COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID DUR REPORT
JANUARY 2023

TEPLIZUMAB-MZWV (TZIELD)
TO DELAY ONSET OF (STAGE 3) TYPE 1 DIABETES MELLITUS
UPDATE

Original report: August 2021
Report update: December 2022
Report delivered: January 2023

Drug Regimen Review Center

Lauren Heath, PharmD, MS, BCACP, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Monet Luloh, PharmD, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Medical Writer
Joanne LaFleur, PharmD, MSPH, Executive Director

University of Utah College of Pharmacy, Drug Regimen Review Center

CONTENTS

LIST OF TABLES

ABBREVIATIONS

A1c	Glycated hemoglobin, or hemoglobin A1c
AACE	American Association of Clinical Endocrinology
AAP	American Academy of Pediatrics
ACE	American College of Endocrinology
ADA	American Diabetes Association
AE	Adverse event
BMI-z	Age-specific body mass index
BSA	Body surface area
CBC	Complete blood count
CD3	Cluster of differentiation 3
CI	Confidence interval
CMV	Cytomegalovirus
CRS	Cytokine release syndrome
DB	Double-blind
DKA	Diabetic ketoacidosis
EBV	Epstein-Barr virus
ES	Endocrine Society
FPG	Fasting plasma glucose
FDA	U.S. Food and Drug Administration
GDM	Gestational diabetes mellitus
HR	Hazard ratio
ICER	Institute for Clinical and Economic Review
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
ISPAD	International Society for Pediatric and Adolescent Diabetes
IQR	Interquartile range
IV	Intravenous
JDRF	Juvenile Diabetes Research Foundation
LFTs	Liver function tests
mAB	Monoclonal antibody
N	Number of participants
OGTT	Oral glucose tolerance test
PBO	Placebo
R	Randomized
RCT	Randomized controlled trial
SR	Systematic review
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TEP	Teplizumab
TTE	Time to event
USPSTF	U.S. Preventative Services Task Force
Vs	Versus
ZnT8	Anti-zinc transporter 8

1.0 INTRODUCTION

The purpose of this report is to review efficacy and safety information for the intravenous (IV) monoclonal antibody, teplizumab-mzwv (Tzield), that was recently approved by the US Food and Drug Administration (FDA) for *delaying* the onset of type 1 diabetes (T1D) in individuals 8 years or older at risk for T1D.[1] **Teplizumab is the first FDA-approved disease-modifying therapy for people at risk for clinical T1D.[1,2]** This report updates a previous report from 2021 on the same topic.

T1D is thought to occur due to a combination of dysfunctional insulin-producing pancreatic beta cells and T-cell mediated destruction of those beta cells, ensuing dependency on exogenous insulin for survival.[3] Peak incidence occurs during childhood (10-14 years old),[4,5] but onset may occur at any age.[6] T1D is usually diagnosed once symptomatic hyperglycemia occurs, which coincides with the loss of a significant number of functional beta cells.[7] FDA-approved therapies for T1D include insulin and pramlintide.[8] These medications manage metabolic complications of T1D, but do not modify the cause of T1D.

In 2015, the American Diabetes Association (ADA), Endocrine Society, and Juvenile Diabetes Research Foundation (JDRF) published a classification system for the course of T1D.[7] This classification system identifies 2 pre-clinical stages before patients meet criteria for clinical T1D: Stage 1 (positive for 2+ autoantibodies associated with T1D) and Stage 2 (positive for 2+ autoantibodies and dysglycemia that does not yet meet criteria for hyperglycemia and overt T1D). Clinical T1D is considered Stage 3 of the disease. Prior to clinical T1D (Stage 3), patients are usually asymptomatic.[7] Nearly all patients with Stage 1 or 2 T1D will eventually progress to Stage 3 or clinical T1D.[7,9,10] Teplizumab is specifically indicated for Stage 2 T1D.[1] There are no FDA-approved therapies for Stage 1 T1D.

Teplizumab has been in clinical development since the late 1990s. Initial studies were conducted among newly diagnosed Stage 3 T1D patients, with the goal of preserving functional pancreatic beta cells.[11] Although benefits on biomarkers indicating continued insulin production (C-peptide) were observed, development for Stage 3 T1D was halted after a phase 3 clinical trial failed to meet its primary clinical endpoint.[11] Later, the T1D TrialNet group completed a phase 2 study of teplizumab in close relatives of persons with established T1D. Most of these at-risk individuals met criteria for Stage 2 T1D, having evidence of immune-mediated destruction of beta cells and dysglycemia not yet meeting clinical criteria for T1D. Results showed that a single 14-day course of teplizumab could delay the onset of overt Stage 3 T1D in these at-risk individuals.[12] On November 17, 2022, after the sponsor provided the FDA with updated safety information and pharmacokinetic data,[13] teplizumab was approved for the delay of T1D (Stage 3) among people ages 8 years or older with Stage 2 T1D.[14] Teplizumab is also under study for patients with recent-onset Stage 3 T1D[15]; however, the FDA has not yet reviewed it for this indication.[14]

Teplizumab is an anti-CD3 humanized monoclonal antibody that is administered as an IV infusion. Table 1 summarizes prescribing information for teplizumab. It is given as a single 14-day course, dose-adjusted according to body surface area,[1] and is up-titrated over the first 4 infusions to minimize the risk of adverse reactions, including cytokine release syndrome (CRS).[2] The mechanism of action is not fully understood, but teplizumab is thought to play a role in correction of overactive T cells contributing to pancreatic islet cell autoimmunity.[1]

Table 1. Overview of Teplizumab-mzwv Prescribing Information[1]

	Prescribing Information
Indication	**To delay onset of clinical T1D among people 8 years of older with Stage 2 T1D[a]** • Laboratory confirmation of diagnosis and safety parameters, and administration of age-appropriate vaccinations are recommended before use
Dosage Information[b]	**One-time 14-day course**; cumulative dose of about 11,240 µg/m² given as follows: • Days 1-4: 65, 125, 250 and 500 µg/m² on days 1-4, respectively (up-titration to avoid side effects) • Days 5-14: 1,030 µg/m² once daily May pause administration for 1-2 days for severe CRS; as appropriate, resume consecutive remaining doses to complete 14-days. **Missed doses:** In the event of a missed dose, resume dosing where it was left off and administer remaining infusions on sequential days until completion of the 14-day regimen. Do not deliver 2 doses on the same day.
Dosage forms and administration	• 2 mg/2 mL single-dose vial • Dilute 2 mL of vial contents with 18 mL of 0.9% sodium chloride to prepare a solution of 100 mcg/mL teplizumab; prepare an infusion bag with the appropriate daily dose by using a syringe to add the necessary amount of diluted 100 mcg/mL teplizumab solution to 25 mL of a 0.9% sodium chloride polyvinylchloride infusion bag. Unused teplizumab solution should be discarded. • **Premedication with an NSAID or APAP, an antihistamine, and/or antiemetic is recommended** during the first 5 days of the 14-day course, and on additional days as needed. • Administer each dose as a 30-minute or longer IV infusion ○ Start infusion within 2 hours of preparation, and complete infusion within 4 hours of preparation
Description and mechanism of action	• Recombinant humanized anti-CD3 monoclonal antibody • Binds to the epsilon chain of CD3, a co-receptor present on T cells that is part of the signaling component of T cells and thought to be an immune system modulator

[a] ***Patients should have Stage 2 T1D*** *with evidence of seropositivity for ≥ 2 diabetes-related autoantibodies (eg, anti-GAD, insulin, IA-2, ZnT8A, islet cell) and dysglycemia (eg, 2-hr plasma glucose of 140-199 mg/dL[16]). OGTT is the recommended test for dysglycemia, though other glycemic tests can be considered if OGTT is inaccessible. Patients should NOT have Stage 3 T1D (ie, overt hyperglycemia) or have a history suggestive of type 2 diabetes mellitus.*

[b] *In the updated protocol of the pivotal study of teplizumab (TN-10), the dose was determined based on body surface area (in m^2) using the Mosteller formula.[12,17]*

Abbreviations: APAP, acetaminophen; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; m, meters; OGTT, oral glucose tolerance test; T1D, type 1 diabetes.

As specified in the product labeling, prescribers should document that a patient intended for teplizumab treatment meets the following criteria for Stage 2 T1D: at least two positive pancreatic islet cell autoantibodies, and dysglycemia without overt hyperglycemia. Additionally, prescribers should order a complete blood count with differential and liver enzyme tests to confirm that patients do not

have serious cytopenia or liver abnormalities. During the single 14-day course of teplizumab, the manufacturer recommends laboratory monitoring, including white blood cell counts and liver enzymes. Patients should receive age-appropriate vaccinations prior to teplizumab therapy owing to the potential for a reduced vaccine response after receiving teplizumab, and the lack of data for use of teplizumab in proximity to vaccinations.[1]

Table 2 summarizes recommendations for laboratory monitoring prior to and during teplizumab use, according to prescribing information.

Table 2. Recommended Laboratory Screening and Monitoring Before and During Teplizumab Therapy[1]

Laboratory Test/ Parameter(s)	Pre-treatment Screening		Monitor during Treatment[a]	
	Screen	*Use is recommended against for patients with any of the following:*	**Monitor**	*STOP treatment for any of the following:*
Hemoglobin	✓	Hemoglobin ≤ 10 g/dL		
Lymphocyte count	✓	Lymphocytes <1000 cells/µL	✓	Lymphocytes <500 cells/µL for ≥ 1 week
Platelet count	✓	Platelets <150,000 cells/µL		
Neutrophil count	✓	ANC <1,500 cells/µL		
AST, ALT, and bilirubin	✓	AST or ALT >2x ULN, or bilirubin >1.5x ULN	✓	AST or ALT >5x ULN, or bilirubin >3x ULN
Other	✓	Serious or chronic active non-localized skin infection, including acute CMV and EBV, or others		

[a] *Based on warnings and precautions from the prescribing information.*

Abbreviations: ALT, alanine aminotransferase ; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GAD, glutamic acid decarboxylase 65; IA-2, insulinoma-associated antigen 2; OGTT, oral glucose tolerance test; T1D, Type 1 diabetes mellitus; ULN, upper limit of normal; x, times; ZnT8, zinc transporter 8.

2.0 METHODS

This report includes evidence from randomized controlled trials (RCTs) or systematic reviews (SRs) of RCTs regarding use of teplizumab. Some observational studies that reported longitudinal follow-up data from patients that received teplizumab as part of an RCT were included also. Additional evidence, including prior clinical trials of teplizumab for use among patients with recent-onset T1D, were reviewed for supportive efficacy and safety information.

Information pertaining to teplizumab was obtained from an Embase search (see Appendix A). The Agency for Healthcare Research and Quality website for evidence-based reports (https://www.ahrq.gov/research/findings/evidence-based-reports/search.html) and Institute for Clinical and Economic Review (ICER) website (https://icer.org/)were additionally searched for relevant information about teplizumab or screening for T1D. Prescribing information for teplizumab and information from the FDA advisory committee's review of teplizumab were on Provention Bio, Inc.'s website (https uneventionbio.com/). Registered clinical trials for teplizumab were searched on ClinicalTrials.gov. Additional references were located based on scanning the reference list of identified studies and clinical practice guidelines. We searched for information pertaining to the prevalence or incidence of stages of T1D on the Center for Disease Control (CDC) website and PubMed.

A search for relevant practice guidelines with information about screening and treatment of **pre-symptomatic T1D** (ie, Stage 1 and 2 T1D) was performed, focusing on US-based or international consensus guidelines. The websites of the following organizations were searched: American Diabetes Association (ADA), American Association of Clinical Endocrinology (AACE)/American College of Endocrinology (ACE), International Society for Pediatric and Adolescent Diabetes (ISPAD), American Academy of Pediatrics (AAP), Endocrine society (ES), and US Preventative Services Task Force (USPSTF).

3.0 DISEASE OVERVIEW

3.1 Pre-symptomatic Type 1 Diabetes Mellitus (T1D)

Advances in the understanding of the pathogenesis and natural history of T1D have led to describing T1D on a disease continuum. Prior to symptomatic T1D, which is when T1D is usually diagnosed, most patients have evidence of autoimmunity and eventually, metabolic disturbances.[7] In 2015 the ADA, Endocrine Society, and JDRF published a classification system for the stages of T1D.[7] This system, and characteristics of each stage are summarized in Table 3. In the T1D continuum, patients progress from having pancreatic islet-cells autoimmunity markers, to considerable loss of pancreatic beta-cell function and manifestation of overt T1D clinical symptoms that spurs a diagnosis of T1D at Stage 3. [7] Of note, a small proportion of patients that develop T1D do not have evidence of autoimmunity; these cases are often referred to as idiopathic T1D.[18]

The **pre-Stage 1** phase describes individuals with genetic risk factors for developing T1D. Specific human leukocyte antigen (HLA) genotypes account for about 30-50% of the genetic risk of T1D; remaining genetic risk is attributed to non-HLA genes.[7] Individuals with a family history of T1D account for approximately 15% of new T1D diagnoses.[7] A first-degree relative with T1D increases individual risk for developing T1D approximately 15-fold.[19] Environmental factors (eg, maternal/intrauterine factors,

viruses, diet) may also contribute to the development of T1D; however, their role is not well understood so these factors are not yet incorporated into T1D staging.[7]

Stage 1 T1D is characterized by evidence of autoimmunity without any evidence of glucose intolerance (ie, normoglycemia). Autoimmunity is defined as 2 or more antibodies to T1D-related antigens (eg, insulin/proinsulin, glutamic acid decarboxylase [GAD], insulinoma antigen 2[IA-2], and/or zinc transporter 8 [ZnT8]).[7] During this stage, there is pancreatic beta-cell stress and there may be a slight decline in functional beta cells; however, there is not yet evidence of dysglycemia due to compensatory insulin production.[7,9] Among children with genetic risk factors and stage 1 T1D, the 10-year risk of developing T1D is about 70%, and lifetime risk approaches 100%.[9,10] As beta-cell destruction continues, Stage 2 T1D develops.

