# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761183Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Division of Risk Management (DRM)**
**Office of Medication Error Prevention and Risk Management (OMEPRM)**
**Office of Surveillance and Epidemiology (OSE)**
**Center for Drug Evaluation and Research (CDER)**

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| **Application Type** | BLA |
| **Application Number** | 761183 |
| **PDUFA Goal Date** | November 17, 2022 |
| **OSE RCM #** | 2022-1413 |
| **Reviewer Name(s)** | Till Olickal, Ph.D., Pharm.D. |
| **Team Leader** | Naomi Boston, Pharm.D. |
| **Associate Director for REMS Design and Evaluation** | Laura Zendel, Pharm.D., BCPS |
| **Review Completion Date** | October 20, 2022 |
| **Subject** | Addendum to DRISK Review to determine if a REMS is necessary, dated July 01, 2021. |
| **Established Name** | teplizumab-mzwv |
| **Trade Name** | Tzield |
| **Name of Applicant** | Provention Bio, Inc. |
| **Therapeutic Class** | CD3-directed monoclonal antibody |
| **Formulation(s)** | 2 mg/2 mL (1 mg/mL) injection in a 2mL single-dose vial |
| **Dosing Regimen** | Administer by intravenous infusion in a 14 consecutive day course.<br>The dose is calculated based on the patient's body surface area (BSA) and administer according to the following regimen: Dose 1: 65 mcg/$m^2$; Dose 2: 125 mcg/$m^2$; Dose 3: 250 mcg/$m^2$; Dose 4: 500 mcg/$m^2$ and Doses 5-14: (b) (4) mcg/$m^2$. |

# 1 Introduction

This review is an addendum to the Division of Risk Management's (DRM) deferral memo, dated June 4, 2021 and review dated July 01, 2021[1], to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) teplizumab-mzwv is necessary to ensure the benefits outweigh the risks of risk of cytokine release syndrome (CRS), serious infections, hypersensitivity reactions, lymphopenia, increase in liver enzymes and vaccinations. Provention Bio, Inc. resubmitted a Biologic Licensing Application (BLA) 761183 for teplizumab-mzwv with the proposed indication to delay the clinical type 1 diabetes in Stage 2 patients (at-risk individuals), after receiving a Complete Response (CR) letter on July 2, 2021, due to the Office of Clinical Pharmacology (OCP), Divisions of Cardiorenal and Endocrine Pharmacology and Pharmacometrics (DCEP) and the Office of Pharmaceutical Quality (OPQ) deficiencies.[2] DRM completed a review in the first cycle and concluded that based on the risk-benefit profile, a REMS was not needed.[1]During this review cycle, the clinical team noted that there are no changes to the safety profile of teplizumab based on the safety update data from the resubmission; therefore, the decision on the need for a REMS remains unchanged. Based on the data available, teplizumab-mzwv appeared efficacious in its primary outcomes. The clinical reviewer recommends approval of teplizumab-mzwv to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes.[3] Stage 2 type 1 diabetes was defined as having both of the following:[3]

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

This application is under review in the Division of Diabetes, Lipid Disorders, and Obesity (DDLO). The Applicant did not submit a proposed REMS or risk management plan with this application.

# 2 Background

## 2.1 PRODUCT INFORMATION

Teplizumab-mzwv is an NME BLA type 351(a) pathway application. It is an anti-CD3 humanized immunoglobulin G-1 (IgG1) monoclonal antibody. The mechanism by which teplizumab-mzwv prevents or delays clinical onset of Stage 3 T1D involves binding to CD3, a cell surface antigen present on T lymphocytes. The binding to CD3 leads to partial agonistic signaling and deactivation of auto-reactive T lymphocytes and leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood. Higher counts of exhausted CD8+ T cells have been shown to correlate with clinical response and have been linked to delayed progression to Stage 3 T1D in the natural course of the disease.[3] Teplizumab-mzwv will be supplied as 2 mg/2 mL (1 mg/mL) injection in a 2mL single-dose vial. The dose is calculated based on the patient's body surface area (BSA) and administer according to the following regimen: Dose 1: 65 mcg/$m^2$; Dose 2: 125 mcg/$m^2$; Dose 3: 250 mcg/$m^2$; Dose 4: 500 mcg/$m^2$ and Doses 5-14: (b) (4) mcg/$m^2$. The regimen is administered as a 30-minute intravenous infusion over 14

consecutive days. Teplizumab-mzwv was granted breakthrough therapy designation on August 02, 2019. Teplizumab-mzwv is not currently approved in any jurisdiction.

### 2.2 REGULATORY HISTORY

The Applicant was issued a Complete Response letter on July 2, 2021, for the OCP and the OPQ deficiencies. During the Type B meeting that was held for IND 100262 (at-risk population, the IND associated with pre-BLA 761183) on January 25, 2022. The purpose of this meeting was to discuss and obtain agreement on the Sponsor's proposed clinical pharmacology data package as well as the clinical contents for the BLA 761183 resubmission. Additionally, at this meeting the Agency recommended that the Sponsor propose an alternative full 14-day dosing regimen to match the $AUC_{inf}$ and/or $C_{trough}$ exposures between the Lilly and AGC products, using PK simulations from the PROTECT study and individual PK parameters of the Agency-recommended model in response to the CR.[6]

The new drug application for teplizumab-mzwv, BLA 761183, was submitted February 17, 2022, by Provention Bio, Inc. for a second review cycle, which included a 13-month safety update, a proposal for 4 alternative dosing regimens with safety justification for the proposed regimens as well as requested pharmacokinetic (PK) comparability data with requested analyses of concentration-CD3 occupancy analyses, anti-drug antibody (ADA) comparisons between clinical trial and manufactured products.[6]

## 3 Benefit and Risk Assessment

The benefit and risk assessment were contained in the July 2021 DRM review for this product.[1] Patients in the teplizumab-mzwv group received a total drug exposure equivalent to the Agency recommended total teplizumab-mzwv drug exposure.[3] The clinical reviewer stated that the benefit-risk integrated assessment is unchanged from the original conclusion contained in the clinical review[4], dated July 2 2021.[6]

DRM evaluated risks of CRS, infections, lymphopenia, increase in liver enzymes and immunizations in a review dated July 01, 2021, and determined that a REMS was not needed to ensure the benefits of teplizumab-mzwv outweigh the risks.[1]

