Health Monitor®

# Clinician Update

## Pediatric Type 1 Diabetes

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## PRECLINICAL TYPE 1:

# Why early screening is critical

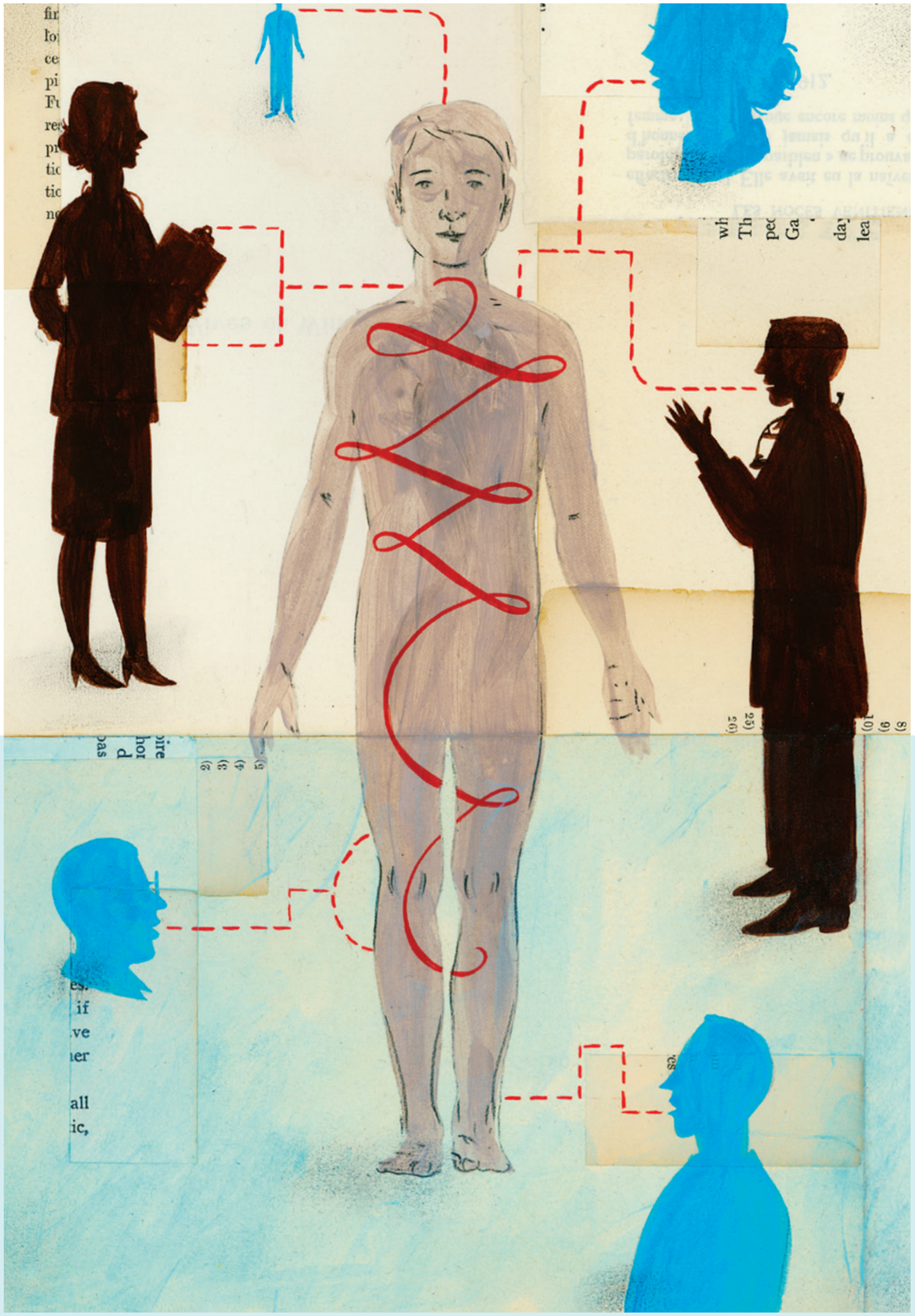
**The potential to delay progression to insulin-dependent type 1 diabetes, as well as the importance of avoiding diabetic ketoacidosis in undiagnosed patients, underscores why timely screening and referral to a specialist are more important than ever.**

**For children and their families, a diagnosis of type 1 diabetes requires insulin therapy and major lifestyle changes** that impact nearly every area of their lives. What's more, the autoimmune disease often is not diagnosed until a person is hospitalized for life-threatening complications, particularly diabetic ketoacidosis (DKA).

However, research has shown there is an asymptomatic period before the typical presentation of type 1, which has led to groundbreaking clinical trials and one approved therapy to delay progression of the disease—and subsequently delay the need for insulin. In fact, the standard of care for type 1 diabetes is rapidly changing, thanks to the approval of the first monoclonal antibody to delay the onset of clinical type 1 diabetes by a median of 2 years.[1,2] (For more on this therapy, see p. 8.)

*Continued on next page* ►

Illustration by Donna Grethen / Ikon Images



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## Staging the progression of disease

The risk for progression to type 1 diabetes is built on the detection of diabetes-related autoantibodies, says pediatric/adult endocrinologist Rayhan Lal, MD, Assistant Professor of Medicine (Endocrinology) and Pediatric Medicine (Endocrinology) at Stanford University.

"Type 1 diabetes consists of three stages. Stage 1 is a long preclinical period characterized by the presence of two or more positive autoantibodies and no alteration in blood glucose," Dr. Lal says. "Stage 2 includes early dysglycemia, which may be identified on a glucose tolerance test or other parameters but is otherwise asymptomatic. Stage 3 is overt type 1 diabetes with hyperglycemia." (For criteria that defines each stage, see Figure 1.)