In **Stage 2 T1D**, there is evidence of 2 or more islet autoantibodies and impaired glucose tolerance without overt hyperglycemia. Various methods for identifying dysglycemia have been proposed including impaired fasting plasma glucose (FPG), impaired plasma glucose (PG) after an oral glucose tolerance test (OGTT), elevations in hemoglobin A1c (A1c), and impaired first-phase insulin response (FPIR) after an IV glucose tolerance test.[9] Reference ranges are listed below. Common criteria for dysglycemia were developed from cohorts of adult patients with type 2 diabetes (T2D), so applicability to T1D and children is sometimes debated.[7] At Stage 2 T1D, the 5-year risk of developing T1D is about 75%, and lifetime risk approaches 100%.[9,10]

Proposed definitions of dysglycemia (present in Stage 2 T1D):

- ADA criteria for adults and children[16,20]: FPG of 100-125 mg/dL; 2-hr plasma glucose of 140-199 mg/dL; or an A1c of 5.7-6.4% or ≥ 10% increase in A1c
- 2015 ADA/JDRF/ES scientific statement (identifies criteria that have been used in some clinical studies): FPG ≥ 100 mg/dL or ≥ 110 mg/dL; after an OGTT, 2-hr plasma glucose ≥ 140 mg/dL, or ≥ 200 mg/dL after 30, 60, or 90 minutes; or A1c ≥ 5.7%[7]

Note that teplizumab prescribing information recommends confirming dysglycemia with an OGTT unless that testing method is not available.[1]

Stage 3 T1D (ie, clinical or symptomatic T1D) occurs once a patient is symptomatic and/or meets criteria for hyperglycemia as defined by clinical practice guidelines[7,9] Patients at this stage usually require treatment with insulin.[9] Refer to section 3.4 for details on the diagnosis of Stage 3 T1D.

A general consensus is that nearly 100% of individuals meeting criteria for Stage 1 T1D will eventually be diagnosed with Stage 3 T1D.[7,10] However, the time of progression through these stages is variable and may occur over months or decades.[7] Among patients with two or more islet autoantibodies (ie, Stage 1 or 2), the rate of progression to T1D is about 11% per year.[19] Age, the specific autoantibodies present, the number of different autoantibodies, and metabolic status are examples of factors that influence the risk of progression.[21] Among children, progression is particularly fast when autoantibodies are detected prior to age 3, and for specific high-risk HLA genotypes (HLA DR3/DR4-DQ8).[19] Adults 18 years or older with multiple islet autoantibodies may progress more slowly, with a 5-year risk of Stage 3 T1D of approximately 15%.[21]

Table 3 outlines the T1D staging system and characteristics of each T1D stage.

Table 3. Description of Type 1 Diabetes Stages based on the 2015 ADA, JDRF, and Endocrine Society Scientific Statement[7] and Additional Supportive Information

Increasing loss of functional β cells[a] →			
Stages	**Stage 1**	**Stage 2**	**Stage 3 (T1D)[b]**
≥ 2 autoantibodies[c]	X	X	X (may be present; includes idiopathic T1D)
Dysglycemia[d]		X	X Hyperglycemia
Symptoms	Pre-symptomatic	Pre-symptomatic	Usually symptomatic
5-year risk for reaching stage 3[e,9]	44%	75%	--
10-year risk for reaching stage 3[e,9]	70%	--	--
Lifetime risk for reaching stage 3[e,9]	Approaches 100%	Approaches 100%	--
Clinical development of teplizumab	*Not studied in this subset*	***FDA-approved** among people ≥ 8 years old*	*In phase 3 clinical trial for patients with autoantibodies (results anticipated in mid-2023)[14]*

[a]*Disease progression is a non-linear process. The most precipitous decline occurs during the later phases of Stage 2 (approximately 6 months before overt hyperglycemia and diagnosis of Stage 3 T1D).[10,22] Some residual beta-cell function remains at T1D diagnosis.[22]*

[b]*"Stage 4" is recognized by some organizations. The International Society of Pediatric and Adolescent Diabetes (ISPAD) defines Stage 4 as "long standing type 1 diabetes." (page 20)[19]*

[c]*Islet autoantibodies, including glutamic acid decarboxylase 65 (GAD65) or just glutamic acid decarboxylase (GAD), tyrosine phosphatase-like insulinoma antigen 2 or islet antigen 2 (IA-2), (pro)insulin, and zinc transporter 8 autoantibodies[7,19]*

[d]*The ADA identifies dysglycemia for Stage 2 as either IFG or IGT. Listed examples that meet this criterion include FPG of 100-125 mg/dL, 2-h plasma glucose of 140-199 mg/dL after OGTT, or an A1c of 5.7-6.4% or > 10% increase in A1c.[18,20]*

[e]*Supported by cohort studies of children (often from birth) with genetic risk factors. Risk for developing T1D is heterogeneous and known to differ according to various factors (eg, age and the specific antibodies present).[21]*

Abbreviations: A1c, glycated hemoglobin; ADA, American Diabetes Association; FDA, US Food and Drug Administration; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; JDRF, juvenile diabetes research foundation; OGTT, oral glucose tolerance test; T1D, type 1 diabetes.

Overall, this staging system may be useful for clinical trials and for potential precision medicine to match treatments to the appropriate stage of disease.[9] During the pre-clinical T1D stages (ie, Stage 1 and Stage 2) when a patient does not yet require insulin, the variable rate of progression to Stage 3 T1D could pose a therapeutic dilemma regarding the risks versus benefits of an early disease-modifying treatment. Goals of targeting these earlier stages are to prevent or delay progression to clinical T1D.[9] Teplizumab has been studied in patients with Stage 2 T1D who have a relative with T1D.[12] A phase 3 trial for patients with Stage 3 is in progress,[15] but a prior phase 3 trial failed to meet its primary endpoint.[23,24]

3.1.1 Autoantibodies

Over 90% of people newly diagnosed with T1D have antibodies to various proteins from or on pancreatic islet cells.[6] These antibodies, including those against insulin, islet cell, glutamic acid decarboxylase (GAD or GAD65), insulinoma-associated protein 2 (IA-2) [also called tyrosine phosphatase IA-2], and zinc transporter 8 (ZnT8), are referred to as islet or diabetes-related autoantibodies, or simply autoantibodies.[10,25] In most patients who develop T1D, autoantibodies develop sequentially.[26] Usually insulin autoantibodies develop first,[7] but sometimes GAD65 develops first.[26] Other antibodies (eg, IA-2 or ZnT8) do not usually develop first.[7] The order in which autoantibodies appear may depend on genetic risk factors[10] and/or age of disease onset.[27] Among children, quantifying the autoantibody level may improve prediction of T1D progression compared to autoantibody seropositivity alone[28]; autoantibody titer level may also be indicative of the rate of progression to clinical T1D.[27] Evidence suggests that the presence of 2 or more different autoantibodies, regardless of family history of T1D, indicates that the individual will eventually develop T1D.[10] However, a small proportion of patients who are initially positive for multiple autoantibodies may experience a reversion of positivity. In one study, among 3,284 multiple-antibody positive individuals who were relatives of someone with T1D, autoantibody reversion occurred in 134 (4.1%) of cases. Factors associated with reversion include older age, lower antibody titers, and fewer positive autoantibodies (ie, 2 versus 3).[29] The presence of a single autoantibody does not necessarily mean that an individual will develop T1D. Based on a cohort of children tracked from birth, the probability of developing T1D within 20 years among individuals with 1 positive autoantibody is approximately 10%.[6]

Standard tests for GAD, insulin, ZnT8, and IA-2 antibodies have been FDA-approved.[30-34] See Appendix B for the sensitivity and specificity of these tests according to the manufacturer. Current procedural terminology (CPT) codes corresponding to tests for various diabetes-related autoantibodies are also available; see Appendix C for information about Utah Medicaid clinician orders for these tests.

3.1.2 C-peptide Biomarker

The C-peptide biomarker was used as supportive evidence to investigate the effect of teplizumab on pancreatic beta-cell function. When proinsulin is cleaved and released from pancreatic beta cells, equimolar parts of C-peptide (a 31- amino-acid) and endogenous insulin are secreted. Unlike insulin that degrades rapidly, C-peptide has a longer half-life and is useful for **assessment of pancreatic beta-cell function**.

The normal plasma concentration of C-peptide in a healthy individual is approximately 0.3-0.6 nmol/L in a fasted state, and 1-3 nmol/L higher after eating. Measurement of C-peptide requires a sensitive assay; it may be less accurate in the presence of anti-insulin antibodies (appears higher) and among individuals with chronic kidney disease due to some renal elimination. C-peptide can be measured in the serum following glucagon stimulation, a mixed meal, or oral glucose; or upon urinary collection.[35] Some experts have advocated for the mixed meal tolerance test (MMTT) as the gold-standard.[35] In 2001, an ADA workshop group recommended either the MMTT or glucagon simulation test (GST).[36] For both the MMTT and GST the cutoff for an abnormal C-peptide reading is usually less than 0.2 nmol/L.[35] Longitudinal follow-up of C-peptide levels among individuals at-risk for T1D that later develop clinical

T1D suggest that C-peptide levels are usually stable between 24 to 6 months prior to diagnosis, decline rapidly in the 6 months prior to diagnosis, and decline further in the 12-month period after diagnosis.[22]

Residual, persistent detection of stimulated C-peptide levels may be clinically significant among patients with T1D.[37] In patients with T1D, higher C-peptide levels have been associated with a lower risk for retinopathy, microalbuminuria, and hypoglycemia.[38] Despite evidence from clinical studies supporting use of C-peptide to define diagnoses (eg, to help differentiate between T1D and type 2 diabetes [T2D]), and for prognostic value or therapeutic response,[35] its use is not readily defined in clinical practice guidelines. Neither the 2022 ADA guideline nor the 2022 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guideline provides a formal recommendation for measuring C-peptide for the diagnosis of specific types of diabetes mellitus.[16,25]

Advisory committee documents from the FDA regarding teplizumab state that C-peptide can be used as supportive evidence of effectiveness and may predict clinical benefit; however, is not sufficient on its own to prove efficacy for delaying T1D. The FDA highlighted that "…C-peptide is not a validated surrogate biomarker for clinical benefit, as the quantitative relationship between improvement in C-peptide and delay of T1D is not well defined." (page 12)[2]

3.2 Estimates of the Incidence of T1D and Prevalence of Pre-symptomatic T1D

It is difficult to estimate the incidence or prevalence of Stage 2 T1D, in part because generalized screening for diabetes autoantibodies in asymptomatic individuals is not part of the current standard of care.[16] One research foundation estimates that there are approximately 300,000 people with pre-symptomatic T1D (Stage 1 or Stage 2) in the US, based on the incidence of T1D, the size of the US population, and a 5-year conversion rate of approximately 44% to Stage 3 T1D.[39] Provention Bio, Inc., the sponsor of teplizumab, estimates the prevalence of Stage 2 T1D in the US to be 200,0000, of whom 30,000 (15%) are direct relatives of people with clinical T1D.[14]

Table 4 provides information about the incidence of T1D among children in Utah and adults in the US. In addition, the table includes an estimate of the prevalence of Stage 2 T1D based on the Fr1DA study, a German public health screening of 90,632 children between 2 and 5 years old with and without a family history of T1D (ie, general population).[40]

As illustrated in this table, T1D is a uncommon condition, with mean incidence of about 25.7 persons per 100,000 among Utah youth.[5] Compared to youth, T1D occurs less frequently in US adults, although there is a paucity of data about the incidence in this older population.[4] The prevalence of pre-symptomatic T1D (ie, Stage 1 or Stage 2) is poorly characterized; one study of German children estimated that 0.02% of screened children met criteria for Stage 2 T1D.[40]

Table 4. Estimate of the Incidence of T1D or Prevalence of Patients At-risk for T1D

Demographic category	Mean incidence
Incidence (per 100,000 person-years) of T1D in Utah youth (95% CI)[a,5]	
Age 0-4 years	18.68
Age 5-9 years	31.59
Age 10-14 years	39.06
Age 15-19 years	14.70
All ages 0-19 years	25.67 (24.57 – 26.75)
Incidence (per 100,000 person-years) of T1D among US adults ages 18-44 years (95% CI)[b,4]	
Men	17.5 (16.4 – 18.8)
Women	13.6 (12.4 – 14.9)
Estimates of children 2-5 years old at risk for T1D in the Fr1DA study[c,40]	
Pre-symptomatic T1D, n (%; 95% CI)	280 (0.31%; 0.27 – 0.35)
Stage 1 T1D	196 (0.22%)
Stage 2 T1D	17 (0.02%)

[a]*Based on Utah youth (≤ 19 years old) who received care at Intermountain or University of Utah Healthcare between 1998 and 2015.*

[b]*A study of active duty US military members between 1990 and 2005. There is a paucity of data about the incidence of T1D in US adults.*

[c]*Based on screening 90,632 children ages 2-5 years old between 2015 and 2019 in Bavaria, Germany. Children were considered to have pre-symptomatic T1D if they had 2 or more different islet autoantibodies (IAA, GADA, IA-2A, ZnT8A). Stage 2 T1D patients had abnormal glucose tolerance in addition to positive autoantibodies. The total number of individuals with Stage 1 or Stage 2 T1D does not add up to the total because 41 children were not staged, and 26 children were diagnosed with Stage 3 T1D.*

Abbreviations: CI, confidence interval; GADA, glutamic acid decarboxylase; IAA, insulin antibodies; IA-2A, islet antigen-2; T1D, type 1 diabetes mellitus; ZnT8A, zinc transporter 8.

