CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	November 17, 2022
Reviewer(s):	Po-Yin Chang, PhD Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MHS, MPH Division of Epidemiology I
Division Director:	Wei Hua, MD, PhD, MS, MHS Division of Epidemiology I
Subject:	Active Risk Identification and Analysis (ARIA) Sufficiency Assessment for Safety Surveillance of Teplizumab-mzwv
Drug Name(s):	TZIELD (Teplizumab-mzwv)
Application Type/Number:	BLA 761183
Submission Number:	59
Applicant/sponsor:	Provention Bio
TTT #:	2022-2279

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	Cytokine release syndrome	Serious infection	Hyper-sensitivity	Lympho-proliferative disorders	Malignancy	Pregnancy-related adverse events	Birth and developmental outcome
-Initial							
-Interim							
-Final	X	X	X	X	X	X	X
Source of safety concern							
-Peri-approval	X	X	X	X	X	X	X
-Post-approval							
Is ARIA sufficient to help characterize the safety concern?							
-Yes							
-No	X	X	X	X	X	X	X
If "No", please identify the area(s) of concern.							
-Surveillance or Study Population	X	X	X	X	X	X	X
-Exposure							
-Outcome(s) of Interest	X			X	X	X	X
-Covariate(s) of Interest						X	X
-Surveillance Design/Analytic Tools							

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Teplizumab-mzwv (also known as PRV-031), a first-in-class, anti-CD3 humanized monoclonal antibody that binds to the CD3-ε epitope of the T cell receptor, is proposed to delay the onset of type 1 diabetes mellitus (T1D) in high-risk individuals. The U.S. Food and Drug Administration (FDA) granted teplizumab a Breakthrough Designation on November 7, 2019.

On April 14, 2020, the Applicant (Provention Bio) submitted Biologics License Application (BLA) 761183 for TZIELD (proposed propriety name for teplizumab injection), seeking an indication of delay or prevention of clinical T1D in at-risk individuals,[a] in a rolling review under section 351(a) of the Public Health Service Act. On November 2, 2020, the Applicant completed the submission of BLA 761183. The Applicant has proposed a 14-day intravenous (IV) dosing regimen, involving a 4-day ramp up of the following body surface area-based doses (51 μg/m^2 on Day 1; 103 μg/m^2 on Day 2; 207 μg/m^2 on Day 3; and 413 μg/m^2 on Day 4), followed by repeated body surface area-based doses of 826 μg/m^2 on Days 5 to 14.

On May 27, 2021, FDA held an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting to discuss the safety, efficacy, and proposed indication of teplizumab.[1] The majority of Committee members agreed that the benefits of teplizumab outweigh the risks, in support of approval to delay clinical T1D. The Committee agreed that the product should be restricted to at-risk populations in the clinical program (i.e., individuals ages ≥8 years who have a first degree relative with T1D, at least two positive diabetes-related autoantibody tests, and dysglycemia from oral glucose tolerance test (OGTT) but not overt diabetes), with the exception of including individuals who are non-relatives of patients with T1D.[2]

On July 2, 2021, FDA issued a Complete Response Letter, listing major concerns of non-comparability of pharmacokinetics in a bridging study and an unacceptable drug stability in real-time stability studies, among other concerns.[3] These major concerns were identified during the review process and were not discussed in the May 27, 2021 EMDAC meeting.

On February 16, 2022, the Applicant re-submitted BLA761183, seeking approval of TZIELD for an indication of delay clinical T1D in at-risk individuals.

The clinical team recommends the following indication:[4]

- TZIELD is indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D

The following provides the clinical and diagnostic backgrounds of three stages of T1D.

- Individuals with stage 1 T1D have two or more islet autoantibodies and are normoglycemic.
- Individuals with stage 2 T1D have two or more T1D-associated islet autoantibodies and have glucose intolerance, or dysglycemia, from loss of functional β-cell mass.[5] Dysglycemia in stage 2 T1D has been defined by (1) impaired fasting plasma glucose ≥100 mg/dL or

[a] In the original BLA submitted on April 14, 2020, the Applicant proposed an indication of delay or prevention of clinical type 1 diabetes in at-risk individuals. In the BLA re-submitted on February 16, 2022, the Applicant proposed an indication of delay of clinical type 1 diabetes in at-risk individuals.

≥110 mg/dL; (2) impaired glucose tolerance, with 2-h plasma glucose ≥140 mg/dL after a 75-g OGTT, or glucose levels ≥200 mg/dL at intermediate time points (30, 60, 90 min) on OGTT; (3) and/or HbA1c ≥5.7%.

- Individuals with stage 3 T1D have the typical clinical symptoms and signs of T1D, which may include polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis (DKA), and others.[5] In the SEARCH for Diabetes in Youth study (the SEARCH study), an estimated incidence of stage 3 T1D in U.S. youths age <20 years was 21.7 cases per 100,000 youths per year in 2011–2012.[6]

1.2. Describe the Safety Concern

The clinical development program for teplizumab identified imbalances in cytokine release syndrome, serious infections (including reactivation of Epstein-Barr virus [EBV]), and hypersensitivity reactions between the teplizumab-exposed group and the control group.[4]

Given teplizumab's action to engage T-cells and to cause lymphopenia, cytokine release syndrome and serious infections were not unexpected.[4] The majority of cytokine release syndrome cases identified in the teplizumab program were mild to moderate without requirement for intervention other than antipyretics. Serious infections were more frequent in the teplizumab than the control group. At 3-6 months after receiving teplizumab, 59% of patients developed anti-drug antibodies, which may be partially contributing to hypersensitivity reactions. These three safety outcomes will be labeled in Warnings and Precautions if the BLA is approved.

Additionally, because of the teplizumab's immunomodulation mechanism, there are theoretical concerns of potential longer-term risks including lymphoproliferative disorders caused by EBV reactivation or other malignancy due to immunosuppression. Nonclinical findings in chimpanzees support a potential risk for lymphoproliferative disorders with teplizumab, as non-neoplastic B-cell lymphoproliferative disease associated with an EBV-like virus and accompanied T-cell immunosuppression was observed at high doses of teplizumab. In the clinical development program, lymphoproliferative disorders were not observed among the pooled safety population with T1D, and an increased risk of general malignancy was not identified.

In mice exposed to the murine analog to teplizumab at the highest dose during pregnancy, increased resorptions in fetuses were reported. A pre-and post-natal study in mice demonstrated reduction in T cell populations and increases in B cells in the offspring on post-natal days 10 and 84, as well as a reduction of the primary IgM/IgG and secondary IgG response in post-natal assessment of immune system function. Please refer to Division of Pediatric and Maternal Health (DPMH) review for details.[7]

In the clinical studies for teplizumab, the Applicant identified and provided information of 17 pregnancies, including 12 pregnancies in teplizumab-exposed subjects and five pregnancies in control subjects. The 12 teplizumab-exposed pregnancies ended with eight normal neonates,[b] two elective abortions, one spontaneous abortion, and one loss to follow-up. The DPMH reviewer considered that the case of spontaneous abortion was complicated by Grave's disease and T1D.[7] None of the cases of abortion (elective or spontaneous) reported congenital malformations.

[b] One of the eight neonates was born 34 weeks gestation and discharged at six weeks of age in healthy condition.

Although data in clinical trials did not report malformations or high rates of spontaneous abortion, the DPMH reviewer concluded that clinical data are too limited to make any conclusions regarding reproductive safety.[7]

The premarket safety data are not sufficient to fully characterize the above-mentioned safety concerns or signals. Should this BLA be approved, FDA would seek to monitor the above-mentioned adverse reactions in a 10-year teplizumab user registry. The registry should also collect information for pregnancy-related adverse events (e.g., preeclampsia and gestational diabetes through the first year postpartum) and birth and developmental outcomes (including major congenital malformations through the infant's first year of life, spontaneous abortions, stillbirths, and small-for-gestational-age infants) in teplizumab-exposed pregnant women.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	Cytokine release syndrome	Serious infection	Hyper-sensitivity	Lympho-proliferative disorders	Malignancy	Pregnancy-related adverse events	Birth and developmental outcome
Assess a known serious risk							
Assess signals of serious risk							
Identify unexpected serious risk when available data indicate potential for serious risk	X	X	X	X	X	X	X

1.4. Statement of Purpose

The purpose of this memo is to evaluate whether the Sentinel Active Risk Identification and Analysis (ARIA) system is sufficient to assess the following safety concerns or signals of TZIELD for at least 10 years in a cohort of at least 150 subjects with stage 2 T1D.

- Cytokine release syndrome
- Serious infections
- Hypersensitivity
- Lymphoproliferative disorders
- Risk of malignancy
- Pregnancy-related adverse events through the first year postpartum

- Birth and developmental outcomes through the infant's first year of life

The cohort study of interest will estimate the incidence of outcome events in subjects with stage 2 T1D who receive teplizumab or comparator drug (to be determined).

1.5. Effect Size of Interest or Estimated Sample Size Desired

A cohort of at least 150 subjects receiving Teplizumab.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population will be comprised of individuals with stage 2 T1D. Stage 2 T1D is a pre-symptomatic condition prior to the onset of symptomatic, stage 3 T1D. The estimated number of U.S. patients with stage 2 T1D is unknown and is expected to be very small.[4]

2.2 Is ARIA sufficient to assess the intended population?

No, ARIA system is likely insufficient to capture the target population of patients with stage 2 T1D for two reasons:

- Currently, there is no ICD-10 diagnosis codes specific for stage 2 T1D.
- Laboratory testing results are needed to identify stage 2 T1D. The current ARIA system includes results of fasting plasma glucose and HbA1c, although the completeness and timing of available data relative to treatment initiation is unknown. However, the ARIA system lacks laboratory testing results for islet autoantibodies and OGTT.

3 EXPOSURES

3.1 Treatment Exposure(s)

If approved, exposure to TZEID will likely be adequately captured via NDC codes and/or procedure codes.

3.2 Comparator Exposure(s)

To be determined.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify exposure of TZIELD.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interests include the following:

- Cytokine release syndrome

- Serious infections
- Hypersensitivity reactions
- Lymphoproliferative disorders
- Risk of malignancy
- Pregnancy-related adverse events (such as preeclampsia and gestational diabetes) through the first year postpartum
- Birth and developmental outcomes (including major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age infants) through the infant's first year of life

4.2 Is ARIA sufficient to assess the outcome of interest?

AIRA is likely sufficient to assess serious infections and hypersensitivity.

AIRA is likely insufficient to assess cytokine release syndrome, lymphoproliferative disorders, malignancy, pregnancy-related adverse events, and birth and developmental outcomes.

(1) Sentinel has led a validation study and found acceptable accuracy of claims-based algorithm for **serious infections**.[8] **Hypersensitivity reactions** including anaphylaxis or those other than anaphylaxis, may be captured with moderate accuracy using administrative claims data.[9,10]

(2) ARIA system could identify **malignancy outcomes** using sensitive diagnosis codes, and a validated algorithm for lymphoma is available in Sentinel.[11] However, ARIA capabilities currently exclude clinical review of primary patient records for validation of malignancy outcomes. Data linkage to population-based cancer registries are currently unavailable in ARIA system. The risk of malignancy is intended to be assessed during a 10-year follow-up. ARIA typically has only 2-3 years of follow-up. In the Sentinel database, roughly 26% of the patients (56.6 million patients) have cumulative enrollment for over 5 years by July 2022.[12]

(3) Validated claims-based algorithms for **cytokine release syndrome and lymphoproliferative disorders** seem unavailable.

(4) Sentinel is considered sufficient for signal identification regarding **pregnancy and birth related outcomes**. However, detailed case narratives are deemed necessary for validation of such outcomes should a signal be identified. ARIA system lacks access to detailed information for pregnancy-related adverse events (e.g., preeclampsia and gestational diabetes) and birth and developmental outcomes (e.g., congenital malformation, spontaneous abortions, stillbirths, and small-for-gestational-age infants).

5 COVARIATES

5.1 Covariates of Interest

Covariates of interest may include demographics, such as age and gender.

For pregnancy-related and birth and developmental adverse outcomes, covariates of interest may include smoking, alcohol consumption, occupational exposure, and illicit drug use.

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA system is insufficient to assess covariates of interest for pregnancy-related adverse events and birth and developmental adverse outcomes because key covariates of interest (e.g., smoking, alcohol use, illicit drug use) are not generally well captured in claims data.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The design of interest is a cohort study.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA is sufficient for cohort studies to assess the question of interest.

7 NEXT STEPS

We determine that the Sentinel ARIA will be insufficient to evaluate the safety of TZIELD for various reasons, including inability to adequately identify the study population, inability to adequately ascertain some outcomes of interest, inability to identify certain covariates of interest, and inability to provide 10 years of follow-up data. The proposed PMR language, as of November 10, 2022:

Conduct an observational registry study to assess the long-term safety of teplizumab in patients with Stage 2 type 1 diabetes. The study should evaluate cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders and the risk of malignancy. The registry will also collect information on women exposed during pregnancy to assess for adverse events related to pregnancy through the first year postpartum, and birth and developmental outcomes through the infant's first year of life. 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.