However, it's important to keep in mind that autoantibodies identify the risk but not the speed of progression to Stage 3, and the rate of progression for each individual may vary considerably. Regardless, one thing is certain: "With two or more positive autoantibodies, a person is guaranteed to develop type 1 with sufficient time," says Dr. Lal. In fact, two decades of research involving more than 160,000 relatives of people with type 1 diabetes showed that for patients with either Stage 1 or Stage 2, the lifetime risk of developing Stage 3 approaches 100%.[2]

## Screening to keep children safe

Screening for preclinical type 1 is important for several reasons, says Anastasia Albanese-O'Neill, PhD, APRN and Director of Community Screening & Clinical Trial Education at JDRF (Juvenile Diabetes Research Foundation at *jdrf.org*). These include the following:

**Avoid diabetic ketoacidosis (DKA).**
Albanese-O'Neill explains, "It's been demonstrated across multiple research studies over 40 years that type 1 diabetes risk screening and follow-up monitoring can significantly reduce the risk of DKA at diagnosis from 30% to less than 4%. Given the additional health risks

**Figure 1.**

### Type 1 diabetes progression, stage by stage

Type 1 diabetes actually begins well before exogenous insulin is needed. Joint guidelines from JDRF, the Endocrine Society and the American Diabetes Association classify each distinct stage as the following:[4]

| STAGE 1 | STAGE 2 | STAGE 3 |
|---|---|---|
| ≥2 pancreatic islet autoantibodies | ≥2 pancreatic islet autoantibodies | ≥2 pancreatic islet autoantibodies |
| Normoglycemia | Dysglycemia, such as:<br>• glucose tolerance test, 140 to 199 mg/dL<br>• fasting glucose, 100 to 125 mg/dL<br>• A1C, 5.7 to 6.4% | Hyperglycemia |
| No symptoms | No symptoms | Symptoms (e.g., polyuria, polydipsia, weight loss) |

**"Good candidates for general population screening are children ages 1 to 17."**
*—Anastasia Albanese-O'Neill, PhD, APRN*

Illustration by Donna Grethen / Ikon Images

and complications associated with DKA at diagnosis, this health benefit alone is an important reason to screen."

**Ensure referral to an endocrinology specialist.** With the approval of a monoclonal antibody to delay onset of the disease, "it's impossible to know if a patient is at risk for type 1 diabetes and eligible for this treatment unless you screen them," says Albanese-O'Neill—and promptly refer patients to an endocrinologist for further assessment and monitoring.

**Ease anxiety and allow time for diabetes education.** "In the past, caregivers and individuals receiving the news would often desperately search for ways to avoid the development of Stage 3 type 1 diabetes," says Dr. Lal. However, behavioral interventions to delay progression, such as reducing carbohydrate consumption, are based on weak or no evidence, he says. "We have seen cases where this pressure has even precipitated disordered eating in patients," notes Dr. Lal. "Fortunately, with appropriate referral, we can help keep patients safe and educate them and their families about what they can do to prepare for the eventual changes and the option of treatment to delay the onset of type 1."

## Red flags for screening: younger age and family history

First-degree relatives of a person with type 1 diabetes, such as siblings, children and parents, have up to 15 times higher risk for type 1 diabetes than those without, Albanese-O'Neill says. That makes them good candidates for screening, but it is important to remember that about 85% to 90% of people have no family history of type 1 diabetes at diagnosis.

In addition, approximately 75% of patients diagnosed with type 1 are under the age of 18 years.[3,4] Therefore, Albanese-O'Neill says, "Good candidates for general population screening are children ages 1 to 17."

In addition, diabetes experts are starting to advocate for screening all patients regardless of age and family history. "As autoantibody assays become more cost-effective and therapy to delay progression becomes more widely available, general population-level screening is also becoming a consideration," says Dr. Lal.

## Steps for in-office screening

The American Diabetes Association updated their 2023 guidelines to include a recommendation to screen people who have relatives with type 1 diabetes.[3] Some insurance companies will cover the cost of screening for type 1 autoantibodies, but there are also free screening programs for eligible patients. Albanese-O'Neill says screening for first-degree relatives can take place at a doctor's office.

**What tests to order**

Autoantibody tests are easy to order, says Dr. Lal. The relevant blood autoantibodies are:

- GAD65 (glutamic acid decarboxylase 65)
- IA-2 (islet antigen 2)
- IAA (insulin autoantibody)
- ZnT8 (zinc transporter 8)

**Tip:** For patients who have family members with type 1, the practitioner can code these laboratory orders to the ICD-10 code Z83.3 (family history of diabetes).

**If results are positive**

"Follow up immediately with an endocrinologist for confirmatory testing, to get a monitoring plan in place and to discuss treatment options," stresses Albanese-O'Neill. "Current clinical guidelines recommend anyone with positive antibodies follow up with a pediatric or adult endocrinologist."

**If results are negative**

If the patient is under the age of 18, future rescreening should occur. ADA guidelines recommend that children who do not test positive for diabetes-related autoantibodies continue to get rescreened every year until age 18.[3]

## Referral to free screening programs

If a patient's insurance will not cover the cost of screening for type 1 autoantibodies, experts recommend connecting them with free screening programs, including:

**TrialNet (*trialnet.org*):** This international network of doctors and researchers offers free screening for family members of people with type 1 diabetes. Candidates must not have been previously diagnosed with diabetes and must fall into one of these three categories:

- Between the ages of 2.5 and 45 and have a parent, sibling or child with type 1 diabetes.
- Between the ages of 2.5 and 20 and have an aunt, uncle, cousin, grandparent, niece, nephew, or half-brother or sister with type 1 diabetes.
- Between the ages of 2.5 and 45 and have previously tested positive for at least one autoantibody related to type 1 diabetes.

**T1Detect (*jdrf.org/T1Detect*):** This JDRF program offers resources, options, links to experts and information on why and how to get screened and next steps after screening.

**Autoimmunity Screening for Kids (ASK; *askhealth.org*):** Free screening for type 1 diabetes and celiac disease offered by the Barbara Davis Center for Diabetes at the University of Colorado is available to all children ages 1 to 17 in the United States, including those with no family history of either disease. Screening is also available for adults.

*—by David Levine*

**"With two or more positive autoantibodies, a person is guaranteed to develop type 1 with sufficient time."**
*—Rayhan Lal, MD*

## References


1. Sims EK, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med.* 2021;13(583):eabc8980.
2. TrialNet. Type 1 diabetes staging classification opens door for intervention. Published December 16, 2023. Available at *trialnet.org*.
3. American Diabetes Association. Addendum. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care.* 2023;46(suppl):S19-S40.
4. Insel RA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care.* 2015;38(10):1964-1974.

# INSIGHT ON THE FIRST THERAPY TO DELAY ONSET OF TYPE 1

**For patients 8 years and older, there is a novel agent that may delay the need for chronic insulin for a median of 2 years—but the only way to determine eligibility is with prompt screening for preclinical stages of type 1 diabetes.**

**When the FDA approved the first disease-modifying therapy for type 1 diabetes** in 2022, it marked the beginning of a new era in not only treatment but also screening practices. "In the past, when there were no FDA-approved options for intervention, screening had to be offered carefully with the knowledge that, other than limited clinical trials, the best management included monitoring blood sugars in an asymptomatic individual in the hope of detecting dysglycemia before frank hyperglycemia developed," explains Rabab Jafri, MD, a pediatric endocrinologist at the Texas Diabetes Institute at The University of Texas at San Antonio. "This may have caused increased anxiety for a family, and interpretation of screening test results had to be carefully performed," she says.