3.3 Summary of Guideline Recommendations about Pre-symptomatic Type 1 Diabetes

A summary of US-based or international consensus guidelines that relate to screening for pre-symptomatic T1D or treatment of pre-symptomatic T1D are included in Table 5. The ADA mentions that screening for various islet cell autoantibodies may be considered to identify people with pre-symptomatic T1D, either in the setting of clinical research or as an option for individuals with a first-degree family member (ie, parents or sibling) with T1D based on moderate quality of evidence.[16] Generally, this translates to a lack of screening for pre-symptomatic T1D in routine clinical practice, since the recommendation is optional and not strongly worded. The 2022 ADA guideline acknowledges that the presence islet autoantibodies can identify those who may develop clinical T1D and could expedite diagnosis of T1D before the patient is symptomatic (eg, before a presentation with diabetic ketoacidosis). However, the lack of treatment options for pre-symptomatic T1DM at the time of guideline publication precluded recommending screening in the general population of people without a

first-degree relative with T1D.[16] The 2018 International Society for Pediatric or Adolescent Diabetes (ISPAD) guideline about stages of T1D lacks a recommendation regarding screening or interventions for pre-symptomatic T1D other than in clinical research settings.[19] The 2022 AACE/ACE guideline does not provide any information or recommendations about screening for T1D before the onset of symptoms.[25]

Table 5. Selected Guideline Recommendations about Screening for Type 1 Diabetes or Treatment of Pre-symptomatic Type 1 Diabetes

Professional Organization and Guideline	Recommendations (Evidence Grade)

American Diabetes Association (ADA)
 	
Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes; 2022[a16]
	• Screening for pre-symptomatic type 1 diabetes (T1D):
	  ○ Assessing risk of non-symptomatic T1D with autoantibody tests (for antibodies to insulin, GAD, islet antigen 2, or ZnT8 autoantibody is recommended for a clinical trial, or "…can be considered an option in first-degree family members of a proband with type 1 diabetes" (page S21) (B).[b]
	• Pre-symptomatic T1D (ie, Stage 1 or Stage 2 T1D):
	  ○ Counsel individuals positive for islet autoantibodies regarding their risk for developing T1D, and symptoms of diabetes including DKA. (Not Graded)

International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents; 2018[a19]	Screening and Intervention for pre-symptomatic T1D (ie, Stage 1 or Stage 2): • Conduct screening and intervention in the setting of clinical research (E). • Provide appropriate counseling and information about clinical research regarding prevention of T1D to individuals who test positive for genetic or immunological markers for T1D (E). • Screen at-risk individuals (ie, family member of patient with T1D) with an initially negative autoantibody profile "…in research studies" (page 21) [19] annually until adulthood. (Not Graded)

[a]*Evidence rating from ADA 2022 and ISPAD 2018 guidelines:*

- *A (highest level of evidence): based on well-designed randomized clinical trials, well-conducted meta-analysis of randomized controlled trials, or very strong nonexperimental evidence*
- *B (moderate level of evidence): based on well-conducted observational studies (cohort or case-control), or meta-analysis of observational studies*
- *C (low level of evidence): based on poorly controlled or uncontrolled studies, or conflicting evidence where the majority supports the recommendation*
- *E (No clinical evidence): based on expert consensus or clinical experience*

[b]*Proband is not defined in the guideline. According to the TN-10 trial protocol, a proband referred to someone "…diagnosed with diabetes before age 40 and started on insulin therapy within one year of diagnosis." (page 18)* [17]

Abbreviations: ADA, American Diabetes Association; DKA, diabetic ketoacidosis; GDM, gestational diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes; ZnT8, zinc transporter 8.

For those testing positive for diabetes-related autoantibodies, the ADA recommends providing counseling about their risk for developing T1D and symptoms of diabetes.[16] The focus of the counseling among antibody-positive individuals is on preventing complications associated with the onset of T1D such as diabetic ketoacidosis.[41] ISPAD also recommends providing affected individuals with information about clinical trials for the prevention of T1D.[19]

Clinical practice guidelines do not yet include any recommendations for therapeutic interventions for patients with pre-symptomatic T1D (ie, prior to Stage 3 clinical T1D).[16,19,25] Upon FDA approval of teplizumab, the ADA Chief Scientific and Medical Officer released a short, positive press statement on how teplizumab advances opportunities for patients and families affected by T1D; however, the statement did not include formal recommendations or a position regarding prescribing of teplizumab.[42]

3.4 Diagnosis and Management of Stage 3 Type 1 Diabetes Mellitus

T1D is a heterogeneous condition and is the most common form of diabetes diagnosed among children,[43] although onset can occur at any age.[6,16] Children usually present with symptoms of hyperglycemia (eg, polyuria, polydipsia, weight loss) while the presentation in adults is more variable.[6,16] Complications of T1D include acute conditions that can be life-threatening (eg, ketoacidosis or severe hypoglycemia) and long-term complications such as microvascular or macrovascular disease.[6] Approximately one third of children present with diabetic ketoacidosis.[6]

There are not yet any FDA-approved disease-modifying therapies for the treatment of T1D. Treatment of overt or symptomatic T1D currently depends on replacing the lack of insulin production with exogenous insulin to prevent death.[20] The ADA and AACE/ACE recommend either multiple daily injections including both prandial and basal insulin, or a continuous insulin infusion for most patients with T1D, including adults, children, and adolescents.[8,20,25] Pramlintide (Symlin) is the only non-insulin therapy approved for T1D, indicated for T1D patients on mealtime insulin who do not reach glycemic goals despite optimal insulin use.[44] There is insufficient evidence for the use of pramlintide in children with T1D.[20] Exercise and dietary management are adjunctive treatments for T1D.[43] Islet cell transplantation can be considered for patients with severe complications (eg, recurrent ketoacidosis or severe hypoglycemia) or those undergoing a renal transplant.[8]

3.4.1 Diagnosis of Type 1 Diabetes (ie, Stage 3)

The general diagnosis of diabetes mellitus is based on symptoms coupled with laboratory criteria demonstrating overt hyperglycemia. T1D can be clinically differentiated from other types (eg, T2D, monogenic diabetes) based on patient history and characteristics combined with laboratory tests such as an islet autoantibody panel,[25] and possibly a C-peptide plasma or urinary test.[20] The AACE/ACE 2022 guideline gives a very strong recommendation to screen for autoantibodies (GAD65, IA-2, ZnT8 and/or insulin) to support a diagnosis of T1D.[25] Approximately 85 to 95% of patients with T1D have diabetes-related autoantibodies at diagnosis.[20] Insulin secretion, based on the marker C-peptide, is usually decreased or absent.[16,20] C-peptide levels can also be variable or decreased in other presentations of diabetes.[20]

Laboratory criteria for diagnosis of clinical T1D Stage 3)[16,20,25]:

- Fasting plasma glucose (FPG) ≥126 mg/dL
- 2-hr plasma glucose ≥200 mg/dL after a 1.75 g/kg up to 75 g[20] oral glucose tolerance test
- Hemoglobin A1c ≥ 6.5% using a standardized and certified assay
- Random plasma glucose ≥ 200 mg/dL if symptomatic

When symptomatic (eg, polyuria, polydipsia, polyphagia, fatigue) or in a hyperglycemic crisis, a random plasma glucose ≥200 mg/dL, or blood glucose meeting the criteria above is diagnostic for diabetes.[16,20,25] In asymptomatic individuals, laboratory results should be confirmed with repeat testing.[16,20,25]

4.0 MECHANISM OF ACTION OF TEPLIZUMAB

The exact mechanism of action of teplizumab among patients at-risk for T1D is not fully understood. Teplizumab is thought to play a role in the temporary correction of overactive T cells contributing to pancreatic islet cell autoimmunity. Under normal conditions, the regulatory immune system (including regulatory T cells among other cell types) would help prevent development of self-reactive T cells.[45] Thus, an imbalance between activation and regulation of the immune system may contribute to the development of T1D.[46]

Teplizumab binds to the cluster of differentiation 3 (CD3) protein on T cells, a component of the T-cell receptor complex (TCR). This is thought to result in partial agonist activity leading to a rebalancing between activation and regulation of the immune system,[46] perhaps through changes to the composition of T-cell subsets.[47] Observed effects include decreases in effector self-reactive T cells, and increases in the number/function of regulatory T cells.[46] Responders to teplizumab exhibit increased partially exhausted" KLRG1+TIGIT+CD8+ T cells,[12,48] a subset of effector CD8+ T cells after teplizumab therapy.[46] Exhausted T cells may have reduced effector functionality (eg, less secretion of chemokines) yet retain some functions.[49]

Provention Bio, Inc., the drug's sponsor, proposes that teplizumab induces conversion of inappropriately self-reactive T cells, that contribute to development of T1D, into the less responsive, exhausted CD8+ T cells. Further, they posit that this occurs *somewhat* selectively to spare other types of T cells (eg, regulatory and memory T cells). This could be clinically important because "…the preservation of beta cells is achieved without long-term impact on immune competence." (page 32) [46]

The effect of teplizumab treatment includes at least short-term lymphopenia in most patients. Teplizumab occupies CD3 receptors, leading to removal of CD3 receptors from the surface of T cells.[46] This is associated with transient lymphopenia, with the nadir expected around the 5th day of the 14-day regimen, and a return to baseline by day 28 for most patients.[2] The mean terminal elimination half-life of teplizumab is about 4.5 days in a 60 kg patient.[1]

5.0 SUMMARY OF TEPLIZUMAB CLINICAL TRIALS

A single pivotal randomized controlled trial (RCT), referred to as TN-10, evaluated teplizumab in patients with Stage 2 T1D at-risk for clinical T1D.[12] Six additional phase 2-3 RCTs previously evaluated use of teplizumab in a different population, those with recent-onset T1D, which remains an off-label use. Overall, these studies included participants ranging from approximately 7 to 49 years of age with most studies reporting a planned follow-up of 1-2 years.[23,24,50-54] One RCT of patients with recent-onset T1D reported a median follow-up of 7.3 years for a subset of patients.[55] Follow-up of participants of the pivotal TN-10 trial is still ongoing; a recent publication reports a median of 923 days of follow-up.[56] **The TN-10 trial supports the efficacy of teplizumab to extend the time to diagnosis of T1D by a median of at least 2 years**.[12,56] Information from previous clinical trials in the T1D population suggests that teplizumab may be effective at preserving the function of pancreatic beta cells.[23,24,50-54] Adverse events

frequently occur during the time of administration of teplizumab and seem relatively consistent across these trials. Whether there are long-term safety risks is not known. Details about these clinical trials are summarized in the following sections.

5.1 Pivotal Phase 2 Trial (TN-10) in Patients with Stage 2 T1D

TN-10 was a randomized, double-blind, placebo-controlled trial[12] designed to determine if a single 14-day course of IV teplizumab could delay the onset of T1D compared to placebo. The primary efficacy outcome was time to clinical diagnosis of T1D (ie, Stage 3 T1D).[12] Refer to Table 6 for a summary of the TN-10 trial results, and extended follow-up of the TN-10 trial by Sims et al.

The TN-10 trial targeted patients with Stage 2 T1D (most patients had 2 or more diabetes-related autoantibodies and dysglycemia) who were 8 to 45 years of age and relatives of persons with T1D. Patients meeting criteria for a diagnosis of T1D diabetes were excluded. Additionally, patients with an active infection, or chronic infection including with hepatitis B or C, human immunodeficiency virus, or tuberculosis were excluded. Patients with cytopenia, or liver function abnormalities, or those receiving immunosuppressive therapies were additionally excluded.[12] See Appendix D for full inclusion and exclusion criteria. In total, 76 patients (44 that received teplizumab) were enrolled in the trial. The median age for participants treated with teplizumab was 14 years (range 8 – 49 years); the majority, 72% (55/76), were under 18 years of age. All participants had at least 2 different diabetes autoantibodies (either anti- GAD65 [glutamic acid decarboxylase 65], micro insulin, anti-IA-2 [islet antigen 2], ICA [islet-cell autoantibody], or anti-ZnT8 [zinc transporter 8]) that were confirmed within 6 months of study drug administration. The majority (71%) of participants were positive for 3 or more autoantibodies.[12] Most patients had dysglycemia supported by a confirmed oral glucose tolerance test (OGTT); however, among the patients under 18 years old that required a single OGTT test to determine study eligibility per the trial protocol, 6 patients had a normal OGTT result and 2 had an overt hyperglycemic result on the day of randomization.[12] Key limitations of the TN-10 trial include the small number of patients, and generalizability concerns related to the eligibility criteria. One noted concern is whether the results could be extended to all Stage 2 T1D patients regardless of family history.