At the time of this review, labeling negotiations were ongoing with the Applicant. If approved, labeling will also include the following risks in the Warnings and Precautions section along with the risks of cytokine release syndrome (CRS), lymphopenia and increase in liver enzymes, infections, and immunizations that are evaluated in a review dated July 01, 2021.[1,3]

*Serious Infections:*

In clinical trials, bacterial and viral infections have occurred in teplizumab-mzwv-treated patients. Teplizumab-mzwv-treated patients had a higher rate of serious infections (2.7%) than control-treated patients (0%) in clinical trials. Labeling instructs that patients be closely monitor for signs and symptoms of infection after administering teplizumab-mzwv. Labeling also instructs to treat appropriately, and discontinue teplizumab-mzwv, if serious infection develops.[3]

*Hypersensitivity Reactions:*

Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm have occurred in teplizumab-mzwv-treated patients in clinical trials. In the safety update, AEs with the PT of 'hypersensitivity' were reported in 1/327 (0.3%) of PROTECT subjects and no patients in the TN-10 Extension study. The sponsor performed an additional analysis at the request of the Agency (received 6/14/2022, SDN 63) which revealed 2/327 (0.6%) of PROTECT subjects reporting the PT of 'infusion related reaction.' These 3 AEs were mild to moderate in severity, considered by the investigators to be related to study drug and recovered despite continued treatment with study drug.[6] The clinical reviewer stated that there were no reported adverse events with the following PTs: 'anaphylaxis,' 'drug hypersensitivity,' 'immune reaction' or 'serum sickness' reported in either the PROTECT or TN-10 Extension studies. There were no SAEs of rash in the safety update. Rash was noted as one of the common AEs for the PROTECT study 81/327 (24.8%).[6] Labeling instructs to discontinue the use of teplizumab-mzwv and treat promptly, if severe hypersensitivity reactions occur.[3] The clinical reviewer stated that the safety update information does not change the original safety conclusions with respect to hypersensitivity/rash.[6]

# 4 Discussion of Need for a REMS

Teplizumab-mzwv is an anti-CD3 humanized IgG1 monoclonal antibody, with the proposed indication in the first cycle of review for the delay or prevention of clinical T1D in at-risk individuals. On February 17, 2022, the Applicant resubmitted the BLA 761183 for teplizumab-mzwv with the proposed indication to delay the clinical type 1 diabetes in Stage 2 patients (at-risk individuals). The clinical reviewer stated that TN-10, which was an adequate and well-controlled, randomized, placebo-controlled trial, successfully demonstrated the treatment effect of teplizumab-mzwv in delaying T1D diagnosis in at-risk patients.[4] At the time of this review, labeling negotiations were ongoing with the Applicant. Based on the efficacy and safety information currently available, if approved, the clinical reviewer recommends teplizumab-mzwv to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes.[1,3,4,5,6] Stage 2 type 1 diabetes was defined as having both of the following[3]:

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

2. Dysglycemia on oral glucose tolerance testing.

The risks associated with teplizumab-mzwv include CRS, serious infections, lymphopenia, hypersensitivity reactions, and vaccinations. DRM evaluated risks of CRS, infections, lymphopenia and increase in liver enzymes and immunizations in a review dated July 01, 2021, and determined that a REMS was not needed to ensure the benefits of teplizumab-mzwv outweigh the risks.[1] The Clinical Review of Class 2 Resubmission stated that the safety update information does not change the original safety conclusions with respect to CRS or the integrated assessment of safety in any meaningful way.[6] The Clinical Reviewer also commented that there are no changes to the safety profile of teplizumab based on the safety update data from the resubmission; there should not be any changes related to

safety from the resubmission on February 17, 2022, that would prompt a difference in the previous REMS decision.[a] At the time of this memorandum, the safety profile of teplizumab-mzwv has not changed.

# 5 Conclusion & Recommendations

Based on the analysis detailed in the REMS review dated July 1, 2021, and the absence of new safety data in the resubmissions following the Complete Response letters, DRM and DDLO maintain our determination that a REMS is not needed to ensure the benefits of teplizumab-mzwv outweigh its risks.

Should DDLO have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

# 6 References


[1] Olickal T. Division of Risk Management's (DRM) review to determine if a REMS is necessary for teplizumab-mzwv, BLA 761183, dated July 1, 2021. [Reference ID: 4820603]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 28, 2022.

[2] Division of Diabetes, Lipid Disorders, and Obesity (DDLO). Complete Response for teplizumab-mzwv, BLA 761183, dated July 02, 2021. [Reference ID: 4821208]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 28, 2022.

[3] Draft Prescribing Information for teplizumab-mzwv as currently edited by the FDA, last updated October 10, 2022.

[4] Wood Heickman LK. Division of Diabetes, Lipid Disorders, and Obesity (DDLO). Clinical Review for teplizumab-mzwv, BLA 761183, dated July 02, 2021. [Reference ID: 4821376]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 28, 2022.

[5] Wood Heickman LK. Safety Review Presentation. Mid-Cycle Meeting, dated May 20, 2022.

[6] Wood Heickman LK. Division of Diabetes, Lipid Disorders, and Obesity (DDLO). Clinical Review of Class 2 Resubmission for teplizumab-mzwv, BLA 761183, dated July 14, 2022. [Reference ID: 5013528]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed July 15, 2022.


[a] Wood Heickman LK to Olickal T. (E-mail communication from DDLO Clinical Reviewer to DRM RMA), dated June 23, 2022.

