing a sBLA for the Stage 3 TID indication based on the current data. FDA recommended that the Sponsor request a Type C meeting to discuss the design of the postmarket study to verify clinical benefit. FDA also emphasized that although our preference is for the Sponsor to have initiated the confirmatory trial prior to the approval action, per FDA's guidance for industry - *Expedited Programs for Serious Conditions—Drugs and Biologics*, in cases where it is not clear until shortly before or after submission of a marketing application for accelerated approval, there should be, at a minimum, agreement on the design and conduct of the study before approval.

Post-Meeting Comment on General FDA Comments:
Sponsors planning to use novel surrogate endpoints as primary efficacy endpoints should consult with FDA through a type C meeting. You may refer to the document, *Considerations for Discussion of a New Surrogate Endpoint(s) at a Type C PDUFA Meeting Request*[2] and the FDA guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,* for further information on the guidelines for the format and content of the meeting package.[3] Unlike other Type C meeting requests, a complete meeting background package is due at the time of the meeting request.

It is not a regulatory requirement to have agreement on the study design and endpoints of the postmarket study to verify clinical benefit; however, it would be more challenging to review a sBLA for accelerated approval without such agreement. FDA recommends that the Sponsor engage as soon as possible with the Agency on developing the study.

Question 1: A description and listing of the planned contents for Modules 1, 2, and 5 are included in the briefing package.

Does the Agency agree that the proposed contents adequately support filing the Efficacy sBLA?

FDA Response to Question 1: **It is premature to provide agreement on the adequacy of the proposed contents to support a sBLA submission. For details regarding this determination, see the general comment above.**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 1:
We appreciate the Agency's feedback. No discussion is needed.

Meeting Discussion on Question 1:

[2] https://www.fda.gov/media/119154/download?attachment
[3] https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/early-engagement-fda-discuss-novel-surrogate-endpoints-november-27-2018-issue

No discussion occurred.

Question 2: A summary of the clinical pharmacology data to be submitted in the complete sBLA package, including the population PK (popPK) modeling data analysis plan, is included in the briefing package.

Does the Agency agree that the proposed clinical pharmacology content adequately supports the filing of the sBLA?

FDA Response to Question 2: **Yes. Overall, the clinical pharmacology content including popPK analysis plan seems reasonable. However, we want to emphasize the following additional comments:**

1. **In the PROTECT study, we recommend assessing the anti-drug antibodies (ADA) titer effect on clearance (CL) for both products (separate and common ADA effect) as a time-varying covariate (e.g., using last observation carried forward (LOCF) or interpolation between measurements), instead of a constant covariate (i.e., maximum observed Ln (ADA titer)).**

2. **Estimate the ADA titer effect on CL separately for the TN-10 study and the PROTECT study and provide the individual random effects (eta) versus covariate plots by study and treatment course.**

3. **In addition to the external graphical evaluation in step 1 and step 2, we recommend to re-estimate and refine the PK models during the different steps (and after fixing PK parameters from course 1 in step 2). Evaluate the ADA effect on CL for course 2, as ADA titers and ADA titer effect on CL is expected to be much higher and significant during course 2 of treatment.**

4. **Provide a summary table of ADA titers and neutralizing ADA (NAB) titers by product, visit and treatment course for the PROTECT study. Separate the course 2 visits for patients who received course 2 at 12 months instead of 6 months after randomization.**

5. **When evaluating the differences in exposure between the Eli Lilly and AGC Biologics product you need to include C_{trough} after the last dose of each course.**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 2:

We appreciate the Agency's feedback.
With respect to comment #4, neutralizing antibodies (NAb) were evaluated using a validated qualitative method. A quantitative NAb assay has not been developed for

teplizumab. Therefore, the summary table will include NAb expressed as reactive/non-reactive and not by titers. No discussion is needed.

Meeting Discussion on Question 2:
No discussion occurred.

Question 3: The results for the efficacy and safety endpoints from the PRV-031-001 (PROTECT) study are included in the briefing package.

Does the Agency agree that the results support the filing of the sBLA?

FDA Response to Question 3: **No, we do not agree, see our general comment for recommended steps that should be completed before submitting an sBLA.**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 3:
Provention Bio Response:
We would like to discuss this comment during the meeting. Please refer to our slides.

Meeting Discussion on Question 3:
No discussion occurred.