After a median follow-up of 745 days, treatment with teplizumab significantly delayed progression to clinical T1D by about 24 months (48.4 months with teplizumab vs 24.4 with placebo (PBO); HR 0.41; 95% CI, 0.22 to 0.78) in the intention-to-treat analysis. Overall, a T1D diagnosis occurred in 43% of the teplizumab group compared to 72% in the PBO group. Results were robust to multiple sensitivity analyses.[12] Pre-specified analyses suggest most patient subgroups (ie, age, sex, body mass index and glucose levels) similarly benefited from treatment with teplizumab. There may be differences based on stratification by anti-ZnT8 autoantibody status and human leukocyte antigen DR3 or DR4 status;[12] however, these subgroup results are likely underpowered and should be considered exploratory. Using advanced modeling methods of glucose and C-peptide changes from a subset of the TN-10 trial population with sufficient OGTT data (92% at 3 months and 89% at 6 months), Sims et al showed that teplizumab helped prevent pancreatic β-cell decline within 3 months compared to placebo, and the protective effect lasted for at least 6 months after the single teplizumab course.[57] The Sims et al modeling study appears to be a secondary analysis of TN-10 trial data that may have been designed after-the-fact, so findings should be interpreted as exploratory.[57]

After extended follow-up with a median of 923 days (range 74 to 3119), there was a significant delay in progression to diagnosis of T1D by approximately 32 months (59.6 months with teplizumab vs 27.1 months with PBO; HR, 0.457; P = 0.01) and diagnosis of T1D occurred in 50% (22/44) of teplizumab-treated patients compared to 78% (25/32) of participants in the PBO group.[56] There were 13 participants who had extended follow-up data for over 5 years. Of these participants, 8 teplizumab-treated patients vs 2 PBO-treated patients remained T1D free.[56]

In the safety analysis of all 76 participants, significantly more adverse events related to dermatologic, blood, or bone marrow occurred among patients that received teplizumab compared to placebo. A spontaneously resolving rash was observed in 36% of teplizumab-treated patients compared to 3% in the placebo group (P<0.001).[12] As expected post-teplizumab treatment, transient lymphopenia was observed, reaching a nadir at day 5 and resolving by day 45 in nearly all patients.[12] Blood or bone marrow events occurred in significantly more patients treated with teplizumab than with placebo (75% vs 6%, P<0.001), and lymphopenia accounted for 75% of grade 3 adverse effects within the first 30 days.[12] Infection is a potential risk with teplizumab treatment; however, the reported rates of infection during the study overall were similar between groups (11% with teplizumab vs 9% with placebo).[12]

Along with infection, reactivation of certain viruses has been reported with anti-CD3 monoclonal antibodies.[58] Some cases of Epstein Barr virus (EBV) and cytomegalovirus (CMV) reactivation occurred in the TN-10 trial. Several weeks after teplizumab administration, 8 participants had quantifiable EBV DNA and 1 participant had CMV DNA present compared to no events with placebo. Reactivation seemed transient, and only one patient with detectable EBV levels was symptomatic.[12] Cytokine release syndrome has been previously reported with teplizumab[59]: 2 teplizumab-treated patients (5%) reported constitutional symptoms compared to 0 placebo-treated patients.[12] Additionally, 2 teplizumab-treated patients (5%) compared to no placebo-treated patients reported allergic or immunologic adverse events.[12] Some risk of these events may have been mitigated by the use of prophylactics (eg, ibuprofen and an antihistamine) prior to the teplizumab infusion as well as for symptomatic treatment per the study protocol. The potential for long-term adverse effects, including theoretical concerns related to infections or malignancies are unknown. Additionally, authors did not report information about the development of antibodies against teplizumab.

Table 6. Details of the Teplizumab Phase 2 Pivotal Trial, TN-10

Population	Interventions, # participants (n)	Summary of selected efficacy and safety results
TN-10 trial Herold, KC et al.; 2019[12]: a phase 2, R, DB, PBO-controlled trial		
Children and adults aged 8 to 45 years with stage 2 pre-T1D (with ≥ 2 diabetes-related autoantibodies within prior 6 months and dysglycemia) who are relatives of patients with T1D. (See Appendix D for list of full inclusion and exclusion criteria.)	**Intervention (n=44):** TEP as an outpatient 30-minute minimum IV infusion for 14 consecutive days. Patients were pre-medicated with ibuprofen and an antihistamine on days 1–5, then as-needed for fever, headache, arthralgia, rash, or malaise. **Dose (per BSA):** Day 1: 51 µg/m² of BSA Day 2: 103 µg/m² Day 3: 207 µg/m² Day 4: 413 µg/m² Days 5 – 14: 826 µg/m² **Comparator (n=32):** PBO (saline) as an outpatient 30-minute minimum IV infusion for 14 consecutive days as outpatients.	• 93% of TEP patients and 88% of PBO patients completed the trial; incompletion was due to laboratory abnormalities (n=4), rash (n=1), or IV access issues (n=2). • Follow-up: median 745 days (range 74 to 2683); >3 years for 75% of patients. • **Efficacy Results:** ○ Median time from randomization to diagnosis of T1D (primary endpoint, TEP vs PBO): 48.4 mo vs 24.4 mo [HR, 0.41; 95% CI, 0.22 to 0.78; two-sided P=0.006]. ▪ Results from 3 pre-planned sensitivity analyses were consistent with the primary analysis. ○ T1D diagnosis: TEP 19/44 (43%) vs PBO 23/32 (72%). ▪ Most profound TEP effects during first year; number of participants diagnosed during first year: TEP 3/44 (7%) vs PBO 14/32 (44%) [unadjusted HR, 0.13; 95% CI, 0.05 to 0.34]. ○ Annualized Rate of T1D Diagnosis: TEP 14.9% per year vs PBO 35.9% per year. • **Safety Results:** ○ Spontaneously resolving rash: TEP 16/44 (36%) vs PBO 1/32 (3%); P<0.001. ○ Blood/bone marrow AE: TEP 33/44 (75%) vs PBO 2/32 (6%); P<0.001. ▪ Lymphopenia: Lymphocyte counts decreased to a nadir on day 5 [total decrease, 72.3%; IQR, 82.1 to 68.4; P<0.001]. Lymphopenia resolved by day 45 in all patients except for 1 patient whose counts returned to normal on day 105. Lymphopenia accounted for 75% (15/20) of grade 3 AE in first 30 days. ○ Infection: TEP 5/44 (11%) vs PBO 3/32 (9%); TEP 8 events vs PBO 5 events. ○ EBV reactivation: ▪ No. of EBV-seropositive participants at trial entry: TEP 16 vs PBO 14. ▪ No. of participants with EBV reactivation after treatment: TEP 8 vs PBO 0; one TEP patient was symptomatic on day 38. ▪ EBV DNA levels decreased below quantification between 43 to 134 days (mean 77 days). ○ CMV reactivation: ▪ No. of CMV-seropositive participants at trial entry: TEP 10 vs PBO 7. ▪ No. of participants with CMV reactivation after treatment: TEP 1 vs PBO 0. ▪ CMV DNA was undetectable by day 42. ○ AE occurring in >5% of participants [TEP %, PBO %]: ▪ Pain [11%, 9%]; gastrointestinal [9%, 9%]; metabolic or laboratory [9%, 6%]; pulmonary or upper respiratory [9%, 0%]; constitutional symptoms [5%, 0%]; allergy or immunologic [5%, 0%]; endocrine [0%, 6%]. • **Prespecified Efficacy Subgroup Analysis:** ○ Autoantibodies: Absence of anti-ZnT8 antibodies was associated with a greater response to TEP [HR, 0.07; 95% CI, 0.02 to 0.26] compared to those with anti-ZnT8. ○ HLA type: Presence of HLA-DR4 [HR, 0.20; 95% CI, 0.09 to 0.45] and absence of HLA-DR3 [HR, 0.18; 95% CI, 0.07 to 0.45] were associated with a greater response to TEP. ○ Pre-treatment C-peptide: Although not necessarily statistically significantly different, patients with below-median C-peptide values (<1.75 nmol/L) may have a more robust response to teplizumab than those with above median C-peptide. ○ Age/gender/BMI-Z/glucose levels: Results were relatively consistent regardless of age, gender, BMI-Z scores, or glucose levels.

Abbreviations: AE, adverse events; BMI-Z, body mass index for age; BSA, body surface area; CI, confidence interval; CMV, cytomegalovirus; DB, double-blind; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; HR, hazard ratio; IQR, interquartile range; IV, intravenous; L, liter; mAB, monoclonal antibody; mo, months; n, number of participants; nmol, nanomoles; No., number; OGTT, oral glucose-tolerance tests; PBO, placebo; pmol, picomoles; R, randomized; TEP, teplizumab; T1D, type 1 diabetes; TTE, time to event; vs, versus; ZnT8, anti–zinc transporter 8.

Table 6. Details of the Teplizumab Phase 2 Pivotal Trial, TN-10

Population	Interventions, # participants (n)	Summary of selected efficacy and safety results
Sims, EK et al.; 2021[56]: Extended follow-up data from TN-10 trial (above)		
See Herold et al. TN-10 trial. Study reported extended follow-up data, and performed post-hoc analyses to assess beta-cell function and glycemic parameters by pooling data from other studies.	See Herold et al. TN-10 trial.	• **Efficacy Results:** ○ Extended median follow-up duration: 923 days (range, 74 – 3119). ○ Median time from randomization to diagnosis of T1D (primary endpoint): TEP 59.6 months vs PBO 27.1 months [HR, 0.457; P = 0.01]. ○ T1D diagnosis: TEP 22/44 (50%) vs PBO 25/32 (78%): ▪ 10/13 participants who had 5+ years of follow-up data were not diagnosed with Stage 3 T1D: TEP n=8 vs PBO n= 2. ○ C-peptide response (not a prespecified analysis): Use of TEP resulted in a greater mean C-peptide AUC when compared to PBO [1.96 (IQR 1.48, 2.61) pmol/ml vs 1.68 (IQR 1.32, 2.11) pmol/ml; p=0.006 after adjustment for age and baseline C-peptide AUC. • **Safety Results:** ○ Additional safety results were not reported.

Abbreviations: AE, adverse events; BMI-Z, body mass index for age; BSA, body surface area; CI, confidence interval; CMV, cytomegalovirus; DB, double-blind; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; HR, hazard ratio; IQR, interquartile range; IV, intravenous; L, liter; mAB, monoclonal antibody; mo, months; n, number of participants; nmol, nanomoles; No., number; OGTT, oral glucose-tolerance tests; PBO, placebo; pmol, picomoles; R, randomized; TEP, teplizumab; T1D, type 1 diabetes; TTE, time to event; vs, versus; ZnT8, anti–zinc transporter 8.

5.2 Clinical Trials among Patients with New-onset Stage 3 T1D

Prior "failed" clinical development of teplizumab included studies among patients with a new clinical T1D diagnosis. Evidence about this study population, potential efficacy of teplizumab to preserve pancreatic beta-cell function (as measured by C-peptide), and safety are included in Appendix E. Six prior randomized controlled trials [RCT] (phases 2-3) evaluated teplizumab versus control or placebo to treat patients with a new diagnosis of T1D.[23,24,50-54] One additional study (Perdigoto et al. 2019) that is longitudinal follow-up of a proportion of patients from a prior RCT (thus an observational study) is additionally included.[55] Three of these trials were double-blinded and used a placebo control (Delay, Protégé, Protégé Encore)[23,24,50,54] while the other studies (Study 1, Herold et al. 2009, and AbATE) were open-label controlled trials (eg, usual care without placebo administration) which may introduce bias.[51-53] Three of the studies were stopped prematurely which may additionally introduce bias: one trial due to accidental higher exposure to teplizumab due to improper administration that was associated a greater incidence of adverse effects than previously observed,[52] the second (Protégé) due to lack of significance on its primary endpoint,[23,24] and the third trial (Protégé Encore) was stopped due to the failure of Protégé.[50] In total, approximately 957 patients participated in the trials with about 719 exposed to teplizumab. The general patient population included individuals between age 7 to 35 years who were recently diagnosed with TD within the prior 1 to 12 months.[23,24,50-54] The planned duration of the trials was 1 to 2 years.[23,24,50-54] Extended follow-up of a median of 7.3 years for a proportion of patients from one phase 2 trial (AbATE) has been published.[55] It is important to note the dosing strategy for teplizumab differs across these studies, and many differ in comparison to the TN-10 trial. The phase 2 trials, AbATE and Delay, are like TN-10, which used one course of teplizumab as a 14-day regimen of a similar dose.[53,54] The phase 1/2 trial (study 1) differed due to use of a 12-day regimen and weight-based dosing instead of body surface area[51] while the phase 2b trial[52] and phase 3 trials planned to administer more than 1 course of teplizumab.[23,50]

In Appendix E, we included C-peptide level presentation-related efficacy information from these trials because the FDA considered it as supportive evidence for the approved indication of teplizumab. However, C-peptide-related outcomes were not the primary outcome for all studies, and multiple studies may either not be powered to detect changes in this outcome. In all the trials, stimulation of C-peptide was assessed by using a mixed-meal tolerance test[23,24,51-54]; however, analytical methods to quantify changes in C-peptide varied, complicating comparison across the studies. While not all C-peptide-related results were statistically significant, overall the trials suggest that use of teplizumab may preserve C-peptide levels within 1 to 2 years after administration compared to control. [23,24,50-54] The administered dose of teplizumab may affect outcomes nonetheless. In the phase 3 Protégé trial, in exploratory analyses, benefits on adjusted change in C-peptide area under the curve (AUC) from baseline, compared to placebo, was observed for the highest dose (2 courses of teplizumab for 14-days at ~9034 μg/m²), but not with the shorter course (6 days) or lower cumulative dose (~2985 μg/m² per course).[23,24] Longer follow-up of a subset of patients for a median of 7.3 years after a single course of teplizumab suggests that some initial teplizumab "responders" (ie, minor C-peptide change from baseline) may experience durable effects for a duration beyond 1-2 years.[55] This suggests a signal of benefit of teplizumab in terms of preserving pancreatic beta-cell function; however, there are significant limitations on these results including use of post-hoc analyses, lack of power, generalizability to patients with earlier stages of T1D, and questions about the validity of C-peptide as a surrogate measure.

