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New Drug Evaluation: teplizumab-mzwv, injection

Date of Review: April 2023
Generic Name: teplizumab-mzwv

End Date of Literature Search: 01/04/23
Brand Name (Manufacturer): Tzield™ (Provention Bio, Inc)

Dossier Received: yes

Plain Language Summary:

- This review evaluates a new medicine called teplizumab that the U.S. Food and Drug Administration (FDA) approved to delay onset of type 1 diabetes. The FDA approved teplizumab only for people that have a high chance of developing type 1 diabetes.
- Type 1 diabetes is a disease where the body's immune system mistakes its own healthy cells as foreign and attacks them. This destroys pancreas cells that make insulin and causes high blood sugar.
- In people who were at risk of getting type 1 diabetes, teplizumab delayed the occurrence of diabetes by approximately two years compared to placebo or no treatment.
- A study showed that teplizumab did not improve blood sugars for people who already have diabetes.
- Teplizumab side effects were rash, blood problems, headache and liver problems.
- We recommend that only diabetes specialists, called endocrinologists, prescribe teplizumab. We also recommend teplizumab be prescribed only to people who are at high risk of type 1 diabetes.

Research Questions:

1. What is the evidence for efficacy for teplizumab in delaying the progression of type 1 diabetes (T1D) in people that are at high risk of developing the disease?
2. What is the harms evidence associated with the use of teplizumab?
3. Are there specific subpopulations that would be more likely to benefit from the use of teplizumab?

Conclusions:

- The efficacy and safety of teplizumab was evaluated in two, phase 2, placebo-controlled trials and one phase 3 trial.[1–3]
- There is moderate quality of evidence that teplizumab delays the progression to T1D in people with stage 2 T1D at high risk of developing T1D (e.g., relative with diabetes, immunogenic markers and abnormal glucose tolerance) for approximately two years.[1]
- One phase 2 trial demonstrated preservation of c-peptide levels, which are indicative of endogenous insulin production, in those receiving teplizumab after 2 years of treatment compared to no treatment, based on low quality of evidence.[2]
- There is low quality evidence from a single phase 3 trial that teplizumab does not reduce insulin needs in people recently diagnosed with T1D.[3]

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- The most common adverse reactions associated with the use of teplizumab are rash, lymphopenia, leukopenia, headache and cytokine release syndrome (CRS).[4]
- There is insufficient long-term evidence for the use of teplizumab. Results are most applicable to those people that are White and under the age of 18 years of age who are at high risk of developing diabetes.

Recommendations:
- Implement prior authorization criteria to limit use to people with stage 2 T1D and high risk of progression to stage 3 T1D (**Appendix 2**).

Background:
Diabetes is characterized by a hemoglobin A1c (HbA1c)of 6.5% or higher and associated with symptoms such as polydipsia, polyuria, weight loss, fatigue, and diabetic ketoacidosis (DKA).[5] People with diabetes have an increased risk of morbidity and mortality, and diabetes is the seventh leading cause of death in the United States (US).[6] There are two types of diabetes; T1D and type 2 diabetes. Type 1 diabetes is autoimmune mediated beta-cell destruction resulting in loss of insulin production while type 2 diabetes (T2D) is a non-autoimmune loss of beta-cell insulin secretion, often coinciding with insulin resistance and metabolic syndrome.[5] Type 2 diabetes more commonly occurs in adulthood and T1D often presents in childhood or adolescents. People with T1D often present with polydipsia, polyuria, weight loss and lower body mass index (BMI). Up to half of those with T1D are diagnosed after an episode of diabetic ketoacidosis (DKA).[5] People with T2D are often above their optimal BMI, are diagnosed at an older age and don't often present with DKA.