Question 4: Based on the efficacy and safety data from the PRV-031-001 (PROTECT) study, a treatment regimen consisting of two 12-day courses (cumulative dose of 9 mg/m^2 per course) is proposed for the treatment of newly diagnosed Stage 3 clinical type 1 diabetes indication.

Does the Agency agree?

FDA Response to Question 4: **In general, we agree that the preliminary safety data you provided from the PROTECT study supports a treatment regimen consisting of two 12-day courses with a cumulative dose of 9 mg/m^2 per course and that the efficacy data shows that the treatment regimen has an effect on the primary endpoint. However, it remains unclear that the treatment regimen will have an effect on a clinically meaningful endpoint per our general comments above.**

We also note that you have included in your background package subgroup analyses demonstrating comparable efficacy of the AGC Biologics product (i.e. Tzield, approved for use in stage 2 T1D) to the Eli Lilly product based on C-peptide preservation in subgroup analyses, with difference (teplizumab-placebo) in least squares (LS) means of 0.130 (95%CI 0.063, 0.198, p<0.001) versus 0.149 (95%CI 0.089, 0.209, p<0.001) respectively. Whether the efficacy and safety data from the PROTECT study support your conclusion that the current commercial

Tzield (ACG Biologics) product is safe and effective for your proposed dosing regimen in the intended population will be a review issue.

In a future sBLA submission, we recommend that you present your intended labeled dosing regimen, complete with the intended timing of the second treatment course, along with analyses supporting the efficacy and safety of the current commercial product (AGC Biologics) in the dose and regimen proposed, including appropriate PK analyses by formulation. Additionally, given that the formulations used across clinical studies were unclear and the bioequivalence study (PRV-031-004) failed to demonstrate comparable PK exposure between Eli Lilly and AGC Biologics formulations, we recommend you flag the formulation used for each subject for each dosing day and throughout the treatment duration in your exposure/dosing database for the PROTECT (PRV-031-001) study and other clinical studies supporting the future sBLA and also summarize the formulation information in Section 2 Summary of Biopharmaceutics. If data allow, conduct an exposure-response analysis to justify the impact of PK exposure on efficacy and safety.

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 4:
We appreciate the Agency's feedback. No discussion is needed.

Meeting Discussion on Question 4:
No discussion occurred.

Question 5: We propose to submit (b) (4)

Does the Agency agree?

FDA Response to Question 5: **We do not agree with your proposal (b) (4) As discussed in our general comment, we recommend that you obtain FDA agreement on what study or studies will constitute substantial evidence of effectiveness for the new indication (treatment of Stage 3 T1D) prior to obtaining agreement on the contents of your ISE and write the ISE specifically for the new proposed indication. For the clinical trials ultimately chosen to support a conclusion of effectiveness, we ask that you provide enough detail in the ISE to understand critical aspects of the study design and the study findings, including treatment compared, sample size, population studies, number and location of study sites, study drug dose and regimen, treatment duration,**

analysis methods, and results for primary and important secondary endpoints of each study for our review. We refer you to the FDA guidance for industry, *Integrated Summary of Effectiveness*.

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 5:
We appreciate the Agency's feedback. We fully intend to write an ISE specifically for the new proposed indication. For further details, please refer to our response to the general comment. No discussion is needed.

Meeting Discussion on Question 5:
No discussion occurred.

Question 6: The Integrated Summary of Safety (ISS) to be included in the sBLA includes (b) (4) as described in the briefing package.

Does the Agency agree?

FDA Response to Question 6: **You are proposing to add safety data from (b) (4) While we agree with the inclusion of the proposed studies in your ISS, we recommend that you create several safety pools for analysis. Your primary safety pool should contain the intended treatment population (new- or recent-onset T1D), excluding TN-10 and subjects receiving open-label teplizumab. Additionally, we recommend a safety pool containing only subjects in the intended population (Stage 3 T1D) receiving the marketed product formulation (AGC Biologics).**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 6:
We appreciate the Agency's feedback.
For clarification, our understanding is that the following safety pools are requested.

- *The proposed population described above*
- *The primary safety pool will contain the intended treatment population (new- or recent-onset T1D), excluding TN-* (b) (4)
    - *For additional clarification, the following patients will be excluded per the Agency's request:*
        - (b) (4)

- [redacted] (b) (4)

- *A safety pool containing only subjects in the intended population (Stage 3 T1D) receiving the marketed product formulation (AGC Biologics).*

Please confirm our understanding.

