NEW DRUG APPROVAL

Brand Name	Tzield™
Generic Name	teplizumab-mzwv
Drug Manufacturer	Provention Bio, Inc.

New Drug Approval

FDA approval date: November 17, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA) 761183

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. Insulin is an essential anabolic hormone that exerts multiple effects on glucose, lipid, protein, and mineral metabolism, as well as growth. Importantly, insulin allows glucose to enter muscle and adipose cells, stimulates the liver to store glucose as glycogen and synthesize fatty acids, stimulates the uptake of amino acids, inhibits the breakdown of fat in adipose tissue, and stimulates the uptake of potassium into cells. People with T1DM require life-long insulin replacement therapy. Without insulin, diabetic ketoacidosis (DKA) develops and is life-threatening.

Epidemiology: Epidemiological studies estimate a prevalence of 1 in 300 children in the United States with an increasing incidence of 2%-5% annually worldwide.

Efficacy

The effectiveness of Tzield™ was investigated in a randomized, double-blind, event-driven, placebo-controlled study (Study TN-10; NCT01030861) in 76 patients, 8 to 49 years of age with Stage 2 type 1 diabetes. Stage 2 type 1 diabetes was defined as having both of the following:

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

In this study, patients were randomized to receive Tzield™ or placebo once daily by intravenous infusion for 14 days. Patients in the Tzield™ group had a total drug exposure that was comparable to the total drug exposure achieved with the recommended total Tzield™ dosage. The primary efficacy endpoint in this study was the time from randomization to development of Stage 3 type 1 diabetes diagnosis.

Baseline Patient Characteristics: In this study, 45% were female; 97% White, 1% Asian, and 1% reported multiracial background; 3% were Hispanic or Latino ethnicity; and 95% were from the United States. The median age was 14 years (72% were <18 years old) (Table 1).

Table 1: Baseline Age Characteristics of Adults and Pediatric Patients 8 Years of Age and Older with Stage 2 Type 1 Diabetes (Study TN-10)[1]		
	Tzield™ (N=44)	Placebo (N=32)
Age Group		
≥ 18 Years	34%	19%
< 18 years	66%	81%
Pediatric Age Group Quartiles		
8 to <11 years	21%	25%
11 to <14 years	27%	31%
14 to <18 years	18%	25%

[1] Intent to treat (ITT) population

Baseline Disease Characteristics: Table 2 displays the baseline disease characteristics in Study TN-10.

