New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Tzield™ (teplizumab-mzwv) [Provention Bio and Sanofi]** (TEE-zeeld)
Dosage Formulations:	Single-dose vial for injection: 2 mg per 2 mL
FDA Approval Date: **FDB File Date:**	FDA: November 17, 2022 FDB: November 27, 2022
Indication:	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.
Mechanism of Action:	Teplizumab-mzwv binds to CD3 (a cell surface antigen present on T lymphocytes). The mechanism may involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.

Dose/ Administration:	Administer Tzield by intravenous infusion (over a minimum of 30 minutes), using a body surface area (BSA)- based dosing, once daily for 14 consecutive days as follows:
	
	Day 1: 65 mcg/m^2
	Day 2: 125 mcg/m^2
	Day 3: 250 mcg/m^2
	Day 4: 500 mcg/m^2
	Days 5 through 14: 1,030 mcg/m^2
	
	<u>Recommendations Regarding Missed Dose(s):</u> if a planned Tzield infusion is missed, resume dosing by administering all remaining doses on consecutive days to complete the 14-day treatment course. Do not administer two doses on the same day.
	
	<u>Preparation</u>:
	• Using aseptic technique, remove 2mL of Tzield from the vial and slowly add to 18mL of 0.9% Sodium Chloride injection.
	• Using an appropriately sized syringe, withdraw the volume of diluted Tzield solution required for that day's calculated dose.
	• Slowly add the contents of the syringe containing the Tzield dose to a 25mL 0.9% Sodium Chloride injection PVC infusion bag.
	• Start Tzield infusion within 2 hours of preparation. If not used immediately, store the infusion solution at room temperature and complete infusion within 4 hours of the start of preparation.
	
	<u>Other important information:</u>
	• Consider pretreatment for the first 5 days of dosing with a non-steroidal anti-inflammatory drug (NSAID) or acetaminophen, an antihistamine, and/or an antiemetic.
	• Tzield has not been studied and may interfere with the immune response to vaccination and decrease vaccine efficacy. Administer all age-appropriate vaccinations prior to starting Tzield. Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to Tzield treatment, during treatment, or 6 weeks after completion of treatment. Live-attenuated vaccinations are not recommended within the 8 weeks prior to Tzield treatment, during treatment, or up to 52 weeks after treatment.
	• Use of Tzield is not recommended in patients with
	  ○ Lymphocyte count < 1,000/mcL
	  ○ Hemoglobin < 10 g/dL
	  ○ Platelet count < 150,000/mcL
	  ○ Absolute neutrophil count < 1,500/mcL
	  ○ ALT or AST > 2 times the upper limit of normal (ULN)
	  ○ Bilirubin > 1.5 x ULN