## "A landmark breakthrough"

That all changed with the FDA approval of a monoclonal antibody to delay the onset of clinical type 1 diabetes, notes Dr. Jafri. "This therapy binds to CD3, a cell surface marker on T cells. It was FDA-approved to delay progression to Stage 3 type 1 diabetes in certain people who have Stage 2," she says. Specifically, the disease-modifying therapy is indicated for delaying the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes, which is defined as having two or more diabetes-related autoantibodies, dysglycemia and no symptoms of diabetes (for more on screening and staging of type 1, see p. 2).

As a result of this approval, the American Diabetes Association updated its 2023 guidelines to include a recommendation to consider this disease-modifying therapy in certain individuals who meet the criteria above.[1]

"This really was a landmark breakthrough," says pediatric endocrinologist Mary Pat Gallagher, MD, of the Pediatric Diabetes Center at Hassenfeld Children's Hospital at NYU Langone Health. While the agent's precise mechanism of action is not known, "it appears to retrain the arm of the immune system that has erroneously identified the islets in the pancreas as foreign," explains Dr. Gallagher. "We are trying to stop that and induce tolerance." The agent is admin-

Illustration by Donna Grethen / Ikon Images

> "This really was a landmark breakthrough. It appears to retrain the arm of the immune system that has erroneously identified the islets in the pancreas as foreign."
>
> —*Mary Pat Gallagher, MD*

istered in a single course that requires 30-minute daily infusions for 14 consecutive days.

## Most extensive data for a disease-modifying therapy

The novel agent was FDA approved on the basis of a phase 2 double-blind trial in which 44 participants were randomly chosen to receive the investigational drug while 32 received the placebo.[2] Participants were relatives of patients with type 1 diabetes who were at least 8 years of age and had Stage 2 (preclinical) type 1 diabetes. Following active treatment, participants were monitored with oral glucose tolerance tests at 3 and 6 months, then every 6 months, to identify those who progressed to Stage 3 type 1 diabetes.

The study, published in the *New England Journal of Medicine*, found that treatment significantly delayed the onset of Stage 3 type 1 diabetes. After a median follow-up time of approximately 4 years, the results showed:

- Participants who were given the drug went roughly 2 years longer before the onset of Stage 3 type 1 diabetes vs. the placebo group.
- The median time of progression to clinical disease was 48.4 months with active treatment vs. 24.4 months with placebo.
- By the end of the study, 55% of those given active treatment had not been diagnosed with Stage 3 type 1 diabetes vs. 28% of those given placebo.

Illustration by Donna Grethen / Ikon Images

These trial results are the most extensive data in type 1 diabetes disease modification with a single agent to date, according to a recent analysis in *Diabetes Care*.[3] Dr. Gallagher believes that the roughly 2-year delay in the onset of Stage 3 type 1 diabetes associated with the treatment in this study "makes it absolutely worth" considering this therapy for appropriately chosen patients. She is quick to add that 2 years was only the median delay, and that some patients may respond better than others with a longer duration of time before development of Stage 3 type 1 diabetes. Moreover, until people with Stage 2 type 1 diabetes who receive the monoclonal antibody are followed long term, the potential benefit will remain unknown—and that it's conceivable that some patients will never progress to clinical type 1 diabetes, says Dr. Gallagher.

In the study, the most common adverse effects were skin rash, headache and transient leukopenia or lymphopenia. However, infection rates were similar in the two treatment groups.

## Barrier to treatment: lack of screening and referral

While the novel therapy is groundbreaking, many patients who may be eligible are not being offered this option. The main barrier is lack of screening and referral. The pivotal *New England Journal of Medicine* study recruited relatives of people known to have type 1 diabetes for a good reason: They are 15 times more likely than others to develop the disease themselves.[4] However, it is important to note that 85% to 90% of newly diagnosed cases do not have a family history, according to JDRF.

What's more, people who are eligible for the agent because they have undiagnosed Stage 2 type 1 diabetes are asymptomatic. "So they're walking around with positive autoantibodies and mildly elevated blood sugar levels, often unaware that they are at risk for clinical type 1 diabetes," says Dr. Gallagher. Because there are currently no universal screening programs for type 1 diabetes, the disease is usually diagnosed only after a patient has transitioned to Stage 3 type 1 and has symptoms—which may include diabetic ketoacidosis, a dangerous and life-threatening complication.

"Screening the general population will be necessary to identify most of the people who can benefit from this therapy," says Dr. Gallagher, who notes that Stage 2 type 1 diabetes can occur in people of all ages and that one-third of people with type 1 diabetes are over age 30. Organizations such as JDRF are leading a drive to institute universal screening for type 1 diabetes. Until then, family members of people with type 1 diabetes are obvious candidates for screening, and Dr. Gallagher adds that any patient who has previously tested positive for autoantibodies, such as for celiac disease, should also be considered for screening.

## More advances on the horizon

The novel agent could eventually become an option for a wider patient population. A recent phase 3 trial published in the *New England Journal of Medicine* found that newly diagnosed type 1 diabetes patients treated with the drug preserved greater beta cell function (as measured by C-peptide levels) than patients who received placebo.[5] Preserving some beta cells and producing as much natural insulin as possible, says Dr. Gallagher, "is like having a cushion that helps a patient experience many fewer episodes of hypo- and hyperglycemia."

This potential use for patients with Stage 3 type 1 diabetes represents exciting possibilities for the future, Dr. Jafri notes. "The rate of progression to the third and final stage is variable yet inevitable, but even then, the role of an intervention in delaying progression can be significant," Dr. Jafri says. "Studies are being conducted in patients who have progressed to the final stage as well as those who were relatively recently diagnosed with type 1 diabetes. It will be interesting to see if certain interventions can reduce or even eliminate insulin needs for any given amount of time." ●

*—by Tim Gower*

## References


1. **American Diabetes Association. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2023. *Diabetes Care.* 2023;46(suppl): S41-S48.**
2. **Herold KC, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med.* 2019;381(7):603-613.**
3. **Herold KC, et al. Teplizumab: a disease-modifying therapy for type 1 diabetes that preserves β-cell function. *Diabetes Care.* 2023;46(10):1848-1856.**
4. **Type 1 Diabetes TrialNet. Frequently Asked Questions. Available at trialnet.org.**
5. **Ramos EL, et al. Teplizumab and β-cell function in newly diagnosed type 1 diabetes. *N Engl J Med.* 2023;389(23):2151-2161.**


## VACCINE ALERT

Prior to starting a course of the disease-modifying agent, ensure that a patient has received all age-appropriate vaccinations, as the treatment may interfere with immune response and decrease vaccine efficacy, says pediatric endocrinologist Mary Pat Gallagher, MD, of the Pediatric Diabetes Center at Hassenfeld Children's Hospital at NYU Langone Health. She also notes that after completion of therapy, the patient's endocrinologist will determine a schedule for monitoring the patient's response to therapy. Dr. Gallagher recommends follow-up at 1 week, then 1 month, then every 3 months.