REFERENCE

1. FDA Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Teplizumab BLA 761183. https://www.fda.gov/media/149388/download. Published May 27, 2021. Accessed.

2. U.S. Food and Drug Administration. Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting. May, 27, 2021. https://www.fda.gov/media/151795/download. Published May 27, 2021. Accessed.

3. U.S. Food and Drug Administration. Complete Response: BLA 761183 Teplizumab. Reference ID: 4821208. July 2, 2021.

4. Wood-Heickman LK. Clinical Review: BLA 761183 Tzield/Teplizumab (PRV-031). Reference ID: 5013528. February 17, 2022.

5. Insel RA, Dunne JL, Atkinson MA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care.* 2015;38(10):1964-1974.

6. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. *New England Journal of Medicine.* 2017;376(15):1419-1429.

7. Roca C. BLA 761183 PRV-031 (teplizumab). Division of Pediatric and Maternal Health Review. Reference ID: 4770036. March 29, 2021.

8. Lo Re III V, Carbonari DM, Jacob J, et al. Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies. *Pharmacoepidemiology and Drug Safety.* 2021;30(7):899-909.

9. Schneider G, Kachroo S, Jones N, et al. A systematic review of validated methods for identifying hypersensitivity reactions other than anaphylaxis (fever, rash, and lymphadenopathy), using administrative and claims data. *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl 1:248-255.

10. Bann MA, Carrell DS, Gruber S, et al. Identification and Validation of Anaphylaxis Using Electronic Health Data in a Population-based Setting. *Epidemiology.* 2021;32(3):439-443.

11. Epstein MM, Dutcher SK, Maro JC, et al. Validation of an electronic algorithm for Hodgkin and non-Hodgkin lymphoma in ICD-10-CM. *Pharmacoepidemiol Drug Saf.* 2021;30(7):910-917.

12. U.S. FDA Sentinel Initiatives. Key Database Statistics.

https://www.sentinelinitiative.org/about/key-database-statistics. Published July 5, 2022. Accessed.

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/s/

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GERALD J DALPAN
11/17/2022 01:42:40 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 16, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761183
Product Name and Strength:	Tzield (teplizumab-mzwv) injection, 2 mg per 2 mL (1 mg/mL)
Applicant/Sponsor Name:	Provention Bio, Inc. (Provention)
OSE RCM #:	2020-2286-4
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Provention submitted revised container label and carton labeling for Tzield on November 15, 2022. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container label and carton labeling for Tzield (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Of note, Provention provided responses to each of the recommendations and agreed to implement the proposed revisions.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Conrad, A. Review of Revised Label and Labeling Memorandum for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Oct 14. RCM No.: 2020-2286-3.

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/s/

ARIANE O CONRAD
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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 Medical Policy

PATIENT LABELING REVIEW

Date:	November 2, 2022
To:	Supendeep Dosanjh Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TZIELD (teplizumab-mzwv)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761183
Applicant:	Provention Bio, Inc.

1 INTRODUCTION

On October 30, 2020, Provention Bio, Inc., submitted for the Agency's review Biologics License Application (BLA) #761183 for TZIELD (teplizumab-mzwv) injection, for intravenous use indicated for the delay or prevention of clinical type I diabetes in at-risk individuals.

On November 20, 2020, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TZIELD (teplizumab-mzwv) injection, for intravenous use.

Due to outstanding clinical, pharmacology, and Chemistry, Manufacturing Controls (CMC) deficiencies, DDLO issued a Complete Response (CR) letter on July 2, 2021, and DMPP deferred to comment on the Applicant's patient labeling at that time.

On February 16, 2022, Provention Bio, Inc., resubmitted for the Agency's review BLA #761183 for TZIELD (teplizumab-mzwv) injection. The Applicant considers this resubmission a complete response to the deficiencies outlined in the CR letter dated July 2, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on March 28, 2022, for DMPP and Office of Prescription Drug Promotion (OPDP) to review the Applicant's proposed Medication Guide (MG) for TZIELD (teplizumab-mzwv) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft TZIELD (teplizumab-mzwv) MG received on February 16, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 24, 2022.
- Draft TZIELD (teplizumab-mzwv) Prescribing Information (PI) received on February 16, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 24, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MARIA T NGUYEN
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DMPP-OPDP review of teplizumab-mzwv (TZIELD) BLA 761183 MG

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 28, 2022

To: Supendeep Dosanjh, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity Products (DDLO)

Melinda Wilson, Associate Director for Labeling, (DDLO)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for TZIELD™ (teplizumab-mzwv) injection, for intravenous use

BLA: 761183

In response to DDLO's consult request dated March 25, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for Tzield.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling obtained from SharePoint on October 27, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed MG will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 25, 2022, and we do not have any comments.

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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/s/

ANKUR S KALOLA
10/28/2022 10:41:26 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 14, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761183
Product Name and Strength:	Tzield (teplizumab-mzwv) injection, 2 mg per 2 mL (1 mg/mL)
Applicant/Sponsor Name:	Provention Bio, Inc. (Provention)
OSE RCM #:	2020-2286-3
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Provention submitted revised container label and carton labeling for Tzield on October 12, 2022. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container label and carton labeling for Tzield (Appendix A) to determine if they are acceptable from a medication error perspective. Of note, the revisions are in response to recommendations that were made by other members of the review team. Our previous label and labeling review determined that the proposed Tzield container label and carton labeling were acceptable.[a] In addition, we note that the sponsor is no longer planning to pursue (b) (4) per carton presentation that we reviewed previously so they have only resubmitted the one vial, 10 vials, and 14 vials per carton presentations for review.

2 CONCLUSION

We reviewed the resubmitted labels and labeling for Tzield to determine if they are acceptable from a medication error perspective. The Tzield vial label is acceptable; however, we do have recommendations for the proposed Tzield carton labeling in Section 3 for Provention. Of note, the sponsor made changes to the net quantity statement on the carton labeling to make it read (b) (4) instead of the prior phrasing "single dose vials" and

[a] Conrad, A. Review of Revised Label and Labeling for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 May 4. RCM No.: 2020-2286-2.

they did not provide their rationale for this change. We determined that this phasing could be inaccurate and confusing, so we provide a comment for the sponsor to address this concern.

3 RECOMMENDATIONS FOR PROVENTION BIO INC.

We recommend the following be implemented prior to approval of this BLA:

A. Carton Labeling (10 count, 14 count)

1. We note that you propose to revise the [redacted] instead of the prior phrasing "single dose vials". We note that the revised phrasing is inaccurate because the vials are the single dose containers [redacted] Therefore, we recommend that you revise the proposed phrasing to read [redacted]
2. We note that you added the statements [redacted] and "Store in the original carton to protect from light." per our earlier recommendations. However, we note that these statements are [redacted] and may be combined for readability. Therefore, we recommend revising these statements to read as follows: "Dispense and store in the original container to protect from light."

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 6, 2021

To: Lauren Heickman, M.D.
Division of Diabetes, Lipid Disorders, and Obesity Products (DDLO)

Elisabeth Hanan, Regulatory Project Manager, (DDLO)

Monika Houstoun, Associate Director for Labeling, (DDLO)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for Tzield (teplizumab-mzwv)

BLA: 761183

This memo is in response to DDLO's labeling consult request dated November 19, 2020. Reference is made to a Complete Response letter that was issued on July 2, 2021. Therefore, OPDP defers comment on the proposed labeling at this time, and request DDLO submit a new consult request during the subsequent review cycle. If you have any questions, please contact name of OPDP reviewer at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

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CONSULT REVIEW MEMORANDUM

Date:	June 17, 2022
Date Request Received:	June 7, 2022
Consult number:	ICCR00851446
Application number:	IND 102629, BLA 761183
Requestor:	Supendeep Dosanjh, PharmD, MLRHR, CSP, Regulatory Project Manager, CDER/OND/ORO/DROCHEN
Consultant:	Jessica Chu, Ph.D., Scientific Reviewer, DCTD/OHT7/OPEQ/CDRH
Through:	Leslie Landree, Ph.D., Diabetes Diagnostic Devices Branch Team Lead, DCTD/OHT7/OPEQ/CDRH
Applicant:	Provention Bio, Inc.
Product name:	Teplizumab (PRV-031)

CONSULT REQUEST

On 1/27/2021, FDA issued preliminary comments to IND 102629 stating that teplizumab may require companion diagnostic device(s) for its safe and effective use because autoantibody testing is necessary to identify the indicated population. During the original submission (BLA 761183, PDUFA date 7/2/2021), FDA met with CDRH and OND Policy to discuss whether this new biologic met the requirement for a companion diagnostic. However, the team deferred a final determination as FDA was planning to issue a Complete Response (CR) letter. Now that the Applicant has submitted their response to the CR letter, we request that CDRH consult again continue discussing this question.

Current Thoughts of DDLO:
The sponsor is seeking an indication for the prevention of clinical “stage 3” type 1 diabetes in patients with preclinical “stage 2” type 1 diabetes, defined as patients with dysglycemia who are positive for 2 of the following 4 potential autoantibodies: glutamic acid decarboxylase 65 autoantibodies (GADA), insulinoma-associated-2 autoantibodies (IA-2A), insulin autoantibodies (IAA), zinc transporter-8 autoantibodies (ZnT8A).

At this point. DDLO considers stage 2 and stage 3 T1D to be stages of the same disease (with the same underlying pathophysiology) and represent different time points along the same disease continuum. This is because both stage 2 and stage 3 T1D are composed of patients with the same disease process, with stage 3 T1D only differing from stage 2 T1D by the severity/degree of progression, namely the severity of dysglycemia, which determines the presence of clinical symptoms. Pancreatic islet autoantibody testing is routinely available and used as part of standard of care for diagnosis of stage 3 T1D, and therefore this testing is also considered standard of care for stage 2 T1D. Additionally, at this point, we believe that it is possible to create an indication statement that identifies the clinical stage, without specifying the need for a specific diagnostic test. This is because there are FDA-cleared antibody tests for use in T1D patients which are currently commercially available and have very low rate of false positives

(high specificity) and when used in combination (requiring 2 or more positives) have even lower false positive rates. Moreover, patients are only diagnosed as having Stage 2 T1D if there is also dysglycemia on oral glucose tolerance testing. However, we wish to continue the discussion that began during the original submission and seek your expert opinion on this regulatory matter.

BACKGROUND

In October 2020, CDRH and CDER held an internal meeting to discuss that a companion diagnostic would be required for safe and effective use of teplizumab based on the sponsor stating that islet autoantibody testing will be required to identify the appropriate patient population upon future marketing of the drug. Also, the TN-10 trial ("Anti-CD3 mAb (teplizumab) for prevention of diabetes in relatives at-risk for Type 1 diabetes mellitus") identified at-risk subjects as patients with dysglycemia who had at least two positive autoantibodies.

Following this internal meeting, CDER sent a letter to the sponsor indicating that teplizumab will require companion diagnostic device(s) for its safe and effective use since islet autoantibody testing is needed for selection of appropriate patients for therapy. The letter stated that the sponsor should co-develop the companion diagnostic device(s) for contemporaneous approval with the drug and recommended that the sponsor discuss a proposed plan for co-development of the device(s) with the Agency.

In December 2020, in response to this letter, the sponsor requested a teleconference to discuss the applicability of FDA's *In Vitro Companion Diagnostic Devices* guidance document to Type 1 Diabetes Mellitus (T1DM) autoantibody testing and the requirement for companion diagnostic device(s) for safe and effective use of teplizumab in Stage 2 T1DM. The sponsor also wanted to discuss available T1DM autoantibody tests and the use of these tests in the diagnosis of T1DM.

In ICCR00045321, CDER requested input from CDRH regarding whether a companion diagnostic device is necessary for safe and effective use of PRB-031 (teplizumab) for the proposed indication of 'delay or prevention of clinical type 1 diabetes in at risk individuals' based on the information that the sponsor submitted in their teleconference request. CDRH did not agree with the sponsor's position that companion diagnostic devices are not needed for safe and effective use of teplizumab and maintained the position that the sponsor should co-develop companion diagnostic devices for the safe and effective use of teplizumab. Please see CDRH's consult review memo associated with ICCR00045321.

Ahead of the February 1, 2021 teleconference with the sponsor, the following preliminary comments were provided to the sponsor:

- Question 1: Given that T1D autoantibody testing is used to identify T1D in clinical practice, whereas dysglycemia is used to identify patients with Stage 2 T1D, the target population for administration of teplizumab, Provention does not consider T1D autoantibody tests to be companion diagnostics for the safe and effective use of teplizumab. Does the Agency agree?

- FDA Response to Question 1: We agree that T1D autoantibody testing is commonly used in clinical practice to confirm the diagnosis of stage 3 T1D, and there are currently FDA-cleared autoantibody tests for the intended use of "aid in the diagnosis of T1D." However, it is unclear whether these clearances also cover the identification of stage 2 T1D, the intended population for PRV-031 for the proposed intended use for PRV-031. Furthermore, we understand that definitive staging depends on the presence of dysglycemia, but T1D autoantibodies are also required, as you state in your response to our information request dated September 11, 2020. Therefore, T1D autoantibodies appear to meet the definition of a companion diagnostic should language instructing providers to select patients on the basis of antibody status be included in the future labeling for PRV-031.