The prior clinical trials among patients with established T1D suggest similar potential adverse events as those observed during the TN-10 (see adverse events listed in Appendix E). An exception is events of diabetic ketoacidosis and hypoglycemia which could also be related to management of patients with T1D with insulin.[23,53] Similar to in the TN-10 trial, in general, adverse effects occurring during treatment with teplizumab (eg, rash, lymphopenia, viral reactivations) were transient.[23,51,53] Little information is known about potential long-term risks such as malignancy and infection. The reported information from these studies is somewhat reassuring about the risks for infection within 2 years,[23,24,51,53,54] and limited information of up to 7 years also does not suggest longer-term risk.[55] A few cases of neoplasm were reported in one study that may or may not be related to teplizumab.[53] Development of anti-teplizumab antibodies after a single course of teplizumab was reported in 2 of these trials.[23,51] This immunogenicity was associated with increased clearance of teplizumab in one trial; however, whether this correlates with decreased efficacy of teplizumab is unclear.[23]

6.0 PLACE IN THERAPY

6.1 Standard of Care and Proposed Benefits of Disease-modifying Therapy

T1D is associated with significant psychosocial distress.[39] Individuals living with T1D face life-threatening complications such as diabetic ketoacidosis (DKA) and severe hypoglycemia.[6] In children diagnosed with T1D at a young age, T1D is associated with longitudinal declines in cognitive function potentially related to hyperglycemia.[60] DKA occurs commonly at diagnosis of clinical T1D, and a single episode of moderate to severe DKA has been associated with worse cognitive function in young children.[61] Further, patients living with T1D are at risk for other long-term microvascular and macrovascular complications such as nephropathy, retinopathy, and atherosclerosis.[6] The hazard for cardiovascular disease events, including the hazard of death due to coronary artery disease, cerebrovascular disease, or peripheral vascular disease, is increased approximately 3- to 7-fold among T1D patients compared to the general population.[62]

Teplizumab is indicated to delay the onset of clinical (Stage 3) T1D in individuals with Stage 2 T1D.[1] Potential advantages of delaying the onset of Stage 3 T1D includes increasing the number of years without T1D, and the possibility of delaying complications, which may improve lifespan.[39]

The 2022 ADA guideline, which predates FDA approval of teplizumab, does not provide any recommendations for pharmacotherapies for treatment of pre-symptomatic T1D.[8,16,43] Based on moderate quality of evidence, the ADA recommends screening asymptomatic individuals for T1D with autoantibodies (anti-insulin, GAD, islet antigen 2, or ZnT8) either in the setting of a clinical trial, or optionally, if they have a first-degree family member with T1D.[16] If at-risk patients are identified, the standard of care is to continue to monitor and provide education.[16] Monitoring may enable earlier diagnosis of Stage 3 T1D prior to acute complications such as diabetic ketoacidosis.[16] Thus, an alternative to teplizumab is closer monitoring (ie, more frequent blood-glucose testing) of at-risk patients.

A recent survey study suggests that most parents with children at elevated risk of T1D would choose to receive a treatment that could delay time to dependence on insulin. In this study, 98% of the

approximately 1500 parents surveyed chose to treat under some hypothetical circumstance, and 58% always selected a treatment irrespective of potential treatment risks (eg, infection).[63] This suggests that there may be patient interest in receiving teplizumab.

The approval of teplizumab, a medication that delays T1D disease progression, may impact future guideline recommendations for screening the general population for T1D autoantibodies. However, given the low incidence of T1D in the general population and the lack of guidance on how to respond to a positive autoantibody result, experts anticipate various barriers needing to be addressed before clinical practice adopts routine screening of the general population.[10] Access to autoantibody testing, the balance of sensitivity and specificity of current autoantibody tests, and ease of interpretation of these tests are additional barriers to widespread testing.[64] TrialNet, a major group of T1D researchers, points to engagement of primary care providers as an important step for screening the general population; they consider children and adolescents to be the population with the greatest unmet need.[65]

6.2 Targeting a T1D Stage and Alternative Disease-modifying Therapies

6.2.1 Proposed Target for Value of a Disease-modifying Therapy for T1D

A 2020 white paper from the JDRF T1D Fund aimed to describe "the full economic value of novel therapies for T1D" (page 5); this paper highlighted several desirable characteristics for a novel T1D medication aimed at delaying onset of Stage 3 T1D[39]:

- Safety > disease burden; particularly for treatment of patients that are not yet symptomatic
- Response rate >50%
    - Definition of response rate is not provided (inferred meaning is the proportion of patients with prevention or delay of clinical T1D at some timepoint)
- Response duration; a delay of at least 5 years is preferred, but according to the expert survey, "…2 years of efficacy duration is highly valuable" (page 19)[39]

Teplizumab trends toward meeting some of these efficacy markers in the pivotal TN-10 trial, with a delay in median time to T1D diagnosis of approximately 32 months in extended follow-up.[12,56]

6.2.2 Targeting Particular Stages of T1D

Teplizumab is FDA-approved for people with Stage 2 T1D.[1] Prior clinical trials of disease-modifying therapy for T1D have typically enrolled patients with a particular stage of T1D. Goals of therapy, the acceptability of certain side effects, and the appropriateness of trial endpoints likely vary by stage of T1D.[39] According to an expert opinion review, preclinical studies suggest that monoclonal antibodies aimed at modifying the T1D disease progression may only be effective at a particular stage of pre-T1D.[66] Regarding teplizumab, teplizumab investigators have suggested that it may be less effective during earlier stages in the disease process (eg, Stage 1 T1D),[12,56] as "…an active autoimmune response is needed for the actions of an anti-CD3 monoclonal antibody...." (page 8)[12] based on pre-clinical data. In the TN-10 trial, the greatest response occurred among patients with lower C-peptide levels at baseline[12]; this is characteristic of further progression toward clinical T1D.[66] A similar effect was observed in

preclinical animal studies that showed an anti-CD3 therapy was most effective in mice with a recent onset of T1D, but not earlier.[67]

6.2.3 Alternative Disease-modifying Therapies for T1D

Teplizumab is the only FDA-approved, disease-modifying therapy for any stage of T1D. However, other therapies, some of which are FDA-approved for other indications, have been studied in clinical trials with varying degrees of benefit. A full review of these therapies is beyond this report's scope. Like teplizumab, most other products aim to modify autoimmunity by systemically targeting either T-effector cells, B cells, or cytokine responses.[3,6] Some studies tried to induce tolerance to a specific antigen such as oral insulin or GAD65 in patients at risk for T1D.[3]

Golimumab (Simponi), is under study in clinical trials of patients with Stage 2 T1D.[68] Golimumab is a subcutaneous human monoclonal antibody that blocks the actions of tumor necrosis factor alpha and is already FDA-approved as a chronic treatment for other autoimmune disorders.[69] Abatacept and hydroxychloroquine, both FDA-approved therapies for other autoimmune disorders,[70,71] are under study for the delay or prevention of T1D (Stage 3) among people with Stage 1 T1D.[72,73]

In more recent trials of patients with newly diagnosed T1D, in addition to teplizumab, the following are examples of therapies that have demonstrated efficacy in preserving C-peptide levels: rituximab,[74] otelixizumab (another anti-CD3 monoclonal antibody),[58] abatacept,[75] alefacept,[76] low-dose anti-thymocyte globulin (ATG),[77] and golimumab.[78] Recently in a phase 2 trial, the combination of anti-interleukin-21 and liraglutide also showed benefit in preserved C-peptide levels among patients with recent onset T1D.[79] According to expert opinion by Greenbaum et al published in 2019, while short-term benefits have been observed for patients with recent-onset T1D, "…positive effects have not been sustained and are not yet sufficient to warrant routine use of immunotherapy in clinical practice." (page 26)[10]

The teplizumab sponsor, Provention Bio, Inc., is also pursuing teplizumab for use in patients with newly diagnosed (Stage 3) T1D. This ongoing phase 3, randomized, placebo-controlled trial (called the PROTECT trial, NCT03875729) enrolled 300 patients ages 8-17 years old with a T1D diabetes diagnosis within the previous 6 weeks and a peak C-peptide value ≥0.2 pmol/mL at baseline, in conjunction with diabetes-related autoantibodies.[14,15] Patients randomized to teplizumab will receive it as daily infusions for 12 days per course, for 2 courses 6 months apart. The primary efficacy endpoint is difference in C-peptide area under the curve values 18 months after baseline.[15] The sponsor anticipates results from this trial by mid-2023.[14]

Preliminary observational data showed teplizumab induction with or without other immunotherapies was associated with a longer time to requiring insulin after a beta-cell transplant among people with T1D.[80] Provention Bio, Inc. may also pursue teplizumab for use among beta-transplant recipients.[14]

7.0 SAFETY

Information in the following sections summarizes teplizumab prescribing information (eg, warnings and precautions) with additional details from teplizumab review documents from the 2021 FDA advisory committee meeting. In the briefing for the advisory committee, the FDA reviewed safety information from the pivotal TN-10 trial as well as from 4 prior trials among patients with a recent diagnosis of T1D (ie, AbATE, Delay, Protégé, and Protégé Encore). Administration of a second course of teplizumab to participants occurred in some of these prior trials, but the FDA focused only on safety information from administration of the first course, which would be most like the approved use of teplizumab. Together, this comprises 729 people exposed to teplizumab and 213 exposed to control across all trials. The median follow-up time of teplizumab-treated patients was 888 days (interquartile range [IQR], 656 to 1519) from the TN-10 trial, and 189 days (IQR 182 to 536) from the other trials.[2]

7.1 Common Adverse Effects (AEs)

In the pivotal TN-10 trial, the most common AEs (reported in at least 2 individuals at a rate of >0.5% among teplizumab-treated patients during and up to 28 days after completion of teplizumab therapy) were as follows (reported as the percent of patients in teplizumab arm vs the placebo arm)[1]:

- Lymphopenia (73% vs 6%)
- Rash (36% vs 0%; eg, rash erythematous, rash macular, rash papular, rash maculo-papular, rash pruritic)
- Leukopenia (21% vs 0%)
- Headache (11% vs 6%)
- Neutropenia (5% or 7%* vs 3%)
- Increased alanine aminotransferase (5% vs 3%)
- Nausea (5% vs 3%)
- Diarrhea (5% vs 0%%)
- Nasopharyngitis (5% vs 0%)

7.2 Warnings and Precautions per Prescribing Information

7.2.1 Cytokine Release Syndrome (CRS)

CRS is a potential AE associated with immunotherapies caused by release of inflammatory cytokines. Some symptoms of CRS include fever, malaise, rash, and in worse cases, hypotension and hypoxia.[2] The combined incidence of CRS in clinical trials (ie, among people with pre-T1D or T1D) up to 28 days after the last dose of teplizumab was greater among teplizumab-treated patients (5%) versus control (0.8%); 13% of these cases were rated as severe.[1] According to the FDA advisory committee review, no cases resulted in death or required an intensive care unit admission.[2]

* There is conflicting information about the incidence of neutropenia among teplizumab-treated patients in the TN-10 trial according to prescribing information (one section reports 5% whereas another reports 7%).

To mitigate the risk for CRS, teplizumab prescribing information recommends:

- Administer premedication (antipyretic plus antihistamine and/or antiemetic) before treatment.
- During treatment, monitor liver function tests (LFTs). Stopping treatment is recommended in the case of serious LFT abnormalities during treatment (ie, AST [aspartate aminotransferase] or ALT [alanine transaminase] > 5x the upper limit of normal [ULN], or bilirubin > 3x the ULN).
- Treat emergent CRS symptoms.
- Temporarily pausing teplizumab (for 1-2 days) or discontinuing treatment may be considered for severe CRS cases.

7.2.2 Serious Infections

Owing to the immunomodulatory effects of teplizumab, infections are a potential AE. In the pivotal TN-10 trial, the incidence of serious infections at any time was greater during or after receipt of teplizumab (9%) compared to placebo (0%). Prescribing information recommends avoiding use of teplizumab among people with active serious infections or chronic infections in places other than localized skin before use. This includes active cases (per laboratory or other evidence) of acute Epstein-Barr virus (EBV) or cytomegalovirus (CMV).[1]

Teplizumab should be discontinued if a serious infection emerges during its use.[1]

7.2.3 Lymphopenia

Lymphopenia is an expected AE owing to the impact of teplizumab on T cells; its occurrence was common among teplizumab clinical trials (ie, among pre-T1D and T1D populations), occurring in about 78% of teplizumab-treated versus 11% of control recipients. Serious lymphopenic events were less common in clinical trials; 0.9% of patients treated with teplizumab had severe (lymphocytes <500 cells/µL) and prolonged (>1 week) lymphopenia. In rare cases, lymphopenia led to teplizumab discontinuation. [1]

Current clinical evidence suggests most patients will experience a lymphocyte nadir on day 5 and return to baseline values by week 6 (ie, while still completing the teplizumab treatment course). [1] According to information for the FDA advisory committee review, 2 serious adverse events related to lymphopenia had been reported; one case of a very low nadir and the other due to hospitalization for acute gastritis after a familial exposure to infection.[2]

Leukocytes should be monitored during teplizumab therapy. Teplizumab should be discontinued for emergent, prolonged, severe lymphopenia.[1]

7.2.4 Hypersensitivity Reactions

Hypersensitivity reactions (eg, serum sickness, angioedema, urticaria, rash) have occurred in association with teplizumab therapy.[1] According to information for the FDA advisory committee review, serious allergy or hypersensitivity AEs were reported among 0.3% of teplizumab-treated vs 0% of control patients [2]

Rashes have been commonly associated with teplizumab, occurring in approximately 47% of teplizumab-treated patients compared to 14.7% of control patients.[2] Most were described as "macular, papular, or maculo-papular subtypes" (page 50) that were non-serious and did not require treatment for resolution.[2] Serious rash AE occurred in 0.3% of teplizumab-treated patients compared with 0% of control patients. Numerically, more patients that received teplizumab developed urticaria compared to control (1.9% vs 1.2%). Overall, one urticarial rash secondary to CRS was rated as serious, and required hospitalization and treatment.[2]

Teplizumab should be discontinued in the case of an emergent, serious hypersensitivity reaction.[1]

7.2.5 Vaccinations

Since there is a lack of information about the theoretical risk that teplizumab could affect adjacent immune responses, it is recommended for patients to receive age-appropriate vaccinations before receiving teplizumab. Furthermore, the safety of administering live vaccines among people who received teplizumab is unknown.[1]

Vaccinations should not be administered during the 14-day teplizumab treatment course. Furthermore, prescribing information recommends administering any inactive or mRNA vaccines > 2 weeks before and live vaccines > 8 weeks before starting teplizumab treatment. Once teplizumab therapy is complete, inactive or mRNA vaccines may be considered after 6 weeks, and live vaccines may be considered after 52 weeks.[1]

7.3 Additional Safety Information

The following summarizes additional safety information from teplizumab prescribing information, or from teplizumab summary documents prepared by the teplizumab manufacturer or FDA for the FDA advisory committee meeting in 2021. Although some of the information may be related to labeled warnings////precautions in prescribing information, most of the details from the FDA advisory committee documents mentioned below were not included in the prescribing information. We include these additional details to supplement the official warnings/precautions found in the prescribing information (see Section 7.2).