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**Division of Risk Management (DRM)**
**Office of Medication Error Prevention and Risk Management (OMEPRM)**
**Office of Surveillance and Epidemiology (OSE)**
**Center for Drug Evaluation and Research (CDER)**

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| **Application Type** | BLA |
| **Application Number** | 761183 |
| **PDUFA Goal Date** | July 02, 2021 |
| **OSE RCM #** | 2020-796 |
| **Reviewer Name(s)** | Till Olickal, Ph.D., Pharm.D. |
| **Team Leader** | Naomi Boston, Pharm.D. |
| **Division Director** | Cynthia LaCivita, Pharm.D. |
| **Review Completion Date** | July 1, 2021 |
| **Subject** | Review to determine if a REMS is necessary |
| **Established Name** | teplizumab-mzwv |
| **Trade Name** | Tzield |
| **Name of Applicant** | Provention Bio, Inc. |
| **Therapeutic Class** | CD3-directed monoclonal antibody |
| **Formulation(s)** | 2 mg/2 mL (1 mg/mL) injection in a 2mL single-dose vial |
| **Dosing Regimen** | Administer by intravenous infusion in a 14 consecutive day course.<br>The dose is calculated based on the patient's body surface area (BSA) and administer according to the following regimen: Dose 1: 51 mcg/$m^2$; Dose 2: 103 mcg/$m^2$; Dose 3: 207 mcg/$m^2$; Dose 4: 413 mcg/$m^2$ and Doses 5-14:826 mcg/$m^2$. |

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# EXECUTIVE SUMMARY

This review provides additional analysis beyond what was included in the Division of Risk Management's (DRM) deferral memo, dated June 4, 2021, to the address the Division of Hematology Malignancies 1 (DHM1) recommendation for a REMS for the risk of cytokine release syndrome (CRS) and to determine whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity teplizumab-mzwv (Tzield) is necessary to ensure the benefits outweigh its risks.

Provention Bio, Inc. submitted a Biologic Licensing Application (BLA) 761183 for teplizumab-mzwv with the proposed indication for the delay or prevention of clinical type 1 diabetes in at-risk individuals. Although the serious risks associated with the use of teplizumab-mzwv include transient lymphopenia and increase in liver enzymes, infection and immunizations, the risk of CRS is the focus of this review. The applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information as follows: Warnings and Precautions, a Medication Guide and Patient Counseling Information.

Type 1 diabetes (T1D) is the second most common chronic disease of childhood, although the disorder may develop throughout the life span. The life-expectancy of individuals with younger-onset disease is on average 16 years shorter than non-diabetic individuals. There are currently no treatments approved for Stage 2 (presymptomatic) T1D. Therefore, there is a clear need for therapeutic strategies with new alternative modalities. Based on the data available, teplizumab-mzwv appeared efficacious in its primary outcomes. The risks of transient lymphopenia and increase in liver enzymes, infection and immunizations will be communicated and managed through labeling.

The DRM and Division of Diabetes, Lipid Disorders, and Obesity (DDLO) discussed if a REMS was necessary to ensure the benefit of teplizumab-mzwv outweighed the risk of CRS. In the clinical trial, CRS occurred in less than 6% of patients treated with teplizumab-mzwv, with the majority, 80%, experiencing mild to moderate CRS (Grade 2 or lower). No patients required the use of intravenous fluid, pressors, supplemental oxygen. The risk of CRS should be able to be managed with premedications (nonsteroidal anti-inflammatory drug (NSAID), an antihistamine, and an anti-emetic) as described in the Dosage and Administration section of the draft label and if needed a temporary pause of dosing for 1-2 days. In addition, teplizumab-mzwv is administered by intravenous infusion as part of a 14-day regimen and it is expected that patients will receive treatment in inpatient or outpatient infusion settings under the care of a health care provider. For teplizumab, although CRS is included in the Warning and Precautions of the draft label, DDLO determined based on the available data that the risk of CRS did not rise to the level of a boxed warning.

At this time, based on the available safety data, DRM's recommendation is that a REMS is not necessary to ensure the benefits of teplizumab-mzwv outweigh the risks for CRS.

The recommended regulatory action at this time per the clinical review team is a complete response (CR). This recommendation is based on the lack of comparability between the clinical trial and to-be-marketed drug products and facility deficiencies. Please consult DRM if additional safety information becomes available when the Applicant addresses the deficiencies in the CR letter.

# 1 Introduction

This review provides additional analysis beyond what was included in the Division of Risk Management's (DRM) deferral memo, dated June 4, 2021[1], to address the Division of Hematology Malignancies 1 (DHM1) recommendation for a REMS to address the risk of cytokine release syndrome (CRS) and to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) teplizumab-mzwv is necessary to ensure the benefits outweigh the risks of risk of cytokine release syndrome (CRS). Provention Bio, Inc. submitted a Biologic Licensing Application (BLA) 761183 for teplizumab-mzwv with the proposed indication for the delay or prevention of clinical type 1 diabetes in at-risk individuals.[2] The Applicant did not submit a REMS with this application but proposed describing the risks in the Prescribing Information as follows: Warnings and Precautions, a Medication Guide, as well as in the Patient Counseling Information.

# 2 Background

## 2.1 PRODUCT INFORMATION

Teplizumab-mzwv is an NME BLA type 351(a) pathway application.[a] It is an anti-CD3 humanized immunoglobulin G-1 (IgG1) monoclonal antibody. The precise mechanism by which teplizumab-mzwv prevents or delays clinical onset of type 1 diabetes mellitus (T1D) is unknown, but is presumed to involve binding to CD3, a cell surface antigen present on T lymphocytes. Following cell surface binding to T lymphocytes, teplizumab-mzwv leads to an increase in the number of regulatory T cells and of exhausted CD8+ T cells in peripheral blood. Higher counts of exhausted CD8+ T cells have been shown to correlate with clinical response to and have been linked to delayed progression to clinical T1D in the natural course of the disease.[2] Teplizumab-mzwv will be supplied as 2 mg/2 mL (1 mg/mL) injection in a 2mL single-dose vial. The dose is calculated based on the patient's body surface area (BSA) and administer according to the following regimen: Dose 1: 51 mcg/$m^2$; Dose 2: 103 mcg/$m^2$; Dose 3: 207 mcg/$m^2$; Dose 4: 413 mcg/$m^2$ and Doses 5-14:826 mcg/$m^2$.[b] The regimen is administered as a 30 minute intravenous infusion over 14 consecutive days. Teplizumab-mzwv was granted breakthrough therapy designation on August 02, 2019. Teplizumab-mzwv is not currently approved in any jurisdiction.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for teplizumab-mzwv (BLA 761183) relevant to this review:

- 02/12/2010: Investigation New Drug IND 102629 submission for MGA031, PRV-031 received.
- 08/02/2019: Breakthrough Therapy designation granted.
- 11/02/2020: BLA 761183 submission for teplizumab-mzwv with the proposed indication for the delay or prevention of clinical type 1 diabetes in at-risk individuals, received.
- 02/12/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for teplizumab-mzwv.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 04/02/2021: The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) issued a" Deficiencies Preclude Discussion" letter stating that the Agency identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.[3]
- 04/30/2021: The Office of Clinical Pharmacology, Divisions of Cardiorenal and Endocrine Pharmacology and Pharmacometrics recommended a Complete Response action for the BLA 761183 until the sponsor can adequately address the issue related to lack of comparability between the clinical trial and to-be-marketed drug products. A pharmacokinetic (PK) bridging study in healthy volunteers was conducted to compare the to-be-marketed formulation with the clinical trial formulation. The results failed to show PK comparability between the two products as their total and partial exposures differed significantly, despite a comparable Cmax after the 30-minute intravenous infusion.[4]
- 05/24/2021: The Office of Pharmaceutical Quality (OPQ) recommended a Complete Response for regulatory action based on the submission[5] based on concerns with that the data provided are not sufficient to support a conclusion that the manufacture of Tzield is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. In addition, there were facility deficiencies that have not been resolved as of 5/14/2021.
- 05/27/2021: The Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC)[6] was convened to discuss the strength of the overall evidence to conclude effectiveness has been established, clinical meaningfulness of the observed median 2-year delay of onset of T1D, the safety issues identified in the clinical development program and whether the demonstrated benefit of teplizumab-mzwv outweigh the risks. The EMDAC vote was 10 "Yes" and 7 "No" as answers to the voting question, does the information provided in the background documents and presentations by the Applicant and FDA show that the benefits of teplizumab outweigh the risks in support of approval to delay clinical type 1 diabetes mellitus?
- 06/24/2021: Meeting between the DRM and OND clinical team to discuss the risk mitigation measures for teplizumab-mzwv.

# 3 Therapeutic Context and Treatment Options

## 3.1 Description of the Medical Condition

T1D is a serious medical condition caused by T-cell mediated autoimmune destruction of the pancreatic beta cells. The resulting loss of pancreatic beta cells leads to impaired insulin production and secretion, and impaired glucose metabolism.[6] The American Diabetes Association estimates that about 1.6 million Americans have type 1 diabetes, and about 64,000 patients, including both adults and children, are newly diagnosed with type 1 diabetes yearly.[7, c] Type 1 diabetes is the second most common chronic disease of childhood, although the disorder may develop throughout the life span. The life-expectancy of individuals with younger-onset disease is on average 16 years shorter than non-diabetic individuals. Mortality in type 1 diabetes is still increased two- to eightfold, which is reflected by a loss of life

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

expectancy at age 20 years of approximately 12 years. Cardiovascular disease is the main driver of morbidity and mortality in people with type 1 diabetes.[8, d]

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Insulin, discovered nearly a century ago, is still the mainstay of treatment for Stage 3 T1D.[9] Pramlintide[10], an amylin-mimetic, is approved for adjunctive therapy, in addition to insulin, to help improve glycemic control. Types of insulin include short-acting (regular) insulin, rapid-acting insulin, intermediate-acting (NPH) insulin, and long-acting insulin. Insulin can be administered by intermittent injection, or by a pump that can administer a continuous (basal) rate of rapid-acting insulin and bolus doses responding to carbohydrate intake and blood glucose measurements. An implanted pump, referred to as an artificial pancreas, was approved by the FDA in 2016.[11] The risk of developing symptomatic type 1 diabetes can be identified and quantified, the disease can be characterized into well-defined stages, and the rate of progression to symptomatic disease can be predicted with appreciable accuracy.[12,13,6] There are currently no treatments approved for Stage 2 T1D. The Applicant's development program is based on the disease model[12] that a therapy targeting Stage 2, which could inhibit the inflammation and destruction of beta cells before they are rendered unrecoverable would delay the onset of clinical disease.[6,13] Therefore, there is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for these patients.

## 4 Benefit Assessment

The efficacy of teplizumab-mzwv for the delay or prevention of clinical type 1 diabetes in at-risk individuals were evaluated in in a randomized, double-blind, placebo-controlled study (TN-10; NCT01030861) in 76 patients 8 to 49 years of age who were identified as at-risk for T1D (or at Stage 2 in T1D), defined as having two or more T1D-related autoantibodies (anti-GAD, micro insulin, anti-IA-2, islet cell antibody [ICA], anti-ZnT8) and abnormal glucose tolerance in a 2-hour oral glucose tolerance test (Fasting plasma glucose ≥110 mg/dL and <125 mg/dL, or 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or 30, 60, or 90-minute value on OGTT ≥200 mg/dL).[2,6] Please refer to Dr. Lauren Wood-Heickman's review for a detailed clinical review of efficacy.

The following section is a summary of relevant efficacy information to date for teplizumab-mzwv. The primary efficacy endpoint was the time from randomization to clinical T1D diagnosis. Criteria for T1D onset were based on glucose testing or the presence of unequivocal hyperglycemia with acute metabolic decompensation, such as DKA.[6] T1D was diagnosed in 20 (45%) of the patients who received teplizumab and in 23 (72%) of those who received placebo. The median time to clinical T1D diagnosis was 49.5 months in the teplizumab group and 24.9 months in the placebo group, for a difference of 24.6 months. The hazard ratio for the time to clinical T1D diagnosis was 0.41 (95% CI: 0.22 to 0.78), which was statistically significant as shown in Table 1.[14,6 e]

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

**Table 1: Primary Analysis Results for Time to T1D onset**[14,6,e]

| | Teplizumab | Placebo |
|---|---|---|
| | N=44 | N=32 |
| **Numberers and Rates of Events by End of Follow-up** | | |
| **Number of patients diagnosed with T1D** | 20 (45%) | 23 (72%) |
| **Number of censored patients** | 24 (55%) | 9 (28%) |
| **Censored for reaching trial end** | 22 (50%) | 8 (25%) |
| **Censored for discontinuation from study** | 2 (5%) | 1(3%) |
| **Time to Event Summary Statistics** | | |
| **Median time to T1D onset (months)** | 49.5 | 24.9 |
| **Primary Analysis** | | |
| **Hazard ratio (95% CI)** | 0.41 (0.22, 0.78) | |
| **P-value** | 0.0066 | |

The initial TN-10 study design included plans to assess treatment effect on secondary efficacy endpoints, such as C-peptide AUC from a 2-hour OGTT. Changes were made, however, regarding the OGTT monitoring schedule; in the final version of the protocol, it was specified that subjects were *not* to be followed up for 2-hour OGTT monitoring and C-peptide data collection upon T1D diagnosis. In addition, there were varying lengths of patients' participation as is expected in a time-to-event study design. These design limitations caused informative censoring and rendered analysis results of available C-peptide data uninterpretable.[6]

# 5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the Applicant. The following section is a summary of relevant safety information to date for teplizumab-mzwv.