  However, we acknowledge that the diagnosis stage 2 T1D may be well understood to future prescribers of PRV-031, and therefore, specification of autoantibody testing in the labeling may not be required for the safe and effective use of PRV-031.

  Therefore, we are continuing to discuss internally the requirement for a companion diagnostic(s) for PRV-031. Given these uncertainties, you should consider seeking additional advice from the Agency on the process of companion diagnostic development, as it remains possible it will be required as a postmarketing commitment. In addition, should a companion diagnostic be required, you may need to bridge the performance of the assays used in the clinical trials to the companion diagnostic devices.

On May 27, 2021, an Endocrinologic and Metabolic Drugs Advisory Committee Meeting was held to discuss the safety and efficacy of BLA 761183 for teplizumab intravenous infusion. The meeting included a discussion of the sponsor's proposed indication statement "Teplizumab is for the delay of clinical type 1 diabetes mellitus (T1D) in at-risk individuals." The committee was asked to discuss how the indicated population should be described to ensure that the expected benefit(s) of teplizumab will outweigh the risks of treatment. It was noted that the TN-10 trial was conducted in individuals ages 8 and older and enrolled relatives of patients with T1D with two or more positive autoantibodies and dysglycemia. The committee agreed that based on the data presented, the indication should be restricted to the population that was studied, although some committee members recommended that the indication not be restricted to relatives of patients with T1D but instead should include both non-relatives and relatives meeting the criteria for stage 2 T1D.

On June 16, 2022, members of the CDRH team met with members of the CDER team to better understand how stage 2 T1D is defined clinically and if clinicians would be able to identify a patient population representative of the population studied in the TN-10 pivotal trial based only on identifying the clinical stage in the drug labeling. CDER provided the following summary after the meeting:

1. Stage 2 and Stage 3 type 1 diabetes differ only in disease severity or disease progression. 100% of Stage 2 T1D patients will eventually transition to Stage 3 in their lifetime. By the time of progression to Stage 3, patients have suffered enough autoimmune mediated cellular damage to result in insulin deficiency and hyperglycemia.

2. Stage 2 T1D is well defined and recognized by professional societies responsible for the care for T1D patients (JDRF, Endocrine Society, American Diabetes Association). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321245/
3. Stage 2 T1D was the population studied in the pivotal trial TN-10. The only difference was that the study population was identified through active surveillance of families with T1D. Family history is not part of the Stage 2 T1D definition and does not impact the safety or efficacy of teplizumab. Use of teplizumab in Stage 2 T1D is consistent with the AC recommendations.
4. We know of no clinical reason why the performance (specificity or sensitivity) of any FDA approved autoantibody assay would differ by disease status or by disease progression for T1D.
5. Many autoimmune diseases are diagnosed with the assistance of autoantibody assays (e.g., systemic lupus erythematosus, grave's disease, rheumatoid arthritis). We are not aware that FDA requires that all disease modifying drugs require companion diagnostics to be developed, even if such assays are diagnostic components of the condition.

COMMENTS TO CDER

Below is our current thinking based on the information you have provided. We look forward to further discussion at our planned meeting on June 22, 2022.

You have indicated that you believe it is possible to create an indication statement that identifies the clinical stage, without specifying the need for a specific diagnostic test because there are commercially available, FDA-cleared antibody tests for use in T1D patients that have high specificity when used individually and even higher specificity when used in combination. You have described that patients are only diagnosed as having Stage 2 T1D if they have two positive autoantibodies in addition to dysglycemia on oral glucose tolerance testing.

Even if the indication statement did not specify a need for certain tests, autoantibody testing would still be necessary (though not sufficient) to determine patient eligibility for teplizumab since it is a key determinant in the staging of T1D. Thus, these tests would meet the definition of companion diagnostic devices. They would be essential for the safe and effective use of teplizumab because they would identify patients in whom teplizumab has been studied for safety and effectiveness (i.e., patients with two or more autoantibodies and dysglycemia, but not meeting criteria for the diagnosis of T1D). These are the patients most likely to benefit from teplizumab treatment, and there is insufficient information about the safety and effectiveness of teplizumab in any other population. Moreover, we have concerns with restricting the drug indication to clinical stage. Though a panel of pediatric endocrinologist experts you surveyed indicated that they are comfortable in identifying stage 2 T1D patients and clinicians are familiar with the clinical guidelines for the staging of T1D, it is not clear that they would correctly identify the population in whom teplizumab has been studied for safety and effectiveness. This is because autoantibody testing for T1D staging is not considered standard of care (as you described during our June 16, 2022 teleconference) and these tests are not routinely recommended in clinical practice (as noted in the clinical review for BLA761183). Additionally, for currently available autoantibody tests, there is a lack of standardization (the Islet Autoantibody Standardization Program is in its infancy and autoantibody tests do not compare

well to one another), and their performance in the teplizumab intended use population is uncertain (laboratory developed tests have not been reviewed by FDA and as described below, the performance of cleared tests has been established in a different patient population).

It may be possible to specify FDA cleared autoantibody tests in the indication and/or drug labeling if there is sufficient data to support the performance of these cleared tests in the teplizumab intended use population (e.g., sensitivity and specificity of the cleared tests when tested with samples of patients eligible for teplizumab treatment and samples of patients not eligible for teplizumab treatment, respectively; information to bridge the sensitivity and specificity performance of the laboratory developed tests used in the TN-10 trial to the cleared tests). However, it is not clear if this information is available. Cleared autoantibody tests were cleared with the intended use of "aid in the diagnosis of Type 1 diabetes mellitus", which is different from a test used to screen for individuals with Stage 2 T1DM eligible for teplizumab treatment. Clinical sensitivity for these cleared tests was determined by assessing true positive test results for samples from diagnosed T1D patients and clinical specificity was determined by assessing true negative test results for samples from patients with non-target diseases (e.g., type 2 diabetes, metabolic syndrome, autoimmune diseases, infection, renal disease, testicular cancer, kidney disease). It is not clear that the sensitivity of the cleared tests would be the same for diagnosed T1D patients (studied in the cleared submissions) vs. stage 2 T1D patients and that the specificity of the cleared tests would be the same in the non-target disease groups (studied in the cleared submissions) vs. patients suspected of Stage 2 T1DM but determined to be ineligible for the drug.

Without information to understand the performance of the cleared tests in the teplizumab intended use population, we are unable to conclude that cleared tests have high specificity (low false positive rate) in the teplizumab intended use population. Additionally, we are not aware of data showing the performance of these tests when used in combination, so we are unable to conclude that cleared tests have even higher specificity when used in combination. Sufficient data to support the performance of FDA-cleared tests in the teplizumab intended use population would be needed to determine whether or not available, FDA-cleared assays could be referenced in teplizumab's label in lieu of requiring a postmarketing commitment for a companion diagnostic.

Jessica Chu -S
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Jessica Chu, Ph.D.
Scientific Reviewer
DCTD/OHT7/OPEQ/CDRH

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Signing on behalf of Jessica Chu from CDRH

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 4, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761183
Product Name and Strength:	Tzield (teplizumab-mzwv) injection, 2 mg per 2 mL (1 mg/mL)
Applicant/Sponsor Name:	Provention Bio, Inc. (Provention)
OSE RCM #:	2020-2286-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Provention submitted their response to a complete response (CR) letter for Tzield (teplizumab-mzwv), under BLA 761183, on February 17, 2022. In addition, Provention resubmitted proposed labels and labeling for Tzield (Appendix A) with their response to the CR, which we reviewed to determine if they are acceptable from a medication error perspective. Of note, we evaluated the proposed labels and labeling for Tzield in prior labeling reviews completed before the BLA received a complete response (CR) on July 2, 2021.[a,b] Our reviews determined that the Tzield carton labeling and container label were acceptable at that time; however, we confirmed that our comments for the prescribing information (PI) were not communicated to the sponsor. In addition, we note that the sponsor is currently proposing two additional carton presentations (i.e., one vial per carton and (b) (4) per carton) that were not submitted for review before.

[a] Conrad, A. Label and Labeling Review for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Feb 26. RCM No.: 2020-2286.
[b] Conrad, A. Review of Revised Label and Labeling Memorandum for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Mar 24. RCM No. 2020-2286-1.

2 CONCLUSION

We reviewed the resubmitted labels and labeling for Tzield to determine if they are acceptable from a medication error perspective. After communicating the comments documented in our prior labeling review to the review team again[a], we determined that the PI is acceptable. Our review of the Tzield container label and carton labeling determined that our prior labeling recommendations were addressed. Therefore, we have no additional recommendations at this time.

APPENDIX A. LABEL AND LABELING RECEIVED ON FEBRUARY 17, 2022

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Tzield label and labeling submitted by Provention.

Prescribing Information: \\CDSESUB1\evsprod\bla761183\0059\m1\us\draft-label-text.docx

Container label:

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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 Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	April 30, 2021
To:	Elisabeth Hanan Senior Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	TRADENAME (teplizumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761183
Applicant:	Provention Bio, Inc.

1 INTRODUCTION

On October 30, 2020, Provention Bio, Inc. submitted for the Agency's review a Biologics License Application (BLA) #761183 for TRADENAME (teplizumab) injection, for intravenous use, indicated for the delay or prevention of clinical type I diabetes in at-risk individuals.

On November 20, 2020, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRADENAME (teplizumab) injection, for intravenous use.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for TRADENAME (teplizumab) injection, for intravenous use.

2 CONCLUSIONS

Due to outstanding clinical, pharmacology, and Chemistry, Manufacturing, and Controls (CMC) deficiencies, DDLO plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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CDER Clinical Consult Review
Division of Hematological Malignancies 1

Referenced Application:	**BLA 761183**
Applicant:	**Provention Bio, Inc.**
Drug(s):	**PRV-031 (teplizumab)**
Consult Requested:	**4/1/21**
Desired Completion Date:	**4/27/21**
Primary Reviewer:	Emily Jen, MD, PhD
Team Leader:	Donna Przepiorka, MD, PhD
Division Director:	R. Angelo de Claro, MD

Product Information:
PRV-031, a humanized anti-CD3ε monoclonal antibody, is being developed as an immuno-suppressive agent for the delay or prevention of clinical type 1 diabetes in at-risk individuals. For the proposed indication, treatment consists of a single 14-day course of PRV-031.

Reason for Consultation (from the consult request):
On November 2, 2020, DDLO received the final rolling submission to complete the BLA for filing. There is a planned AC meeting on May 27, 2021. In anticipation of this AC, DDLO requests input from DHM1 for the following issues:

1) Input on the assessment of severity for the cases of observed infusion reactions/cytokine release syndrome among PRV-031 treated subjects, and advice about risk mitigation strategies in the post-marketing setting.

2) Advice regarding a registry trial to further evaluate the safety signal of Epstein-Barr virus (EBV) reactivations, the potential for lymphoproliferative disease/malignancy and whether surveillance is needed

Materials Reviewed:
- BLA 761183 – ISS, patient narratives, ISS dataset, ISI, Clinical Study Reports
- Response to 18 Feb Request for Information on cytokine release syndrome (CRS)
- Module 2.4 Nonclinical Overview
- Relevant literature

Clinical Trials of Teplizumab in the ISS

Study	Design	Teplizumab Regimen	Number of Subjects
TN-10 (Pivotal Trial)	Randomized, double-blind, placebo-controlled trial	Single 14-day step-dose course 51-826 μg/m^2/day	32 placebo 44 teplizumab
Protégé CP-MGA031-01	Two-part randomized, double-blind, placebo-controlled dose-ranging trial	Up to 2 courses of 3 different step-dose regimens	Segment 1: 38 teplizumab Segment 2: 98 placebo 415 teplizumab
Encore CP-MGA031-03	Randomized, double-blind, placebo-controlled, dose-ranging trial	Up to 2 courses of 3 different step-dose regimens	62 placebo 192 teplizumab
AbATE ITN027	Randomized, 2-arm, open-label, controlled, 2-arm trial	Two 14-day step-dose courses 51-826 μg/m^2/day	25 control 52 teplizumab
Delay NCT00378508	Randomized, double-blind, placebo-controlled trial	Single 14-day step-dose course 51-826 μg/m^2/day	27 placebo 31 teplizumab

Questions for the Consultant:

1. *Please provide a summary of CRS that can be used as a reference for the AC backgrounder materials or verify that our current summary is accordance with current DHM1 understanding of CRS.*

   Review:

   - Drug-induced CRS is a clinical diagnosis based on fever ≥ 38.0º C with or without hypotension and/or hypoxia with a temporal relationship to a treatment with a drug mechanistically known to provoke production of proinflammatory cytokines.[1]
     - CRS can start within minutes or hours of the first dose up to 14 days after infusion depending on the product.
     - Constitutional symptoms (headache, fatigue, arthralgias, myalgias), nausea or rash are common but not required for diagnosis of CRS.
     - Severe cases may include respiratory failure, hypotension requiring vasopressors, cardiac dysfunction, renal failure, elevated transaminases, and disseminated intravascular coagulation. CRS may result in fatal multi-organ failure.
     - Laboratory findings can include cytopenias, elevated creatinine and liver enzymes, abnormal coagulation parameters, and elevated CRP and ferritin, but these can be highly variable and nonspecific or may lag after clinical changes. Therefore, diagnosis of CRS does not rely on laboratory findings.
     - Inflammatory cytokines (TNFα, IL-6, IFNγ) are elevated, but these data are often not available in real time for diagnosis.