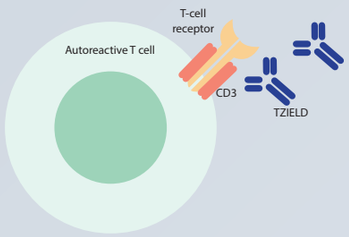
# Tzield® (teplizumab-mzwv)

Injection | 2 mg/2mL

The first innovative biologic therapy in T1D since the discovery of insulin 100 years ago.

**TZIELD is the first and only disease-modifying treatment indicated to delay the onset of Stage 3 type 1 diabetes (T1D). TZIELD is appropriate for adult and pediatric patients aged 8 years and older with Stage 2 T1D.**

## TZIELD was designed to target the underlying autoimmune process of T1D[1]




- TZIELD is an anti-CD3 monoclonal antibody that binds to CD3 antigens on the surface of the T cells, which leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.[1]
- The mechanism of action may involve the partial agonistic signaling and deactivation of autoreactive T cells that target pancreatic beta cells.[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.
- **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.
  - o Administer live vaccines at least 8 weeks prior to treatment. Live vaccines are not recommended during treatment, or up to 52 weeks after treatment.
  - o 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.

## Identifying and staging autoimmune T1D early can give your patients more time to[2]:

| | |
|---|---|
| **Potentially Delay Stage 3:** | Postpone the burden of disease management and have more time to prepare for Stage 3 for appropriate patients[2] |
| **Look for symptoms:** | Be more vigilant for symptoms of hyperglycemia and diabetic ketoacidosis (DKA)[2] |
| **Seek Treatment:** | Utilize TZIELD to potentially delay the onset of Stage 3 T1D (insulin-dependent) for appropriate patients[2] |

## Type 1 diabetes can happen at any age[3-5]: It's important to screen for pancreatic islet autoantibodies (AAbs) through a blood test:

**up to 15x greater**

Relatives of T1D patients, since they have up to 15x higher risk of developing T1D vs. general population[5]

Autoantibody screening along with blood glucose monitoring has been found to reduce the risk of DKA at Stage 3 T1D onset[7,8,9]

Those with certain other autoimmune diseases[6]

If the results show two or more AAbs, the life-time risk of progressing to Stage 3 T1D approaches 100%. It's not a question of if, but when[7,8]

**Consider screening and staging at-risk patients to see if TZIELD may be an appropriate treatment option[1]**

**Visit TZIELDHCP.com or scan here to read about the TN-10 Clinical Study and extended follow-up along with our Safety Profile.**

### IMPORTANT SAFETY INFORMATION (continued)

### 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.

**Please see brief summary of Prescribing Information on following pages.**

**References: 1.** TZIELD Prescribing Information. Provention Bio, Inc; 2023. **2.** Edelman S. Early intervention by family physicians to delay type 1 diabetes. *J Fam Pract.* 2023:72(6 suppl):S19-S24. **3.** Fang M, Wang D, Echouffo-Tcheugui JB, Selvin E. Age at diagnosis in U.S. adults with type 1 diabetes. *Ann Intern Med.* 2023;176(11):1567-1568. **4.** Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: A scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care.* 2015;38(10):1964-1974. **5.** Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes.* 2018;19 (suppl 27):20-27. **6.** Popoviciu MS, Kaka N, Sethi Y, et al. Type 1 diabetes mellitus and autoimmune diseases: A critical review of the association and the application of personalized medicine. *J Pers Med.* 2023;13(3):422. **7.** Elding Larsson H, Vehik K, Bell R, et al. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. *Diabetes Care.* 2011;34(11):2347-2352. **8.** Barker JM, Goehrig SH, Barriga K, et al; DAISY study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care.* 2004;27(6):1399-1404. **9.** Greenbaum CA. A Key to T1D Prevention: Screening and Monitoring Relatives as Part of Clinical Care. Diabetes. 2021;70(5):1029-1037

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TZIELD is manufactured by Provention Bio, A Sanofi company MAT-US-2404115-v1.0-05/2024

sanofi

**TZIELD®** **Rx Only**
**(teplizumab-mzwv) injection, for intravenous use**

**Brief Summary of Prescribing Information**

## 1 INDICATIONS AND USAGE

TZIELD is indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes *[see Dosage and Administration (2.1)]*.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

Select adult patients and pediatric patients 8 years of age and older for TZIELD treatment who have a diagnosis of Stage 2 type 1 diabetes.

- Confirm Stage 2 type 1 diabetes by documenting:
  - At least two positive pancreatic islet cell autoantibodies
  - Dysglycemia without overt hyperglycemia using an oral glucose tolerance test (if an oral glucose tolerance test is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate)
- Ensure the clinical history of the patient does not suggest type 2 diabetes.

### 2.2 Laboratory Evaluation and Vaccination Prior to Initiation

- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests.
- Use of TZIELD is not recommended in patients with *[see Warnings and Precautions (5)]*:
  - Lymphocyte count less than 1,000 lymphocytes/mcL
  - Hemoglobin less than 10 g/dL
  - Platelet count less than 150,000 platelets/mcL
  - Absolute neutrophil count less than 1,500 neutrophils/mcL
  - Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times 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
- Administer all age-appropriate vaccinations prior to starting TZIELD *[see Warnings and Precautions (5.5)]*:
  - Administer live-attenuated (live) vaccines at least 8 weeks prior to treatment.
  - Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment.

### 2.3 Important Preparation and Premedication Instructions

The following are important preparation and premedication instructions:

- Must dilute TZIELD prior to use *[see Dosage and Administration (2.5)]*.
- Premedicate prior to TZIELD infusion for the first 5 days of dosing with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic *[see Warnings and Precautions (5.1)]*. Administer additional doses of premedication if needed.

### 2.4 Recommended Dosage and Administration

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.

Recommendations Regarding Missed Dose(s)

If a planned TZIELD infusion is missed, resume dosing by administering all remaining doses on consecutive days to complete the 14-day treatment course.