	○ Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV) ○ Active serious infection or chronic active infection other than localized skin infections
Disease State Clinical Highlights:	Approximately 1 million to 1.5 million Americans have T1D, which is one of the most common diseases of childhood, with the annual incidence is 22.3 per 100,000 amongst children and adolescents (overall incidence is 15 per 100,000 people). Approximately 45 percent of children present with childhood-onset T1D before 10 years of age. The age of presentation has a bimodal distribution, with peaks at 4 to 6 years of age and between 10 and 14 years of age. Type 1 diabetes results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans. Several clinically useful serum autoantibodies can be detected, including islet cell antibodies (ICA), insulin autoantibodies (IAA), antibodies to glutamic acid decarboxylase (GAD), antibodies to tyrosine phosphatase-like proteins such as insulinoma-associated protein (IA-2, ICA512), and antibodies to the zinc transporter 8 (ZnT8). Sixty to 80 percent of patients with newly diagnosed type 1 diabetes have ZnT8 autoantibodies. In addition, 26% of subjects with antibody negative (insulin, GAD, IA-2 and ICA) type 1 diabetes have ZnT8 autoantibodies. Risk of T1D is highest in those with multiple autoantibodies (40 percent risk of developing T1D within first five years of life versus 3 percent in those with single autoantibodies). The lifelong risk of T1D is markedly increased in close relatives of a patient with type 1 diabetes, averaging approximately 6 percent in offspring, 5 percent in siblings, and 50 percent in identical twins (versus 0.4 percent in subjects with no family history). In genetically susceptible persons, T1D progresses through asymptomatic stages before the development of overt hyperglycemia. In stage 1, patients have normal blood glucose levels but possess beta cell autoimmunity (≥2 islet autoantibodies). In stage 2, metabolic responses to a glucose load are impaired and patients start to show dysglycemia. Other metabolic indexes - for example, the level of glycosylated hemoglobin - remain normal, and insulin treatment is not needed. Patients remain asymptomatic in stage 2, which may lead to delay in diagnosis until stage 3 when signs and symptoms including polyuria, polydipsia, weight loss, and lethargy are recognized. However, diabetic ketoacidosis (DKA) is often the initial presentation for T1D, especially in children younger than six years of age because it may be difficult to recognize the symptoms of hyperglycemia. Stage 4 marks longstanding T1D. Insulin administration is the core treatment for all patients with T1DM, however, hypoglycemia is the most common acute complication of T1D in childhood. Severe and acute hypoglycemia can lead to acute and permanent neurologic complications. DKA is a common and potentially life-threatening complication of T1D. Vascular complications, such as nephropathy, retinopathy, neuropathy, and cardiovascular disease) typically become clinically apparent in adulthood, however the pathogenesis begins at disease onset.
Drug Clinical Highlights:	<u>Contraindications:</u> none <u>Warnings/Precautions:</u> • Cytokine Release Syndrome (CRS) ○ Prior to Tzield, consider premedicate with antipyretics, antihistamines and/or antiemetics. ○ Monitor liver enzyme during treatment; discontinue in patients who develop elevated ALT or AST > 5 times the upper limit of normal (ULN), or bilirubin > 3 x ULN. ○ Treat symptoms of CRS with antipyretics, antihistamines and/or antiemetics. If severe CRS develops, consider temporarily pausing dosing for 1-2 days (and administer the remaining doses to complete the full 14-day course on consecutive days) or discontinuing treatment.

- In clinical trials, CRS was reported in 5% of Tzield-treated patients compared to 0.8% of control-treated patients during the treatment period and through 28 days after the last study drug administration. CRS manifestations included fever, nausea, fatigue, headache, myalgia, arthralgia, increased ALT, increased AST, and increased total bilirubin. These manifestations typically occurred during the first 5 days of treatment.

- Serious Infections
  - Bacterial and viral infections have occurred in Tzield-treated patients. In clinical trials, Tzield-treated patients had a higher rate of serious infections (3.5%) than control-treated patients (2%), including gastroenteritis, cellulitis, pneumonia, abscess, sepsis.
  - Use of Tzield is not recommended in patients with active serious infection or chronic infection other than localized skin infections.
  - Monitor patients for signs and symptoms of infection during and after Tzield treatment. If serious infection develops, treat appropriately, and discontinue Tzield.
- Lymphopenia
  - In clinical trials, 78% of Tzield-treated patients developed lymphopenia compared to 11% of control-treated patients. For most Tzield-treated patients who experienced lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pre-treatment values within two weeks after treatment completion and without dose interruption.
  - Severe lymphopenia (<500 cells/mcL) lasting 1 week or longer occurred in 0.9% of Tzield-treated patients. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells/mcL lasting 1 week or longer) develops, discontinue Tzield.
- Hypersensitivity Reactions
  - Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in Tzield-treated patients. If severe hypersensitivity reactions occur, discontinue use of Tzield and treat promptly.

<u>Pregnancy/Lactation:</u>

- Although there are insufficient data to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes, monoclonal antibodies can be actively transported across the placenta, and Tzield may cause immunosuppression in the utero-exposed infant. To minimize exposure to a fetus, avoid use of Tzield during pregnancy and at least 30 days prior to planned pregnancy.
- There are no data on the presence of Tzield in either human or animal milk, the effects on the breastfed child, or the effects on milk production.