Type 1 diabetes accounts for approximately 10% of the diabetes diagnoses, with an estimated occurrence of 64,000 new cases annually in the US.[7] In some people with genetic predisposition to T1D, progression through stages of asymptomatic loss of insulin production occurs before overt hyperglycemia. Stages are defined based on different clinical and laboratory parameters (**Table 1**).[5] Development of autoantibodies occurs in Stage 1. Stage 2 is characterized by impaired metabolic response to glucose but normal levels of glycosylated hemoglobin; supplemental insulin is not required. In stage 3 T1D, people develop hyperglycemia with clinical symptoms leading to the need for life-long exogenous insulin.[8] People with characteristics of stage 2 disease, immunologic markers of T1D and abnormal glucose tolerance, are at high risk for progression to stage 3 and development of hyperglycemia symptoms over time. Development of hyperglycemia requiring insulin for management usually occurs within 6 years of development of autoantibodies. The FDA states that the conversion rate to stage 3 T1D to be 25% at 6 months, 60% at 2 years and 75% at 4 years in those individuals with dysglycemia and stage 2 T1D.[8] The lifetime risk for developing T1D is near 100% in high-risk individuals.[8] Caucasians have a higher prevalence of T1D with children, teens and young adults most commonly diagnosed. The most common ages of diagnosis is between 4 and 7 years of age. Family history is the most common risk factor.

Table 1. Type 1 Diabetes Staging[5]

	Stage 1	Stage 2	Stage 3
Characteristics	▪ Autoimmunity ▪ Normoglycemia ▪ Presymptomatic	▪ Autoimmunity ▪ Dysglycemia ▪ Presymptomatic	▪ Automimmunity ▪ Overt hyperglycemia ▪ Symptomatic
Diagnostic Criteria	▪ Multiple islet cell autoantibodies ▪ No IGT or IFG	▪ Islet cell autoantibodies (usually multiple) ▪ Dysglycemia: IFG and/or IGT ▪ FPG 100-125 mg/dL	▪ Autoantibodies may become absent ▪ Diabetes by standard criteria

		▪ 2-h PG 140-199 mg/dL ▪ HbA1c 5.7-6.4% or ≥10% increase in HbA1c	
Abbreviations: FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; 2-h PG = 2 hour plasma glucose			

Individuals that have the persistent presence of two or more islet autoantibodies are almost 100% likely to develop diabetes.[5] Determinants of progression include; age of first detection of autoantibody, number of autoantibodies, autoantibody specificity and autoantibody titers.[5] Several autoantibodies have been linked to the development of T1D. Exogenous insulin administration causes all individuals to develop insulin autoantibodies and should not be used to determine the presence of immune mediated diabetes. Glutamic acid decarboxylase (GAD) antibodies have been identified in approximately 70% of those with T1D.[9] Insulinoma-associated protein 2 (IA-2) is also commonly found in individuals with T1D and usually appears later than GAD or other autoantibodies to insulin. Zinc transporter (ZnT8) has been identified as a autoantigen in 60-80% of those with T1D, which appears later and is lost soon after the onset of T1D.[9] Islet cell antibodies (ICA) are present with insulin producing pancreatic beta cells are injured and are used to estimate the risk of T1D. Microinsulin autoantibodies (mIAA) are least commonly associated with other antibodies and rarely is indicative of the development of diabetes if it is the only antibody present.[10]

There are several immunologic treatment options in development to prevent the progression to T1D by preserving beta-cell function.[1] Chronic immunosuppressive therapies, such as cyclosporin, have been studied as an option for delaying the loss of insulin secretion. Fc receptor non-binding anti-CD3 monoclonal antibodies, like teplizumab and otelixizumab (in development), target CD8+ lymphocytes that contribute to the destruction of beta-cells and have demonstrated the most promise.[1]