Meeting Discussion on Question 6:
No discussion occurred.

Post-Meeting Comment on Question 6:
Yes, your understanding of the requested safety pools is correct.

Question 7: [redacted] (b) (4)

Does the Agency agree?

FDA Response to Question 7: **No, we do not agree. As with your ISE and ISS, we request that your ISI be written specifically to support this new indication and we ask that you provide additional supportive immunogenicity analyses in patients with recent-onset T1D using the intended commercial product using the proposed dosing regimen. In contrast to the Stage 2 T1D indication, we note that the Stage 3 T1D indication requires 2 courses of teplizumab, and preliminary evidence suggests that the second course is associated with greater immunogenicity. Thus, we recommend that you address this issue in your ISI.**

We also note that your previously submitted statistical analysis plan (SAP) for the PROTECT study (version 5.0, dated March 17, 2023) does not contain sufficient detail outlining your intended immunogenicity analyses. We therefore recommend you submit a more detailed immunogenicity analysis SAP for the PROTECT study. For the PROTECT study, in addition to evaluating the effect of immunogenicity on C-peptide AUC preservation, we recommend you evaluate the impact of immunogenicity on HbA1c.

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 7:
We appreciate the Agency's feedback. No discussion is needed.

Meeting Discussion on Question 7:
No discussion occurred.

Question 8: We plan to place the textual portions of the ISE and ISS in Module 2.7.3 and 2.7.4, respectively. The integrated analysis tables, figures, and listings will be located in Module 5.3.5.3 Integrated Summaries of Effectiveness and Safety. Thus, the ISE and ISS in Module 5.3.5.3 will contain only the statistical outputs and datasets, and Modules 2.7.3 and 2.7.4 will contain hyperlinks to the specific tables, figures, and listings located in Module 5.3.5.3.

Does the Agency agree?

FDA Response to Question 8: **We agree with your plan. However, we request that you submit and clearly indicate the location of the program files used to produce the analyses and results presented in your ISE and ISS.**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 8:
We appreciate the Agency's feedback. No discussion is needed.

Meeting Discussion on Question 8:
No discussion occurred.

Question 9: We do not plan to provide a 120-day safety update.
Does the Agency agree?

FDA Response to Question 9: **Although not required by regulations, providing a 120-day safety update would aid in the evaluation of your sBLA as the PROTECT Extension study is ongoing.**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 9:
We appreciate the Agency's feedback. We will provide a 120-day safety update from the PROTECT Extension study. No discussion is needed.

Meeting Discussion on Question 9:
No discussion occurred.

2.2. Regulatory Question

Question 10: We propose to update the approved USPI by annotating only the new text.
Does the Agency agree?

FDA Response to Question 10: **We interpret this question to mean you intend to update the currently approved United States Prescribing Information (USPI) for teplizumab (using tracked changes) with new text in support of your new indication. We are generally in agreement with this approach.**

Sponsor's Response (received by email on August 28, 2023) to Preliminary Comments Question 10:
We appreciate the Agency's feedback. No discussion is needed.

Meeting Discussion on Question 10:
No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[4] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[5]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the

draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to identify uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[9] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Further discussion on the design of the confirmatory trial is needed if the Sponsor elects to use the accelerated approval pathway for submission of their sBLA.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit type C meeting request to discuss an accelerated approval pathway with a proposal for a confirmatory trial	Sponsor	TBD

6.0 ATTACHMENTS AND HANDOUTS

[8] https://www.fda.gov/media/85061/download
[9] https://www.fda.gov/media/124795/download

- Attached slides presented by Sponsor at the meeting and delivered via email on August 28, 2023.
- Attached document with Sponsor's responses to FDA preliminary comments delivered via email on August 28, 2023.

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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/

JOHN M SHARRETTS
09/28/2023 02:01:49 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100262

MEETING MINUTES

Provention Bio, Inc.
Attention: Sharon Rowland, Ph.D., RAC
SVP Global Regulatory Affairs & Quality
308 Foster Knoll Drive
Joppa, MD 21085

Dear Dr. Rowland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for teplizumab.

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2018. The purpose of the meeting was to discuss the clinical, nonclinical, and CMC topics related to phase 3 development and to obtain feedback on any potential BLA filing issues for teplizumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Martin White, M.S., Regulatory Project Manager at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B (EOP)
Meeting Category: End of Phase 2

Meeting Date and Time: December 13, 2018, 12:00 PM – 1:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 100262
Product Name: teplizumab

Indication: (b) (4)

Sponsor Name: Provention Bio, Inc.