<u>Clinical Studies:</u>

- PROTÉGÉ study (NCT00385697: Teplizumab for treatment of type 1 diabetes): multi-center, randomized, placebo-controlled trial in patients aged 8 to 35 years who were diagnosed with T1D for 12 weeks or fewer.
  - Key Inclusion Criteria:
    - Age 8 to 35 years
    - Body mass of at least 36 kg
    - Diagnosed with type 1 diabetes mellitus for 12 weeks or fewer
  - Patients were randomly assigned (2:1:1:1 ratio) to receive treatment in one of four parallel groups:
    - 14-day course of escalating doses of intravenous teplizumab, with a total cumulative dose of about 9034 mcg/m^2 (14-day full-dose group)
    - 14-day course of escalating doses of intravenous teplizumab, with a total cumulative dose of about 2985 mcg/m^2 (14-day low-dose group)
    - 6-day course of escalating doses of intravenous teplizumab plus 8 days of intravenous placebo, with a total cumulative dose of about 2426 mcg/m^2 (6-day full-dose group)

        - 14-day course of intravenous placebo (placebo group). All treatments were repeated at week 26.
    - Primary Outcome and Conclusions:
        - Change in insulin use from baseline did not differ between the 14-day full-dose group and placebo.
        - The proportion of patients who achieved HbA1C of less than 7% and insulin use of less than 0.25 units/kg per day was greater in the 14-day full-dose group than in the placebo group for the study overall. A similar effect was seen at HbA1C of less than 6.5% and insulin use of less than 0.25 units/kg per day (p=0·02).
        - Rash, the most common clinical adverse event in the teplizumab groups, occurred in a higher proportion of patients than in the placebo group. With median onset at day 6 (Interquartile range [IQR] 5–11), rash was usually mild to moderate (218/220 [99%]), self-limited in all but one patient, most often maculopapular (132/220 [60%]), and sometimes pruritic 56/220 (25%).
        - The effect of teplizumab was only seen with the highest dose (two courses of 17 mg, 6 months apart, in a 70 kg individual on the basis of a cumulative dose of 90,343mcg/m^2 and a body surface area of 1.92 m^2), yielding a cumulative dose per cycle that was half that in the previous study of teplizumab.
        - Larger treatment effects were associated with younger age and earlier treatment.
        - Findings of this study showed that teplizumab had a treatment effect on preserving C-peptide secretion and therefore allowing glycemic control to be achieved at a lower insulin dose, particularly in selected, prespecified subgroups.
            - An exploratory analysis of the Protégé study suggested that future studies of teplizumab may have increased success in preventing decline in beta-cell function (as measured by C-peptide) and providing glycemic control at reduced doses of insulin if the target population is recently diagnosed patients and children.
- TN-10 (NCT01030861: Teplizumab for Prevention of Type 1 Diabetes in Relatives “At-risk”): phase II, randomized, placebo-controlled, double-blind trial in relatives of patients with T1D who did not have diabetes but were at high risk of developing clinical disease.
    - Key inclusion criteria:
        - Between the age of 8 to 45 years
        - Relative of a proband with T1D (proband is an individual diagnosed with diabetes before age 40 and started on insulin therapy within one year of diagnosis)
            - If the proband is a second or third degree relative (niece, nephew, aunt, uncle, grandchild, cousin), the study participant must be 8 to 20 years of age
        - An abnormal glucose tolerance by OGTT confirmed within 7 weeks of baseline
            - Fasting plasma glucose (FPG) ≥ 110 mg/dL, and < 126 mg/dl or
            - Two hour plasma glucose ≥ 140 mg/dL, and < 200 mg/dl or
            - 30, 60, or 90 minute value on OGTT ≥200mg/dl
        - At least 2 diabetes-related autoantibodies confirmed to be present on two occasions, including anti-GAD65, anti-ICA512, anti-insulin (MIAA), and ICA.
            - Confirmation of 2 positive autoantibodies must occur within the previous six months but confirmation does not have to involve the same 2 autoantibodies.
        - Weigh at least 26 kg at randomization
    - Key exclusion criteria:
        - Diagnosis of diabetes
        - Overt hyperglycemia (FPG ≥ 126 mg/dL or 2 hour plasma glucose ≥ 200 mg/dL)
        - Lymphopenia, neutropenia, thrombocytopenia, anemia, elevated AST/ALT or INR
        - History of infectious mononucleosis within the 3 months prior to enrollment
        - Laboratory or clinical evidence of acute infection with EBV or CMV

- Serological evidence of current or past HIV, Hepatitis B or Hepatitis C infection
- Other autoimmune disease (asthma or atopic disease requiring chronic treatment, untreated hypothyroidism, active Graves' disease) or chronic use of steroids or other immunosuppressive agents
- Prior OKT®3 (Muromonab-CD3) or other anti-CD3 treatment
- Administration of a monoclonal antibody within the year before randomization

- Total of 76 participants (55 [72%] of whom were ≤18 years of age) underwent randomization — 44 to the teplizumab group and 32 to the placebo group.