There is insufficient data on the most optimal outcome to measure the effectiveness of immunotherapy in people with T1D. The measurement of C-peptide is used in some studies to predict insulin levels and the progression to T1D.[11] C-peptide levels are an indication of endogenous insulin production. C-peptide is not metabolized by the liver, and therefore, is a better determinant of insulin production than glucose levels. Low levels of C-peptide are indicative of no or low insulin production by the pancreas and need for exogenous insulin. Important short-term outcomes of progression to T1D include risk of hyperglycemia and DKA and longer term outcomes are retinopathy, kidney disease, and cardiovascular disease.[12] Studies have shown that those who are diagnosed with T1D at an older age have higher C-peptide levels and lower risk of morbidity associated with clinical T1D.[11, 13]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Teplizumab was approved by the FDA in November of 2022.[4] Teplizumab is a CD-3 directed antibody indicated for use in adults and pediatric patients 8 years of age and older with Stage 2 T1D to delay the onset of Stage 3 T1D. Teplizumab should be used in people that have a confirmed diagnosis of Stage 2 T1D by documentation of at least two positive pancreatic islet autoantibodies (e.g., GAD autoantibodies, IAA, IA-2, ZnT8 and ICA) in those who have dysglycemia without overt hyperglycemia when using an oral glucose tolerance test (OGTT) or alternative method if OGTT is not available.[4] Teplizumab should not be used for T2D or gestational diabetes and patient clinical history should be reviewed prior to initiation to ensure the patient has not already developed clinical symptoms of diabetes indicative of stage 3 diabetes. Teplizumab is given as a one-time treatment course of an intravenous (IV) infusion over at least 30 minutes, once daily for 14 days. A complete blood count and liver enzyme tests should be performed prior to starting teplizumab. Teplizumab has been associated with

cytokine release syndrome (CRS), and premedication before each teplizumab infusion, for the first five doses, is recommended. Pre-medications include oral nonsteroidal anti-inflammatory (NSAIDs) or acetaminophen, an antihistamine and and/or an antiemetic.

Teplizumab was evaluated in one good quality phase 2 trial, one poor quality phase 2 trial (AbATE) and one fair quality phase 3 trial (PROTÉGÉ) (**Table 5**).[1–3] Only one of these trials provided evidence for the approved indication of delaying the onset of Stage 3 T1D in those with stage 2 T1D.[1] Participants in this phase 2 trial were identified through the TrialNet Natural History Study. This study offers risk screening for relatives of people with T1D as well as clinical studies that test ways to slow down and prevent disease progression. Eligible participants had to be at high risk of developing diabetes, which was defined as people who have relatives with T1D and confirmed presence of autoantibodies (**Table 2**). Participants were also required to have a degree of dysglycemia on an OGTT (defined as a fasting glucose level of 110 to 125 mg per deciliter [6.1 to 6.9 mmol per liter], a 2-hour postprandial plasma glucose level of at least 140 mg per deciliter [7.8 mmol per liter] and less than 200 mg per deciliter [11.1 mmol per liter], or a postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter on two occasions, within 52 days before enrollment).[1] The median age of study participant was 13.5 years, median HbA1c 5.2%, and 55% of participants were male.[1] Seventy-six participants were randomized to placebo or teplizumab given as one course of treatment over 14 days.[1] Dosing of teplizumab was the following in the phase 2 trials: 51 mcg/m^2 on day zero, 103 mcg/m^2 mcg on day one, 207 mcg/m^2 mcg area on day two, 413 mcg/m^2 on day three, 826 mcg/m^2 area on days four through 13. This regimen is comprised of slightly lower doses throughout taper and final dose compared to teplizumab labeling which recommends titration up to the highest dose of 1,030 mcg/m^2 for days 5 through 14.[1] Pre-medications were given to both the treatment and placebo group.

Participants in the Herold trial were followed for 745 days.[1] The median time to progression to T1D was longer in people treated with teplizumab compared to placebo, 48.4 months versus 24.4 months (hazard ratio [HR] 0.41; 95% CI, 0.22 to 0.78; p-value = 0.006).[1] The percentage of people that progressed to T1D was lower in people randomized to teplizumab compared to placebo, 43% versus 72%.[1] The progression to diabetes was highest in the first year after treatment compared to the second or third year following treatment. Diagnosis of T1D occurred in 7% of people taking teplizumab compared to 44% in the placebo group in the first year.[1] The FDA determined that the delay in the development of T1D by two years is clinically meaningful due to the benefits in quality of life, and a reduction in risk of complications.[8] Those diagnosed at an earlier age are more likely to develop diabetic ketoacidosis and DKA.