Meeting Chair: Lisa B. Yanoff, M.D.
Meeting Recorder: Martin White, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology
Products Lisa B. Yanoff, MD, Director (Acting)
Mitra Rauschecker, MD, Clinical Team Lead (Acting)
Suchitra Balakrishnan, MD, Clinical Reviewer
Todd Bourcier, PhD, Non-Clinical Supervisor
David Carlson, PhD, Non-Clinical Reviewer
Pamela Lucarelli, Chief, Project Management Staff
Martin White, MS, Regulatory Project Manager
Arati Kamath, PhD, Regulatory Project Manager

Office of Biostatistics
Yun Wang, PhD, Statistical Team Lead
Jiwei He, PhD, Mathematical Statistician

Office of Clinical Pharmacology, Office of Translational Sciences
Sury Sista, PhD, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology
Mei-Yean Chen, Pharm.D., BCOP, Risk Management Analyst

SPONSOR ATTENDEES
Eleanor Ramos, MD; Chief Medical and Operating Officer; Provention Bio, Inc.
Mark Rigby, MD, PhD; VP Clinical Development; Provention Bio, Inc.
(b) (4)
Consultant for Provention Bio, Inc.
(b) (4) Consultant for Provention Bio, Inc.
(b) (4) Consultant for Provention Bio, Inc.
(b) (4) Consultant for Provention Bio, Inc.
(b) (4)
Consultant for Provention Bio, Inc.
Francisco Leon, MD, PhD; Chief Scientific Officer Provention Bio, Inc.
Chantal Petit, PhD; VP Project Management; Provention Bio, Inc.
Sharon Rowland, PhD, RAC; SVP Regulatory Affairs & Quality; Provention Bio, Inc.
Ashleigh Palmer; Chief Executive Officer; Provention Bio, Inc.

Attending via Teleconference:
Paul Dunford; Executive Director of Translational Medicine; Provention Bio, Inc.

1.0 BACKGROUND

IND 100262 was submitted on July 25, 2006, by MacroGenics for teplizumab, which is a humanized IgG1 monoclonal antibody, with a proposed indication (b) (4)

Previous FDA-MacroGenics major meetings/designations:

- On December 20, 2005, a Pre-IND Meeting was held with DMEP under PIND (b) (4).
- On July 25, 2006, IND 100262 was filed for an indication of treatment of recent-onset Type 1 Diabetes.
- On September 29, 2006, orphan-drug designation was granted by the FDA for teplizumab for treatment of recent-onset type 1 diabetes.
- On January 9, 2012, a Type C Meeting was held with DMEP to review data from Protocol CP-MGA031-01 (the Protégé study): *A Phase 2/3, Randomized, Double-Blind, Multicenter, Multinational, 4-Arm, Controlled, Dose- Ranging Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus*. The primary purpose of the meeting was to review Protégé data with FDA and to discuss and seek concurrence with FDA on (1) the plan to conduct a new phase 3 study, (2) a proposed primary endpoint for a new phase 3 trial and (3) a path toward BLA filing for a recent onset T1DM treatment given the results of the Protégé study.

- (b) (4) [redacted]

In May 2018, teplizumab was acquired by Provention Bio, Inc. Provention Bio continues to develop teplizumab for treatment of recent-onset T1D.

The purpose of this meeting is to discuss the clinical, nonclinical, and CMC topics related to phase 3 development of teplizumab and to obtain feedback on any potential BLA filing issues for teplizumab.

FDA sent Preliminary Comments to Provention Bio, on December 7, 2018.

2.0 DISCUSSION

2.1 CMC

Question 1: Provention Bio acquired teplizumab from MacroGenics Inc. in May 2018. As a consequence, Provention Bio plans (b) (4) [redacted] A draft outline of a comparability plan for the new supply is included in the briefing package.

Does the Agency agree that this plan is acceptable?

FDA Response to Question 1: **No, we do not agree.**

We recommend that you submit a more detailed comparability protocol for the transfer of the manufacturing processes to the new manufacturing facility once it is available. Ultimately, the acceptability of drug manufacturing processes, manufacturing process controls, compatibility, etc. will be determined upon review of the license application.