The safety of teplizumab-mzwv was evaluated in randomized, controlled trials including a study in pre-symptomatic diabetic individuals (Stage 2) and in multiple studies in patients with newly diagnosed type 1 diabetes (T1D) (Stage 3). In total 1018 patients, 791 treated with teplizumab-mzwv, from 5 studies were pooled into a safety database.[2] The most common adverse events reported in ≥30% were lymphopenia (79.9%), leukopenia (63.3%), neutropenia (39.6%), blood bicarbonate decreased (38.3%) and rash (34.5%).[2]

**Deaths**

There were three deaths reported in the teplizumab-mzwv development program. All three deaths were reported for patients with T1D who were randomized to teplizumab-mzwv, with two deaths occurring during the follow up period of the Protégé trial and one occurring in the follow-up period of the Protégé Extension Study. A 20-year-old female patient died from DKA, 9 months after her last dose of teplizumab-mzwv. A 27-year-old male died of complications related to an anterior wall myocardial infarction 15 months after receiving the last dose of study drug. A 24-year-old female died of unknown causes 26 months after the last dose of study drug. The clinical reviewer noted that on review of this patient's narrative, an acute episode of abdominal pain, vomiting, and diarrhea treated by a local doctor preceded her death; It is unlikely these deaths are causally related to teplizumab-mzwv because of the long latency between dosing and the events. Furthermore, the etiologies were disparate and

inconsistent with the mechanism of action of the drug.[6]

**Serious Adverse Events (SAE)**

The serious adverse event with the largest risk difference between teplizumab-mzwv (n=18/773;2.3%) and control (n=1/245;0.4%) was diabetic ketoacidosis, or DKA. A causal relationship between teplizumab-mzwv and DKA is unclear, but importantly, in TN-10, which enrolled at-risk patients, there were no reported events of DKA at the time of onset of diabetes. In addition, hypoglycemic seizure (n=6/773;0.8% vs n=0/245) and hypoglycemia (n=13/773;1.7% vs n=3/245;1.2%) occurred more frequently with teplizumab vs. control, respectively; however the clinical reviewer noted that these events are expected to occur in patients with T1D using insulin but not in the at-risk population, therefore, the clinical relevance of these events is unclear.[15] Infection (n=26/773;3.4% vs n=5/245;2%), cytokine release syndrome (n=5/773;0.6% vs n=0/245), and hepatic injury (n=4/773;0.5% vs n=0/245), were also reported more frequently with teplizumab-mzwv. The clinical reviewer noted that these results are not unexpected as they are consistent with teplizumab-mzwv's mechanism of action. [15][15]

If approved, labeling will include the following risks in the Warnings and Precautions section:

## 5.1 CYTOKINE RELEASE SYNDROME (CRS)

Teplizumab-mzwv can cause CRS. Symptoms may include fever, nausea, fatigue, myalgia, and malaise, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and typically occurs during the first 5 doses of teplizumab-mzwv. Draft labeling includes that CRS can be managed by treatment with anti-pyretics (eg, NSAIDs] or acetaminophen), antihistamines and/or anti-nausea medications. Draft labeling states to consider temporary pause of dosing for 1-2 days, if disabling signs and symptoms occur and can resume after improvement or resolution of symptoms. With more serious cases of cytokine release syndrome (Grade 3 or 4 CRS), hypotension or hypoxia may occur requiring intervention (intravenous fluid, pressors, supplemental oxygen); however, no patients required the use of intravenous fluid, pressors, supplemental oxygen in the clinical trial.

CRS was reported in <6% of treated subjects, with majority, 80% experiencing mild to moderate CRS (Grade 2 or lower) during clinical trial.[2] There were 41 total CRS cases observed based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading system. Out of 41 cases, 39 cases (5%) were reported with teplizumab-mzwv (N=773) and 2 cases (0.8%) were reported with control arm (N=245). Ten of the cases caused treatment interruption or permanent discontinuation. The patients experiencing CRS were broadly consistent with the overall treatment population, although slightly older, and more males reported CRS. The median duration of the CRS event was 3 days and started 3 days into the treatment cycle. The majority (83%) of CRS cases were grade 1 and 2. The remaining 7 cases were grade 3, and 5/7 of the grade 3 cases were also reported as SAEs. An excess of 4.2 cases (95% CI: 2.3 to 6.1) of any grade of CRS was observed per 100 patients treated. The excess cases were primarily grades 1 and 2, with close to 1 excess case of grade 3 CRS per 100 patients.[6]

(b) (4)

[redacted]

2

## 5.2 (b) (4)

In pooled clinical trial data approximately 80% of patients receiving teplizumab-mzwv had transient lymphopenia. Severe lymphopenia (<500 per $m^3$) that lasted for 7 days or longer occurred in less than 1% of patients receiving teplizumab-mzwv. 0.5% patients receiving teplizumab-mzwv permanently discontinued treatment due to lymphopenia. In most patients, circulating lymphocyte counts began to recover after Day 5 of the treatment course, without dose interruption, and returned to pre-treatment values within 4 weeks. Labeling instructs not initiate treatment with teplizumab-mzwv for individuals with preexisting lymphopenia (<1000 lymphocytes/µL).[2]