Table 2. Autoantibodies Present at Baseline in Participants in the Teplizumab Studies

Autoantibodies	Teplizumab	Placebo
Phase 2 Study[1]		
GAD65	40 (91%)	28 (88%)
Micro insulin (mIAA)	20 (45%)	11 (34%)
IA-2	27 (61%)	24 (75%)
ICA	29 (66%)	28 (88%)
ZnT8	32 (73%)	24 (75%)
Phase 2 Study (AbATE)[14]		
GAD-65	40 (76.5%)	24 (95.7%)
IA-2	51 (98.0%)	24 (95.7%)
Micro insulin (mIAA)	37 (70.6%)	18 (73.9%)
ZnT8	45 (86.3%)	16 (65.2%)
Phase 3 Study (PROTÉGÉ)[3]		

GAD-65	375 (89%)	89 (91%)
Human insulin	370 (88%)	88 (90%)
Islet cell 512	231 (56%)	53 (54%)
Abbreviations: GAD65 = glutamic acid decarboxylase 65; IA-2 = insulinoma-associated antigen 2 antibody; ICA = islet cell autoantibody; ZnT8 = zinc transporter 8		

In the second phase 2 trial (AbATE), participants were newly diagnosed with T1D (stage 3) and had positive autoantibodies.[2] The mean age of participants was 12 years and 59% were White.[2] Patients were followed for 2 years.[2] This open-label, phase 2 study evaluated the effect of teplizumab on C-peptide levels.[2] At 2 years, people receiving teplizumab had less reduction in C-peptide levels compared to no treatment, -0.28 mmol/L versus -0.46 mmol/L ; p=0.002), which suggests preservation of beta-cell function. However, there were no significant differences in HbA1c levels between the groups.[2]

In the phase 3 trial (PROTÉGÉ) eligible participants were diagnosed with T1D within the previous 12 weeks or less, were a mean age of 7 years and had a mean HbA1c of 8.25%.[3] Total insulin mean insulin dose was 0.65 U/kg per day at baseline.[3] During the study the investigators were advised to titrate insulin to an HbA1c of 6.5% or lower and an insulin dose of at least 0.25 U/kg per day. The dose of teplizumab was: teplizumab 14-day full dose (total dose of 9,034 mcg/m^2 over 14 days; repeated at week 26), teplizumab 14-day low dose (total dose of 2,985 mcg/m2 over 14 days; repeated at week 26), teplizumab 6-day full dose (total dose of 2,426 mcg/m2 over 6 days, followed by 8 days of placebo; repeated at week 26).[3] The composite outcome of the percentage of participants with insulin use of less than 0.5 units/kg per day and HbA1c less than 6.5% at one year.[3] Results were reported at one year as prespecified by the study protocol; however, the study duration was two years.[3] The results for the primary composite outcome were not significantly different between the teplizumab groups compared to placebo. The composite of patients with insulin use of less than 0.5 U/kg per day and HbA1c of less than 6.5% at 1 year, after 14 days of therapy, was 19.8% (n=41) for teplizumab full dose, 13.7% (n=14) for teplizumab low dose, 20.8% (n=22) for teplizumab 6-day full dose, and 20.4% (n=20) for placebo. Secondary outcome results were considered exploratory because the primary composite outcome did not reach statistical significance.

Limitations to the studies are the small sample sizes, use in predominately White populations, and strict inclusion criteria. There is consistent evidence from two studies that teplizumab does not improve outcomes in participants that have been recently diagnosed with T1D. A phase 3 study for the treatment of early-onset T1D is underway (PROTECT, NCT03875729) and may inform additional indications for teplizumab. There is insufficient evidence for a second course of teplizumab; however this is being evaluated in ongoing studies.

Clinical Safety:

Common adverse reactions experienced with teplizumab are presented in **Table 3**.[4] Teplizumab is associated with CRS which occurred in 2% of participants in trials compared to 0.0% of placebo treated participants.[4] Teplizumab should be discontinued in those people who have liver enzyme elevations 5 times of upper limit of normal. If severe CRS occurs, pausing dosing should be considered. Teplizumab should not be used in people with serious or chronic infection and teplizumab should be discontinued if a serious infection occurs. Serious infections (e.g. cellulitis, gastroenteritis, pneumonia, and wound infection) occurred in 9% in people taking teplizumab versus 0% in people taking placebo, during treatment and through 28 days after the last dose of study drug was given.[4] Lymphopenia has been associated with teplizumab use and should be discontinued in severe lymphopenia (<500 cells/μL) that persists for 1 week or longer. The average largest reductions in lymphocyte counts occurred at 5 days with return to baseline levels at week 6. Anemia has been associated with teplizumab compared to placebo, occurring in 27% and 23% of patients, respectively. Thrombocytopenia occurred in 13% of teplizumab treated patients and in 5% of those taking placebo.[4] Rash was a common, though generally not serious, adverse reaction and often would spontaneously resolve. Age-appropriate vaccines should be given to all people taking teplizumab before initiation of therapy. Teplizumab may cause fetal harm and patients should be advised to take appropriate precautions up to 30 days before becoming pregnant and during pregnancy.

Results from an open-label extension study of Protégé are available. However, the FDA determined that limited conclusions could be drawn from this data due to dramatic differences in follow up between teplizumab and placebo groups with a 1.4-fold longer median follow-up time in the teplizumab group.

Table 3. Teplizumab Adverse Reactions in Adult and Pediatric Patients Occurring in 5% or more of Patients.[4]

Adverse Reaction	Placebo (n=32)	Teplizumab (n=44)
Lymphopenia	6%	73%
Rash	0%	36%
Leukopenia	0%	21%
Headache	6%	11%
Neutropenia	3%	5%
Increased alanine aminotransferase	3%	5%
Nausea	3%	5%
Diarrhea	0%	5%
Nasopharyngitis	0%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) T1D diagnosis
2) Time to T1D diagnosis
3) HbA1c
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Median time to progression to clinical T1D
2) C-peptide levels
3) Composite outcome of daily insulin use and HbA1C levels below specified thresholds

Table 4. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	Binds to CD3 (a cell surface antigen on T-lymphocytes). Partial agonistic signaling and deactivation of pancreatic deactivation beta cell autoreactive T lymphocytes. Teplizumab increases the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.
Oral Bioavailability	NA
Distribution and Protein Binding	2.27 L
Elimination	Not described
Half-Life	4.5 days
Metabolism	Catabolic pathways into small peptides

Abbreviations: L – Liter; NA – not applicable

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Herold, et al[1] DB, Phase 2, PC, RCT	1. Teplizumab 51 mcg per square meter of body surface area on day zero, 103 mcg/m^2 on day one, 207 mcg/m^2 on day two, 413 mcg/m^2 on day three, 826 mcg/m^2 on days four through 13. Doses given as an IV infusion 2. Saline IV infusion Median follow-up: 745 days (2 years)	Demographics: Median age: 13.5 years Male: 55% Median HbA1c: 5.3% Median glucose: 160 mg/dL[2] Sibling with T1D: 57% White: 97% Key Inclusion Criteria: - Non-diabetic relatives of people with T1D - Ages 8 years to 45 years - At high risk for development of diabetes - Two or more diabetes related autoantibodies detected in two samples obtained within 6 months before randomization - Evidence of dysglycemia* during an OGTT Key Exclusion Criteria: - Clinically important medical histories - Abnormal laboratory chemical values - Abnormal blood counts (n=76)	ITT: 1. 44 2. 32 PP: 1. 41 2. 28 Attrition: 1. 3 (7%) 2. 4 (12%)	Median time to progression to clinical T1D based on OGTT : 1. 48.4 months 2. 24.4 months HR 0.41 (95% CI, 0.22 to 0.78) p-value = 0.006 Secondary Endpoint: T1D Diagnosis at year 1: 1. 3 (7%) 2. 14 (44%) HR 0.13 (95% CI, 0.05 to 0.34) P-value not provided	NA 37%/ 3	Dermatologic or skin (rash): 1. 16 (36%) 2. 1 (3%) Blood or bone marrow (lymphopenia): 1. 33 (75%) 2. 2 (6%) Infection: 1. 5 (11%) 2. 3 (9%) Pain: 1. 5 (11%) 2. 3 (9%) Cytokine Release Syndrome: 1. 1 (2%) 2. 0 (0%) Discontinuations due to adverse events: 1. 3 (7%) 2. 4 (13%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1 and stratified by those less than 18 years and those 18 and over. Randomization numbers and tables were done by the trial coordinating center. All participants in the teplizumab group were White compared to 93.8% in the placebo group. There were 15% more participants in the placebo group that were under the age of 18 years. Performance Bias: (low) Double-masked. Differences in adverse event rates could lead to unblinding. Detection Bias: (low) Efficacy and safety analysis was done by an independent medical monitor. Attrition Bias: (low) Attrition rates were low in both groups. Results were measured via ITT analysis and missing data will be assumed to be missing completely at random (MCAR) and no method will be used to impute missing data. Reporting Bias: (high) Due to slower than expected enrollment, the protocol was changed to detect a 60% lower risk of T1D in the teplizumab compared to placebo (instead of 50%) resulting in enrollment of 71 participants compared to 144. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results are most applicable to young adolescents that are White. The majority of patients were less than 18 years of age in the teplizumab and placebo groups, 66% and 81%, respectively which is consistent with age of onset for T1D. Intervention: Teplizumab dose was appropriate based on previous studies. Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D. Outcomes: Time to development of T1D is an appropriate outcome for a therapy used for this purpose. Setting: Thirty one sites in the United States, Canada, Australia and Germany.