(b) (4) [redacted]

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 2: Provention Bio may request an End-of-Phase 2 CMC meeting after the details of the new manufacturing facility are arranged in order to confirm the acceptability of the process, specifications, process validation plans and the stability program to support commercial supply and to discuss other potential CMC issues.
Does the Agency agree?

FDA Response to Question 2: **Yes, the Agency recommends that you request an End-of-Phase 2 meeting specifically to discuss CMC issues. It may be helpful to schedule this meeting after preliminary data has been generated from your proposed manufacturing process and once the comparability plan is finalized to have a more productive discussion of what will be required to demonstrate comparability of material produced at your new manufacturing sites.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

2.2 Nonclinical Questions

Questions 3: Teplizumab is a monoclonal antibody. The ICH Guideline S6 R(1) Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals states that standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still

be needed depending upon duration of clinical dosing, patient population, and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.) The need for a product-specific assessment of the carcinogenic potential for biopharmaceutical should be determined with regard to the intended clinical population and treatment duration (see the guidance S1A The Need for Carcinogenicity Studies of Pharmaceuticals.)

Teplizumab falls within the category of biotechnology-derived pharmaceuticals and has several product-specific characteristics that suggest carcinogenicity studies are not warranted: a) the clinical use is expected to be short (two 12-day courses, each course administered 6 months apart); b) Direct testing of teplizumab in standard rodent carcinogenicity models is inappropriate due to lack of binding of teplizumab to rodent CD3; c) The surrogate anti-murine CD3 antibody used in pre-clinical pharmacology and toxicology studies (251055), has limited utility in chronic dosing due to increased hypersensitivity and anaphylactic reactions observed with long term repeat dosing. Therefore, taken together Provention Bio believes that a carcinogenicity study is not warranted, and this would be consistent with ICH guidelines.

(1) Does the Agency agree?

(2) If the Agency agrees, should Provention Bio submit a formal request for waiver of carcinogenicity studies to the CDER ECAC committee?

FDA Response to Question 3: **We agree a carcinogenicity assessment is not needed given the intended duration of drug exposure. As review divisions determine the need for carcinogenicity assessments, a waiver request for the CDER ECAC is not needed.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 4: Due to the limited binding of teplizumab to CD3 in non-human species suitable for reproductive toxicology studies, reproductive toxicity studies were conducted in mice using a surrogate monoclonal antibody (251055) that binds to the murine CD3ε. Does the Agency agree that the completed reproductive toxicity studies are adequate for submission in a BLA?

FDA Response to Question 4: **Yes, we agree that the completed reproductive toxicity studies are adequate for submission in a future BLA.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 5: A tabular overview of Provention Bio's nonclinical program for the indication of treatment of recent-onset T1D is provided in the briefing package.

Does the Agency agree that the outlined nonclinical studies are adequate to support the successful filing of a BLA and that no additional non-clinical studies are needed?

FDA Response to Question 5: **We agree that no additional non-clinical studies are needed to support filing of a BLA, unless unanticipated issues arise in your program that are addressable by non-clinical approaches.**

Discussion:
The sponsor accepted FDA's response.

Additional Nonclinical Discussion:
During the meeting, DMEP asked if there were plans to alter the dosing regimen in the future. Provention Bio responded that only the proposed dosing regimen is being investigated at this time. The Division noted that additional nonclinical evaluation would likely be needed to support a chronic, recurring dosing regimen for teplizumab.

2.3 Clinical Questions

Questions 7: Does the Agency agree on the overall design of the phase 3 clinical trial, PRV-031-001 (PROTECT study), a randomized (2:1), double blind, placebo-controlled study in approximately 300 subjects (200 teplizumab:100 placebo) where randomization will be stratified by age and peak C-peptide at screening, and in which the target study population are participants between 8 and 17 years of age with newly diagnosed T1D (within 6 weeks of diagnosis) and a peak stimulated C-peptide ≥ 0.2 pmol/mL at screening from a 2 hour MMTT?