   - Monoclonal antibody-induced CRS can occur via multiple mechanisms.[2]
     - When engaged with cognate antigen, antibodies with an intact Fc may cross-link the Fc-receptor and activate monocytes and macrophages, resulting in cytokine production. In the ISI, the Applicant noted that the Fc region mutations in PRV-031 should minimize Fc receptor and C1q binding, and thus reduce the risk of immune cell activation through the Fc receptor.
     - T-cell agonists, including agonistic anti-CD3 antibodies, may also activate T-cells directly with subsequent secretion of cytokines that may cascade to other inflammatory cells.

   - There are multiple grading systems for CRS in use (see Appendix A). Grading is frequently based on the presence of fever not attributable to other cause with or without hypoxia and/or hypotension in addition to the level of intervention required for hypoxia or hypotension.

   DHM1 Response: Please see comments in tracked changes on the attached AC backgrounder excerpt.

[1] Shimabukuro-Vornhagen A, et al. (2018) Cytokine release syndrome. J Immunother Cancer 6: 56.
[2] Bugelski PJ, et al. (2009) Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol 5:499 - 521.

2. *Please provide your assessment regarding the cases of CRS observed with PRV-031 use and comment on if they represent CRS or rather transient infusion reactions?*

Applicant-Reported CRS Events (from the consult request)

	Placebo/Control	PRV-031	Δ risk (%)	95%CI	RR (95% CI)
CRS by CTCAE v3.0 GUIDELINES ***N***	**245**	**791**			
Any Grade CRS, CTCAE	3 (1.2%)	46 (5.8%)[1]	4.6	(2.5, 6.7)	4.75 (1.49, 15.14)
Grade 1 CRS, CTCAE	1 (0.4%)	18 (2.3%)	1.9	(0.6, 3.2)	5.58 (0.75, 41.59)
Grade 2 CRS, CTCAE	2 (0.8%)	22 (2.8%)	2.0	(0.4, 3.6)	3.41 (0.81, 14.4)
Grade 3 CRS, CTCAE	0	7 (0.9%)	0.9		
CRS by ASTCT GUIDELINES					
Any Grade CRS, ASTCT	32 (13.1%)	172 (21.7%)	8.7	(3.6, 13.8)	1.66 (1.17, 2.35)
Grade 1 CRS, ASTCT	23 (9.4%)	140 (17.7%)	8.3	(3.8, 12.8)	1.89 (1.25, 2.87)
Grade 2 CRS, ASTCT	9 (3.7%)	37 (4.7%)	1.0	(-1.8, 3.8)	1.27 (0.62, 2.59)
Grade 2 CRS + Hypotension	7 (2.9%)	32 (4.0%)	1.2	(-1.3, 3.7)	1.42 (0.63, 3.18)
Grade 2 CRS + Hypoxia	2 (0.8%)	7 (0.9%)	0.1	(-1.2, 1.4)	1.08 (0.23, 5.17)
Grade 2 CRS + Both Hypoxia & Hypotension	0	2 (0.3%)	0.3	(-0.1, 0.6)	

[1] Note, one subject had events meeting criteria both grade 1 and 2 CRS

Review:

a. Cytokine Release Syndrome

- Nonclinical data:
  - Circulating TNFa, IL-6, IL-10, and IFNg increased dose-dependently following single PRV-031 SC dose in chimpanzees; peak levels observed 6 hours post-dose (0.1 to 10 mg/kg).
  - Circulating IL-6 and IL-12 increased slightly in mice following single SC dose surrogate antibody (0.65 or 19.5 mg/kg).
  - Animal models with cross-reactive target antigens were limited in availability.
  - MGA031-HL003 (in vitro study of cytokine induction in PBMCs)
    - OKT3 (murine precursor to PRV-031) bound CD3 receptor
    - No significant differences in cytokine induction towards PRV-031 vs OKT3 in PBMCs from healthy volunteers or patients with psoriasis

- In patients with newly-diagnosed T1D treated with PRV-031, serum IL-6 and TNFa peaked after the 2nd dose[3]

- The ISS population included 1,018 patients ages 8-49 years at high risk for or with Type I diabetes mellitus treated with PRV-031 or placebo/control. Patients were treated inpatient vs outpatient at the discretion of the investigator. The dataset did not identify whether treatment was inpatient or outpatient for a given patient/dose, but comments in the narratives imply that many patients were being treated outpatient.

[3] Herold, et al. (2002) Anti-CD3 Monoclonal antibody in new-onset type 1 diabetes mellitus. NEJM 346:1692-8.

- CRS adjudication was based on data in adcrs.xpt, adae.xpt, advs.xpt, and narratives linked in ISS.
  - CRS screening criteria:
    - Preferred Term Cytokine release syndrome reported within 14 days of initiation of therapy (Period 1 or Period 2) OR
    - Documented fever (a report of Grade 1 pyrexia in adae.xpt was considered evidence of $T \geq 38^{o}C$ even if advs.xpt did not have a recorded temperature),
    - With or without hypotension and/or hypoxia, AND
    - Presentation of signs/symptoms of CRS within 14 days of initiation of therapy (Period 1 or Period 2)
  - Upon review of the narrative and/or additional data elements, patients were excluded if they had documented concurrent infections as a potential secondary cause of symptoms; in the absence of documented infections, signs/symptoms were considered at least possibly related to CRS.
  - Grading was based on ASTCT Consensus Criteria (see Appendix A)

Limitations of the data:

- There are few data provided that describe the observed cytokine production profile after treatment with the proposed PRV-031 regimen, so it is not clear when the risk of CRS would be greatest. Therefore, the types and frequency of safety monitoring for CRS may not have been sufficient to fully characterize the risk.

- Clinical manifestations of CRS and infusion-related reactions (IRR) may overlap, and if the diagnostic criteria in the protocol were not prespecified, the reporting may not be accurate.

- Adjudication was somewhat limited by the fact that most subjects had no or only non-informative narratives and no or minimal ARs documented in adae.xpt. Some had comments such as "Temperature at home not captured." Several patients with Applicant-reported Grade 3 CRS by CTCAE had no other documentation of the event.

- ASTCT Grade ≥ 2 CRS is based on the types of interventions required. However, no data on concomitant medications were included in the dataset. In the absence of data/documentation on interventions/supportive care medications, Grade 2 vs 3 vs 4 could not be confirmed for most cases. All cases with documentation of fever and hypotension and/or hypoxia were adjudicated as Grade 2+. Hypoxia was reported by PT dyspnea or cough or descriptions of dyspnea/bronchospasm or oxygen requirement in the narratives.

- Although cytokine levels were not included in the dataset, a few patients with more comprehensive narratives had IL-6 and TNFa increases reported following treatment with PRV-031.

Analysis results:

- Sixteen duplicate entries and 6 events with a start date more than 14 days from the start of the treatment period were excluded from the analysis.

- There were 279 potential episodes of CRS within the first 14 days of treatment identified in 230 patients.

- Of the 58 episodes of CRS by CTCAE reported by the Applicant in 49 patients, 40 cases could not be confirmed due to lack of supporting data. This included 5 of the 8 events of CTCAE Grade 3 CRS which could not be determined to have been CRS by objective criteria.

- Of the other 221 cases in 183 patients, CRS was excluded for 22 cases after evaluation of the information in the narratives or additional reported adverse events.

- DHM1 grading was limited to at most Grade 2+ when there was hypotension or hypoxia and insufficient data to assign a specific grade.

- DHM1 identified 217 cases of CRS in 184 patients. Table 1 shows a summary of the final DHM1 adjudication of patients who developed CRS.

Table 1. ISS Safety Population – CRS by ASTCT Grading – DHM1 Adjudication

	PRV-031 N = 791*	**Control/Placebo N = 245**
Any Grade	160 (21%)	25 (10%)
Grade 1	124 (16%)	21 (9%)
Grade 2+	36 (5%)	4 (2%)
- Fever + hypoxia	4 (1%)	0
- Fever + hypotension	28 (4%)	4 (2%)
- Fever + hypotension + hypoxia	4 (1%)	0

*Includes 18 patients who crossed over from control and received PRV-031 in Period 2
For patients with more than one CRS event, only worst grade shown
Includes one patient with CRS after both control and PRV-031
Source: DHM1 Consult Reviewer

- Of the cases adjudicated by DHM1 to be CRS:

  - The median time to onset of the episode was 4 days (range, 1-14)

  - Duration of CRS could not be determined reliably, since the end dates for some signs or symptoms of CRS were not available for many reported adverse events. However, most cases appeared to have resolved within a week.

  - Thirty-three patients met criteria for CRS twice (once in each treatment period).

    - 29 patients treated with PRV-03 had multiple episodes of CRS:
      - 22 had Grade 1 CRS twice
      - 3 had Grade 2+ CRS twice (fever + hypotension)
      - 4 had Grade 1 once and Grade 2+ once

    - 3 patients in the control arm met criteria for Grade 1 CRS twice

    - 1 patient had Grade 1 CRS while receiving control and Grade 1 CRS after crossing over to treatment with PRV-031 (Delay (b) (6))

- Three additional patients in the control arm crossed over to treatment with PRV-031 and experienced subsequent Grade 1 CRS events (Delay-(b) (6)

Main discrepancies between FDA and Applicant adjudication of CRS:

- Of the patients with CRS reported as a Preferred Term according to CTCAE that DHM1 adjudicated as not CRS:
  - Most patients had constitutional symptoms only or no documentation of any signs/symptoms of CRS.
  - Seven patients had rash as the only symptom identified. These patients may fall under IRR.

- Of the screening cases adjudicated by DHM1 as not CRS, several had rash as the only documented sign/symptom; although these patients did not meet criteria for CRS, these still represent possible IRR.

- There are background levels of these signs/symptoms as seen in the control arm.
  - There were four patients in the control arm who had fever + hypotension, but none had additional documentation available to confirm potential causes for these findings. The Applicant's alternative for all four was "Possible viral infection".

In summary, the nonclinical data demonstrate the ability of PRV-031 to stimulate production of cytokines from T cells, elevations in proinflammatory cytokines were reported in patients treated with PRV-031, and the clinical manifestations of CRS were observed more frequently in patients treated with PRV-031 that with placebo. Therefore, one can conclude that CRS is a potential adverse reaction of PRV-031. It is not possible to fully describe the severity of CRS in the population due to missing information.

b. Hypersensitivity Reactions

Anaphylaxis and serum sickness/vasculitis are two major acute infusion reactions that can be caused by monoclonal antibodies.[4]

Anaphylaxis is produced by vasoactive mediators (e.g., histamine) released by mast cells and basophils activated by IgE bound with cognate antigen. Clinical manifestations include pruritus, flushing, angioedema, stridor, wheezing, abdominal cramping, and/or hypotension. Onset is generally within minutes to hours of the start of drug administration, but because this reaction requires prior antigen exposure, it usually occurs with the second or later dose.

In the ISS, there were no reports of the Preferred Term Anaphylaxis. In the SMQ analysis there was 1 (0.4%) patient in the control arm with urticaria and 14 (1.8%) patients who developed urticaria (n=12), periorbital edema (n=1) or swelling of the face (n=1) during treatment with PRV-031. Two patients had 3 episodes within the same course. The median time to first episode was 4 days (range 3-11 days).

[4] Pichler WJ. (2021) Drug hypersensitivity: Classification and clinical features. Accessed 4/26/2021 at https://www.uptodate.com/contents/drug-hypersensitivity-classification-and-clinical-features?source=history_widget

Although some manifestations of anaphylaxis in general and the expected timing of onset overlap with those of CRS, the events observed in the clinical trials were limited to angioedema, which can be distinguished from CRS. The limited data, however, do not preclude the possibility that cases with hypotension may occur with postmarket use of the drug and be confused with CRS. The differentiation is important, since discontinuation of therapy would be warranted in true cases of anaphylaxis.

Type III hypersensitivity reactions (serum sickness/vasculitis) are mediated by antigen-antibody complexes. Depending on the form, clinical manifestations may include fever, rash, arthralgias, glomerulonephritis, and lymphadenopathy. Timing generally occurs weeks after start of treatment, since development of anti-drug antibodies are needed to generate the syndrome. Onset may occur more rapidly upon re-exposure, such as a repeat later course.

In the ISI, the Applicant reported that 50-92% of patients developed ADA during the first course of PRV-031 across the various treatment regimens, and that the ADA incidence was as high as 100% when a second course was administered. There was one report of serum sickness on Cycle 1 Day 22 in a patient treated with PRV-031 in Study TN-10 and no reports of the term vasculitis in the ISS. The Applicant reported that rash occurred more frequently in patients treated with PRV-031 than with placebo, but a correlation with development of ADA was not consistent across trials (Appendix B).