7.3.1 Immunogenicity

According to teplizumab prescribing information, during the pivotal TN-10 trial, anti-drug antibodies were observed in about 57% of patients, of whom 46% developed neutralizing antibodies after a single treatment course. Anti-teplizumab antibodies were associated with rashes in the trial; however, the impact on treatment effectiveness is unknown.[1]

7.3.2 Liver Function Test Abnormalities

Liver function test elevations, including aspartate aminotransferase (AST), alanine transaminase (ALT) and bilirubin, have been observed during treatment with teplizumab. The sponsor posits that these effects could be related to the effects of cytokines on the liver.[46]

According to the FDA, only 2 cases in clinical trials met criteria for possible drug-induced liver injury (bilirubin >2x the upper limit of normal [ULN] and ALT >3x ULN); both cases were considered likely unrelated to teplizumab due to alternative explanations. However, serious hepatic injury AE was reported among 0.5% of teplizumab patients versus 0% of control patients.[2]

7.3.3 Viral Illness Including Reactivation of Latent Virus

Modulation of T cells has been associated with reactivation of some viruses. For example, Epstein-Barr virus (EBV) reactivation is associated with another experimental anti-CD3 therapy.[58] Of note, patients with active infections, certain chronic infections (eg, hepatis B or C, human immunodeficiency virus), or a positive tuberculosis purified protein derivative (ppd) test were excluded from the TN-10 trial.[12]

Some types of infections occurring in clinical trials included:

- EBV-related illness: More EBV-related events (including mononucleosis-like illness) emerged among patients treated with teplizumab compared to control (8.8% vs 4.5%; risk difference [RD] 4.3%, 95% confidence interval [CI] 1.0–7.6%). Analysis by the FDA suggests that teplizumab treatment was not associated with an increase in EBV-related primary infections; however, EBV viremia occurred significantly more with teplizumab than control (3.1% vs 0.4%; RD 2.7%, 95% CI 1.2 – 4.2%). In the TN-10 study, follow-up of 9 patients that developed EBV viremia suggests that it is transient, as each of these patients had a reduced viral load within 3 to 12 months after receipt of teplizumab.[2]
- Herpes infections (including 'oral herpes' and 'herpes simplex'): Few events occurred, but numerically more patients receiving teplizumab reported these events than controls (7, 0.9% vs 1, 0.4%).[2]
- Varicella zoster virus infections: Few events occurred, but numerically more patients receiving teplizumab reported these events than controls (9, 1.2% vs 1, 0.4%).[2]
- CMV infections (including "CMV infection" or "CMV positive test"): Few events occurred, but numerically, more patients receiving teplizumab reported these events than controls (9, 1.2% vs 2, 0.8%).[2]

7.3.4 Malignancies

Since teplizumab modulates the immune system, there is a theoretical risk for malignancies. Whether a one-time, short-term treatment with teplizumab increases the risk is unknown. One malignancy (melanoma) was reported in a patient who received teplizumab; however, this patient also had a history of pre-malignant lesions, and the overall contribution of teplizumab was unclear.[2] In the 2021 FDA advisory meeting documents, the FDA pointed out that "It is important to note that the clinical safety data submitted in the BLA [biologics license application] are not sufficient to evaluate the potential risk of malignancy because of the short duration of follow-up as well as the relatively young age of the safety population." (page 56)[2]

7.3.5 Other Adverse Events (AE)[2]

- **Death**: Three deaths occurred in the prior studies, and none occurred in TN-10. The deaths (one due to DKA, one from myocardial infarction, and one unknown) all occurred 9-26 months after the last teplizumab infusion. The FDA considered these unlikely to be related to teplizumab.

- **Other AE rated as serious that may or may not have been related to teplizumab** (reported in at least 2 individuals at a rate of >0.1% in treatment group; teplizumab vs placebo): diabetic ketoacidosis [DKA] (2.3% vs 0%), hypoglycemic seizure (0.8% vs 0%), CRS (0.6% vs 0%), hypoglycemia (1.7% vs 1.2%), splenic rupture (0.3% vs 0%), thrombosis (0.3% vs 0%), suicidal ideation/suicide (0.3% vs 0%), dizziness/balance issues/falls (0.3% vs 0%), abdominal pain (0.3% vs 0%), fracture (0.5% vs 0.4%), and leukopenia (0.5% vs 0.4%)
    - DKA and hypoglycemic serious events were observed in prior trials of patients with T1D but not in the TN-10 trial of patients with pre-T1D. However, according to the drug sponsor, patients were not followed in the study after development of clinical T1D.[46]
- **AE leading to withdrawal from the pivotal trial:** In the TN-10 trial, 3 patients withdrew (1 who received teplizumab and 2 who received placebo) due to laboratory abnormalities; the participant receiving teplizumab experienced ALT elevation and a pruritic rash. The events resolved after discontinuation of treatment. Events leading to withdrawal in the prior T1D studies included decreased white blood cell counts (1.5%), decreases in hemoglobin (1.8%), transaminase elevations (5.6%), CRS (1%), and thrombocytopenia (1%). Some of these cases required hospitalization.

8.0 PHARMACOKINETICS AND USE IN SPECIAL POPULATIONS

The terminal half-life of teplizumab is about 4 days. It is not anticipated that steady-state teplizumab concentrations will occur during the single, 14-day course of therapy. Metabolism is dependent on catabolism of teplizumab into smaller peptides. Available clinical data suggest that teplizumab pharmacokinetics will be similar regardless of age (up to 35 years), sex, or race.[1]

Pharmacokinetic drug interactions are not expected. Teplizumab does cause an expected transient lymphopenia in most patients.[2] Most patients recover quickly (within approximately 28 days of starting teplizumab)[2]; however, interactions owing to additive effects with other immunosuppressive medications that could also predispose the patient to infections are theoretically possible. While not advised against in the prescribing information (the issue is not mentioned), It may be prudent to avoid concurrent use with other immunosuppressants if possible. Administration of vaccines directly prior to, during, or directly after teplizumab therapy is not recommended (see Section 7.2.5).[1]

Regarding special populations, subgroup analyses of combined teplizumab data (TN-10 trial and T1D supportive trials) by the FDA do not suggest differences in adverse effects based on sex.[2] The teplizumab sponsor indicated the possibility of slight differences in some adverse effects (rash and vomiting) among children younger than 18 years old compared to adults[46]; however, teplizumab prescribing information concluded that the safety profile is similar between children and adults in the indicated population (ie, people 8 years or older with Stage 2 T1D).[1] In the TN-10 trial, significant differences in efficacy were not observed based on age, sex, or body mass index, but the study was underpowered to detect any differences in subgroups.[2] There is a lack of information about use of teplizumab in patients younger than approximately 8 years old, and older than about 49 years old.[12] Additionally, it is recommended to avoid teplizumab during pregnancy and lactation (for up to 20 days after teplizumab therapy completion). Teplizumab is not recommended for use in patients with liver dysfunction at baseline.[1]

Table 7 summarizes and recommendations for teplizumab use in special populations from prescribing information.

Table 7. Recommendations for Teplizumab-mzwv Use in Special Populations[a,1]

Renal impairment	No information reported.
Hepatic impairment	Not recommended for patients with baseline LFT abnormalities: AST or ALT >2x ULN, or bilirubin >1.5x ULN.
Pediatric patients	• Studied in pediatric patients 8 years or older (children 8 to 17 years old were 72% of patients in the TN-10 trial).[2] • Safety profile in children ages 8 or older considered comparable to adults.
Older adults	The maximum enrollment age allowed in the TN-10 clinical trial was 45 years old; the max age of a patient was 49.5 years old.[12] No significant differences based on age subgroups (including 19.4 to 49.5 years old as the max age group) were observed in the TN-10 clinical trial.[2] There is not a maximum indicated age for use of teplizumab.

Pregnancy and breastfeeding	• **Pregnancy**: There is limited human data. However, as a monoclonal antibody, teplizumab may be transferred through the placenta and may theoretically cause immunosuppression in the neonate (this effect was observed in mouse pups). **Use during pregnancy is not recommended.**
	  ○ The TN-10 trial excluded pregnant patients.[12]
	• **Breastfeeding**: There is a lack of human data about the transfer of teplizumab into breast milk and effects on the infant. As a monoclonal antibody, it is expected that teplizumab could be secreted into milk.
	• The manufacturer advises weighing the risks versus benefits of administration; temporarily discarding pumped breast milk for 30 days after completion of teplizumab therapy may be considered.
	  ○ The TN-10 trial excluded lactating patients.[12]

[a]Information is primarily from the prescribing information (package insert); supplemental details are from the 2021 FDA or sponsor advisory meeting documents, or the pivotal clinical trial.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CD3, cluster of differentiation 3; CYPs, cytochrome P450 enzymes; FDA, US Federal Drug Administration; LFTs, liver function tests; PD, pharmacodynamic; PK, pharmacokinetic; SS, steady state; ULN, upper limit of normal.

9.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION (PA) CRITERIA

The DUR board may consider implementing PA criteria for teplizumab-mzwv (Tzield) to ensure that prescribing is according to the current FDA-approved indication.

Some criteria that may be considered include the following:

- Patient should be **8 years of age or older.**
  - Teplizumab is FDA-indicated for ages 8 and older.[1] This is congruent with the youngest age enrolled in the pivotal phase 2 trial, TN-10.
- The patient should have a **diagnosis of Stage 2 type 1 diabetes mellitus (T1D)** as evidenced by seropositivity for at least 2 different diabetes-related autoantibodies, and elevated blood glucose (dysglycemia) without overt hyperglycemia. May also consider an attestation field that the **patient does not meet criteria for a diagnosis of clinical T1D (Stage 3 T1D)**.

  Criteria for Stage 2 T1D[7] is as follows:
  - Presence of ≥2 different islet autoantibodies
    - Teplizumab prescribing information does not specify which diabetes-related autoantibodies should be tested, nor does it specify the proximity of the positive autoantibody seropositivity relative to teplizumab administration.
      - May consider requiring a positive result within reasonable proximity before starting teplizumab. In the TN-10 trial, two positive tests for 2 or more autoantibodies from 2 samples were required, with one positive test within the prior 6 months.[12]
      - Autoantibodies tested in the TN-10 trial[12]: anti-insulin (mIAA); anti-GAD65 (glutamic acid decarboxylase 65); anti-ICA512 (islet cell antigen), also commonly referred to as islet antigen-2 or insulinoma-associated protein (IA-2)[81]; anti-ZnT8 (zinc transporter 8); and ICA (islet cell antibodies).
  - Evidence of dysglycemia without meeting criteria for hyperglycemia (ie, for diagnosis of clinical, Stage 3 T1D):
    - Teplizumab prescribing information recommends confirming dysglycemia with an oral glucose tolerance test (OGTT), unless that glycemic test is unavailable.[1]
    - There is not universal agreement on dysglycemic criteria. The 2022 ADA guideline recommends the following: fasting plasma glucose (FPG) of 100-125 mg/dL; 2-hr plasma glucose of 140-199 mg/dL; or a hemoglobin A1c of 5.7-6.4% or > 10% increase in hemoglobin A1c.[16,20]
    - In the TN-10 pivotal trial, an abnormal oral glucose tolerance test (OGTT) was required. Accepted evidence of dysglycemia included a FPG of 110-125 mg/dL, a 2-hr plasma glucose of 140-199 mg/dL, or a 30-, 60-, or 90-minute post-OGTT plasma glucose level ≥200mg/dL.[12] Sufficient evidence for patients <18 years old included a single dysglycemic result, while those 18 or older had to have 2 consecutive positive results, with one occurring within 7 weeks before the start of the trial.[12]

- Consider restricting patients to a single course of teplizumab (14 infusions total)
  - To delay onset of Stage 3 T1D, teplizumab has been approved as a single 14-day course of therapy (plus allowances for slight delays for resolving adverse effects during administration). The total recommended dose, given over 14 days and dosed based on body surface area, is approximately 11,240 μg/m².[1]
  - The efficacy and safety of additional courses of therapy have not been established. Moreover, a considerable number of patients in the pivotal trial developed neutralizing antibodies to teplizumab after a 1st course[1]; studies must be conducted to prove that there are significant clinical benefits to additional courses of therapy. Notably, teplizumab is under study for 2 courses of therapy among people with Stage 3 T1D (a different potential population),[15] with top-line results from a phase 3 trial expected by mid-2023.[14]
- Consider requiring provider attestation to the completion of recommended laboratory screening (eg, for significant hematologic or hepatic abnormalities) before therapy (as shown in Table 2).