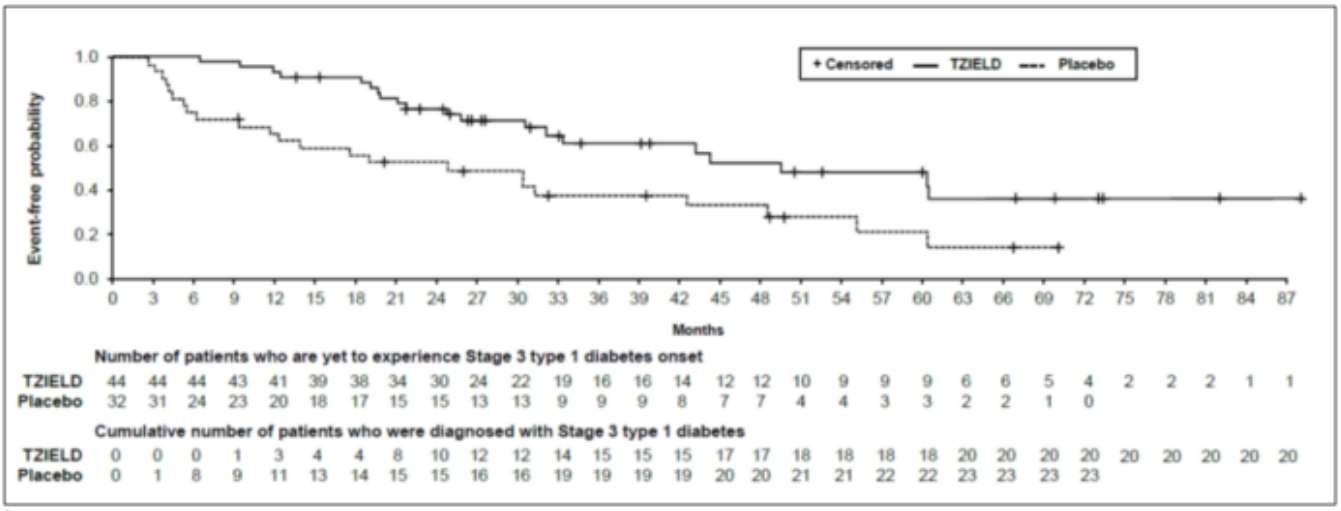
Table 2: Baseline Disease Characteristics of Adults and Pediatric Patients 8 Years of Age and Older with Stage 2 Type 1 Diabetes (Study TN-10)[1]		
	Tzield™ (N=44)	Placebo (N=32)
Glucose, mg/dL2		
median (min, max)	165 (115, 207)	154 (103, 200)
HbA1c, %		
median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)
HLA-DR4		
Missing	5%	0
Absent	34%	34%
Present	61%	66%
HLA-DR3		
Both DR3 and DR4	25%	22%
DR3 only	23%	25%
DR4 only	36%	44%
Missing	5%	0
Neither DR3 nor DR4	11%	9%
Autoantibodies Positive (N)		
1	2%	0
2	27%	22%
3	25%	
4	27%	
5	18%	19%
Autoantibody Type Positive		
GAD65	91%	88%
IAA	43%	34%
IA-2A	59%	75%
ICA	66%	88%
ZnT8	73%	75%

[1] Intent to treat (ITT) population

[2] The glucose data are area under the time-concentration curve (AUC) values from the oral glucose tolerance test Abbreviations: HbA1c=hemoglobin A1c, SD=standard deviation, HLA = human leukocyte antigen, GAD65=Glutamic acid decarboxylase 65 (GAD) autoantibodies, IAA=Insulin autoantibody, IA2A=Insulinoma-associated antigen 2 autoantibody, ZnT8A=Zinc transporter 8 autoantibody, ICA=Islet cell autoantibody.

Efficacy Results: In Study TN-10, Stage 3 type 1 diabetes was diagnosed in 20 (45%) of the Tzield™-treated patients and in 23 (72%) of the placebo-treated patients. A Cox proportional hazards model, stratified by age and oral glucose tolerance test status at randomization, demonstrated that the median time from randomization to Stage 3 type 1 diabetes diagnosis was 50 months in the Tzield™ group and 25 months in the placebo group, for a difference of 25 months. With a median follow-up time of 51 months, therapy with Tzield™ resulted in a statistically significant delay in the development of Stage 3 type 1 diabetes, hazard ratio 0.41 (95% CI: 0.22 to 0.78; p=0.0066) (Figure 1).
Study TN-10 was not designed to assess whether there were differences in the effectiveness between subgroups based on demographic characteristics or baseline disease characteristics.

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



[1] ITT population

Safety: Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache.

Safety

ADVERSE EVENTS

Common Adverse Reactions: Table 3 presents common (≥ 5%) adverse reactions that occurred during treatment and through 28 days after the last study drug administration in Study TN-10. Adverse reactions observed in pediatric patients 8 years and older who received Tzield™ were consistent with those reported in adult patients in this study.