The data suggest that Type III hypersensitivity reactions may be possible in the postmarket period, but due to the delayed onset, they are not likely to be confused with CRS.

DHM1 Response: Cytokine release syndrome (CRS) is a class effect of monoclonal antibody T-cell agonists. Both nonclinical and clinical data indicate that treatment with PRV-031 results in elevated IL-6 and TNFa levels. In the clinical trials included in this BLA, CRS requiring intervention other than antipyretics was rare but did occur following treatment with PRV-031. However, it is not possible to fully describe the severity of CRS in the population due to missing information.

In the clinical setting, CRS and some forms of infusion related reactions (IRR) are difficult to distinguish because the clinical manifestations and timing overlap. The high number of false positive calls and the additional cases of possible CRS identified by the screening algorithm suggest that even the trained investigators could not clearly differentiate CRS from other types of IRR. Additional education may be needed.

See attached data file for our adjudication of CRS.

3. *In terms of the severity and frequency of CRS observed with PRV-031 use, please provide an expert opinion on whether DHM1 has any specific recommendations on ways to help mitigate this risk for the CRS events/infusion reactions observed in the PRV-031 program. For the clinical trials included in the ISS, Ibuprofen (or similar non-steroidal anti-inflammatory (NSAID) drug) and antihistamine were administered prophylactically prior to PRV-031 infusion on the first 5 days of treatment. Further dosing of ibuprofen, antihistamines, and/or acetaminophen were recommended to be used as needed for fever, malaise, headache, arthralgia, or rash. Please comment on if this premedication regimen appears to be adequate given what is known about the CRS events/infusion reactions observed in the PRV-031 program.*

Review:

Use of an intra-patient step-dosing (incremental dose increases during the first cycle) until the target maintenance dose is reached is a common method to mitigate the risks of CRS or infusion reactions. The Applicant has already incorporated this strategy in their treatment schedule.

Pretreatment with antihistamines and acetaminophen are often reported in the literature as "prophylaxis for CRS". However, although these drugs are used commonly for prevention of IRR, they do not address the mechanism of cytokine release and would not be effective in preventing the occurrence of CRS. Premedication with corticosteroids can be used to reduce the incidence of severe CRS, but there are potential complications from the corticosteroids themselves.

In this BLA:

- PRV-031 was administered with step-dosing: doses increased from Dose 1 through Dose 5 with the same dose maintained for Doses 5-14.
- Per protocol, NSAIDs and antihistamines were to be administered prophylactically prior to PRV-031.

Limitations of the data:

- No data were provided in the ISS dataset to allow for analysis of the use of specific medications for prophylaxis or treatment of CRS.
- Interventions could not be confirmed. Lack of escalation of care was extrapolated from CTCAE Grade 3 CRS x 8 cases, no Grade 3+ CRS by ASTCT grading per Applicant (response to IR), no fatal outcomes, no ICU admissions, and no patients requiring a vasopressor or experiencing significant hypoxia per narratives.

DHM1 Response: Premedication with NSAIDs and antihistamines would not prevent CRS. However, these were used as premedication in the clinical trials, and they may have a role in mitigation of IRR. We recommend inclusion of instructions for premedication with NSAIDs and antihistamines in the USPI that are the same as those used in the protocol.

Given the low incidence of severe CRS as reported by the Applicant in the clinical trials, few patients requiring hospitalization, and no patients requiring escalation of care, the data do not support additional premedication guidelines. We would not recommend use of corticosteroids as prophylaxis in this population.

We recommend education for patients and providers on the risks, diagnosis and management of CRS after treatment with PRV-031 as a means to mitigate severe CRS (see response to Question #5).

4. *Please provide an assessment of the EBV reactivations and the potential risk for lymphoproliferative disease/malignancy in the 'at risk for T1D' patient population and whether long-term surveillance is recommended*

Review:

- Patients who are immunocompromised are at increased risk for development of lymphoproliferative disorders (LPD) compared to the general 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.[5]

    - Time to onset of LPD is highly variable, but can be as short as months in, for example, the patients after hematopoietic stem cell transplantation. The risk appears to wane with time when immunosuppressive therapy is reduced or removed and T cell function recovers.[6]

    - In most cases, LPD follow reactivation of a latent EBV infection rather than new EBV infection. This circumstance may vary by age due to the cumulative risk of EBV infection with time.

- Nonclinical findings support a potential risk for LPD with PRV-031:
    - There was mortality in chimpanzees treated at 10 mg/kg due to non-neoplastic B-cell lymphoproliferative disease resulting from reoccurring infection with EBV-like virus and T-cell immunosuppression.

- In trials of otelixizumab, another anti-CD3 monoclonal antibody, for the treatment of patients with Type 1 diabetes, there were patients who developed transient symptomatic EBV infections, but there were no reports of LPD.[7]

In the BLA:

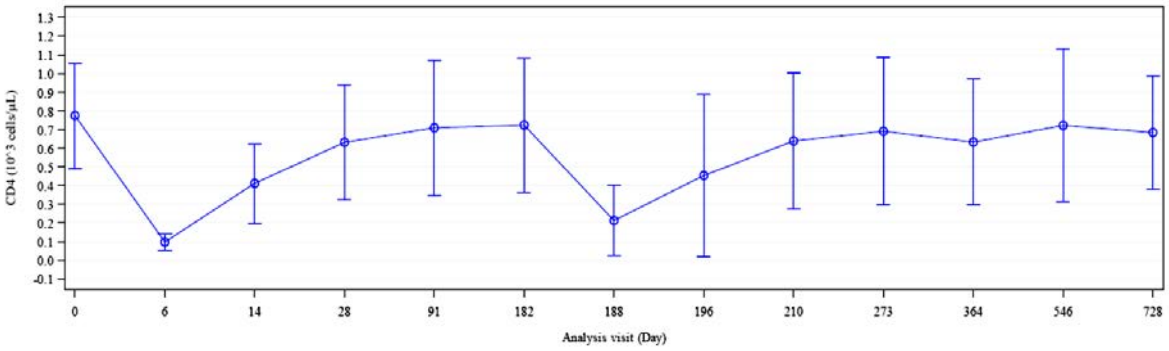
- T-cell immunosuppression occurred following treatment with PRV-031.

    - Circulating CD3 lymphocytes were reported to be 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 (Figure 1), but rare patients had CD4 counts less than 0.2 Gi/L as late as 3-6 months after treatment.

[5] 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.
[6] Styczynski J, et al. (2016) Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematol 101:803-811; Berti A, et al. (2018) EBV-induced lymphoproliferative disorders in rheumatic patients: A systematic review of the literature. Joint Bone Spine 85: 35-40; Lau E, et al. (2021) Analysis of Post-Transplant Lymphoproliferative Disorder (PTLD) Outcomes with Epstein–Barr Virus (EBV) Assessments—A Single Tertiary Referral Center Experience and Review of Literature. Cancers 13:899-915.
[7] Keymeulen B et al. (2005) Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes. NEJM 352:2598-2608.

Figure 1. Absolute CD4+ Lymphocytes over Time (Protege Segment 1)



Source: BLA 761183 ISI Figure 3.1.4

- Monitoring of EBV IgG and IgM titers and EBV viral DNA was conducted at day 20, week 6, and months 3, 12, 24, 36, and 48.
  - EBV reactivation by grouped term (Appendix C) in adae.xpt was reported in 42 (8%) patients out of 528 patients who were EBV IgG positive at baseline. All 42 patients had been treated with PRV-031. Median time to reactivation was 28 days (range: 14 – 722); time > 30 days after last dose for 12 patients
  - Increases in the lab tests in adlb.xpt for EBV DNA, EBV PCR, and EBV viral load over baseline were reported for 41 patients (all treated with PRV-031) who were EBV IgG positive at baseline. Median time to first increase was 28 days (range:19 – 722); time > 30 days after last dose for 9 patients

- There were no reports of lymphoproliferative disease in clinical trials (95% CI 0-0.4%).

- One patient who was EBV seropositive at baseline was treated on a single-patient IND and received a 12-day course of PRV-031 (increasing doses starting with 1 mg and increasing to a maximum of 4 mg for a total dose of 43 mg). One month later, the patient was reported to have developed EBV-associated nonmalignant LPD (severe pharyngitis) in the context of islet cell transplantation while on tacrolimus, sirolimus, and etanercept. Given the occurrence of LPD in the setting of immunosuppression and transplantation, association of this case with treatment with PRV-031 is unlikely.

DHM1 Response: The results of the analyses show that EBV reactivation is a clear risk of treatment with PRV-031. Most EBV reactivation events were reported early after treatment with PRV-031. A minority of cases occurred more than 30 days after the end of treatment. The only case of LPD was in a transplant patient receiving multiple immunosuppressive drugs.

Nonetheless, prolonged and profound depletion of CD4 cells was observed in rare cases. Thus, there is a potential for the occurrence of LPD in the postmarket period, but we would estimate that the risk is < 1%, so a registry study may not be practical. However, we do recommend enhanced pharmacovigilance for lymphoproliferative disease (LPD) in the postmarket setting. See Response to Question 6.

Additionally, due to the profound immunosuppression with this drug, a mitigation should be in place to prevent serious infections. See Response to Question 5.

5. Provide any recommendations for product labeling.

   DHM1 Response: See attached draft labeling with suggestions in tracked changes.

   We have recommended language regarding the Warning for cytokine release syndrome. We also recommend addition of a Warning caution against the use of PRV-031 in patients who received a live viral vaccine prior to planned use of PRV-031 and against administration of a live viral vaccine.

   In addition, because PRV-031 will be given in the outpatient setting, we recommend a Medication Guide to inform patients about the signs and symptoms of CRS for which they should contact their healthcare provider.

   Lastly, since the healthcare providers for the intended population are not likely to be experienced with diagnosis and management of CRS, we also recommend a communication REMS informing providers about the risk of CRS.

6. Provide any recommendations for PMRs or PMCs.

   DHM1 Response: Based on our review above, we do not recommend any PMRs or PMCs for CRS or LPD. However, we do recommend enhanced pharmacovigilance for CRS and LPD.

   Recommended text for the action letter:

   Submit for a period of 5 years from the U.S. approval date, all cases of severe, life-threatening or fatal cytokine release syndrome (CRS) and all cases of lympho-proliferative disorder (LPD) reported after treatment with TRADENAME as 15-day alert reports, and provide detailed analyses of CRS and LPD events reported from clinical study and postmarketing reports in your periodic safety reports (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 TRADENAME as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of CRS or LPD reported with TRADENAME should also be provided in the periodic safety report.

Appendix A. Grading Systems for CRS[8,9]

CTCAE v.3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.						

CTCAE v5

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome	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	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. **Navigational Note:** Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache					

ASTCT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[†]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With either:		
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

*Fever = temperature ≥ 38C not attributable to any other cause
CRS grade determined by more severe event: hypotension or hypoxia not attributable to any other cause

[8] Available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
[9] Adapted from Lee DW, et al. (2019) ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 25:625-638.

Appendix B. Potential Type III Reactions by ADA Status[10]

Table 25 Immune-related TEAEs by ADA Status: Protégé Segment 1

	COURSE 1 (number of events/total subjects (percent)				COURSE 2 (number of events/total subjects (percent)			
	ADA+	ADA-	Placebo ADA+*	Placebo ADA-*	ADA+	ADA-	Placebo ADA+*	Placebo ADA-*
Serum sickness	0/24	0/14			0/25	0/6		
Skin & Subcutaneous disorders	14/24 (58.3)	4/14 (28.6)			5/25 (20.0)	2/6 (33.3)		

Table 26 Immune-related TEAEs by ADA Status: Protégé Segment 2, Full 14 Day Regimen

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

Table 35 Immune Related TEAEs by ADA status: Encore Full 14-Day Regimen

	COURSE 1 (number of events/total subjects (percent				COURSE 2 (number of events/total subjects (percent)			
	ADA+	ADA-	Placebo ADA+	Placebo ADA-	ADA+	ADA-	Placebo ADA+	Placebo ADA-
Serum sickness	0/5	0/5	0/0	0/11	0/2	0/0	0/0	0/2
Skin & Subcutaneous disorders	4/5 (80.0)	4/5 (80.0)	2/11 (18.2)	0/11	0/2	0/0	0/0	0/2

Table 40 Immune-Related TEAEs by ADA status: TN-10 Study

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

[10] Adapted from BLA 761183 ISI Tables 25, 26, 35 and 40

Appendix C. EBV AEs Grouped Term

- Epstein-Barr viraemia
- Epstein-Barr virus antibody positive
- Epstein-Barr virus antigen positive
- Epstein-Barr virus infection
- Epstein-Barr virus infection reactivation
- Epstein-Barr virus test positive
- Infectious mononucleosis
- Mononucleosis syndrome

18 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

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Clinical Inspection Summary

Date	4/27/2021
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Lauren Wood Heickman, M.D., Clinical Reviewer Mitra Rauschecker, M.D., Clinical Team Leader Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Elisabeth Hanan, Senior Regulatory Project Manager Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
BLA	761183
Applicant	Provention Bio
Drug	Teplizumab (PRV-031)
NME	Yes
Therapeutic Classification	Humanized FcR non-binding anti-CD3 monoclonal antibody
Proposed Indication	Delay or prevention of clinical type 1 diabetes in at-risk individuals
Consultation Request Date	11/10/2020
Summary Goal Date	5/2/2021
Action Goal Date	7/2/2021
PDUFA Date	7/2/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this biologics license application (BLA) consisted of three domestic sites in addition to the contract research organization (CRO) and the sponsor.