### 2.5 Additional Preparation and Administration Instructions

The following are additional preparation and administration instructions *[see Dosage and Administration (2.2, 2.3, 2.4)]*:

- Inspect TZIELD visually before use (the supplied solution is clear and colorless). Do not use TZIELD if particulate matter or coloration is seen.
- Prepare TZIELD using aseptic technique. Each vial is intended for single dose only.
- Prepare a:
  - Sterile glass vial with 18 mL of 0.9% Sodium Chloride Injection **or**
  - Polyvinylchloride (PVC) infusion bag with 18 mL of 0.9% Sodium Chloride Injection.
- Remove 2 mL of TZIELD from the vial and slowly add to the 18 mL of 0.9% Sodium Chloride Injection. Mix gently by slowly inverting the vial or rocking the infusion bag. The resulting 20 mL diluted solution contains 100 mcg/mL of teplizumab-mzwv.
- Using an appropriately sized syringe (e.g., 5 mL), withdraw the volume of diluted TZIELD solution required for that day's calculated dose from the 100 mcg/mL solution.
- Slowly add contents of the syringe containing the TZIELD dose to a 25 mL 0.9% Sodium Chloride Injection PVC infusion bag. Gently rock the infusion bag to ensure that the solution mixes sufficiently. Do not shake.
- Discard unused portion of remaining diluted TZIELD solution in the sterile glass vial or PVC infusion bag.
- Start the TZIELD infusion within 2 hours of preparation. If not used immediately, store the infusion solution at room temperature [15°C to 30°C (59°F to 86°F)] and complete infusion within 4 hours of the start of preparation. Discard the infusion solution if not administered within 4 hours of preparation.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cytokine Release Syndrome

Cytokine release syndrome (CRS) has been observed in TZIELD-treated patients. 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 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 *[see Adverse Reactions (6.1)]*. To mitigate CRS:

- Premedicate with antipyretics, antihistamines and/or antiemetics prior to TZIELD treatment *[see Dosage and Administration (2.3)]*.
- 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.

### 5.2 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 *[see Adverse Reactions (6.1)]*. 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.

### 5.3 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 per mcL) lasting 1 week or longer occurred in 0.9% of TZIELD-treated patients, and 0.5% of TZIELD-treated patients permanently discontinued TZIELD because of lymphopenia *[see Adverse Reactions (6.1)]*.

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.

### 5.4 Hypersensitivity Reactions

Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in TZIELD-treated patients *[see Adverse Reactions (6.1)]*. If severe hypersensitivity reactions occur, discontinue use of TZIELD and treat promptly.

### 5.5 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 *[see Dosage and Administration (2.2)]*.
- 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.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the Prescribing Information:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Serious Infections *[see Warnings and Precautions (5.2)]*
- Lymphopenia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Placebo-Controlled Study in Patients with Stage 2 Type 1 Diabetes

The data in Table 1 are derived from the placebo-controlled study (Study TN-10) in patients aged 8 years and older with Stage 2 type 1 diabetes (T1D) *[see Clinical Studies (14) in the full prescribing information]*. These data reflect exposure of 44 patients of whom 93% completed the full 14-day treatment course.

Pool of Five Controlled Clinical Studies in Stage 2 Type 1 Diabetes and in an Unapproved Population

Adverse reactions in TZIELD-treated patients were also evaluated in a larger pool of adult and pediatric patients who participated in five controlled clinical studies (including Study TN-10 described above):

- One study in patients with Stage 2 T1D (Study TN-10) *[see Clinical Studies (14) in the full prescribing information]*,
- Three placebo-controlled studies in an unapproved population,
- One open-label standard-of-care controlled study of TZIELD in an unapproved population.

In this pool:

- 773 patients received TZIELD (44 patients with Stage 2 TID and 729 patients from an unapproved population), and
- 245 patients received either placebo or standard of care control (32 patients with Stage 2 T1D and 213 patients from an unapproved population).

In these studies, 436 patients received a 14-day dosing regimen of TZIELD with a total drug exposure that was comparable to the total drug exposure achieved with the recommended dosage *[see Dosage and Administration (2.4)]*, 168 patients received a 14-day course of TZIELD with a lower total TZIELD drug exposure, and 169 patients received a 6-day course of TZIELD with a lower total TZIELD drug exposure. The mean age of TZIELD-treated patients was 17.6 years (median 15 years), 62% were <18 years old (40% age 12 to 17; 21% age 8 to 11), and 64% were male. The population was 72% White, 26% Asian, 1% Black or African American, 1% were multiple or unknown race, and <1% American Indian or Alaska Native; 5% were Hispanic or Latino ethnicity.

Common Adverse Reactions

Table 1 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 1. Common Adverse Reactions* in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 Type 1 Diabetes (Study TN-10)†**

| Adverse Reaction | Placebo N=32 | TZIELD 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% |

*That occurred during treatment and through 28 days after the last study drug administration

†Adverse reactions that occurred in 2 or more TZIELD-treated patients

‡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 *[see Warnings and Precautions (5.1)]*. 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.

In the pool of 5 clinical trials of patients:



- Anaphylaxis (with hypoxia and bronchospasm) was observed in one TZIELD-treated patient who was hospitalized.
- Angioedema (periorbital and facial) was observed in 0.3% TZIELD-treated patients, compared to 0% in control-treated patients. Peripheral and generalized edema was reported in 1.6% of TZIELD-treated patients and 0% of control-treated patients.
- Rash was observed in 48% of TZIELD-treated patients compared to 15% in control-treated patients, with 33 excess cases of rash per 100 patients. The majority of rashes observed with TZIELD treatment were not serious and resolved without intervention; although 0.3% (2/773) of TZIELD-treated patients had a serious rash compared to 0% (0/245) of placebo- treated patients.
- Urticaria was reported in 1.9% of TZIELD-treated patients and in 1.2% of control-treated patients.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

In Study TN-10, rash occurred in 39% of TZIELD-treated patients who developed anti- teplizumab-mzwv antibodies and in 33% of TZIELD-treated patients who did not develop anti- teplizumab-mzwv antibodies *[see Clinical Pharmacology (12.6) in the full prescribing information]*.

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 *[see Warnings and Precautions (5.3)]*.

*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.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Available case reports from clinical trials with TZIELD are insufficient to identify a drug- associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on teplizumab-mzwv, monoclonal antibodies can be actively transported across the placenta, and TZIELD may cause immunosuppression in the utero- exposed infant *(see Clinical Considerations)*. To minimize exposure to a fetus, avoid use of TZIELD during pregnancy and at least 30 days (6 half-lives) prior to planned pregnancy.

TZIELD is not active in rodents. In animal reproduction studies, mice were given a surrogate anti-mouse CD3 antibody subcutaneously during organogenesis through lactation. Pups born to dams administered the murine surrogate antibody during pregnancy showed a reduction in the adaptive immune response consistent with the expected pharmacology *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Report pregnancies to Provention Bio, Inc.'s Adverse Event reporting line at 1-800-633-1610.