	Tzield N = 44	**Placebo N = 32**
Age group		
≥ 18 years < 18 years	34% 66%	19% 81%
Pediatric Age Group Quartiles		
8 to < 11 years 11 to < 14 years 14 to < 18 years	21% 27% 18%	25% 31% 25%
Male sex No. of subjects (%)	25 (56.8)	17 (53.1)
Body Mass Index (kg/m^2)-median (IQR) Z-score -median (IQR)	19.6 (17.3 – 25.4) 0.259 (-0.754 - 1.19)	21.5 (18.2 – 24.7) 0.681 (0.339 – 1.11)
Race – No. of subjects (%)		
White African American Asian	44 (100.0) 0 (0.0) 0 (0.0)	30 (93.8) 0 (0.0) 2 (6.2)
Ethnicity – No. of subjects (%) Non-Hispanic	43 (97.7)	31 (96.9)
Glucose, mg/dL Median (min, max)	165 (115, 207)	154 (103, 200)
HbA1C Median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)
Autoantibodies titer – median		
Anti-GAD65 Micro Insulin Anti-IA-2 ICA Zinc Transporter	240 (76.8 – 464) 0.0070 (0.0020 – 0.028) 52 (0 – 310) 20 (0 – 200) 0.157 (0.0133 – 0.496)	221 (42.3 – 520) 0.0040 (0.0020 – 0.0168) 187 (26 – 253) 80 (20 – 160) 0.096 (0.028 – 0.386)
No. of Autoantibodies Positive (% of total)		
1 2 3 4 5	1 (2.4) 11 (25.0) 12 (27.3) 11 (25.0) 9 (20.5)	0 (0.0) 7 (21.9) 5 (15.6) 14 (43.8) 6 (18.8)
C-peptide AUC Mean, OGTT (nmol/L) Median (IQR)	1.76 (1.47 – 2.18)	1.73 (1.44 – 2.36)

- Patients were randomly assigned to a single 14-day course of teplizumab or placebo, and follow-up for progression to clinical type 1 diabetes was performed with the use of oral glucose-tolerance tests at 6-month intervals.
- Conclusion:
  - Median time to the diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group; the disease was diagnosed in 19 (43%) of the participants who received teplizumab and in 23 (72%) of those who received placebo.

- The hazard ratio for the diagnosis of type 1 diabetes (teplizumab vs. placebo) was 0.41 (95% confidence interval, 0.22 to 0.78; P= 0.006 by adjusted Cox proportional-hazards model).
- The annualized rates of diagnosis of diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group.