Teplizumab-mzwv can cause an increase in liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, with or without elevations in bilirubin, sometimes in association with cytokine release syndrome.[2] In the teplizumab program, 2 cases met the criteria for Hy's law (i.e., having bilirubin >2X ULN and having ALT >3X ULN). Both cases fulfilling Hy's criteria had alternative explanations as one of the patients reported an SAE of biliary dyskinesia, reported approximately 1 year (346 days) after the last teplizumab infusion, with resolution following laproscopic cholecystectomy. The second Hy's law case was associated with a diagnosis of Hepatitis A infection, which occurred 3 months after the last dose of teplizumab, making drug-induced liver injury unlikely.[6] Draft labeling (b) (4) The draft labeling includes to discontinue the treatment in patients who develop elevated ALT or AST greater than 5 times the ULN or bilirubin greater than 3 times the ULN (b) (4)

## 5.3 (b) (4)

In the full integrated summary of safety (ISS), during the period of the 14-day teplizumab infusion, 38 patients (4.9%) reported any infection in the teplizumab group compared to 12 (4.9%) in the control group. During the first treatment cycle and follow up period, 581 infections were reported by 309 patients (40.0%) in the teplizumab group compared to 17 infections among 99 patients (40.4%) in the control group. A slightly higher incidence of serious infections was reported for teplizumab compared to control over the entire observation period of the first treatment cycle (15/773 [1.9%] vs. 4/245 [1.6%]). (b) (4) labeling is not recommending the initiation treatment with teplizumab-mzwv in individuals with active infections. Labeling instructs that patients be closely monitored for the development of signs and symptoms of infections during and after receiving teplizumab-mzwv.[2]

## 5.4 (b) (4)

Since no data are available on either the efficacy or on the risks of secondary transmission of infection by live vaccines in patients receiving teplizumab-mzwv, live vaccines should not be given concurrently with teplizumab-mzwv. In addition, because teplizumab-mzwv may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving teplizumab-mzwv. Limited data are available on the response to vaccinations with inactivated (killed) antigens in patients receiving teplizumab-mzwv.[2]

# 6 Expected Postmarket Use

According to the currently proposed indication, if approved, teplizumab-mzwv will be administered as a 30-minute infusion in inpatient and outpatient settings. It is expected that prescribing will be done by specialists such as pediatric endocrinologists or endocrinologists.

# 7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for teplizumab-mzwv beyond routine pharmacovigilance and labeling that includes Warnings and Precautions, Patient Counseling Information and a Medication Guide to address the risk of CRS, transient lymphopenia and increase in liver enzymes, infection and immunizations.

# 8 Discussion of Need for a REMS

Teplizumab-mzwv is an anti-CD3 humanized IgG1 monoclonal antibody, with the proposed indication for the delay or prevention of clinical T1D in at-risk individuals.[2] When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for teplizumab-mzwv, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Type 1 diabetes is the second most common chronic disease of childhood, although the disorder may develop throughout the life span. As mentioned before, it is estimated that about 64,000 patients, including both adults and children, are newly diagnosed with type 1 diabetes yearly.[7] The life-expectancy of individuals with younger-onset disease is on average 16 years shorter than non-diabetic individuals. Insulin is still the mainstay of treatment for Stage 3 T1D. As there are no treatments approved for Stage 2 T1D that could inhibit the inflammation and destruction of beta cells before they are rendered unrecoverable and would delay the onset of clinical disease; therefore, there is a clear unmet need for additional therapies. Although the serious risks associated with the use of teplizumab-mzwv include transient lymphopenia and increase in liver enzymes, infection and immunizations, the risk of CRS is the focus of this review.

The Division of Hematology Malignancies 1 (DHM1) was consult regarding the risk of CRS.[16] They stated that in the clinical trials submitted for this BLA, CRS requiring intervention other than antipyretics was rare but did occur following treatment with teplizumab-mzwv; however, it is not possible to fully describe the severity of CRS in the population due to missing information. DHM1 review stated that 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. DHM1 also recommend a REMS comprised of a communication plan to inform providers about the risk of CRS, as DHM1 believes that healthcare providers for the intended population are not likely to be experienced with diagnosis and management of CRS.

On June 24, 2021 DRM and Division of Diabetes, Lipid Disorders, and Obesity (DDLO) met to discuss the DHM1 consult review which recommended a REMS comprised of a communication plan for teplizumab-mzwvin to address the risk of CRS [16] and, to determine if such measures are necessary to ensure the benefits outweigh the risks of CRS for teplizumab-mzwv. In considering a REMS for

teplizumab-mzwv, the discussion primarily focused on the severity of the risk of CRS with teplizumab and likely prescribers of teplizumab.

**Severity of the risk:** CRS was reported in <6% of treated subjects, with the majority, 80%, experiencing mild to moderate CRS (Grade 2 or lower) during the clinical trial. There were no fatal outcomes or ICU admissions. No patient required a vasopressors for symptoms of hypotension or experienced significant hypoxia. There were no serious morbidities associated with CRS on review of the CRS specific report forms as well as AE reports.[6] In general, when discussing if a REMS is necessary to ensure the benefits outweigh the risks, we [DRM] recommend that first all the tools in labeling are used to its fullest extent to communicate the risk before determining additional risk mitigation measures are necessary. For teplizumab, although CRS is included in the Warning and Precautions of the draft label, DDLO determined based on the available data that the risk of CRS did not rise to the level of a boxed warning.

**Likely prescribers of teplizumab:** Teplizumab-mzwv will likely be prescribed by specialists (i.e., endocrinologists, pediatric endocrinologists). Teplizumab-mzwv will be administered as an infusion for 14 days in both inpatient and outpatient infusion settings. As the majority of the CRS were grade 1 and 2, staff administering teplizumab-mzwv should be able to manage this risk with premedications (nonsteroidal anti-inflammatory drug (NSAID), an antihistamine, and an anti-emetic) as described in the Dosage and Administration section of the draft label.

The DRM and DDLO discussed if a REMS was necessary to ensure the benefit of teplizumab-mzwv outweighed the risk of CRS. Based on the clinical trial, CRS occurred in less than 6% of patients treated with teplizumab-mzwv, with the majority, 80%, experiencing mild to moderate CRS (Grade 2 or lower). The risk of CRS should be able to be managed with premedications (nonsteroidal anti-inflammatory drug (NSAID), an antihistamine, and an anti-emetic) as described in the Dosage and Administration section of the draft label and if needed a temporary pause of dosing for 1-2 days. In addition, we expect that patients will receive the 30-minute infusion in inpatient or outpatient infusion settings under the care of a health care provider.

