TN-10 SAFETY SUMMARY FOR TZIELD™ (teplizumab-mzwv)

The first and only treatment approved to delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients aged 8 years and older with Stage 2 T1D.[1]

Confirm Stage 2 T1D by documenting at least 2 positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if OGTT is not available. Ensure the clinical history of the patient does not suggest type 2 diabetes.[1]

INDICATION

TZIELD is a CD3-directed monoclonal 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Cytokine Release Syndrome (CRS):** CRS occurred in TZIELD-treated patients during the treatment period and through 28 days after the last drug administration. Prior to TZIELD treatment, premedicate with antipyretics, antihistamines and/or antiemetics, and treat similarly if symptoms occur during treatment. If severe CRS develops, consider pausing dosing for 1 day to 2 days and administering the remaining doses to complete the full 14-day course on consecutive days; or discontinue treatment. Monitor liver enzymes during treatment. Discontinue TZIELD treatment in patients who develop elevated alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.

Please see Important Safety Information throughout and read the accompanying full Prescribing Information and Medication Guide.

Tzield®
(teplizumab-mzwv)
Injection | 2 mg/2mL

TZIELD SAFETY PROFILE (TN-10)

Tzield® (teplizumab-mzwv) Injection | 2 mg/2mL

PIVOTAL TRIAL: TN-10

Study design
The safety and efficacy of TZIELD was investigated in a randomized, double-blind, event-driven, placebo-controlled study in 76 patients, 8 to 49 years of age with Stage 2 type 1 diabetes, defined as having 2 or more T1D-related autoantibodies* and dysglycemia on oral glucose tolerance testing. In this study, Stage 2 patients were randomized to receive TZIELD (N=44) or placebo (N=32) once daily, by intravenous infusion for 14 days.[1]

Primary endpoint
The primary efficacy endpoint in this study was the time from randomization to Stage 3 diagnosis. The primary analysis was conducted when at least 40 Stage 3 T1D diagnoses were made.[1,2]

*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)[1]

The safety profile of TZIELD was also evaluated in a pooled analysis of >750 patients across 5 controlled, clinical studies.[1]

In the pooled analysis, adverse reactions were evaluated in 773 TZIELD-treated patients, and 245 patients received placebo or standard of care (1 study in patients with Stage 2 T1D [Study TN-10], 3 placebo-controlled studies in an unapproved population, and 1 open-label standard-of-care controlled study of TZIELD in an unapproved population). See sections 5.0 and 6.0 of the Prescribing Information for additional safety information from the 5 pooled clinical trials.

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COMMON ADVERSE REACTIONS† IN THE TN-10 TRIAL[1‡]

Adverse Reactions	Placebo (N=32)	TZIELD (N=44)
Lymphopenia	6%	73%
Rash§	0%	36%
Leukopenia	0%	21%
Headache	6%	11%
Neutropenia	3%	5%
Alanine aminotransferase increase	3%	5%
Nausea	3%	5%
Diarrhea	0%	5%
Nasopharyngitis	0%	5%

In the TN-10 trial, greater incidences of adverse reactions were observed in TZIELD-treated patients vs placebo-treated patients[1]:

- Cytokine release syndrome (2% vs 0%, respectively)
- Serious infections‖ (9% vs 0%, respectively)
- Hypersensitivity reactions; serum sickness (2% vs 0%, respectively)
- Lymphopenia (73% vs 6%, respectively)
- Neutropenia (7% vs 3%, respectively)

†Adverse reactions that occurred in 2 or more TZIELD-treated patients.[1]
‡That occurred during treatment and through 28 days of the last TZIELD administration.[1]
§Composite of rash-related terms including rash erythematous, rash macular, rash papular, rash maculo-papular, rash pruritic.[1]
‖Serious infections included cellulitis, gastroenteritis, pneumonia, and wound infection.[1]

Adverse reactions observed in TZIELD-treated pediatric patients (8 years and older) were consistent with those reported in TZIELD-treated adults.