One site (Dr. Gottlieb/Site 7) received a Form FDA 483 with no significant regulatory violations. In general, based on the inspections of the three clinical sites, the CRO and sponsor, the inspectional findings support validity of data as reported by the sponsor under this BLA.

II. BACKGROUND

Provention Bio submitted a new biologics license application (BLA) for teplizumab, an anti-CD3 humanized monoclonal antibody, for the delay or prevention of clinical type l diabetes in at-risk individuals. It has been designated a Breakthrough Therapy and granted rolling review.

Teplizumab is neither marketed, nor the subject of a marketing application, in any country.

Teplizumab was originally developed in the late 1980s, primarily as an investigational therapy for type 1 diabetes mellitus (T1D). Early Phase 2 trials conducted between 1999 and 2005 in newly diagnosed (Stage 3) T1D were conducted by academic investigators and academic consortia, including the Immune Tolerance Network and Type 1 Diabetes TrialNet.

In 2005, teplizumab was acquired by MacroGenics and in collaboration with Eli Lilly, continued the clinical development program. The development of teplizumab in T1D was transferred from MacroGenics to Provention Bio in May 2018. Provention Bio is a publicly traded company as of July 2018. They currently do not have any products in the market.

The results of the TN-10 (At Risk) study *The TrialNet Type 1 Diabetes Protocol TN-10: Anti-CD3 mAb (teplizumab) for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus (T1DM)* form the basis for this BLA.

TN-10
This was a multicenter, double-masked, randomized, placebo-controlled study to determine whether treatment of subjects at high risk for diabetes (in Stage 2) with teplizumab results in delaying or preventing the development of clinical T1D. The study population are individuals with Stage 2 T1D, characterized by the presence of two or more T1D-related autoantibodies on two occasions and dysglycemia. The subjects screened and enrolled in this study were relatives of patients with clinical T1D (Stage 3 disease), had an abnormal 2-hour oral glucose tolerance test (OGTT) at baseline, had to be a participant in the TrialNet Natural History Study (TN-01), and age ≥ 8 years at time of randomization.

Subjects were randomly assigned in a 1:1 ratio (within the two strata defined by age at enrollment: <18 and ≥18 years) to the following two treatment groups:

- Teplizumab (14-day intravenous [IV] infusion) followed by close monitoring for T1D development
- Placebo (14-day IV infusion) followed by close monitoring for T1D development

The primary outcome is the elapsed time from random treatment assignment to the development of diabetes or time of last contact among those randomized.

A total of 30 sites participated in the study. There were 146 subjects screened, 76 subjects enrolled, and 73 subjects who completed the trial. Six subjects were reported to have discontinued study participation prematurely. However, 3 subjects (b) (6) were diagnosed with T1D (i.e., met the primary endpoint) and, therefore, completed the study. Of the other 3 subjects (b) (6) one was lost to follow-up and 2 withdrew consent. The first patient enrolled (b) (6) Data cutoff is November 30, 2018.

The study was conducted by Type 1 Diabetes TrialNet, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). Provention Bio, the current sponsor of the teplizumab development program, conducted full analyses of the data obtained in the study for regulatory submission purposes.

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. **Peter A. Gottlieb, M.D.**
   Barbara Davis Center for Childhood Diabetes
   1775 Aurora Court, Mail Stop A140
   Aurora, CO 80045-2536

   Site: 7

Dates of inspection: January 4 – 11, 2021

There were 18 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. There were 18 subject records reviewed. There was one subject record (b) (6) that was not available on site; it was a screen fail at an affiliate site.

The institutional review board of record was (b) (4)

Dr. Gottlieb is a board-certified endocrinologist who has been conducting research as a principal investigator for approximately 21 years at the Barbara Davis Center for Childhood Diabetes (BDC) and has been with the research department for approximately 26 years. Dr. Gottlieb was contacted by TrialNet to conduct the study. Participants were recruited from the Pathway to Prevention study (TN-01). All study subjects were seen for their study visits onsite. Infusions for pediatric subjects were done at Children's Hospital in Aurora.

Source records were organized, legible, and available. Information was transferred from the paper source records to the electronic case report forms. Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan.
   a. Dr. Gottlieb failed to obtain proper authorization from the medical monitor and

the IRB to administer a peripherally inserted central catheter (PICC) line in Subject (b) (6) This procedure also had to be performed for this subject under general anesthesia. As per protocol Section 4.5.1, Drug Administration, a peripheral intravenous line was to be used.
OSI Reviewer comment: Several communications at the site were reviewed by the FDA inspector, including discussions regarding added risks that a PICC line has in placebo patients. A PICC line had been used in a different subject (b) (6) *and the site received proper approval before the procedure. When the PICC line was placed in that subject, the IRB stated that if any other PICC lines were to be used in the future, a protocol amendment would be required because it changed the risk category of the control arm. Dr. Gottlieb initiated the proper approval process of reaching out to the medical monitor, IRB, and sponsor; however, he moved forward with the procedure before any approval occurred. Dr. Gottlieb acknowledged that the proper approval was not gained prior to the placement of the PICC line in Subject* (b) (6)*. He developed a corrective and preventive action (CAPA) plan to ensure that this mistake would not be repeated in the future. The IRB was also notified and approved the CAPA. There were no complications from the PICC line in Subject* (b) (6)*.*

b. Dr. Gottlieb failed to provide proper oversight to his staff. He had the clinical research coordinator (CRC) and research manager grading adverse events. Per protocol Section 6.1.1, Adverse Events, the investigator must record all adverse events on source documents.
OSI Reviewer comment: Review of the audit trail found that there were seven subjects with 28 adverse events that had the grading changed by the research staff. Dr. Gottlieb stated that he had been aware and agreed with all the changes that the CRC and research manager made; however, he failed to initial next to the changes being made on the source documents. These deviations had occurred years previously (none since 2017) and had been previously identified during non-FDA audits. CAPAs were implemented in collaboration with the TrialNet Coordinating Center and the IRB. The site has new procedures in place to ensure that Dr. Gottlieb is signing off on changes to the source documents, as needed.

2. Failure to maintain proper case histories with respect to observations and data pertinent to the investigation:
   a. Dr. Gottlieb had four subjects missing LDH and direct bilirubin laboratory tests: Subjects (b) (6) for Days 1, 2, 3, 4, 5, 6, 11 and 13.
   OSI Reviewer comment: The initial version of the protocol, which was used to develop the laboratory requisition form at the site, did not include liver function tests (LFTs) in the Schedule of Assessments. This was revised in the protocol September 17, 2012. The research team failed to identify the need to update the laboratory requisition form. This oversight was identified in December 2012. Upon identification of the oversight, the laboratory requisition form was updated and protocol deviations for missed assessments were reported to the TrialNet Coordinating Center and later to the IRB. A CAPA now includes a two-step review for building and amending laboratory requisition forms.

b. Dr. Gottlieb signed off that he had reviewed a laboratory test five days before it occurred. The labs were drawn on 10/25/2012 and he signed off that he reviewed them five days prior on 10/20/2012.
OSI Reviewer comment: The results were faxed to the site on October 25, 2012 and immediately reviewed. Dr. Gottlieb explained that his "5" looked like "0". This was an isolated handwriting legibility issue.

Dr. Gottlieb responded to the Form FDA 483 observations on January 12, 2021; his response was deemed acceptable.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses.

2. Kevan C. Herold, M.D.
YCCI Hospital Research Unit
Yale New Haven Hospital
20 York Street
New Haven, CT 06510-3220*

**Subjects seen at:*
2 Church St. South. Suite 401
New Haven, CT 06519

Site: 2

Dates of inspection: November 30 – December 04, 2020

There were 26 subjects screened (including 4 subjects screened at a different site but were consented at Site 2 for the Intervention/Infusion) and 13 subjects enrolled by the site into the study (plus two transfers from different sites); 15 subjects completed the study. There were 22 subject records reviewed.

The institutional review board of record was Human Investigation Committee, Yale University School of Medicine.

Dr. Herold was a site investigator and the Principal Investigator for the study. He is also the head of the protocol development committee, main author of the protocol, and provided training for the other investigators in the study.

Participants were recruited from the Pathway to Prevention Study (TN-01). Since the subjects for the study can only participate if they were from the TN-01 study, most subjects were consented multiple times at different locations to accommodate the closest location for screening, infusion, and follow-up for the subject.

Subjects were initially screened and infused at Yale Center for Clinical Investigation

(YCCI) Hospital Research Unit. Follow-up visits were conducted at the YCCI Hospital Research Unit and YCCI 2 Church Street South.

The site uses a six-digit subject identification (ID) and subject initials. A Masked ID was used by the sponsor for the statistical analysis activity of the study and included in the data line listings. As this was the first site inspected, it was found that the Subject ID numbers in the clinical study report (CSR) do not match the Subject ID numbers at the sites. A list of all linked numbers was subsequently sent to assist with this site inspection and all other site inspections.

A listing of all transfers during the study was reviewed. Most of the transfers were data transfers (chart electronically transferred) and not necessarily physical transfers of subjects. All subjects and their records were accounted for.

The source records included original paper and printed electronic lab records. Paper records were attributable, legible, contemporaneous, original, accurate, and complete. Source records were compared to the sponsor data line listings. There were no discrepancies. It was noted that six subjects did not have their albumin levels recorded in the CRF nor in the data line listings. It was discovered that the albumin data entry field in the CRF only became available in September 2015.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable for the subject records that were available. The FDA inspector could not verify the primary efficacy of some enrolled subjects because their full source documents are at the site where they were transferred to after their infusion.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. William E. Russell, M.D.
Vanderbilt Eskind Diabetes Clinic
1500 21st Avenue South, Suite 1514
Nashville, TN 37212-3157

Site: 3126

Dates of inspection: December 7 – 14, 2020

There were 21 subjects screened (plus 4 subjects screened at another site) and 16 subjects enrolled into the study; 9 subjects completed the study (3 subjects at the site and 7 subjects at transferred sites). There were 25 subject records reviewed.

The institutional review board of record was Vanderbilt Human Research Protection Program.

Dr. Russell is a member of the Vanderbilt University Medical Center (VUMC) Department of Pediatrics, Director, Division of Endocrinology and Diabetes. He has been with VUMC for approximately 30 years. He is also a member of the TrialNet Clinical Organization at VUMC. All subjects were recruited from the TrialNet TN-01 study.

Source documents were paper records, with limited electronic records that were recorded in the electronic medical record (EMR). The EMR records were printed and placed in the individual subject binders. The electronic records were limited to local laboratory results and the occasional physical exam and nursing notes from infusion days.

The transfer of subjects between sites was evaluated. Some sites were approved by TrialNet to conduct all phases of the inspection (screening, infusion, post-infusion follow-up) and some sites could only perform two aspects (screening and post-infusion follow-up). Once a subject had transferred, the site could no longer update the electronic data capture (EDC) system; therefore, that subject would need to be "transferred" in the system so staff could update the EDC with information. Once completed, the subject would be "transferred" back to the site who had responsibility for the subject. A listing of all transfers during the study was reviewed. All subjects and their records were accounted for.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. **Contract Research Organization:**
   TrialNet Coordinating Center
   Health Informatics Institute at USF
   3650 Spectrum Blvd.
   University of South Florida
   Tampa, FL 33612

Dates of inspection: April 19 – 26, 2021

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, transfer of subjects from one site to another, the evaluation of the adequacy of monitoring and corrective actions taken by the CRO, deviations related to key safety and efficacy endpoints, randomization, quality assurance and audits, standard operating procedures (SOPs), record retention, data management, escalation of issues, and clinical trial oversight.

Type 1 Diabetes TrialNet is an international consortium that the sponsor, Provention Bio,

utilizes to run clinical trials, including study TN-10. The TrialNet study group currently consists of the TrialNet Coordination Center (TNCC), the TrialNet Clinical Network Hub (CNH), the Collaborative Mechanistic Studies Panel, a Chairman's Office, six (6) core clinical laboratories, two (2) Mechanistic core laboratories, a central pharmacy, 19 North American clinical centers, 220 North American affiliate centers, six (6) international clinical centers, and 19 international affiliate centers.

The Health Informatics Institute (HII), established in 2004 as the Pediatric Epidemiology Center, is housed at the University of South Florida (USF) and is comprised of approximately 150 staff members. The TrialNet Coordinating Center (TNCC) is based in the HII. The HII acts in a data and/or clinical coordinating capacity for several large, longitudinal, international studies. The University of South Florida has served as the Coordinating Center for the TrialNet study group since October 2008.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), as co-sponsor, contracted TrialNet and TNCC for the study. NIDDK's clinical trial agreement (CTA) with TrialNet documented each of the firm's responsibilities for the study.