FDA Response to Question 7: **In general, the proposed study design for the PROTECT study seems acceptable.** (b) (4) **Based on our review of the data, the rationale to evaluate patients within 6 weeks of diagnosis of T1 DM and between 8-17 years of age seems reasonable. However, you should consider whether the 2-year follow-up data from the Protégé trial clearly support a baseline C-peptide cut-off of >0.2 pmol/ml vs.** (b) (4) **pmoL/mL. Since the response to teplizumab may depend on C-peptide reserves, if you choose a cutoff for C-peptide that is too low, your study may fail to demonstrate an effect of teplizumab.**

Discussion:
The Division reiterated their concerns as stated above and suggested recruitment of adequate number of subjects with higher C-peptide reserves as these were the subjects

(b) (4)

most likely to demonstrate a response to teplizumab given their greater beta cell reserve. The Division had no additional comments regarding the sponsor's rationale for the C-peptide threshold of > 0.2pmol/ml.

Questions 8: Does the Agency agree that the C-peptide AUC from a 4-hour mixed meal tolerance test (MMTT) at 18 months is an acceptable primary endpoint for the proposed Phase 3 clinical trial, the PROTECT study?

FDA Response to Question 8: **We agree that the C-peptide AUC from a 4-hour mixed meal tolerance test (MMTT) is a reasonable primary endpoint for the proposed phase 3 PROTECT study. Note, however, that although C-peptide AUC is reasonably likely to predict a clinical benefit, it is not a well-validated surrogate for clinical benefit, and we caution you that for teplizumab to be approved for the proposed indication, there should be clinically meaningful differences versus placebo in your other proposed clinical endpoints. Please also see our response to question 9.**

In addition, the 18 month time point for the primary endpoint seems reasonable for the proposed study, but we recommend further discussion with the Agency about your plans to assess the longer-term benefit of teplizumab therapy, e,g. 4 to 5 years and whether you plan to include an extension phase of the study. See also our response to Question 12.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 9: Does the Agency agree on the key clinically relevant secondary endpoints ((b) (4) to support the proposed indication at the time of a BLA submission, and that these parameters should demonstrate trends supporting the primary endpoint but not required to be statistically significant?

FDA Response to Question 9: **In general, we agree that statistical significance or lack thereof is not the key concern regarding demonstrating a favorable benefit risk assessment for teplizumab for the proposed indication. The totality of data should support a clinically meaningful and durable impact on the treatment of early type 1 diabetes, and whether the study provides convincing evidence will ultimately be a review issue. We note that while not required, a statistically significant improvement on HbA1c would provide very convincing evidence for clinical benefit, and we recommend that you consider designing your study with this goal, particularly given that the long-term benefit of establishing a difference in C-peptide AUC at 18 months is unclear.**

Discussion:
The sponsor summarized their response submitted to the Agency on December 10, 2018. The Division continued to recommend that to the totality of the data should support

clinically meaningful and durable benefit for patients with type 1 DM. (b) (4) [redacted] *Finally, it was acknowledged by the sponsor that the Division would need to review the protocol to come to an agreement on the primary and secondary endpoints.*

Questions 10: Does the Agency agree that the Inclusion and Exclusion criteria for the clinical study are adequate?

FDA Response to Question 10: **The inclusion and exclusion criteria appear adequate, please also review our response to question 7.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 11: Does the Agency agree that the existing clinical and population PK support the use of the planned 12-day regimen intended to deliver 9.0 mg/m^2 per course, with a total of 2 courses administered 6 months apart, in the Phase 3 PROTECT study?

FDA Response to Question 11: **Yes, your proposed 12-day regimen intended to deliver 9.0 mg/m^2 per course, with a total of 2 courses administered 6 months apart appears to be supported based on the existing clinical data and population PK modeling and simulations.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 12: Does the Agency agree that the existing safety and tolerability data from participants treated with two 9.0 mg/m^2 course over 14-days 6 months apart (including 207 participants from the Protégé study who received teplizumab and followed for up to 2 years) combined with the safety and tolerability data from the proposed phase 3 PROTECT clinical trial (where approximately 200 participants will be treated with two 9.0 mg/m^2 course of teplizumab over 12-days 6 months apart and followed for 18 months) will constitute an adequate safety database for submission of a BLA?

FDA Response to Question 12: **The safety database seems adequate for a submission of a BLA provided there are no unexpected safety issues that arise during product development, e.g. in the PROTECT trial. However, with this proposal we believe that significant uncertainties will remain about the long-term safety of your product which ultimately would impact the overall benefit risk considerations for the treatment approach to early type 1 diabetes, and these uncertainties would need to be addressed post-marketing if teplizumab were to be approved. We would expect that further robust safety data continue to be collected from patients enrolled in PROTECT and that you proactively consider strategies to provide long-term safety**

data (e.g. extension trials). We recommend further discussion on this point at a future (e.g. pre-BLA) meeting.