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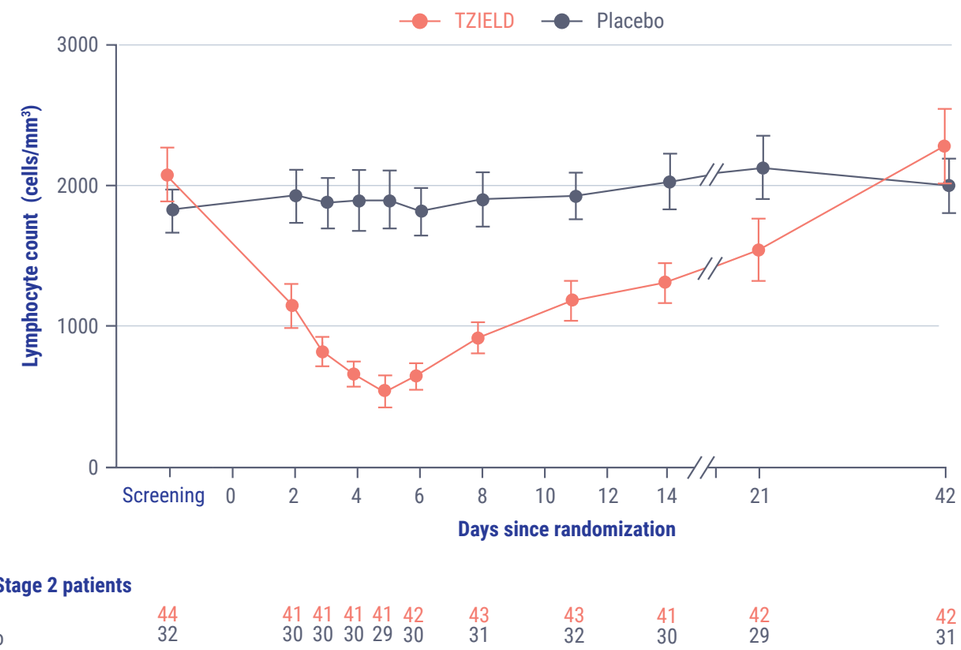
AVERAGE ABSOLUTE LYMPHOCYTE COUNTS IN TREATMENT GROUPS DURING THE FIRST 6 WEEKS AFTER INITIATING TREATMENT[3]



No. of Stage 2 patients										
TZIELD	44	41	41	41	41	42	43	43	41	42	42
Placebo	32	30	30	30	29	30	31	32	30	29	31

Adapted from Herold KC, et al. Means and confidence intervals are shown.

In the TN-10 study, lymphopenia was reported in 73% of TZIELD-treated patients compared with 6% of placebo-treated patients.

Pharmacodynamic effects include lymphopenia with nadir on the 5th day of dosing, during the 14-day course. Known effects were in absence of T cell depletion.[1]

TZIELD-exposure-response relations and time course of pharmacodynamic response for the safety and effectiveness of TZIELD have not been fully characterized.[1]

Most instances of lymphopenia with TZIELD recovered by Week 6.[1]

Lymphopenia occurred in absence of T cell depletion.[1]

TZIELD was not commonly associated with the symptomatic reactivation of EBV or CMV.[3]*

CMV=cytomegalovirus; EBV=Epstein-Barr virus.

*One TZIELD-treated patient in Study TN-10 reported symptoms consistent with reactivation of EBV.[3]

TZIELD-treated patients with detectable EBV and CMV DNA levels in the TN-10 trial:

Epstein-Barr virus (EBV)[3]:	Cytomegalovirus (CMV)[3]:
Of 16 patients with EBV antibodies in the TZIELD group, 8 had quantifiable EBV DNA in whole blood at Week 3 through Week 6. EBV DNA levels decreased to below the level of quantification between Day 43 and Day 134 (mean Day 77).	Of 10 patients with CMV antibodies in the TZIELD group, one had detectable levels of CMV DNA at Day 20. CMV DNA was undetectable by Day 42.