A Participant Identification number (PID) was assigned to each subject as part of their participation in the TN-01 screening trial. PIDs in TrialNet are not specific to one study; therefore, the same person will have the same PID for all the TrialNet studies. In the BLA, Masked ID numbers were provided by NIDDK-TrialNet in lieu of the Subject ID numbers. The datasets supplied to Provention Bio by TrialNet were coded to include the Masked ID only. The use of Subject IDs or Masked IDs was governed in accordance with the NIDDK Data Sharing Policy and the NIDDK-Provention Bio CTA.

Data management was reviewed and there were no issues noted. The USF HII Clinical Trial Management System was used for study TN-10 data capture. The Adverse Events Data Management System (AEDAMS) was used for submitting and reviewing adverse events in real time. The results of tests performed by each central laboratory were transmitted to the TNCC in .csv files. All data was transferred securely.

The randomization and blinding processes were reviewed, and no issues were noted. There were no requests for emergent unblinding for the TN-10 study.

Monitoring of study TN-10 was adequate and acceptable. Source documents were compared to the data in the USF HII Clinical Trial Management System electronic case report forms (CRFs). Data correction were verified at a subsequent monitoring or audit visit. Data inconsistencies were also identified via the Error Reporting and Verification System (ERVS). Query reports were sent to sites on a monthly basis to correct or verify the data entered. Quality assurance (QA) and compliance reports were reviewed by the Project Manager on an ongoing basis and reviewed by the Data and Safety Monitoring Board (DSMB) biannually. Once all participant study visits ended and site and error reconciliation efforts concluded, the database was eligible for locking. The TNCC Executive Director approved the database lock date in writing via a signed database lock approval form.

Transfer of subjects was reviewed. There were 172 subject transfers in the study. While some clinical sites were able to accommodate the lengthy infusion time needed, not every site had the ability and facilities available to infuse study participants. Two separate categories of sites were implemented for the TN-10 study: "recruitment/follow-up sites" and "infusion centers". While most TN-10 transfers occurred between a recruitment/ follow-up site and an infusion center, some were transfers to other sites when subjects moved (such as to another state). If a participant needed to transfer to a different site, the originating site would complete a "Participant Transfer" eCRF to note which site the subject was transferring to and the date of the transfer. The source documents remained at the site where data collection occurred.

For those participants that remained close to the infusion center where they enrolled throughout their study duration, no site transfer was needed, and all study visits were completed at the infusion center. There were 44 subjects that had no transfer.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

5. **Sponsor:**
   Provention Bio
   55 Broad Street, 2nd Floor
   Red Bank, NJ 07701

Dates of inspection: February 3 – 4, 2021

Current inspectional coverage was limited to reviewing Provention Bio's sponsor responsibilities listed in the transfer of responsibilities (TORO) shared with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). A review of how Provention Bio informed investigators of safety reports, monitoring of investigations, investigational product records, and transfer of electronic records from MacroGenics and TrialNet and their correspondences was conducted.

Provention Bio is primarily a virtual company with most of the 57 full-time employees working all over the US. Provention Bio acquired teplizumab from MacroGenics in May 2018. When Provention Bio acquired teplizumab, they also acquired all MacroGenics' responsibilities listed in the TORO. After the publication of the data in June 2019, Provention Bio received the dataset from NIDDK. NIDDK was responsible for registering the study in ClinicalTrials.gov; registration responsibilities were not transferred to Provention Bio.

Once Provention Bio received the dataset, they reviewed the data and compared the results with the initial CSR written by TrialNet in 2019. Provention Bio contracted Statfinn, an IQVIA company, to generate the data analysis for regulatory submission purposes. These

results were the basis of the current TN-10 CSR Addendum. Provention Bio applied for the BLA in accordance to their CTA.

The Global Safety Database was transferred from TNCC to Provention Bio in 2019. Provention Bio contracted [redacted] (b) (4) to host the database. The Master Agreement and Work Orders were reviewed, and no deficiencies were noted.

The safety database includes data from legacy teplizumab studies, and the current clinical Phase 3 PROTECT study (PROvention TlD trial Evaluating C-peptide with Teplizumab) [redacted] (b) (4). Provention Bio is now responsible for updating the investigator's brochure (IB); they have updated the IB since the completion of the TN-10 study due to the ongoing Phase 3 study.

Provention Bio's database is housed in Microsoft Office 365 and managed by the contractor [redacted] (b) (4) The read and write privilege for all Provention Bio employees and contractors were reviewed. No deficiencies were found.

After the study was completed and MacroGenics sold teplizumab to Provention Bio, all drug accountability records were transferred to Provention Bio. The drug accountability records were reviewed, and no deficiencies were noted.

All Provention Bio documents are accessed, reviewed, and stored electronically. The company did not have any type of training for handling electronic records but was developing a training matrix and in the validation stages of a Learning Management System with their training program to begin March 2021. Protocol training of study personnel and monitors was conducted by TrialNet.

The information regarding subject transfers between clinical sites was not available but reported to still be held at TNCC and TrialNet. Therefore, this could not be assessed during the sponsor inspection.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Data from this sponsor appears acceptable.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

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DDLO/Division Director/ Lisa Yanoff
DDLO /Associate Director for Therapeutics/ Patrick Archdeacon
DDLO /Team Lead/Mitra Rauschecker
DDLO /Clinical Reviewer/ Lauren Wood Heickman
DRO /Regulatory Project Manager/ Elisabeth Hanan
OSI/DCCE/Acting Division Director/Kassa Ayalew
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OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 3/29/2021 **Date consulted:** 12/21/2020

From: Catherine Roca MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Diabetes, Lipid Disorders and Obesity (DDLO)

Drug: PRV-031 (teplizumab)

BLA: 761183

Applicant: Provention Dio, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: For the delay and prevention of clinical type I diabetes in at-risk individuals

Materials Reviewed:

- Applicant's submitted background package for BLA 761183
- DPMH Consult request dated December 21, 2020
- DPMH PLLR Review of ILARIS (canakinumab) Kristie Baisden, DO, Medical Officer, June 5, 2020. DARRTS Reference ID 4620300.[1]

[1] The ILARIS review was part of the materials reviewed but was not a source relied upon for the labeling recommendation below.

Consult Question: "DDLO requests input from DPMH on the PLLR sections of the newly proposed labeling for this original 351(a) BLA application."

INTRODUCTION AND BACKGROUND

On November 2, 2020, Provention Bio, Inc. submitted an original BLA application, for PRV-031 (teplizumab) for the delay or prevention of clinical type I diabetes in at-risk individuals. DDLO consulted DPMH on December 21, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

PRV-031 (teplizumab) is a recombinant humanized anti-human CD3 monoclonal antibody that was granted breakthrough therapy designation on August 2, 2019. On November 2, 2020, DDLO received the final rolling submission to complete the BLA for filing.

Drug Characteristics for teplizumab[2]

Drug Class	Anti-CD3 humanized monoclonal antibody
Mechanism of action	Teplizumab prevents the decline in beta cell function. The mechanism of action is unknown, but is thought to involve binding to CD3, a cell surface antigen present on T lymphocytes.
Dosage	Administered by intravenous infusion in a 14 consecutive day course. Dose is calculated based on body surface area (BSA) with total cumulative does of 9 mg/mm^2 Teplizumab is administered according to the following regimen: • (b) (4) 1: 51 µg/m^2 • 2: 103 µg/m^2 • 3: 207 µg/m^2 • 4: 413 µg/m^2 • (b) (4) 5-14: 826 µg/m^2
Molecular weight	Approximately 150 kilodaltons
Protein binding	Not described
Half-life	Terminal half-life of (b) (4) days
Oral Bioavailability	Not described
Serious Adverse Reactions	• Cytokine Release Syndrome (b) (4)

[2] Proposed teplizumab labeling, information verified with Clinical Pharmacology and Pharmacotoxicology on 2/11/2021

REVIEW
PREGNANCY

Nonclinical Experience

In an embryo-fetal developmental toxicity study, pregnant mice were administered the surrogate mAb by subcutaneous injection at dose levels of 0, 0.03, 0.3, or 20 mg/kg on Gestation Days 6, 10, and 14. A treatment-related increase in post-implantation loss occurred in the 20 mg/kg group (7 times the cumulative clinical dose (9 mg/m^2) based on body surface area (BSA)) as indicated by complete resorption of all implantations in 6 out of 26 pregnant mice. In a subsequent pre- and postnatal toxicity study in which the surrogate 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 increased incidence of post-implantation loss was observed at the same high dose.

The reader is referred to the Nonclinical review by Daniel Minck, PhD, and Federica Basso, PhD.

Review of Pharmacovigilance Database

The applicant provided information on pregnancies that occurred during the clinical studies for teplizumab.

Seventeen pregnancies were described; 12 pregnancies in teplizumab subjects and 5 pregnancies in control subjects. (see Appendix A for details) For the teplizumab subjects there were:

- 8 normal neonates
- 2 elective abortions
- 1 spontaneous abortion
- 1 lost to follow-up

Reviewer Comment:
The case of spontaneous abortion was complicated by Grave's disease and Type 1 diabetes. None of the cases of abortion (elective or spontaneous) reported congenital malformations.

Review of Literature

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex[3] using the search terms, "teplizumab" and "pregnancy," "pregnancy outcomes," "congenital anomalies," "stillbirth," and "spontaneous abortion."

There are no data on teplizumab and pregnancy outcomes in the published literature.

Reviewer Comment:
The applicant did not provide a review of the literature, but this reviewer found no papers on teplizumab in any of the literature searches.

[3] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 1/15/2021

LACTATION

Nonclinical Experience

Studies of male and female mice pups on postnatal days 11-13 indicated exposure to teplizumab; however, since levels were not obtained at birth it is unknown if exposure was via the placenta or through milk.[4]

The reader is referred to the Nonclinical review by Daniel Minck, PhD, and Federica Basso, PhD.

Review of Pharmacovigilance Database

Data from the applicant's clinical studies did not reveal any cases related to lactation.

Review of Literature

DPMH conducted a search of *Medications in Mother's Milk,* the Drugs and Lactation Database (LactMed),[5] Micromedex,[6] and of the published literature in PubMed and Embase using the search terms "teplizumab" and "lactation" or "breastfeeding."

There are no data on teplizumab and lactation in the published literature.

Reviewer comment:
The applicant states in draft labeling that (b) (4)

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Fertility and reproductive performance were unaffected in female and male mice that received a murine analog of teplizumab administered by the subcutaneous route at doses up to 7 times the cumulative clinical dose based on body surface area. However, in offspring exposed to teplizumab in utero or via lactation in the pre- and postnatal toxicity study, a reduction in fertility was evident at 20 mg/kg (7 times the cumulative clinical dose based on BSA).

The reader is referred to the Nonclinical review by Daniel Minck, PhD, and Federica Basso, PhD.

Review of Pharmacovigilance Database

No reports of adverse effects related to fertility are reported from the clinical trials.

Review of Literature

[4] Applicant's submitted Preclinical Study report WIL-353232

[5] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[6] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 1/15/2021

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "teplizumab" and "fertility," "contraception," "oral contraceptives," and "infertility."

No reports related to fertility or the effects of teplizumab on hormonal contraception were found in the search.

Reviewer comment:
The applicant did not perform a search of the published literature. This is a new product and there are no published reports related to fertility.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no published data on the effects of teplizumab on pregnancy or neonatal outcomes. Data from the clinical trials did not report malformations or high rates of spontaneous abortion but are too limited to make any conclusions regarding reproductive safety. Nonclinical data during pregnancy report increased resorptions of fetuses in mice exposed to the murine analog to teplizumab at the highest dose administered. A second comparable experiment did not show increased fetal loss. A pre-and postnatal study demonstrated reduction in T cell populations and increases in B cells in the offspring on postnatal days 10 and 84. There was also a reduction of the primary IgM/IgG and secondary IgG response in an assessment of immune system function when evaluated on postnatal days 35 and 84.

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester[7] and may interfere with immune response to infections and live vaccines, such as the rotavirus vaccine. Teplizumab is administered over a single 14-day period; therefore, it could be scheduled to be administered to avoid use during pregnancy. DPMH recommends that to minimize exposure to a fetus, teplizumab use be avoided during pregnancy and at least 30 days (6 half-lives) prior to a planned pregnancy.

Teplizumab is being proposed for a relatively narrow indication, "for the delay and prevention of clinical type I diabetes in at-risk individuals." In discussions with the review division, this is not expected to be a large population, but would include females of reproductive potential. DPMH recommends a postmarketing Single-arm Pregnancy Safety Study (SPSS) to assess major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age infants, and pregnancy complications such as preeclampsia and gestational diabetes in women exposed to teplizumab during pregnancy. This could be done as a stand-alone postmarketing requirement (PMR) or as part of a larger safety registry PMR.