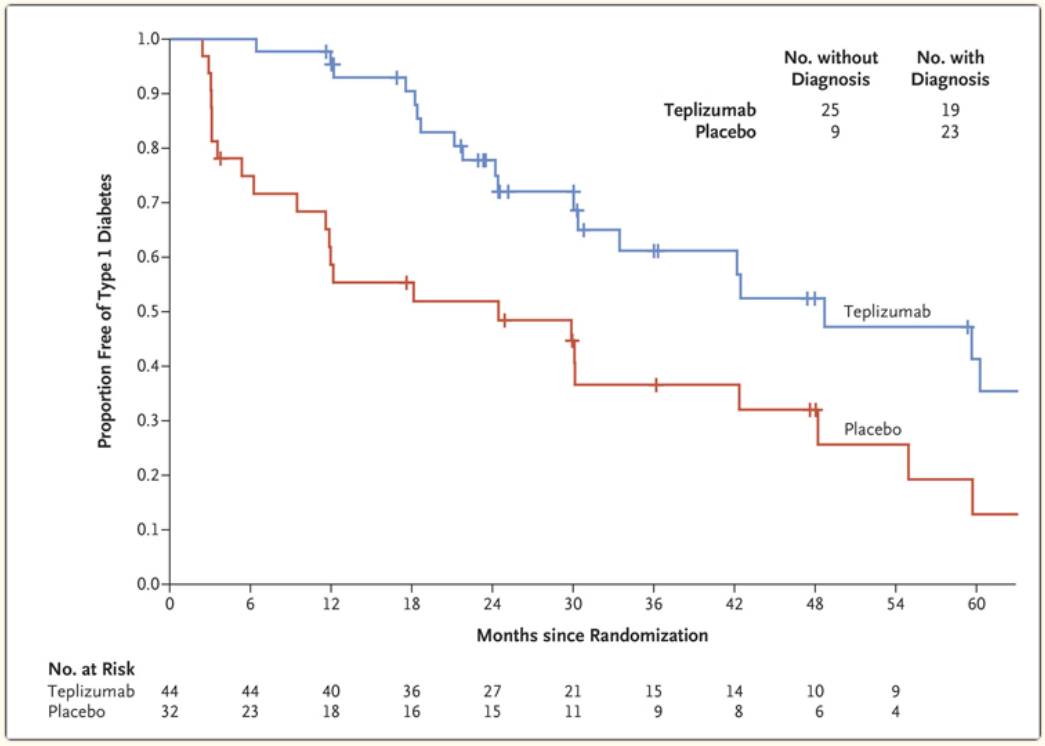
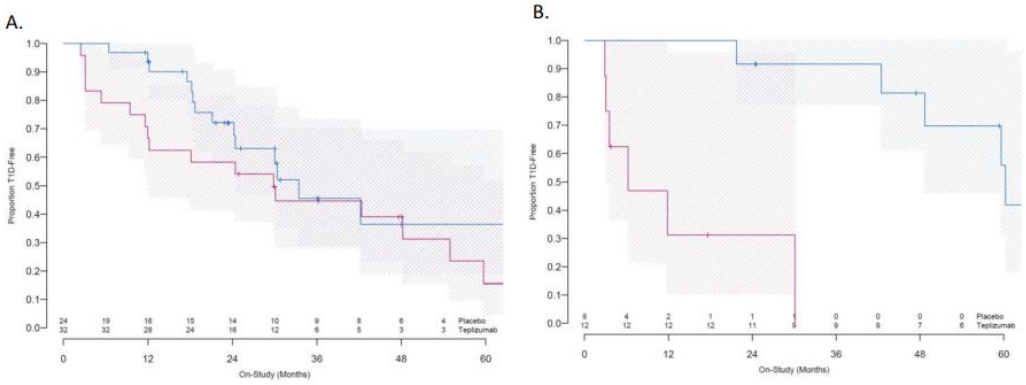


Figure 1.

Effects of Teplizumab on Development of Type 1 Diabetes.

- Subgroup analysis:
  - Anti-ZnT8 were presence in 73% of treatment group and 75% of non-treatment group. The response to teplizumab as compared with placebo was greater among participants without ZnT8 antibodies than among those with these antibodies (hazard ratio, 0.07; 95% CI, 0.02 to 0.26)



Supplementary Appendix Figure S7: The effects of teplizumab treatment in participants with (A) and without (B) anti-ZnT8 antibodies at randomization. The absence of anti-ZnT8 antibody (Hazard ratio: 0.064 for negative, 0.831 for positive) was associated with response to teplizumab. (For each graph ----- = teplizumab, ----- = placebo, + = censored. The number of participants at risk are shown along the X axis. The shaded areas represent the 95% CIs.)