Clinical Considerations

*Fetal/Neonatal Adverse Reactions*

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because teplizumab-mzwv may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to teplizumab-mzwv in utero. There are insufficient data regarding infant serum levels of teplizumab-mzwv at birth and the duration of persistence of teplizumab- mzwv in infant serum after birth to identify a specific timeframe to delay live virus immunizations in infants exposed in utero.

Data

*Animal Data*

In an embryo-fetal developmental toxicity study, pregnant mice were administered a murine surrogate anti-mouse CD3 antibody by subcutaneous injection at dose levels of 0, 0.03, 0.3, or 20 mg/kg on Gestation Days 6, 10, and 14. Increase in post-implantation loss occurred in the 20 mg/kg group, in the presence of maternal toxicity.

In a pre- and postnatal development toxicity study in pregnant mice, in which the murine surrogate antibody was administered every 3 days from gestation day 6 through lactation day 19 at doses of 0, 0.3, 3, or 20 mg/kg, no maternal toxicity or increased incidence of post- implantation loss was observed. Reductions in T cell populations and increases in B cells, and a reduction in the adaptive immune response to keyhole limpet hemocyanin (KLH) were observed in the offspring on postnatal days 35 and 84 at 20 mg/kg. The surrogate antibody was present in the offspring serum at level less than 1.5% that of maternal serum at the high dose. A trend towards reduction in fertility was observed in the offspring of dams administered the murine surrogate antibody at 20 mg/kg. The human relevance of this finding is unknown.

### 8.2 Lactation

Risk Summary

There are no data on the presence of teplizumab-mzwv in either human or animal milk, the effects on the breastfed child, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to teplizumab-mzwv are unknown.

Although the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TZIELD and any potential adverse effects on the breastfed child from TZIELD or from the underlying maternal condition, a lactating woman may interrupt breastfeeding and pump and discard breast milk during treatment and for 20 days after TZIELD administration to minimize drug exposure to a breastfed child.

### 8.4 Pediatric Use

The safety and effectiveness of TZIELD to delay the onset of Stage 3 type 1 diabetes have been established in pediatric patients 8 years of age and older with Stage 2 type 1 diabetes. Use of TZIELD for this indication is supported by evidence from an adequate and well-controlled study (Study TN-10) in adults and pediatric patients 8 years of age and older (including 29 pediatric patients). Adverse reactions observed in pediatric patients 8 years of age and older who received TZIELD were consistent with those reported in adult patients *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of TZIELD have not been established in pediatric patients younger than 8 years of age.

### 8.5 Geriatric Use

Stage 2 type 1 diabetes is largely a condition that occurs in pediatric and younger adult patients. Clinical studies of TZIELD to delay the onset of Stage 3 T1D did not include patients 65 years of age and older.

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**Managing type 1 diabetes (T1D)** is a challenge for any patient, but it's even greater when the person is a child or adolescent. The difficulties that pediatric patients and their families confront is reflected in data suggesting that fewer than one in five T1D patients 18 years or younger consistently achieve the recommended A1C target of 7% or less for youth with T1D.[1]

This underscores why screening for preclinical T1D is critical to help families prepare for the major lifestyle adjustments that clinical (Stage 3) T1D requires. Clinicians who forge strong partnerships with patients and their parents throughout their journey—from screening to diagnosis of Stages 1 and 2 to onset of Stage 3—can help families overcome obstacles to effective T1D management, says University of Utah developmental health psychologist Cynthia Berg, PhD, who studies how adolescents manage chronic illnesses, including diabetes, in the context of their relationships. Cultivation of a trusting relationship between clinicians and their newly diagnosed pediatric patient plus the child's parents is associated with better outcomes, says Berg. Here, she offers strategies to help ensure optimal management of T1D at diagnosis and throughout a patient's life.

## Reassure parents

An important early step in building a relationship with families is to recognize and address concerns parents have about the diagnosis. "Many parents are quite distressed when their child is first diagnosed," says Berg. "The future that they saw their child having is now altered and that can be really stressful." Acknowledge that managing a child's T1D is challenging, says Dr. Berg, but emphasize that it can be normalized and integrated into the family's daily life by creating routines around managing the condition and accepting that challenges may occur.

## Help patients cope with stress

Many individuals with T1D experience their highest lifetime A1C levels in late adolescence and early emerging adulthood (roughly 18 to 24), says Berg. This is also the time when T1D patients report the highest levels of diabetes distress, which arises due to concerns about food and eating, for example, or feeling discouraged about the tasks involved in managing T1D, such as checking one's blood sugar level and determining the proper insulin dosage.

"There are a lot of reasons why that's the case," says Berg. Many patients in this age group find themselves entering higher grade levels with more demanding courses as well as dating and getting a job for the first time. Older teenagers and young adults are preparing for living independently for the first time, either because they're attending college or have moved out of the family home, meaning they no longer have an in-house support team. The demands of a heavy course load, a new job and new social relationships may make management of T1D more difficult.

Berg and colleagues examined how diabetes stressors and the general stressors of daily life (such as problems with schoolwork or arguments with friends) relate to management of the disease in a group of adolescents and emerging adults with T1D. Study participants were asked to record their levels of negative moods (depression, anxiety and anger) and self-care for diabetes in daily diaries for 2 weeks. They also reported on their daily blood glucose values (measured with glucometers). This 2024 study, published in the *Journal of Behavioral Medicine*, found that on days when participants reported more diabetes and general stressors, they also reported lower positive and higher negative moods. On days when they reported higher diabetes stressors, they reported lower self-care and higher blood glucose levels.[2]

Standard medical screening tools or questions during medical exams can help identify patients experiencing diabetes distress. Some patients may benefit from stress-reduction or mindfulness meditation classes, while those reporting high levels of diabetes-related or general stress may benefit from referrals to mental health professionals, advises Berg.

## Address family conflict

A source of stress among adolescents with T1D is conflict with parents, which can interfere with diabetes management. In a 2023 study published in the *Journal of Family Psychology*, Berg and colleagues oversaw a study in which 180 adolescents with T1D (median age 12.9 years) were instructed to record conflicts over diabetes management with their parents in diaries every day for 2 weeks. Participants' diary entries were correlated with daily average blood glucose. The study found that adolescents reporting the most conflict with parents had higher average mean blood glucose levels.[3]

Earlier research by Berg and colleagues found that conflict over diabetes management is more likely in households with parents who have low levels of self-control over their own emotions, cognition and behaviors. Clinicians should encourage parents to adopt a warm and accepting approach when commenting on a child's diabetes management, says Dr. Berg. "Show unconditional love to your child," she tells parents. "Even if they have high A1C, address that with problem-solving rather than with criticism or psychological control."