2. Herold, et al[2] AbATE Phase 2, OL, RCT	1. Teplizumab*: 51 mcg/m^2 on day zero, 103 mcg/m^2 on day two, 206 mcg/m^2 on day three, 413 mcg/m^2 on day four, 826 mcg/m^2 on days five thru 14. Doses given as an IV infusion at diagnosis and after 1 year. 2. No infusion given/no treatment * Ibuprofen, diphenhydramine and acetaminophen premedication given for infusion-related reactions	Demographics: Median age: 12 years Male: 59% Time since diagnosis: 39 days Median HbA1c: 7.6% C-peptide AUC: 0.695 mmol/L Key Inclusion Criteria: - Ages 8 years to 30 years - Diagnosed with T1D within 8 weeks of study enrollment - Positive for anti-GAD65, anti-ICA512 or ICA. Key Exclusion Criteria: - Not described	mITT: 1. 56 2. 27 PP: 1. 52 2. 25 Attrition: 1. 4 (7%) 2. 2 (7%)	C-peptide levels at year 2: 1. -0.28 mmol/L (95% CI, -0.36 to -0.20) 2. -0.46 mmol/L (95% CI, -0.57 to -0.35) HR not provided P=0.002 Secondary Endpoints: HbA1C levels at year 2: 1. 7.5% 2. 7.7% (no CI provided) P=0.093	NA for all	Dermatologic or skin (rash): 1. 43 (83%) 2. 2 (8%) Blood or bone marrow (lymphopenia): 1. 1 (2%) 2. 0 (0%) Upper respiratory tract infection: 1. 32 (62%) 2. 14 (56%) Abdominal Pain: 1. 23 (44%) 2. 6 (24%) Cytokine Release Syndrome: 1. 5 (10%) 2. 0 (0%) Discontinuations due to Adverse Events: 1. 12 (21%) 2. 0 (0%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 2:1 within randomly ordered blocks of six or three. More people in the placebo group compared to teplizumab were male, 64% vs. 53.8%. Performance Bias: (high) Trial was open-label. Laboratory personnel were masked to treatment assignments. Detection Bias: (unclear) Not described. Attrition Bias: (low) Attrition rates were low in both groups. Results were measured via ITT analysis and missing data for the primary endpoint was imputed as zero if previous value was zero and if the value was more than zero then values among those in the same arm were regressed on AUC values from the prior time point. Reporting Bias: (high) Study was conducted per protocol. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results applicable to patients with early stage 3 T1D. Intervention: Teplizumab dose was appropriate based on previous studies. Comparator: No comparator given. Lack of comparator may bias results. Outcomes: C-peptide levels are an appropriate indicator of insulin production; however levels indicative of time to disease progression are unknown. Setting: Six study sites in North America.