Management considerations
Monitor white blood cell counts during the treatment period. If severe lymphopenia develops (<500 cells per mcL lasting 1 week or longer), discontinue TZIELD.[1]

Please see Important Safety Information throughout and read the accompanying full Prescribing Information and Medication Guide.

POTENTIAL ADVERSE REACTIONS AND MANAGEMENT CONSIDERATIONS

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CYTOKINE RELEASE SYNDROME (CRS)

CRS has been observed in TZIELD-treated patients. In Study TN-10, CRS was reported in 2% of TZIELD-treated patients compared to 0% of placebo-treated patients. Symptoms included fever, nausea, fatigue, headache, myalgia, arthralgia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased total bilirubin; and, typically occurred during the first 5 days of treatment.[1]

Management considerations[1]

- Premedicate with antipyretics, antihistamines and/or antiemetics prior to TZIELD treatment for the first 5 days and as needed thereafter
- 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 pausing dosing for 1 day to 2 days and administering the remaining doses to complete the full 14-day course on consecutive days; or discontinuing treatment

SERIOUS INFECTIONS[1]

Bacterial and viral infections have occurred in TZIELD-treated patients including gastroenteritis, cellulitis, pneumonia, abscess, and sepsis. In Study TN-10, serious infections 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.

Management considerations[1]

- Monitor patients for signs and symptoms of infection, during and after TZIELD treatment. If serious infection develops, treat appropriately, and discontinue TZIELD
- Use of TZIELD is not recommended in patients with active serious infections or chronic infection other than localized skin infections

HYPERSENSITIVITY REACTIONS[1]

Acute hypersensitivity reactions, including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm, occurred in TZIELD-treated patients. 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. See *Rash and Hypersensitivity Reactions* (section 6.1) of the Prescribing Information for additional safety information from the 5 pooled clinical trials.

Management considerations[1]

If severe hypersensitivity reactions occur, discontinue use of TZIELD and treat promptly.

VACCINATIONS[1]

The safety of immunization with live-attenuated vaccines in patients receiving TZIELD has not been studied. 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 2 weeks prior to TZIELD treatment, during treatment, or 6 weeks after completion of treatment
- Live-attenuated vaccinations are not recommended 8 weeks prior to TZIELD treatment, during treatment, or up to 52 weeks after treatment

Please see Important Safety Information throughout and read the accompanying full Prescribing Information and Medication Guide.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Serious Infections:** 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 administration. If serious infection develops, treat appropriately, and discontinue TZIELD.
- **Lymphopenia:** Lymphopenia occurred in most TZIELD-treated patients. For most patients, lymphocyte levels began to recover after the fifth day of treatment and returned to pretreatment values within two weeks after treatment completion and without dose interruption. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia develops (<500 cells per mcL lasting 1 week or longer), 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 TZIELD and treat promptly.
- **Vaccinations:** The safety of immunization with live-attenuated (live) vaccines with TZIELD-treated patients has not been studied. TZIELD may interfere with immune response to vaccination and decrease vaccine efficacy. Administer all age-appropriate vaccinations prior to starting TZIELD.
    - Administer live vaccines at least 8 weeks prior to treatment. Live vaccines are not recommended during treatment, or up to 52 weeks after treatment.
    - Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment. Inactivated vaccines are not recommended during treatment or 6 weeks after completion of treatment.

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

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm.
- **Lactation:** A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration.

Before prescribing TZIELD, please read the accompanying Prescribing Information, including patient selection criteria, and Medication Guide.

REFERENCES: 1. TZIELD Prescribing Information. Provention Bio, Inc. **2.** Data on file. Provention Bio, Inc. **3.** Herold KC, Bundy BN, Long SA, et al; Type 1 Diabetes TrialNet Study Group. *N Engl J Med*. 2019;381(7):603-613.

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