	○ Safety: **Adverse Reaction** / **Tzield N = 44** / **Placebo N = 32** Lymphopenia 73% 6% Rash 36% 0% Leukopenia 21% 0% Headache 11% 6% Neutropenia 5% 3% Increased alanine aminotransferase 5% 3% Nausea 5% 3% Diarrhea 5% 0% Nasopharyngitis 5% 0% ▪ Lymphocyte count decreased to a nadir on day 5 (total decrease, 72.3%; interquartile range (IQR), 82.1 to 68.4; P<0.001). A total of 15 (75%) of the 20 grade 3 events in the teplizumab group involved lymphopenia during the first 30 days after administration. Lymphopenia resolved by day 45 in all participants except one; in that participant, the lymphocyte counts returned to the normal range on day 105. ▪ A spontaneously resolving rash, as previously noted, occurred in 16 (36%) of participants who received teplizumab. ▪ The rates of infection were similar in the two treatment groups. ▪ Epstein-Barr virus reactivation: ➢ At trial entry, 30 participants (39%; 16 in the teplizumab group and 14 in the placebo group) had antibodies against EBV. At weeks 3 through 6 after receipt of the trial regimen, there was quantifiable EBV DNA in whole blood in 8 of the seropositive participants - all in the teplizumab group - one of whom had symptoms of pharyngitis, rhinorrhea, and cough on day 38. In these participants, the EBV DNA levels decreased to below the level of quantification between day 43 and day 134 (mean day 77). ➢ At trial entry, 17 participants (10 in the teplizumab group and 7 in the placebo group) had antibodies against cytomegalovirus (CMV). One participant in the teplizumab group who was CMV-seropositive had detectable levels of CMV DNA at day 20, but CMV DNA was undetectable by day 42. • TN-10 extended period follow-up (Teplizumab improves and stabilizes beta cell function in antibody positive high-risk individuals): ○ The average on-study C-peptide AUC was greater in the teplizumab treatment group vs placebo (unadjusted mean (IQR): 1.96 (1.48, 2.61) pmol/ml vs 1.68 (1.32, 2.11) pmol/ml and when adjusted for the age and baseline C-peptide AUC, the differences were highly significant (p=0.006) ○ Higher average on-study C-peptide AUC in individuals that remained diabetes free (compared to those that progressed to T1D). However, there was not a clear drug effect when the average C-peptide levels were compared in those who were diagnosed and remained diabetes free.
Price Per Unit (WAC):	• $13,850 per vial • Estimated course of therapy: $193,900 (average 14 year old patient with BSA = 1.5) • Estimated course of therapy if BSA is greater than 1.942: $332,400
Therapeutic Alternatives:	The standard of care for treating clinical-stage T1D is insulin therapy and glucose monitoring. There are no disease-modifying or preventative therapies available for T1D. Delaying the onset of T1D would be clinically meaningful for individuals at risk of developing T1D because the burden of insulin injection and blood glucose monitoring could be delayed until patients are better able to manage their disease, potentially avoiding long-term complications. Teplizumab is the only late-stage anti-CD3 antibody in development for the delay of T1D.

Prior Authorization Approval Criteria:	**Must meet the following criteria:**
	
	Approval Criteria:
	• Age 8 years or older **AND**
	• Prescribed by or in consultation with an endocrinologist or an appropriate specialist for the treated disease **AND**
	• Diagnosis of Stage 2 type 1 diabetes by documenting:
	  ○ At least 2 positive pancreatic islet cell autoantibodies within 6 months **AND**
	  ○ Abnormal glucose tolerance by oral glucose tolerance test (OGTT) confirmed within 7 weeks of baseline visit using:
	  ▪ FPG greater than 110mg/dL and less than 126 mg/dL **OR**
	  ▪ 2 hour glucose greater or equal to 140 mg/dL and less than 200 mg/dL **OR**
	  ▪ 30, 60, or 90 minute value on OGTT greater than or equal to 200 mg/dL
	• Approval is for one time (14 days).
	
	Denial Criteria:
	• Participant is in Stage 1, 3 or 4 of type 1 diabetes
	• Documented history of type 2 diabetes
	• Participant is currently pregnant
	• Documented previous treatment with teplizumab
	
	Additional Provider Diagnostic/Monitoring Criteria, if desired:
	• Tzield has not been studied in patient who had received other monoclonal antibodies in the previous year.
	• Tzield is not recommended in patients with:
	  ○ Lymphocyte count < 1,000/mcL
	  ○ Hemoglobin < 10 g/dL
	  ○ Platelet count < 150,000/mcL
	  ○ Absolute neutrophil count < 1,500/mcL
	  ○ ALT or AST > 2 x ULN
	  ○ Bilirubin > 1.5 x ULN
	  ○ Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
	  ○ Active serious infection or chronic active infection other than localized skin infections

Implication to State Medicaid Program:	• LOE: 11/17/2034 (Orphan Drug Exclusivity until 11/17/29 and Biologic Data Exclusivity until 11/17/34). • Provention Bio estimates that 30,000 patients may qualify for Tzield treatment at launch. Currently, there are no novel agents in late-stage development for the delay of T1D that would directly compete with Tzield in the near term. • Provention Bio is collaborating with Precigen ActoBio to investigate the combination of Tzield and orally administered AG019 to treat recent-onset T1D (NCT03751007). This potentially stabilizes or improves endogenous insulin production. Submitted results (pending Quality Control review) showed treatment with daily AG019 monotherapy or daily AG019 for 8 weeks in combination with daily IV infusions of teplizumab for 12 days resulted in an HbA1C below 7% for the majority of participants. • PROTECT trial (and PROTECT Extension trial) are active phase III trials to determine whether teplizumab slows the loss and preserves the function of beta cells in children and adolescents 8 to 17 years of age who were recently diagnosed with T1D (Stage 3). Treatment arm will consist of two 12-day courses of teplizumab 6 months apart. • If approved by the FDA, Lantidra™ (donislecel) will be indicated for the treatment of brittle type 1 diabetes mellitus (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy. • Diamyd (diabetes treatment vaccine) is currently in a Phase III trial to improve glycemic control in type 1 diabetes.