Additional considerations for discussion:

- **Regarding use among patients already diagnosed with clinical (Stage 3) T1D**, teplizumab is in phase 3 trials for the use in patients with recent onset T1D.[15] While there have been previous trials in that population that suggest benefits of teplizumab in retaining pancreatic beta-cell function,[23,24,51] the prior phase 3 trial failed to meet its primary efficacy endpoint.[23,24]
- May consider requiring that teplizumab be prescribed by or consultation with an endocrinologist.
- May consider mentioning educational information for prescribers intended to mitigate adverse effects based on prescribing information. For example:
  - According to teplizumab prescribing information, teplizumab is NOT recommended for patients with one of the following characteristics at baseline[1]:
    - Cytopenia, including: lymphopenia (<1000 lymphocytes/μL), anemia (hemoglobin <10 g/dL) thrombocytopenia (<150,000 platelets/μL), or neutropenia (ANC <1,500 neutrophils/μL)
    - Liver function abnormalities (ie, AST/ALT > 2x the upper limit of normal [ULN], or bilirubin >1.5x ULN)
    - Laboratory or clinical evidence of acute Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
    - Active serious infection, or chronic infection (except for localized skin infections)
  - Administer urgently needed vaccinations before teplizumab therapy: give live vaccines ≥ 8 weeks before starting teplizumab, and give inactivated or mRNA vaccines ≥ 2 weeks before teplizumab initiation. After teplizumab therapy completion, inactive/mRNA vaccines may be considered after 6 weeks, and live vaccines may be considered after 52 weeks.[1]
  - Premedicate with an antipyretic, antihistamine, and/or antinausea medication before each teplizumab dose during at least the first 5 days of the treatment regimen.[1]
  - Monitor for and treat emergent cytokine release syndrome (CRS); for severe symptoms, consider pausing treatment for 1-2 days or discontinuing teplizumab.
    - Examples of CRS symptoms: "…fever, nausea, fatigue, headache, myalgia, arthralgia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased total bilirubin." (page 4)[1]

10.0 SUMMARY

Teplizumab-mzwv (Tzield) is an intravenous (IV), humanized anti-CD3 monoclonal antibody thought to work as an immunomodulator to temporarily suppress inappropriate T lymphocyte auto-immunity against pancreatic beta cells.[2,46] A 2015 multi-organization statement classified predictable, pre-clinical type 1 diabetes (T1D) stages (Stage 1 and Stage 2). Both Stage 1 and 2 T1D are characterized by the presence of 2 or more diabetes-related autoantibodies, with Stage 2 T1D patients also requiring evidence of dysglycemia.[7] It is expected that nearly all patients who develop 2 or more autoantibodies, regardless of a family history of T1D, will eventually develop overt (Stage 3) T1D that requires treatment with insulin, but the natural time to conversion to Stage 3 is highly variable.[10] Teplizumab is the first therapy indicated as a one-time 14-day regimen to *delay* the onset of clinical (Stage 3) T1D among individuals 8 years or older with Stage 2 T1D.[1] There are no other FDA-approved disease-modifying therapies for any T1D stage.

A single phase 2 randomized controlled trial (TN-10) of 76 patients with Stage 2 T1D and family history of T1D, ages 8 to 49.5 years old, supports the efficacy of teplizumab for its FDA-approved indication.[12] In the TN-10 trial, administration of a single, 14-day course of teplizumab significantly delayed onset of Stage 3 T1D by a median of about 24 months (HR 0.42, 95% CI 0.22–0.78) compared to placebo after a median follow-up of 745 days.[12] This delay approached 32 months after a median follow-up of 923 days.[56] According to some experts, delaying onset of T1D by at least 2 years may be clinically meaningful as it delays the time to requiring insulin, and may theoretically delay or lower the risk for diabetes-related complications.[39]

In the TN-10 trial, common adverse effects included transient lymphopenia, leukopenia, rash, hepatic enzyme increases, and headache.[12] Labeled warnings and precautions for the use of teplizumab include the risk of cytokine release syndrome (CRS), serious infections, lymphopenia, hypersensitivity reactions, and the recommendation that patients receive age-appropriate vaccinations before receiving teplizumab.[1] White blood cell counts and liver function tests should be monitored during treatment. To mitigate the risk for CRS, patients should receive premedication with appropriate antipyretic and antihistamine and/or antiemetic before teplizumab administration by IV infusion.[1] Owing to its immunosuppressive effect on T lymphocytes, there is a plausible elevated risk for infection. The rate of infection was similar to placebo during overall TN-10 trial follow-up; though, a few cases of transient viral reactivation (eg, EBV and CMV) did occur.[12] Patients with active infections or a history of certain infections (eg, hepatitis B or C) were excluded from the TN-10 trial.[12] Patients with serious or chronic non-localized skin infections should not receive teplizumab.[1]

Efficacy and safety of teplizumab among patients meeting criteria for T1D diagnosis is not yet established. Early studies in this population suggest that teplizumab may help preserve or prevent declines in C-peptide,[23,24,51,53,54] a biomarker that indicates insulin secretion[35]; however, the major phase 3 trial failed to meet its primary efficacy endpoint.[23] A phase 3 trial in patients with recent-onset T1D by the current teplizumab sponsor is ongoing, with results expected by mid-2023.[15]

Clinical practice guidelines, which predated FDA approval of teplizumab, do not yet include recommendations for use of any disease-modifying therapies for initial stages of T1D. To potentially initiate treatment with teplizumab, individuals with Stage 2 T1D must be identified. The 2022 American

Diabetes Association (ADA) guideline and 2018 International Society for Pediatric and Adolescent Diabetes (ISPAD) guideline do not yet strongly recommend screening the general asymptomatic population for diabetes-related autoantibodies, outside of the setting of a clinical trial.[16,19] However, the ADA guideline recommends, as optional, screening first-degree relatives of T1D-diagnosed persons for diabetes-related autoantibodies (anti- insulin, GAD, islet antigen 2 and ZnT8).[16] Only about 15% of patients diagnosed with T1D have a family history of T1D.[7]

Currently, when an individual with pre-clinical T1D (ie, Stage 1 or Stage 2) is identified, guidelines recommend providing education about monitoring for T1D symptoms.[16,19] Identification of patients at-risk for T1D and subsequent education about T1D has been associated with a lower rate of DKA at T1D diagnosis.[82] This (and/or referral for participation in clinical trials) is the current standard-of-care for patients with pre-clinical T1D. The present lack of routine screening in clinical practice may be an initial barrier to routine use of teplizumab; however, with the availability of teplizumab, guideline recommendations may change.

Implementation of prior authorization (PA) to ensure the use of teplizumab for populations with an established acceptable safety and efficacy profile may be considered. Although teplizumab is being studied among people with recent-onset (Stage 3) T1D, it is not yet indicated or under FDA review for use in this population. Some PA considerations are included on page 24.

REFERENCES

1. Tzield (teplizumab-mzwv) injection, for intravenous use. Package Insert. Provention Bio I; 2022. Accessed November 28, 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf

2. U.S. Food and Drug Administration. FDA briefing document for Endocrinologic and Metabolic Drugs Advisory Committee Meeting May 21, 2021. Teplizumab BLA 761183. Prepared April 30, 2021. http://investors.proventionbio.com/events?item=35. Accessed June 2, 2021.

3. von Scholten BJ, Kreiner FF, Gough SCL, von Herrath M. Current and future therapies for type 1 diabetes. *Diabetologia*. 2021;64(5):1037-1048. doi:10.1007/s00125-021-05398-3

4. Imperatore G, Mayer-Davis EJ, Orchard TJ, Zhong VW. Prevalence and Incidence of Type 1 Diabetes Among Children and Adults in the United States and Comparison With Non-U.S. Countries. In: Cowie CC, Casagrande SS, Menke A, et al, eds. National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018.

5. McCullough ML, Wan N, Pezzolesi MG, et al. Type 1 Diabetes incidence among youth in Utah: A geographical analysis. *Soc Sci Med*. 2021;278:113952. doi:10.1016/j.socscimed.2021.113952

6. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391(10138):2449-2462. doi:10.1016/s0140-6736(18)31320-5

7. 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. doi:10.2337/dc15-1419

8. Draznin B, Aroda VR, Bakris G, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S125-s143. doi:10.2337/dc22-S009

9. Insel R, Dutta S, Hedrick J. Type 1 Diabetes: Disease Stratification. *Biomedicine Hub*. 2017;2(Suppl. 1):1-16. doi:10.1159/000481131 https://www.karger.com/DOI/10.1159/000481131

10. Greenbaum C, VanBuecken D, Lord S. Disease-Modifying Therapies in Type 1 Diabetes: A Look into the Future of Diabetes Practice. *Drugs*. 2019;79(1):43-61. doi:10.1007/s40265-018-1035-y

11. Vudattu NK, Herold KC. Treatment of new onset type 1 diabetes with teplizumab: successes and pitfalls in development. *Expert Opin Biol Ther*. 2014;14(3):377-385. doi:10.1517/14712598.2014.881797

12. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. 2019;381(7):603-613. doi:10.1056/NEJMoa1902226

13. Provention Bio, Inc. Provention Bio receives complete response letter (CRL) to biologics license application (BLA) for teplizumab for the delay of clinical type 1 diabetes (T1D) in at-risk individuals. July 6, 2021. http://investors.proventionbio.com/2021-07-06-Provention-Bio-Receives-Complete-Response-Letter-CRL-to-Biologics-License-Application-BLA-for-Teplizumab-for-the-Delay-of-Clinical-Type-1-Diabetes-T1D-in-At-risk-Individuals. Accessed July 14, 2021.

14. Provention Bio I. *Changing Their World, Can Change our World. Investor Information.* . Provention Bio I; 2022: 38 pages. Last Updated November 2022. Accessed November 29, 2022. Available at https://investors.proventionbio.com/home

15. Provention Bio I. Recent-onset Type 1 Diabetes Trial Evaluating Efficacy and Safety of Teplizumab (PROTECT). NCT03875729. ClinicalTrials.gov; 2019. Last Updated August 17, 2022. Accessed November 29, 2022. Available at https://clinicaltrials.gov/ct2/show/NCT03875729

16. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S17-s38. doi:10.2337/dc22-S002

17. Type 1 Diabetes TrialNet. *Anti-CD3 mab (teplizumab) for prevention of diabetes in relatives at-risk for type 1 diabetes mellitus*. Protocol TN-10,. Type 1 Diabetes TrialNet; 2014: 136 pages. Last Updated March 27, 2018. Accessed December 5, 2022. Available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1902226/suppl_file/nejmoa1902226_protocol.pdf

18. Association AD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S15-s33. doi:10.2337/dc21-S002

19. 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. doi:10.1111/pedi.12734

20. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association. *Diabetes Care*. 2018;41(9):2026-2044. doi:10.2337/dci18-0023

21. Jacobsen LM, Bocchino L, Evans-Molina C, et al. The risk of progression to type 1 diabetes is highly variable in individuals with multiple autoantibodies following screening. *Diabetologia*. 2020;63(3):588-596. doi:10.1007/s00125-019-05047-w

22. Bogun MM, Bundy BN, Goland RS, Greenbaum CJ. C-Peptide Levels in Subjects Followed Longitudinally Before and After Type 1 Diabetes Diagnosis in TrialNet. *Diabetes Care*. 2020;43(8):1836-1842. doi:10.2337/dc19-2288

23. Sherry N, Hagopian W, Ludvigsson J, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. 2011;378(9790):487-497. doi:10.1016/s0140-6736(11)60931-8

24. Hagopian W, Ferry RJ, Jr., Sherry N, et al. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. *Diabetes*. 2013;62(11):3901-3908. doi:10.2337/db13-0236

25. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. *Endocr Pract*. 2022;28(10):923-1049. doi:10.1016/j.eprac.2022.08.002

26. Yu L, Rewers M, Gianani R, et al. Antiislet autoantibodies usually develop sequentially rather than simultaneously. *J Clin Endocrinol Metab*. 1996;81(12):4264-4267. doi:10.1210/jcem.81.12.8954025

27. So M, Speake C, Steck AK, et al. Advances in Type 1 Diabetes Prediction Using Islet Autoantibodies: Beyond a Simple Count. *Endocr Rev*. 2021;42(5):584-604. doi:10.1210/endrev/bnab013

28. Ng K, Anand V, Stavropoulos H, et al. Quantifying the utility of islet autoantibody levels in the prediction of type 1 diabetes in children. *Diabetologia*. 2022, 10.1007/s00125-022-05799-ydoi:10.1007/s00125-022-05799-y

29. So M, O'Rourke C, Bahnson HT, Greenbaum CJ, Speake C. Autoantibody Reversion: Changing Risk Categories in Multiple-Autoantibody-Positive Individuals. *Diabetes Care*. 2020;43(4):913-917. doi:10.2337/dc19-1731

30. Tyrosine phosphatase (IA-2) autoantibody assay. January 19, 2018. https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K171731. Accessed July 29, 2021.

31. Autoantibodies, glutamic acid decarboxylase (Gad). November 7, 2007. https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K072135. Accessed July 29, 2021.

32. Insulin autoantibody kit. July 13, 2007. https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K070183. Accessed July 29, 2021.

33. KRONUS Zinc Transporter 8 Autoantibody (ZnT8) ELISA assay. August 2014. https://www.accessdata.fda.gov/cdrh_docs/pdf14/DEN140001.pdf. Accessed July 29, 2021.