3. Sherry, et al[3] PROTÉGÉ DB, MC, Phase 3, PC, RCT	1. Teplizumab 14-day full dose (total dose of 9,034 mcg/m^2 over 14 days) Repeated at week 26 2. Teplizumab 14-day low dose (total dose of 2,985 mcg/m2 over 14 days) Repeated at week 26 3. Teplizumab 6-day full dose (total dose of 2,426 mcg/m2 over 6 days, followed by 8 days of placebo) Repeated at week 26 4. Placebo * All participants were managed with exogenous insulin for T1D Trial duration: 2 years	Demographics: Mean age: 19 years Male: 63.5% Mean HbA1c: 8.25% White: 71% Key Inclusion Criteria: - Age 18 to 35 years - Body mass ≥36 kg - ≤ 12 weeks of diagnosis for clinical T1D and requirement for exogenous insulin (stage 3) - Detectable fasting or stimulated C-peptide - Positive for antibody titers against ICA-512/IA-2, GAD-65 or insulin ≤ 2 weeks of starting insulin therapy Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety - Recent participation in a clinical trial - Recent vaccination - Pregnancy N=516	ITT: 1. 207 2. 102 3. 106 4. 98 PP: 1. 162 2. 79 3. 82 4. 87 Attrition: 1. 45 (22%) 2. 23 (23%) 3. 24 (23%) 4. 11 (11%)	Composite of percentage of patients with insulin use of less than 0.5 U/kg per day and HbA1c of less than 6.5% at 1 year: 1. 41 (19.8%) 2. 14 (13.7%) 3. 22 (20.8%) 4. 20 (20.4%) CI and p-values not provided Secondary Endpoints: Endpoints were considered exploratory because primary outcome was not significant, as prespecified in the protocol	NA for all	Dermatologic or skin (rash): 1. 117 (56%) 2. 58 (57%) 3. 56 (53%) 4. 21 (21%) Cytokine Release Syndrome: 1. 12 (6%) 2. 2 (2%) 3. 8 (8%) 2. 0 (0%) Blood or bone marrow (lymphopenia): 1. 181 (87%) 2. 88 (86%) 3. 85 (80%) 4. 51 (52%) Infection: 1. 94 (45%) 2. 53 (52%) 3. 55 (52%) 2. 54 (55%) Gastrointestinal disorders: 1. 71 (34%) 2. 31 (30%) 3. 44 (42%) 4. 26 (26%) Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (4%) 3. 2 (2%) 2. 1 (1%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Patients were randomized 2:1:1:1 by an interactive telephone system according to a computer-generated block randomization by third party organization. Baseline characteristics were well matched. Performance Bias: (low) Medication were made using a double-dummy design and dosing was double blind. Detection Bias: (low) Data analysis was done by an independent data monitoring committee. Attrition Bias: (unclear) Attrition was high in all teplizumab treatment groups. More patients in treatment groups had missing data compared to placebo. Participants with missing data were designated as non-responders. Reporting Bias: (low) Study conducted according to protocol. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results are most applicable to young adults who are White with a recent diagnosis of T1D. Intervention: Teplizumab dose was appropriate based on previous studies. Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D. Outcomes: Composite of insulin use and A1c appropriate to evaluate clinically significant disease progression. Setting: Eighty-three medical centers in North America, Europe, Israel and India.

Key: * Dysglycemia defined as fasting glucose level of 110 to 125 mg/dL, 2-hour post-prandial plasma glucose level of at least 140 mg per dL and less than 200 mg per dL or an intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per dL on two occasions, within 52 days before enrollment. The protocol was amended to include participants younger than 18 who had a single abnormal OGTT because rates of progression to T1D was similar with or without a confirmatory OGTT.
Abbreviations: AUC = area under the curve; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; GAD = glutamic acid decarboxylase; ITT = intention to treat; ICA = islet-cell antigen; IV = intravenous; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OGTT = oral glucose tolerance test; PC = placebo-controlled; PP = per protocol; T1D = type 1 diabetes.

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3. Sherry N, Hagopian W, Ludvigsson J, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. 2011;378(9790):487-497. doi:10.1016/S0140-6736(11)60931-8.

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Appendix 1: Prescribing Information Highlights

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

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

---------- INDICATIONS AND USAGE----------
TZIELD is a CD3-directed antibody 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 (1).