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 13: Assuming the C-peptide primary endpoint of the proposed phase 3 PROTECT trial is positive with supportive secondary clinical endpoints, does the Agency agree that these data coupled with the positive C-peptide and clinically-relevant results from the (b) (4) studies are adequate to support a BLA submission?

FDA Response to Question 13: **We believe it is premature to provide agreement on the adequacy of the proposed data to support a future BLA submission.** (b) (4) **it appears that you will be relying on PROTECT as the single adequate and well controlled investigation that does not rely on post hoc analyses to support the intended indication. While this may be acceptable [results of** (b) (4) **may also be considered as supportive information for the intended indication], we recommend further discussion with the Agency about data requirements for a BLA once the results from PROTECT are available. Depending on the available data (see our response to Question 9 regarding what constitutes convincing evidence of clinical benefit) further discussions about additional data requirements and/or the appropriate regulatory pathway, e.g. traditional vs. accelerated, may be warranted.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Questions 14: Teplizumab has Orphan designation for treatment of recent-onset T1D. Orphan products are exempt from the requirement of filing a Pediatric Study Plan. Does the Agency agree that because Provention Bio plans to enroll only pediatric participants in the proposed phase 3 PROTECT trial and the target population for the proposed indication is focused on children and adolescents, that a submission of a formal pediatric study plan is not necessary?

(b) (4)

FDA Response to Question 14: **Because this drug product for this indication has an orphan drug designation you are exempt from these requirements. Please refer to Section 3 below.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Additional Clinical Comments:

1. **In your previous submission (SN 0197) dated August 16, 2018, you report three deaths in the Protégé study teplizumab arm, including one listed as "unknown". Submit a patient narrative for this death, since this was not reported in the CSR for the Protégé study (SN0164 to IND 100262, August 3, 2012).**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

Additional Statistical Comments:

2. **We do not agree** (b) (4)

   We recommend that missing values from patients who drop out before the end of treatment period be imputed based on those who similarly discontinue study drug in the same treatment arm but still have their measurements taken at the scheduled visits. You are welcome to propose alternative methods that account for the differences in treatment discontinuation.

Discussion:
(b) (4) *The Agency advised the sponsor to use the recommended multiple imputation approach for missing data in the primary analysis regardless the amount of missing data. The Agency also emphasized the importance of following all patients for all scheduled measurements regardless of early termination of treatment. The sponsor stated they plan to do so.*

3. **The description about sample size calculation in Section 11.3 of the PROTECT protocol is not clear. Please provide step by step procedure on the sample size calculation. Clarify whether the estimate of 0.25 used in the calculation is in the scale of AUC or ln(1+AUC). Specify the mean difference and standard deviation used in the final calculation for sample size. Also, provide justification for the chosen parameters, such as the clinical relevance of your proposed 40% increase in C-peptide response in sample size calculation.**

Discussion:
The Agency agreed that the sponsor's clarification to sample size calculation, received on December 10, 2018, was adequate. The Agency pointed out that the equation in the Palmer et al. (2001) paper, $G = exp(M) - 1$, that transforms geometric mean of AUC to the mean of log(AUC+1) does not hold exactly. The sponsor stated that the transformation used for sample size calculation works well in previous studies and that the small discrepancy does not have much impact.

Post-Meeting Comment: The Agency notes the sponsor's explanation; this will be a review issue.

The Division also stated that the sponsor should submit data to support that a 40% difference in C-peptide AUC vs. placebo correlates with clinical benefit.

4. (b) (4) **You need to propose other sensitivity analysis, such as tipping point analysis or analysis using other imputation methods, to address the impact of missing values.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

5. **You mentioned Hochberg step-up method for addressing multiplicity of the secondary endpoints. Please provide further details in your study protocol and statistical analysis plan. Please also provide details on the statistical model used for each key secondary endpoint in your study protocol and statistical analysis plan. You did not specify a method for analyzing percentage of time participants' blood glucose (BG) levels are within the goal BG range at Week 78.**

Discussion:
The sponsor accepted FDA's response, no discussion occurred.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at

https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

8.0 ACTION ITEMS

There were no action items.

9.0 ATTACHMENTS AND HANDOUTS

Meeting Discussion handout submitted by Provention, Inc. on December 10, 2018.

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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/

LISA B YANOFF
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