- The active ingredient in the vaccine is GAD65, an enzyme that occurs naturally in the pancreatic beta cells that helps them work properly and continue producing insulin.
- Diamyd's vaccine supplements the GAD65 enzyme, aiming to stop this destructive process.

- Phase II/III study of sitagliptin in relatives of patients with T1D is expected to start in December 2022 and to complete in 2027.

References:

1. Tzield™ (teplizumab-mzwv) [package insert]. Red Bank, NJ: Provention Bio, Inc; November 2022
2. Divers J, Mayer-Davis EJ, et.al. Trends in Incidence of Type 1 and Type 2 Diabetes Among Youths - Selected Counties and Indian Reservations, United States, 2002-2015. MMWR Morb Mortal Wkly Rep. 2020 Feb 14;69(6):161-165. doi: 10.15585/mmwr.mm6906a3. PMID: 32053581; PMCID: PMC7017961.
3. G, Bullard KM, Mayer-Davis E, Cowie CC. The prevalence of type 1 diabetes in the United States. Epidemiology 2013;24:773-774
4. Herold KC, Bundy BN, et. al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med. 2019 Aug 15;381(7):603-613. doi: 10.1056/NEJMoa1902226. Epub 2019 Jun 9. Erratum in: N Engl J Med. 2020 Feb 6;382(6):586. PMID: 31180194; PMCID: PMC6776880.
5. Hirsch, I. Pathogenesis of type 1 diabetes mellitus. Up To Date. Available from https://www.uptodate.com/contents/pathogenesis-of-type-1-diabetes-mellitus?search=type%201%20diabetes&topicRef=5816&source=see_link. Updated 8 June 2022. Accessed 2 December 2022.
6. Hirsch, I. Prediction of type 1 diabetes mellitus. Up To Date. Available from https://www.uptodate.com/contents/prediction-of-type-1-diabetes-mellitus?search=diabetes&topicRef=5816&source=see_link. Updated 21 January 2022. Access 2 December 2022.
7. Letvisky LL, Misra M. Complications and screening in children and adolescents with type 1 diabetes mellitus. Up To Date. Available from https://www.uptodate.com/contents/complications-and-screening-in-children-and-adolescents-with-type-1-diabetes-mellitus?search=diabetes&topicRef=5816&source=see_link. Updated 7 March 2022. Access 2 December 2022.
8. Levitsky LL, Misra M. Epidemiology, presentation, and diagnosis of type 1 diabetes mellitus in children and adolescents. Up To Date. Available from https://www.uptodate.com/contents/epidemiology-presentation-and-diagnosis-of-type-1-diabetes-mellitus-in-children-and-adolescents?search=diabetes&topicRef=1791&source=related_link. Updated 20 June 2022. Accessed 2 December 2022.
9. Mobasseri M, Shirmohammadi M, et.al. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. Health Promot Perspect. 2020 Mar 30;10(2):98-115. doi: 10.34172/hpp.2020.18. PMID: 32296622; PMCID: PMC7146037.
10. Nourelden AZ, Elshanbary AA, et.al. Safety and Efficacy of Teplizumab for Treatment of Type One Diabetes Mellitus: A Systematic Review and Meta-Analysis. Endocr Metab Immune Disord Drug Targets. 2021;21(10):1895-1904. doi: 10.2174/1871530320999201209222921. PMID: 33302842.
11. Sherry N, Hagopian W, et.al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. Lancet. 2011 Aug 6;378(9790):487-97. doi: 10.1016/S0140-6736(11)60931-8. Epub 2011 Jun 28. PMID: 21719095; PMCID: PMC3191495.
12. Sims EK, Bundy BN, et.al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med. 2021 Mar 3;13(583):eabc8980. doi: 10.1126/scitranslmed.abc8980. PMID: 33658358; PMCID: PMC8610022.