In general, when discussing if a REMS is necessary to ensure the benefits outweigh the risks, we recommend that first all the tools in labeling are used to its fullest extent to communicate the risk before determining additional risk mitigation measures are necessary. For teplizumab, although CRS is included in the Warning and Precautions of the draft label, DDLO determined based on the available data that the risk of CRS did not rise to the level of a boxed warning.

The DRM and DDLO also discussed, that if approved, it is likely the Applicant will develop materials as part of their outreach to prescribers. DRM is not opposed to communications by the Applicant; however, the review of these materials would be done through the Office of Prescription Drug Promotion (OPDP). If this product was approved, DRM and DDLO discussed potential FDA-driven communications close to the time of approval to highlight this is a novel treatment for T1D and to convey safety information.

DRM and DDLO have determined that based the data currently available, if approved, a REMS is not necessary to ensure the benefits of teplizumab-mzwv outweigh its risks. At the time this review was completed, labeling negotiations were still ongoing with the Applicant. At this time draft labeling for teplizumab-mzwv includes Warnings and Precautions, Patient Counseling Information and a Medication Guide to communicate the safety issues and to manage the risks associated with teplizumab-mzwv.

# 9 Conclusion & Recommendations

At this time of this addendum review, DDLO is recommending a CR on the basis related to lack of comparability between the clinical trial and to-be-marketed drug products and facility deficiencies. Should any changes in efficacy, safety or benefit:risk analysis change with the resubmission of teplizumab-mzwv, DRM should be consulted. This memo serves to close the existing consult request to DRM for teplizumab-mzwv under BLA 761183.

# 10 References

[1] Olickal T. Defer comment on DRM evaluation of the need for a REMS for teplizumab-mzwv, BLA 761183, dated June 4, 2021. [Reference ID: 4806591]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 24, 2021.

[2] Draft Prescribing Information for teplizumab-mzwv as currently edited by the FDA, last updated June 6, 2021.

[3] Deficiencies Preclude Discussions Letter, dated April 02, 2021. [Reference ID: 4773160]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed May 10, 2021.

[4] Thanukrishnan H, Dahmane E, Khurana M and Earp J. Office of Clinical Pharmacology Review for teplizumab-mzwv, BLA 761183, dated April 30, 2021. [Reference ID: 4788416]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed March 1, 2021.

[5] Swisher J. Office of Pharmaceutical Quality. Quality Executive Summary for teplizumab-mzwv, BLA 761183, dated May 24, 2021. [Reference ID: 4796111]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 2, 2021.

[6] FDA Briefing Document, The Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC). May 27, 2021; https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-agenda-information-may-27-2021-meeting-endocrinologic-and-metabolic-drugs-advisory-committee#event-materials

[7] American Diabetes Association. Statistics About Diabetes. https://www.diabetes.org/resources/statistics/statistics-about-diabetes. Accessed June 24, 2021.

[8] Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet (London, England).* 2018;392(10146):477-486.

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[10] Symlin. Prescribing Information (last updated 12/2019).

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[12] 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.

[13] Provention Bio, Inc. Clinical Overview for teplizumab-mzwv, dated September 30, 2020.

[14] Wang Y. Statistical Assessment of Teplizumab Efficacy. EMDAC Presentation, dated May 27, 2021.

[15] WoodHeickman L. Clinical Safety of Teplizumab. EMDAC Presentation, dated May 27, 2021.

[16] Jen E. Division of Hematological Malignancies 1. CDER Clinical Consult Review for teplizumab-mzwv BLA 761183, dated April 28, 2021. [Reference ID: 4787354]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed April 28, 2021.

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**Division of Risk Management (DRM)**

**Office of Medication Error Prevention and Risk Management (OMEPRM)**

**Office of Surveillance and Epidemiology (OSE)**

**Center for Drug Evaluation and Research (CDER)**

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|---|---|
| **Application Type** | BLA |
| **Application Number** | 761183 |
| **PDUFA Goal Date** | July 02, 2021 |
| **OSE RCM #** | 2020-796 |
| **Reviewer Name(s)** | Till Olickal, Ph.D., Pharm.D. |
| **Team Leader** | Naomi Boston, Pharm.D. |
| **Deputy Director** | Doris Auth, Pharm.D. |
| **Review Completion Date** | June 4, 2021 |
| **Subject** | Defer comment on DRM evaluation of the need for a REMS for teplizumab-mzwv |
| **Established Name** | teplizumab-mzwv |
| **Trade Name** | Tzield |
| **Name of Applicant** | Provention Bio, Inc. |
| **Therapeutic Class** | CD3-directed monoclonal antibody |
| **Formulation(s)** | 2 mg/2 mL (1 mg/mL) injection in a 2mL single-dose vial |
| **Dosing Regimen** | Administer by intravenous infusion in a 14 consecutive day course.<br>The dose is calculated based on the patient's body surface area (BSA) and administer according to the following regimen: Dose 1: 51 mcg/$m^2$; Dose 2: 103 mcg/$m^2$; Dose 3: 207 mcg/$m^2$; Dose 4: 413 mcg/$m^2$ and Doses 5-14:826 mcg/$m^2$. |

This purpose of this memo is to defer the Division of Risk Management (DRM) review of the need for a risk evaluation and mitigation strategy (REMS) for teplizumab-mzwv, BLA 761183.

On November 2, 2020, the Applicant submitted BLA 761183 for teplizumab with the proposed indication for the delay or prevention of clinical type 1 diabetes in at-risk individuals. The submission included draft labeling but did not include a REMS.