Lactation

In a pre-and postnatal toxicity study, teplizumab was detected in the serum of the offspring. It is not known if the serum level in offspring reflect in utero and/or lactational exposure. There are no data on the presence of teplizumab in human or animal milk, and the effects of teplizumab on the breastfed infant and on milk production are unknown. Teplizumab is a

[7] Saji F, et al. Dynamics of immunoglobulins at the feto-maternal interface. Rev Reprod 1999; 4:81-89.

monoclonal antibody and human IgG is known to be present in human milk. The effects of exposure of teplizumab to the infant's gastrointestinal tract and potential exposure to the infant are unknown. If teplizumab is present in human milk, it is likely that it will only be present in small amounts given the large molecular weight of the product and will likely to be destroyed in the infant's gastrointestinal tract.

Females and Males of Reproductive Potential

Nonclinical data do not indicate an adverse effect on fertility in male or female animals administered teplizumab, although there was diminished fertility in the offspring at 20 mg/kg (7 times the cumulative clinical dose based on BSA).There are no data on effects of fertility in humans. Nonclinical data during pregnancy, however, report increased resorptions of fetuses in mice exposed to the murine analog to teplizumab. While there were no major congenital malformations (MCMs) or high rates of spontaneous abortion in pregnancies during the clinical trials, data are too limited to make any conclusions about reproductive safety.

POSTMARKETING REQUIREMENT (PMR) RECOMMENDATIONS

- Conduct a descriptive study that collects data in women exposed to teplizumab during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life, including growth and development. Maternal deaths through the first year postpartum will be reported. Results will be analyzed and reported descriptively with interim and final study reports.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

[redacted]

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A

Table 30 Pregnancies: List of Cases in the Teplizumab Clinical Program

Study	Subject ID	Teplizumab vs. control or placebo	Outcome	Last Dosing to conception (approximate)
Protégé	(b) (6)	Control	Pregnancy medically terminated (voluntary)	NA
		Control	No complications	2 months
		Full 14-day	No complications	9 months
		Full 14-day	No complications	9 months
		Full 14-day	No complications	5 months
		Full 14-day	Pregnancy medically terminated on (b) (6)	Before treatment end
		Full 14-day	No complications	>11 months
		Full 14- day	Pregnancy medically terminated	>11 months
		1/3 14 -day	No complications	<1 month
		Full 6-day	No complications	12 months

Study	Subject ID	Teplizumab vs. control or placebo	Outcome	Last Dosing to conception (approximate)
Encore	(b) (6)	Control	No complications; 35 weeks female infant normal	<1 month
		Control	No complications	3 months
		Full 14-day	No complications; 34 weeks healthy male infants	2 months
		Full 6-day	No complications	2 months
		Full 14-day	Lost to follow up	4 months Last dos (b) (6) positive pregnancy test on (b) (6)
Study 1[1]	NA	Control	No complication	17 months
Protégé Extension[1]	(b) (6)	Full 14-day	Abortion spontaneous	20 months

[1] Studies not included in pooled analysis.
[2] Female partners of male subjects.
Abbreviation: NA=not applicable.
Source: Protégé CSR; Encore CSR; Study 1 publications (Herold 2002; Herold 2005).

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 24, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761183
Product Name and Strength:	Tzield (teplizumab-mzwv) injection, 1 mg/mL
Applicant/Sponsor Name:	Provention Bio, Inc. (Provention)
OSE RCM #:	2020-2286-1
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Provention submitted revised container label and carton labeling for Tzield, received on March 22, 2021. Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container label and carton labeling for Tzield (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note that the sponsor responded to each our labeling recommendations for the container label and carton labeling.[b]

2 CONCLUSION

We reviewed the resubmitted labels for Tzield to determine if they are acceptable from a medication error perspective. We confirmed that Provention addressed our prior labeling recommendations and we have no additional recommendations at this time.

[a] Conrad, A. Label and Labeling Review for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Feb 26. RCM No.: 2020-2286.
[b] Provention Bio, Inc. Response to 04 March 2021 Comments on Container and Carton Labeling for teplizumab injection (BLA 761183). Submitted to FDA March 12, 2021. Available via: \\CDSESUB1\evsprod\bla761183\0032\m1\us\response-document.pdf

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	February 26, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761183
Product Name, Dosage Form, and Strength:	Tzield[a] (teplizumab-xxxx)[b] injection, 1 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Provention Bio, Inc. (Provention)
FDA Received Date:	November 2, 2020
OSE RCM #:	2020-2286
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

[a] Conrad A. Proprietary Name Memorandum for Tzield (BLA 761183). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 11. Panorama #: 2020-43721201.

[b] Since the proper name for Tzield has not been determined yet, teplizumab-xxxx is used as the nonproprietary name for this product throughout this review.

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Tzield (teplizumab-xxxx), submitted under BLA 761183 on November 2, 2020, to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), container labels, and carton labeling for Tzield to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI and the proposed carton and container labels. We provide our recommendations below in Section 4.1 for the Division and Section 4.2 for Provention.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Tzield are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

A. Prescribing Information

1. General Comments for the Highlights of Prescribing Information and Full Prescribing Information

   a. We note the use of the error-prone abbreviation (b) (4) to represent micrograms throughout the labeling. We recommend replacing (b) (4) with "mcg" wherever it appears to prevent confusion or misinterpretation.

2. Full Prescribing Information: Dosage and Administration Section 2

   a. Recommendations for Section 2 are noted in track changes below:

2 DOSAGE AND ADMINISTRATION

(b) (4)

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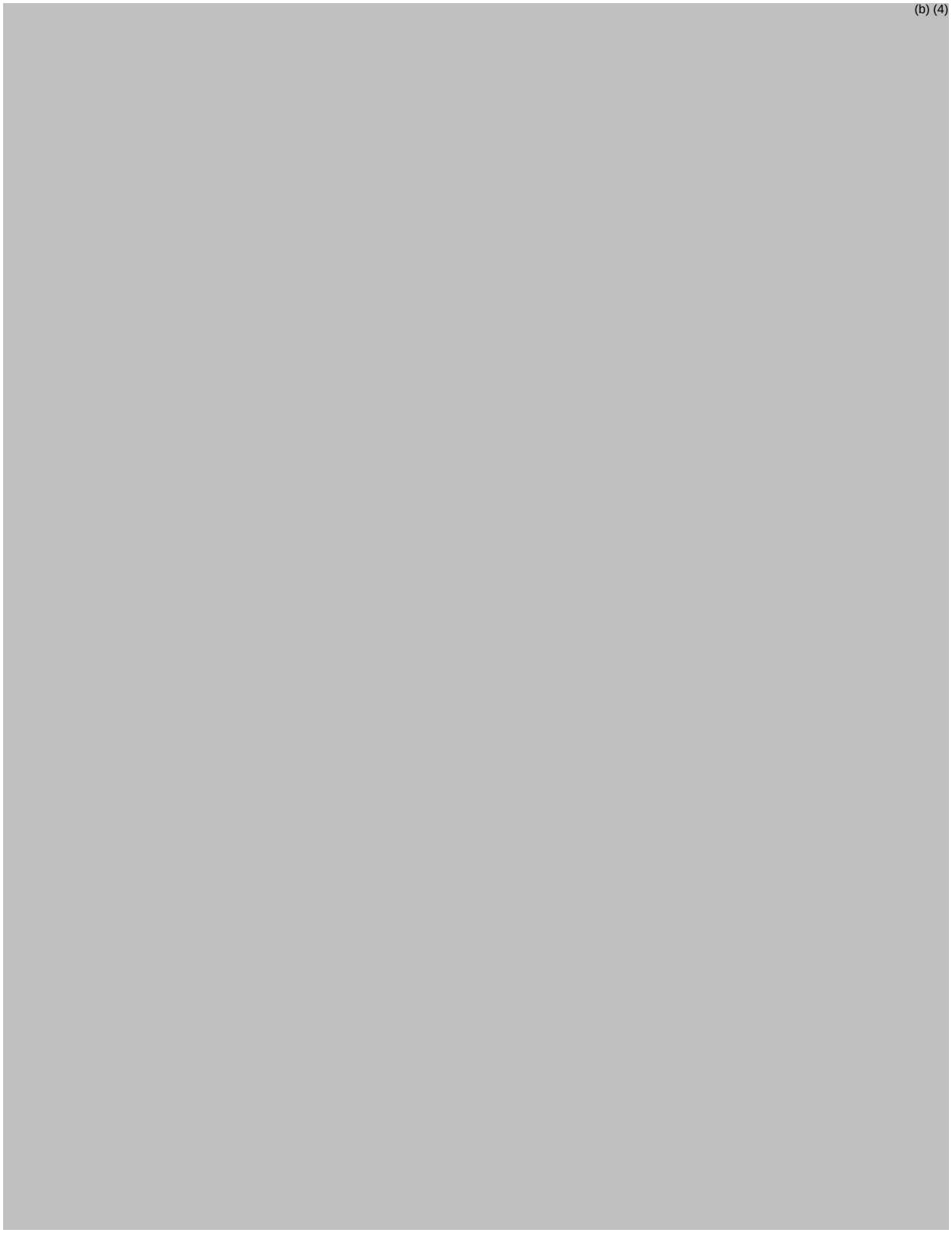

4.2 RECOMMENDATIONS FOR PROVENTION BIO, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We note that the first letter of the proprietary name, Tzield, is not capitalized which may lead to misinterpretation of the proprietary name. Please revise.
2. We note that the nonproprietary name will require a four-letter suffix; however, your proposed labels and labeling lack a placeholder (i.e., teplizumab-xxxx). We request that you add a nonproprietary name placeholder to the proposed labels and labeling for now, which must be replaced with a conditionally approved suffix once determined.
3. The "Rx only" statement appears more prominent than the established name and dosage form on the principal display panel (PDP). Consider removing the bold font from the statement.
4. We note that you intend to use the "MMMDDYYYY" format for this product's expiration date. FDA recommends that the human-readable expiration date on the drug package label appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. In addition, FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date. Please identify the format that you intend to use.

B. Container Labels

1. Considering the curvature of a vial and the size of the proposed label, we note that information that should be stated on the PDP would appear on the side panel of the vial to readers. Therefore, we recommend the following changes to the PDP of your label:
   a. Revise the statements [redacted] (b) (4) to read "For Intravenous Infusion after Dilution" for improved readability and spacing and move this statement to the PDP.
   b. Revise the statement [redacted] (b) (4) to read "2 mL single dose vial—discard unused portion" to minimize the [redacted] (b) (4) and move this statement to the PDP.
   c. We recommend removing or relocating U.S. License information as this information is not required on the PDP.
   d. Consider moving the NDC and "Rx only" to the side panel in order to make room for information that is required to appear on the PDP. For example, you can place the NDC in the space that currently contains the [redacted] (b) (4) statement. Additionally, decrease the prominence of the "Rx Only" statement by removing its bolded font.

2. Revise the [redacted] (b) (4) concentration statement to "1 mg/mL" in accordance with USP General Chapter <7>.

3. Revise the statement [redacted] (b) (4) To read "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F)". We recommend this to increase the readability of this important information on this small label.

C. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a human-readable and machine-readable (2D data matrix barcode) product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We note the human-readable product identifier is available, but it is unclear if the machine-readable product identifier will be included on your product's labeling.
   The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

2. We recommend adding the following statement to the PDP "Store in the original carton to protect from light."

3. Revise the statement [redacted] (b) (4) to read "contains 14 single dose vials—discard unused portion" to minimize the risk of the entire contents of the vial being given as a single dose. In addition, we recommend that you remove [redacted] (b) (4) as we note that these statements appear more prominent than the product strength information on the PDP.

4. We recommend revising [redacted] (b) (4) to read "For intravenous infusion after dilution."

5. We recommend revising the statement [redacted] (b) (4) to read as follows "Dosage: See prescribing information." per 21 CFR 201.55.

6. Add the statement "Dispense in original container to protect from light." to the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tzield received on November 2, 2020 from Provention Bio, Inc.

Table 2. Relevant Product Information for Tzield	
Initial Approval Date	N/A
Nonproprietary Name	teplizumab-xxxx
Indication	the delay or prevention of clinical type 1 diabetes in at-risk individuals
Route of Administration	intravenous (IV) infusion
Dosage Form	injection
Strength	1 mg/mL
Dose and Frequency	[TRADENAME] is administered by intravenous infusion in a 14 consecutive day course. The dose is calculated based on body surface area (BSA), with a total cumulative dose of 9 mg/m^2 administered over 14 consecutive days *[see Clinical Pharmacology (12.3)]* TRADENAME is administered according to the following regimen: • (b) (4) 1: 51 µg/m^2 • 2: 103 µg/m^2 • 3: 207 µg/m^2 • 4: 413 µg/m^2 • (b) (4) 5-14: 826 µg/m^2
How Supplied	2 mL single-dose vials dispensed in cartons containing 10 or 14 vials
Storage	refrigerate at 2°C-8°C (36°F-46°F) in the original carton to protect from light

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,[c] along with postmarket medication error data, we reviewed the following Tzield labels and labeling submitted by Provention Bio, Inc.

- Container label received on November 2, 2020
- Carton labeling received on November 2, 2020
- Prescribing Information and Medication Guide received on November 2, 2020, available from \\CDSESUB1\evsprod\bla761183\0005\m1\us\draft-label-text.docx

B.2 Label and Labeling Images

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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