----------DOSAGE AND ADMINISTRATION----------
- Confirm Stage 2 T1D by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available (2.1).
- In patients who meet criteria for a diagnosis of Stage 2 type 1 diabetes, ensure the clinical history of the patient does not suggest type 2 diabetes (2.1).
- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests. Use of TZIELD is not recommended in patients with certain laboratory abnormalities (2.2).
- Must dilute TZIELD in 0.9% Sodium Chloride Injection, USP. See full prescribing information for detailed preparation and administration instructions (2.3, 2.4, 2.5).
- Premedicate with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic before each TZIELD dose for at least the first 5 days of the 14-day treatment course (2.3).
- Administer TZIELD by intravenous infusion (over a minimum of 30 minutes) once daily for 14 days. See full prescribing information for the dosing schedule (2.4).

---------- DOSAGE FORMS AND STRENGTHS----------
Injection: 2 mg per 2 mL (1 mg/mL) single-dose vial (3).

---------- CONTRAINDICATIONS ----------
None. (4).

---------- WARNINGS AND PRECAUTIONS ----------
- *Cytokine Release Syndrome (CRS):* Premedicate, monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal, and if severe CRS develops consider temporarily pausing dosing (5.1).
- *Serious Infections:* Use of TZIELD is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after TZIELD treatment. If a serious infection develops, discontinue TZIELD (5.2).
- *Lymphopenia:* Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD (5.3).
- *Hypersensitivity Reactions:* If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly (5.4).
- *Vaccinations:* Administer all age-appropriate vaccinations prior to starting TZIELD. See recommendations regarding live-attenuated, inactivated, and mRNA vaccines (2.2, 5.5).

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache (6.1).

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: May cause fetal harm (8.1).
- Lactation: A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration (8.2).

To report SUSPECTED ADVERSE REACTIONS, contact Provention Bio at 1-844-778-2246 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

Teplizumab

Goal(s):

- To optimize the safe and effective use of teplizumab for *prevention* of type 1 diabetes mellitus (T1DM).

Length of Authorization:

- One 14-day treatment course.

Requires PA:

- All provider-administered and pharmacy point-of-sale claims for teplizumab

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is the request for an FDA approved age (e.g. 8 years of age or older)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Has the patient previously been treated with teplizumab (use beyond the original 14 day infusion)?	**Yes:** Pass to RPh. Deny; medical appropriateness. No evidence to support additional doses.	**No:** Go to #3
3. Is the medication prescribed by or in consultation with an endocrinologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
4. Does the patient meet the standard criteria for the diagnosis of type 1 diabetes as determined as having one of the following: - HbA1c of 6.5% or higher **OR** - Fasting plasma glucose (FPG) of 126 mg/dL or higher **OR** - Oral glucose tolerance test (OGTT) of 200 mg/dL or higher?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Have baseline liver function tests and complete blood panel been evaluated in the past 2 months?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Has the patient received, or have contraindications to, all routine immunizations recommended for their age based on provider attestation of immunization history? Note: - Teplizumab labeling recommends administration of live-attenuated vaccines at least 8 weeks prior to treatment and inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment. - Routine vaccinations for patients at least 8 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #7 Document provider attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		

7. Is the person at high risk of developing T1DM (e.g. Stage 2 diabetes) as determined by having the following:
- Presence of two or more diabetes-related autoantibodies (e.g. insulin autoantibodies (IAA), islet cell antibodies (ICA), glutamic acid decarboxylase 65 (GAD) autoantibodies, insulinoma-associated antigen 2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A)) **AND**
- Abnormal glucose confirmed within the last 2 months as determined by one of the following:
  - An abnormal glucose during an OGTT (140-199 mg/dL) **OR**
  - FPG 100-125 mg/dL **OR**
  - HbA1c 5.7-6.4% or ≥10% increase in HbA1c **OR**
  - 2-hour plasma glucose 140-199 mg/dL
 	
Note: Teplizumab is preventative therapy and not approved at this time for people diagnosed with symptomatic T1DM (e.g. Stage 3)
	Yes: Approve for one 14-day course.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 4/23 (KS)
Implementation: 5/1/23