The effectiveness of teplizumab-mzwv was investigated in a randomized, double-blind, placebo-controlled study (TN-10) in 76 patients 8 to 49 years of age who were identified as at-risk for type 1 diabetes mellitus (T1D) (or at Stage 2 in T1D), defined as having two or more T1D-related autoantibodies (anti-GAD, micro insulin, anti-IA-2, islet cell antibody [ICA], anti-ZnT8) and abnormal glucose tolerance in a 2-hour oral glucose tolerance test. The primary efficacy endpoint was the time from randomization to clinical T1D diagnosis. The evaluation of primary endpoint was conducted when a minimum number of 40 T1D events was observed. The change from baseline in C-peptide area under the time-concentration curve (AUC) in a 2-hour oral glucose tolerance test (OGTT) was a secondary endpoint. T1D was diagnosed in 20 (45%) of the patients who received teplizumab and in 23 (72%) of those who received placebo. The median time to clinical T1D diagnosis was 49.5 months in the teplizumab group and 24.9 months in the placebo group, for a difference of 24.6 months. The hazard ratio for the time to clinical T1D diagnosis was 0.41 (95% CI: 0.22 to 0.78), which was statistically significant.[1]

The Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC)[2] was convened on May 27, 2021 to discuss:

a) the strength of the overall evidence to conclude that effectiveness has been established for teplizumab for the proposed indication to delay clinical T1D in at-risk individuals.
b) the clinical meaningfulness of the observed median 2-year delay of onset of T1D demonstrated in study TN-10.
c) the safety issues identified in the clinical development program and the potential for unobserved, longer latency safety issues (e.g., malignancy) given the mechanism of action of teplizumab, and also discussed whether these safety concerns can be adequately mitigated through labeling and/or required postmarketing studies.
d) how the indicated population should be described to ensure that the expected benefit(s) of teplizumab will outweigh the risks of treatment, and any other recommendations for the indication statement.

The voting question presented to the committee was:

> Does the information provided in the background documents and presentations by the Applicant and FDA show that the benefits of teplizumab outweigh the risks in support of approval to delay clinical type 1 diabetes mellitus?

The EMDAC vote was 10 “Yes” and 7 “No” as answers to the voting question above. The committee unanimously agreed that meta-analysis of biomarker, C-peptide data from other controlled trials in patients with existing type 1 disease could not serve as confirmatory

evidence to the pivotal TN-10 study. The views expressed by the committee were the efficacy data were insufficient and outweighed by potential safety concerns, which included an imbalance in diabetic ketoacidosis (DKA) cases in the controlled trials in patients with T1D. In addition, there were no long-term safety data for the TN-10 population. More specifically, committee members stressed that they couldn't fully grasp the long-term malignancies, including the risk of DKA and three deaths documented in the study. The causes of death include DKA and anterior myocardial infarction. The last cause of death was unknown. Several members of the committee articulated that they don't have confidence in a study where only 44 patients were treated with the medication and with the uncertainties that are there in the safety side of things, so a second adequate and well-controlled study needs to be done in order to to decide whether the risk-benefit falls in favor of the benefit and determine the magnitude of the delay. Many panelists believed the proposed indication is too broad and sought to limit the indication according to the population enrolled in TN-10: subjects ages eight to 45 years with two or more positive autoantibodies. Panelists were split on whether to restrict use to only those individuals for whom T1D runs in the family, or to open it up more broadly to all individuals with early Stage 2 disease. In summary, the EMDAC narrowly endorsed teplizumab-mzwv to delay onset of type 1 diabetes, citing a high unmet need and a strong efficacy result on a hard clinical outcome in a small, single trial. Many panelists who voted "Yes" stated that it requires post marketing studies and safety registry/surveillance in order to clearly understand the long-term side effects of the drug. While the committee agreed that a two-year delay of Type 1 diabetes would be significant and clinically meaningful, there were some considerations and reservations regarding teplizumab support. Committee members stated that they needed more safety data in order to adequately inform labeling and required postmarketing studies.

Additional pertinent history includes:

- The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) issued a "Deficiencies Preclude Discussion" letter on April 2, 2020 stating that the Agency identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.[3]

- The Office of Clinical Pharmacology, Divisions of Cardiorenal and Endocrine Pharmacology and Pharmacometrics is recommending a Complete Response action for the BLA 761183 until the sponsor can adequately address the issue related to lack of comparability between the clinical trial and to-be-marketed drug products. A pharmacokinetic (PK) bridging study in healthy volunteers was conducted to compare the to-be-marketed formulation with the clinical trial formulation. The results failed to show PK comparability between the two products as their total and partial exposures differed significantly, despite a comparable Cmax after the 30-minute intravenous infusion. Please refer to Dr. Harisudhan Thanukrishnan's review for a detailed review of identified issues and recommendations.[4]

- The Office of Pharmaceutical Quality (OPQ) is recommending a Complete Response for regulatory action based on the submission[5]:

  *The data submitted in this application are not sufficient to support a conclusion that the manufacture of Tzield is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a chemistry, manufacturing and control*

*(CMC) standpoint, Office of Biotechnology Products (OBP) is recommending a Complete Response letter be issued to Provention Bio, Inc. to outline the deficiencies and the information and data that will be required to support approval.*[5]

*Additionally, this application cannot be approved during this review cycle due to facility deficiencies. As of 5/14/2021, there is a* (b) (4) *proposed for Teplizumab (PRV-031) DP manufacture. During an ongoing inspection of the manufacturing facility, deficiencies were conveyed to the representatives of the facility by investigators from FDA. Satisfactory resolution of the observations is required before this BLA may be approved. OPQ is recommending a withhold status, which will be communicated in the Complete Response letter to Provention to outline the deficiencies.*[5]

Therefore, an evaluation of the need for REMS for teplizumab-mzwv will be undertaken by DRM after the Applicant addresses the deficiencies in the CR letter. Please send DRM a new consult request at such time. This memo serves to close the existing consult request to DRM for teplizumab-mzwv under BLA 761183.

## References


[1] Draft Prescribing Information for teplizumab-mzwv as currently edited by the FDA, last updated April 19, 2021.

[2] FDA Briefing Document, The Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC). May 27, 2021; https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-agenda-information-may-27-2021-meeting-endocrinologic-and-metabolic-drugs-advisory-committee#event-materials

[3] Deficiencies Preclude Discussions Letter, dated April 02, 2021. [Reference ID: 4773160]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed May 10, 2021.

[4] Thanukrishnan H, Dahmane E, Khurana M and Earp J. Office of Clinical Pharmacology Review for teplizumab-mzwv, BLA 761183, dated April 30, 2021. [Reference ID: 4788416]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed March 1, 2021.

[5] Swisher J. Office of Pharmaceutical Quality. Quality Executive Summary for teplizumab-mzwv, BLA 761183, dated May 24, 2021. [Reference ID: 4796111]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 2, 2021.

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