Table 3: Common Adverse Reactions1 in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 Type 1 Diabetes (Study TN-10)[2]

Adverse Reaction	Placebo (N=32)	Tzield™ (N=44)
Lymphopenia	6%	73%
Rash[3]	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%

[1] That occurred during treatment and through 28 days after the last study drug administration

[2] Adverse reactions that occurred in 2 or more Tzield™-treated patients

[3] Composite of rash-related terms including rash erythematous, rash macular, rash papular, rash maculo-papular, rash pruritic

Cytokine Release Syndrome (CRS): In Study TN-10, CRS was reported in 2% of Tzield™-treated patients compared to 0% of placebo-treated patients. Of the 39 Tzield™-treated patients that developed CRS (5% of all Tzield™-treated patients) in the pool of 5 clinical trials, 13% of the CRS cases were serious adverse reactions. Liver transaminase elevations were observed in 56% of Tzield™ -treated patients who experienced CRS: 64% were up to 2.5 times ULN, 32% were more than 2.5 to 5 times ULN, and 4.5% were 5-10 times ULN.

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

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

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions: In Study TN-10, rash occurred in 39% of Tzield™-treated patients who developed antiteplizumab-mzwv antibodies and in 33% of Tzield™-treated patients who did not develop antiteplizumab-mzwv antibodies.

Other Adverse Reactions

- **Lymphopenia:** In Study TN-10, lymphopenia was reported in 73% of Tzield™-treated patients compared to 6% of placebo-treated patients. The average lymphocyte count nadir occurred at Day 5 of treatment, with recovery and return to baseline by Week 6.
- **Neutropenia:** In Study TN-10, neutropenia was observed in 7% of Tzield™-treated patients compared to 3% of placebo-treated patients.
- **Anemia and Thrombocytopenia:** In the pool of 5 clinical trials of patients, anemia was reported in 27% of Tzield™-treated patients compared to 21% of placebo-treated patients, and thrombocytopenia was reported in 13% of Tzield™-treated patients compared to 5% of placebo-treated patients during the 14-day treatment course; recovery occurred within 2 to 4 weeks of treatment. In clinical trials, 1.8% of Tzield™-treated patients discontinued treatment due to hemoglobin less than 8.5 g/dL (or a decrease of more than 2 g/dL to a value less than 10 g/dL), and 1% discontinued Tzield™ due to platelet count less than 50,000 platelets/mcL.
- **Liver Enzyme Elevations:** Liver enzyme elevations were observed in Tzield™-treated patients, both in the context of CRS and in patients without CRS. In the pool of 5 clinical trials, elevated aminotransferases were reported in 25% of Tzield™-treated patients compared to 11% of placebo-treated patients during the 14-day treatment course. On laboratory analysis, 5.1% of Tzield™-treated patients experienced a peak ALT more than 3 times the ULN compared to 0.8% of control-treated patients. Most liver enzyme elevations were transient and resolved 1-2 weeks after treatment; 98% resolved by follow-up week 14.
- **Other Laboratory Abnormalities:** In the pool of 5 clinical trials, other laboratory abnormalities including decreased bicarbonate (15% in Tzield™-treated patients, compared to 7% in placebo-treated patients) and

decreased blood calcium (19% in Tzield™-treated patients, compared to 13% in placebo-treated patients) were noted.

WARNINGS & PRECAUTIONS

Cytokine Release Syndrome: CRS manifestations in Tzield™-treated patients included fever, nausea, fatigue, headache, myalgia, arthralgia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased total bilirubin. These manifestations typically occurred during the first 5 days of Tzield™ treatment. To mitigate CRS:

- Premedicate with antipyretics, antihistamines and/or antiemetics prior to Tzield™ treatment.
- Monitor liver enzymes during treatment. Discontinue Tzield™ treatment in patients who develop elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.
- Treat symptoms of CRS 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.

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. 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™.

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.

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

- Administer all age-appropriate vaccinations prior to starting Tzield™.
- 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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Teplizumab-mzwv binds to CD3 (a cell surface antigen presents on T lymphocytes) and delays the onset of Stage 3 type 1 diabetes in adults and pediatric patients aged 8 years and older with Stage 2 type 1 diabetes. 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

ADULTS

Administer Tzield™ by intravenous infusion (over a minimum of 30 minutes), using a body surface area-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

Do not administer two doses on the same day.

PEDIATRICS

Refer to adult dosing.

GERIATRICS

None

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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