## Consider other barriers to glucose control

When a pediatric patient with T1D transitions to care with an adult endocrinologist and struggles to manage blood glucose levels, "they may be characterized as unmotivated," says Dr. Berg. "But what they're describing is oftentimes low executive function," she says, such as the ability to plan, concentrate, focus and control impulses.[4] Emerging adults who have lower executive function experience a more rapid increase in A1C from ages 18 to 21, on average.[5] Berg's research suggests that lower executive functions may have significant impact on diabetes management after an emerging adult moves out of the family home and is managing diabetes more independently.[6]

Clinicians should consider that lower executive function may be a contributing problem when a young patient is consistently unable to achieve A1C targets despite working closely with a diabetes educator to learn management strategies, says Berg. Referring such patients to a mental health professional for assessment of executive function may be appropriate in some cases, says Berg, but her research shows that most require greater support from their healthcare team and can greatly benefit from the involvement of parents.[7]

## Set "smart" goals

Young adults frequently set goals for T1D management that are too abstract, such as wanting to achieve a low A1C level, says Berg. "Instead, we recommend setting a 'smart' behavioral goal—something very specific and measurable that the patient can do every day," she says. "It's important to work with the individual to identify barriers to meeting those particular goals and how to reduce them."

For example, a clinician might work with the patient

to set a goal of testing blood glucose five times per day, then recommend strategies for anticipating highs or lows and how to counteract them. Fortunately, the availability of continuous glucose monitoring can help encourage patients to check and monitor their glucose levels more frequently on their smartphones with fewer fingerstick tests. Another goal may be set for meals. Many adolescents skip breakfast, which research shows can increase the challenge of controlling blood glucose for the rest of the day, says Berg. For such a patient, you might suggest eating breakfast 3 days a week, then increasing the goal to 4 days, and continue until they have established a habit of eating a morning meal daily. Achieving these daily metrics not only helps manage A1C but gives young patients a boost in self-esteem. "Our participants say, 'I'm so proud of myself for meeting this goal,'" says Berg.

## Schedule a one-on-one with adolescents

While parents will be present with a pediatric patient at most office visits, it's important for clinicians to schedule some separate time with adolescents. "That allows the patient to talk about any issues that they may want to address specifically with their healthcare provider," says Berg, noting that this can accomplish several goals. First, patients will be more likely to see their clinician as their advocate, which may encourage disclosure of risky health practices they would be less likely to reveal to a parent, such as consuming alcohol or smoking marijuana. Also, these conversations can help adolescents become comfortable speaking openly with healthcare providers, which will be essential when a pediatric patient eventually transitions to adult care for T1D.

## Encourage parents to remain involved

Many parents of young people with T1D assume that their involvement in their child's management of the disease diminishes as they slowly enter adulthood. It's usually true that the nature of a parent's involvement changes during this transition, especially if the young person lives independently or has a close romantic partner. "But the more that parents remain available, if needed, helps those young adults," says Berg, who has plans to study the role of supportive text messaging between parents and emerging adults with T1D.

## Help avoid gaps in care

Depending on the clinic, T1D patients transition from pediatric care to adult care at age 18 or 19, or upon graduating high school, with some going up to a year or more with a lapse between appointments. If possible, pediatricians who treat patients transitioning to adult care should arrange for a "warm handoff" with their new primary care provider and, ideally, their adult-care endocrinologist. In addition, advising parents to maintain involvement during this transition by encouraging them to attend the first appointment with the adult-care clinicians, with permission of their child, may be beneficial.

*—by Tim Gower*

"We recommend setting a 'smart' behavioral goal—something very specific and measurable that the patient can do every day."

*—Cynthia Berg, PhD*

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**PATIENT:** LISA, A 32-YEAR-OLD WOMAN WITH HYPOTHYROIDISM, PREDIABETES, GESTATIONAL DIABETES AND A FAMILY HISTORY OF TYPE 1 DIABETES.

# "Screening for early-stage type 1 offers many benefits for families"


PHYSICIAN:

**Rachel Pessah-Pollack, MD, FACE**

*Clinical Associate Professor, Division of Endocrinology, Diabetes & Metabolism, NYU School of Medicine, NYU Langone*


Illustration by Juhee Kim

**History and screening:**
Lisa had been coming to see me for management of her Hashimoto's hypothyroidism. Recently, I had diagnosed her mother with adult-onset type 1 diabetes, and we know that patients who have a first-degree relative with type 1 have a higher risk of also developing the disease. Therefore, before Lisa's next visit, I ordered labs that included screening for diabetes autoantibodies. When Lisa came for her visit, we discussed her lab results. She had a fasting glucose of 119 mg/dL and an A1C of 5.8% but no symptoms of dysglycemia. She had also tested positive for two diabetes autoantibodies (Abs), GAD65 (glutamic acid decarboxylase 65) and islet cell Abs. I explained to Lisa that this meant she had preclinical (Stage 2) type 1 diabetes.

Lisa, who had an 18-month-old daughter, told me that she and her husband wanted a second child and were actively trying to conceive. Understandably, she was concerned about the implications of her diagnosis for herself, her daughter and future family planning. I reassured her that I would follow her closely and evaluate her for progression to Stage 3 type 1. She would also need to be alert for potential signs of diabetes and report them immediately. This monitoring can help her avoid diabetic ketoacidosis (DKA), which can be very dangerous.

**Considerations for the family:**
Given Lisa's history, I stressed the importance of screening her daughter as well as future children and grandchildren, for early-stage type 1 when they reach the appropriate age. The American Diabetes Association recommends yearly screening for children and adolescents ages 1 to 17 who have a first-degree relative with type 1 diabetes.

Until recently, there were no treatments for patients who tested positive for preclinical disease. However, thanks to a landmark trial, a novel monoclonal antibody was recently FDA-approved for delaying onset of clinical (Stage 3) type 1. The drug is approved for patients ages 8 and older with Stage 2 type 1 diabetes—defined as having two or more diabetes autoantibodies, no diabetes symptoms and dysglycemia (fasting glucose 100-125 mg/dL, 2-hour postprandial glucose 140-199 mg/dL and A1C 5.7-6.4%). A patient like Lisa could theoretically consider treatment to delay the onset of Stage 3—but *only* if she deferred becoming pregnant, as the agent has not been studied during pregnancy and therefore is contraindicated in pregnancy. Lisa and I discussed potential treatment to delay her development of type 1, but she chose to proceed with pregnancy and close monitoring given her risk of developing Stage 3 diabetes.

**Summary:**
Lisa's case demonstrates the generational impact of type 1 diabetes and the critical need to screen these high-risk patients for preclinical disease. In addition, the availability of a treatment to delay onset of type 1 is exciting because of the discussions we can now have with our patients about treatment options. That gives us even greater incentive to screen all relatives of a patient who has type 1.

