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

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]

CLINICAL DATA OF TZIELD

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.

STUDY DESIGN OF PIVOTAL TN-10 TRIAL

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 T1D 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]

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.

TZIELD SIGNIFICANTLY DELAYED THE MEDIAN TIME TO THE DEVELOPMENT OF STAGE 3 T1D[1]

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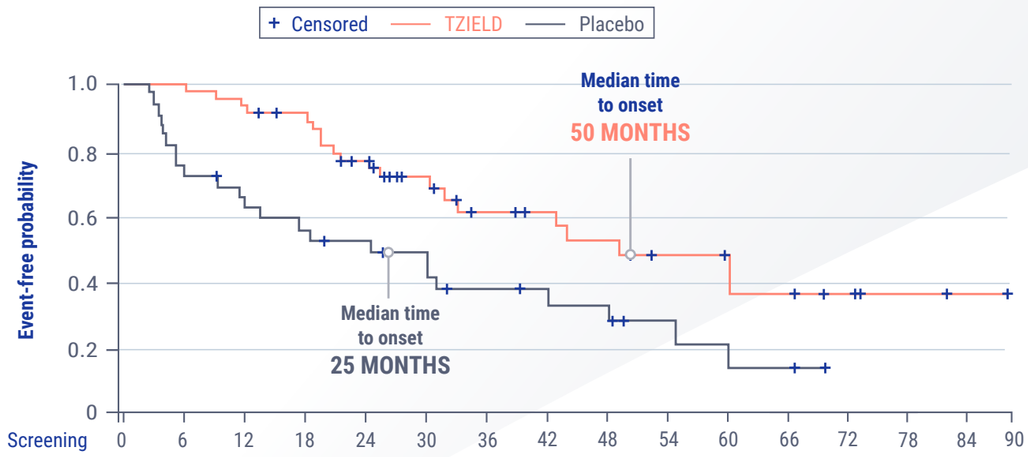
KAPLAN-MEIER CURVE: TIME TO DIAGNOSIS OF STAGE 3 T1D BY TREATMENT GROUP*



No. of patients who have yet to experience Stage 3 T1D onset

TZIELD	44	44	41	38	30	22	16	14	12	9	9	6	4	2	1
Placebo	32	24	20	17	15	13	9	8	7	4	3	2	0		

Cumulative no. of patients who were diagnosed with Stage 3 T1D

TZIELD	0	0	3	4	10	12	15	15	17	18	18	20	20	20	20
Placebo	0	8	11	14	15	16	19	19	20	21	22	23	23		

(HR 0.41; 95% CI, 0.22-0.78, p=0.0066 by adjusted Cox proportional-hazards model)

*Adapted from the TZIELD prescribing information.
Median follow-up time was 51 months.

Median time to onset of Stage 3 T1D was 2x longer in TZIELD-treated patients vs placebo-treated patients.[1]

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

PRIMARY ANALYSIS[1]

~2 YEAR DELAY

In patients with Stage 2 T1D, TZIELD significantly

DELAYED THE MEDIAN TIME TO STAGE 3 T1D

onset by 2 years when compared with placebo

TZIELD	PLACEBO
~4 YEARS (50 months)	~2 YEARS (25 months)

(HR 0.41; 95% CI, 0.22-0.78, *p*=0.0066 by adjusted Cox proportional-hazards model)

TZIELD delayed median time to onset of Stage 3 T1D by 25 months longer than placebo in Stage 2 patients. Median follow-up time was 51 months (range: 74 days to 2683 days).[1,3]

~2x the proportion of TZIELD-treated patients had not progressed to Stage 3 T1D* compared to placebo-treated patients (55% [24/44] and 28% [9/32], respectively) at the time of primary analysis.[1]

*Patients who did not progress to Stage 3 T1D are inclusive of censored patients. Censored patients were those participants still in Stage 2 T1D at the time of analysis, who had not reached the full duration of the observation period.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

EXTENDED FOLLOW-UP ANALYSIS[4]

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2.7 YEAR DELAY

EXTENDED FOLLOW-UP ANALYSIS

In TN-10 trial participants, median time to Stage 3 T1D diagnosis was:

TZIELD	PLACEBO
59.6 MONTHS	27.1 MONTHS

(HR 0.457; *p*=0.01 by adjusted Cox proportional-hazards model)

In the extended follow-up of TZIELD- and placebo-treated patients of the TN-10 trial, the median follow-up time was 923 days (range, 74 days to 3119 days).[4†]

50% of TZIELD-treated patients did not progress to Stage 3 T1D compared with 22% of placebo-treated patients (22/44 and 7/32, respectively) at the end of the extended follow-up analysis.[4]

LIMITATIONS OF EXTENDED FOLLOW-UP

These data are not contained in the Prescribing Information. The TN-10 study was relatively small at the start of the trial and patient numbers decreased throughout follow-up. Patient results may vary.[4]

†The median follow-up time from Sims et al was calculated using time to T1D diagnosis, end of study participation or administration cutoff (end of study). The median follow-up time from the TZIELD Prescribing Information was calculated using the reverse Kaplan-Meier method.

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

SAFETY PROFILE OF TZIELD (TN-10)

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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 observed in TZIELD-treated pediatric patients (8 years and older) were consistent with those reported in TZIELD-treated adults.[1]

*Adverse reactions that occurred in 2 or more TZIELD-treated patients.[1]
†That occurred during treatment and through 28 days after the last study drug 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]

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

LYMPHOPENIA IN TN-10

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.[2,3]

CMV=cytomegalovirus; EBV=Epstein-Barr virus.
Monitor white blood cells counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD.[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).

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

Provention Bio
COMPASS™

A PERSONALIZED PATIENT ASSISTANCE AND SUPPORT PROGRAM WITH HELPFUL RESOURCES.

Our team will provide information about financial assistance options, reimbursement, educational tools and resources, and additional support from the day of enrollment.

Provention Bio COMPASS is a patient support program that helps patients gain access to TZIELD and provides patients with education and resources related to TZIELD. Provention Bio COMPASS is not a healthcare service or an insurance provider and does not provide care coordination. Provention Bio COMPASS and the COMPASS Navigator will not provide medical or treatment advice. Provention Bio COMPASS services are available only to those who have been prescribed TZIELD and are intended for US residents only.

For more information about Provention Bio COMPASS, call 1-844-778-2246, Monday through Friday, 8 AM-8 PM ET.

Enroll your patients to get them started with TZIELD

IMPORTANT SAFETY INFORMATION (cont'd)

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. **4.** Sims EK, Bundy BN, Stier K, et al. *Sci Transl Med*. 2021;13(583):eabc8980.

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