Delaying progression can be especially meaningful to children and their families because of the lifestyle adjustments that treating type 1 diabetes requires. A disease-modifying therapy has the potential to significantly improve quality of life—not just for patients, but for their family members that one day, too, may be diagnosed with early-stage type 1 and be able to delay onset of this autoimmune disease.

**NEW!**
**KOL ON DEMAND VIDEO**
Scan here for more insight on Lisa's case.

# Q

# A

*Expert insight on pediatric type 1 diabetes*

## When test results are positive for Stage 2

**Q: When a patient is diagnosed with preclinical type 1 diabetes, what are the next steps for management?**

**A:** The next step is referral to an endocrinology specialist, preferably a pediatric endocrinologist, which, if done in a timely manner, can assist with expediting further steps in ongoing assessment and management. The endocrinologist can discuss enrolling the child in clinical trials or offer the option of a monoclonal antibody to delay onset of Stage 3 after a discussion of the pros and cons with the family. The family should be informed that enrollment in a clinical trial includes the possibility that a child may be randomized to the placebo arm of the trial and would not receive the active treatment. Therefore, traveling to a clinical site to receive a monoclonal antibody vs. joining a research study that may not result in active treatment should be discussed as that may impact the family's decision-making.

Regardless of whether a family pursues intervention with therapy to delay onset, education on blood sugar monitoring should be provided, including awareness of the symptoms of hyperglycemia (e.g., excessive thirst or urinating more than normal). A diabetes educator, who is typically affiliated with an endocrinologist's practice, is easily able to provide this teaching to the family. There are also many resources available online, including videos and handouts in several different languages that families can peruse at their convenience. Information from the Juvenile Diabetes Research Foundation (*jdrf.org/T1Detect*) and *trialnet.org* are great resources for families to ensure they are aware of their options, have the necessary contacts and can connect with families in a similar situation to derive support.

*–**Rabab Jafri, MD,** pediatric endocrinologist, Texas Diabetes Institute, The University of Texas at San Antonio*

## Helping parents navigate a diagnosis

**Q: When a child is diagnosed with type 1, what are challenges that parents experience?**

**A:** When a child or adolescent receives a diagnosis, parents may feel shock, guilt, anxiety or uncertainty. That's on top of many unanswered questions, including how to best support their child. To help parents cope, I provide comprehensive education about type 1 diabetes and its management. In addition, I advise type 1 diabetes screening for all relatives, especially siblings.

For many parents, the challenge is how to stay actively engaged in their child's diabetes management while at the same time encouraging the child's independence after progression to the clinical stage. They worry how their child can balance their social life and their ability to manage diabetes, both emotionally and practically. I ask parents how involved they want to be in their child's care and, conversely, I ask the child how much they want their parents to be involved. Giving older children and teenagers the opportunity to voice their preferences and take charge reassures parents and eases their concerns. Specialized counselors or therapists can help address parents' emotional distress and offer valuable coping mechanisms. Additionally, emphasizing self-care for parents and connecting them with support groups provides shared experiences and insights, aiding in the transition and helping parents strike a balance in supporting their child's journey.

*–**Joanna Mitri, MD, MS,** Medical Director, Global Education and Advisory Care, Joslin Diabetes Center; Assistant Professor, Harvard Medical School*

Illustration by Donna Grethen / Ikon Images

## Advances in insulin therapy

**Q: What are some recent advances in insulin delivery?**

**A:** Many patients are now benefiting from innovations in delivery devices, such as advanced insulin pump technology and closed-loop systems. Hybrid closed-loop systems, in particular, stand out. By automating the treatment loop, these systems significantly reduce the patient's daily decision-making burden. In addition, they help keep patients within the desired glucose range for longer periods, without requiring extra effort from the user. For instance, if a hypoglycemic episode occurs during sleep, this technology temporarily halts insulin delivery to minimize the duration spent below the target range. Moreover, insulin delivery slows or halts if the sensor predicts an impending hypoglycemic event. Similarly, if the sensor detects a likelihood of glucose levels rising above the target range, the system temporarily adjusts the basal rate or delivers small corrective boluses, or sometimes both.

Transdermal insulin-patches are another insulin-delivery innovation, potentially offering more convenience and ease in administration. Inhaled insulin is another option that is appealing for those seeking a more straightforward insulin delivery method during meals.

*–**Joanna Mitri, MD, MS***

## Glucose monitoring

**Q: What counseling do you provide when a patient starts CGM?**

**A:** One thing I tell patients: This is not going to manage their diabetes for them! Continuous glucose monitoring (CGM) is a tool to help them manage their blood sugar. When selecting a device, it is important to find the right one for each patient. It is also vital for patients and their families to do training with a product representative or educator so they know device capabilities, how to download data to their smartphone, physical placement and sensor rotation. They should also know how to troubleshoot problems–for example, by doing a fingerstick reading to validate the numbers if they are unsure if the device is working properly or if they have an insulin pump and want to make sure their devices are synched. Also, CGM can be less accurate during a hypoglycemic episode, so a fingerstick reading should be done for validation.

*–**Susan VanBeuge, DNP, APRN, FAANP,** Professor in Residence, University of Nevada, Las Vegas, School of Nursing*

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# Clinician Update

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EXAM TOOL

# SCREENING FOR PEDIATRIC TYPE 1 DIABETES (T1D)

Diagnosing preclinical type 1—which is asymptomatic and does not require insulin therapy—is critical not only for avoiding diabetic ketoacidosis in undiagnosed patients but also for ensuring timely referral to an endocrinologist for evaluation and ongoing monitoring. In addition, identifying patients with preclinical (Stage 1 and Stage 2) T1D as early as possible will allow patients and their families the option of starting treatment to delay onset of insulin-dependent (Stage 3) T1D and help them prepare for the significant lifestyle changes that are required for lifelong management. Fortunately, you can identify at-risk patients by taking a few simple steps:

## STEP 1:

**Identify patients at higher risk, including those who:**

- ☐ Have a family history of T1D, especially a sibling or parent with the disease.
- ☐ Have an autoimmune disease, such as celiac disease.
- ☐ Are between 1 and 17 years old (about 75% of those diagnosed with T1D are under age 18).

## STEP 2:

**Order a blood test to screen for pancreatic islet autoantibodies, including:**

- ☐ GAD65 (glutamic acid decarboxylase 65)
- ☐ IA-2 (islet antigen 2)
- ☐ IAA (insulin autoantibody)
- ☐ ZnT8 (zinc transporter 8)

## STEP 3:

**Refer to an endocrinologist if results are positive for ≥2 pancreatic islet autoantibodies.**

SOURCE: The Juvenile Diabetes Research Foundation (JDRF).
For more on T1D risk screening and options for free testing, visit *jdrf.org/T1Detect*.