34. ARUP laboratories. Zinc Transporter 8 Antibody. https://ltd.aruplab.com/Tests/Pub/2006196. Accessed July 29, 2021.

35. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. *Diabetes Ther*. 2017;8(3):475-487. doi:10.1007/s13300-017-0265-4

36. Palmer JP, Fleming GA, Greenbaum CJ, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. *Diabetes*. 2004;53(1):250-264. doi:10.2337/diabetes.53.1.250

37. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003;26(3):832-836. doi:10.2337/diacare.26.3.832

38. Lachin JM, McGee P, Palmer JP. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes*. 2014;63(2):739-748. doi:10.2337/db13-0881

39. JDRF T1D Fund. *White paper. Modeling the Total Economic Value of Novel Type 1 Diabetes (T1D) Therapeutic Concepts*. JDRF T1D Fund: 45 pages. Last Updated January 2020. Accessed June 21, 2021. Available at https://t1dfund.org/modeling-the-total-economic-value-of-novel-type-1-diabetes-therapeutic-concepts/

40. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. *Jama*. 2020;323(4):339-351. doi:10.1001/jama.2019.21565

41. ARUP laboratories. Insulin antibody. https://ltd.aruplab.com/Tests/Pub/0099228. Accessed July 29, 2021.

42. Gabbay R. American Diabetes Association Statment on FDA Approval of Teplizumab. Association AD. 2022. Last Updated November 17, 2022. Accessed December 2, 2022. Available at https://diabetes.org/newsroom/official-statement/2022/american-diabetes-association-statement-on-fda-approval-teplizumab

43. Draznin B, Aroda VR, Bakris G, et al. 14. Children and Adolescents: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S208-s231. doi:10.2337/dc22-S014

44. Symlin (pramlintide acetate) injection for subcuaneous use Package Insert. AstraZeneca Pharmaceuticals LP; 2019. Accessed December 5, 2022. Available at https://medicalinformation.astrazeneca-us.com/home/prescribing-information/symlin-pi.html

45. Bluestone JA, Anderson M. Tolerance in the Age of Immunotherapy. *N Engl J Med*. 2020;383(12):1156-1166. doi:10.1056/NEJMra1911109

46. ProventionBio. Teplizumab for the delay of progression to clinical stage 3 type 1 diabetes in at-risk patients. Sponsor briefing document. Endocrinologic and metaboliic drugs advisory committee. Meeting May 27, 2021. http://investors.proventionbio.com/events?item=35. Accessed June 2, 2021. .

47. Long SA, Thorpe J, Herold KC, et al. Remodeling T cell compartments during anti-CD3 immunotherapy of type 1 diabetes. *Cell Immunol*. 2017;319:3-9. doi:10.1016/j.cellimm.2017.07.007

48. Long SA, Thorpe J, DeBerg HA, et al. Partial exhaustion of CD8 T cells and clinical response to teplizumab in new-onset type 1 diabetes. *Sci Immunol*. 2016;1(5)doi:10.1126/sciimmunol.aai7793

49. Blank CU, Haining WN, Held W, et al. Defining 'T cell exhaustion'. *Nat Rev Immunol*. 2019;19(11):665-674. doi:10.1038/s41577-019-0221-9

50. Daifotis AG, Koenig S, Chatenoud L, Herold KC. Anti-CD3 clinical trials in type 1 diabetes mellitus. *Clin Immunol*. 2013;149(3):268-278. doi:10.1016/j.clim.2013.05.001

51. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes*. 2005;54(6):1763-1769. doi:10.2337/diabetes.54.6.1763

52. Herold KC, Gitelman S, Greenbaum C, et al. Treatment of patients with new onset Type 1 diabetes with a single course of anti-CD3 mAb Teplizumab preserves insulin production for up to 5 years. *Clin Immunol*. 2009;132(2):166-173. doi:10.1016/j.clim.2009.04.007

53. Herold KC, Gitelman SE, Ehlers MR, et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial:

metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes*. 2013;62(11):3766-3774. doi:10.2337/db13-0345

54. Herold KC, Gitelman SE, Willi SM, et al. Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. *Diabetologia*. 2013;56(2):391-400. doi:10.1007/s00125-012-2753-4

55. Perdigoto AL, Preston-Hurlburt P, Clark P, et al. Treatment of type 1 diabetes with teplizumab: clinical and immunological follow-up after 7 years from diagnosis. *Diabetologia*. 2019;62(4):655-664. doi:10.1007/s00125-018-4786-9

56. Sims EK, Bundy BN, Stier K, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med*. 2021;13(583)doi:10.1126/scitranslmed.abc8980

57. Sims EK, Cuthbertson D, Herold KC, Sosenko JM. The Deterrence of Rapid Metabolic Decline Within 3 Months After Teplizumab Treatment in Individuals at High Risk for Type 1 Diabetes. *Diabetes*. 2021;70(12):2922-2931. doi:10.2337/db21-0519

58. Keymeulen B, van Maurik A, Inman D, et al. A randomised, single-blind, placebo-controlled, dose-finding safety and tolerability study of the anti-CD3 monoclonal antibody otelixizumab in new-onset type 1 diabetes. *Diabetologia*. 2021;64(2):313-324. doi:10.1007/s00125-020-05317-y

59. Nourelden AZ, Elshanbary AA, El-Sherif L, et al. Safety and Efficacy of Teplizumab for Treatment of Type One Diabetes Mellitus: A Systematic Review and Meta-analysis. *Endocr Metab Immune Disord Drug Targets*. 2020, 10.2174/1871530320999201209222921doi:10.2174/1871530320999201209222921

60. Mauras N, Buckingham B, White NH, et al. Impact of Type 1 Diabetes in the Developing Brain in Children: A Longitudinal Study. *Diabetes Care*. 2021;44(4):983-992. doi:10.2337/dc20-2125

61. Aye T, Mazaika PK, Mauras N, et al. Impact of Early Diabetic Ketoacidosis on the Developing Brain. *Diabetes Care*. 2019;42(3):443-449. doi:10.2337/dc18-1405

62. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care*. 2014;37(10):2843-2863. doi:10.2337/dc14-1720

63. DiSantostefano RL, Sutphin J, Hedrick JA, Klein K, Mansfield C. Parent Preferences for Delaying Insulin Dependence in Children at Risk of Stage III Type 1 Diabetes. *Diabetes Technol Ther*. 2020;22(8):584-593. doi:10.1089/dia.2019.0444

64. Ross E, Altimus C. *Type 1 Diabetes Autoantibody Screening: A Roadmap for Pediatric Policy Implementation* Milken Institute; 2021: 41 pages. Accessed December 6, 2022. Available at https://milkeninstitute.org/sites/default/files/2021-04/MI_Type%201%20Diabetes%20Autoantibody%20Screening.pdf

65. Sims EK, Besser REJ, Dayan C, et al. Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. *Diabetes*. 2022;71(4):610-623. doi:10.2337/dbi20-0054

66. Ke Q, Kroger CJ, Clark M, Tisch RM. Evolving Antibody Therapies for the Treatment of Type 1 Diabetes. *Front Immunol*. 2020;11:624568. doi:10.3389/fimmu.2020.624568

67. Chatenoud L, Primo J, Bach JF. CD3 antibody-induced dominant self tolerance in overtly diabetic NOD mice. *J Immunol*. 1997;158(6):2947-2954.

68. Janssen Research & Development L. A Study to Evaluate SIMPONI (golimumab) Therapy in Children, Adolescents and Young Adults with Pre-symptomatic Type 1 Diabetes. . NCT03298542. ClinicalTrials.gov; 2017. Last Updated September 16, 2021. Accessed December 1, 2022. Available at https://clinicaltrials.gov/ct2/show/NCT03298542

69. SIMPONI (golimumab) injection for subcuaneous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; revised September 2019.

70. Plaquenil (hydroxychloroquine sulfate) tablets, for oral use Package Insert. Concordia Pharmaceuticals; 2021. Accessed December 1, 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/009768s053lbl.pdf

71. Orencia (abatacept) for injection, for intravenous use. Orencia (abatacept) injection, for subcutaneous use. . Package Insert. Bristol-Myers Squibb Company; 2021. Accessed December 1, 2022. Available at https://packageinserts.bms.com/pi/pi_orencia.pdf

72. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1. NCT01773707. ClinicalTrials.gov; 2013. Last Updated April 15, 2022. Accessed December 1, 2022. Available at https://clinicaltrials.gov/ct2/show/NCT01773707

73. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Hydroxychloroquine in Individuals At-risk for Type 1 Diabetes Mellitus (TN-22). NCT03428945. ClinicalTrials.gov; 2018. Last Updated July 1, 2022. Accessed December 1, 2022. Available at https://www.clinicaltrials.gov/ct2/show/NCT03428945

74. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N Engl J Med*. 2009;361(22):2143-2152. doi:10.1056/NEJMoa0904452

75. Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;378(9789):412-419. doi:10.1016/s0140-6736(11)60886-6

76. Rigby MR, Harris KM, Pinckney A, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. *J Clin Invest*. 2015;125(8):3285-3296. doi:10.1172/jci81722

77. Haller MJ, Long SA, Blanchfield JL, et al. Low-Dose Anti-Thymocyte Globulin Preserves C-Peptide, Reduces HbA(1c), and Increases Regulatory to Conventional T-Cell Ratios in New-Onset Type 1 Diabetes: Two-Year Clinical Trial Data. *Diabetes*. 2019;68(6):1267-1276. doi:10.2337/db19-0057

78. Quattrin T, Haller MJ, Steck AK, et al. Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. *N Engl J Med*. 2020;383(21):2007-2017. doi:10.1056/NEJMoa2006136

79. von Herrath M, Bain SC, Bode B, et al. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol*. 2021;9(4):212-224. doi:10.1016/s2213-8587(21)00019-x

80. Bellin MD, Barton FB, Heitman A, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. *Am J Transplant*. 2012;12(6):1576-1583. doi:10.1111/j.1600-6143.2011.03977.x

81. ARUP laboratories. Islet Antigen-2 (IA-2) Autoantibody, serum. *https://ltd.aruplab.com/Tests/Pub/3001499.* Accessed July 19, 2021.

82. Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. *Pediatr Diabetes*. 2012;13(4):308-313. doi:10.1111/j.1399-5448.2011.00829.x

83. KRONUS. Islet call autoimmunity IA-2 Autoantibody (IA-2Ab) ELISA. https://kronus.com/tech-files/KR18_IA2Ab_ELISA_x1a.pdf. Accessed July 29, 2021.

84. KRONUS. Islet call autoimmunity Zinc Transporter 8 Autoantibody (ZnT8Ab) ELISA. https://kronus.com/tech-files/KR14_ZnT8Ab_ELISA_x1a.pdf. Accessed July 29, 2021.,

85. KRONUS. Glutamic Acid Decarboxylase Autoantibody (GADAb) ELISA. https://kronus.com/tech-files/KR16_GADAb_ELISA_x1a.pdf. Accessed July 29, 2021.

86. KRONUS. Islet call autoimmunity Insulin Autoanttibody (IAA) radioimmunoassay. https://kronus.com/tech-files/KR14_IAA_RIA_x1a.pdf. Accessed July 29, 2021.

87. ARUP Test Directory. https://www.aruplab.com/testing. Accessed July 29, 2021.

APPENDIX A: LITERATURE SEARCH

The following initial search was performed in Embase on June 8, 2021:

> *'teplizumab'/exp OR (teplizumab:ti,ab,kw OR 'prv-031':ti,ab,kw OR 'prv 031':ti,ab,kw OR 'mga031':ti,ab,kw OR 'mga 031':ti,ab,kw OR 'mab hokt3gamma1':ti,ab,kw)*
>
> This search returned 291 results.

The same search string was queried in Embase on November 28, 2022, with the search years restricted to 2021 and 2022 to check for updates to the original report. This updated search returned 44 results.

APPENDIX B: SENSITIVITY AND SPECIFICITY OF FDA-APPROVED ISLET AUTOANTIBODY TESTS

Table B1 lists sensitivity and specificity information for 4 islet autoantibody tests (all from the manufacturer, KRONUS) that are reported as FDA-approved.[30-34] The manufacturer states that each of these tests may be useful to help with a T1D diagnosis[83-86]; however, the IA-2 and ZnT8 tests are not to be used alone to establish diagnosis.[83,84]

Table B1. Manufacturer-reported Sensitivity and Specificity of FDA-approved[30-32,34,81] Islet Cell Autoantibody Tests

Test Name	Sensitivity[a]	Specificity[a]
Glutamic acid decarboxylase autoantibody[b]	83%	99%
Insulin autoantibody[c]	50%	99%
IA-2 autoantibody[d]	58.2%	97.0%
Zinc transporter 8 autoantibody[e]	68%	98%

[a]*Reported as "Clinical Sensitivity & Specificity."[83]*

[b]*Semi-quantitative assay (by ELISA) of human serum. "Useful as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune-medicated diabetes)."[85]*

[c]*Semi-quantitative assay (by radioimmunoassay) of human serum. "Useful as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune-medicated diabetes) in patients who have not received insulin therapy." (The test cannot distinguish between antibodies to endogenous and exogenously administered insulin).[86]*

[d]*Quantitative assay (by ELISA) of human serum. "Useful as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune-medicated diabetes)" when used with other clinical and laboratory data (NOT indicated as a solitary test).[83]*

[e]*Semi-quantitative assay (by ELISA) of human serum. "Useful as an aid in the diagnosis of Type 1 diabetes mellitus (autoimmune-medicated diabetes)" when used with other clinical and laboratory data (NOT indicated as a solitary test).[84]*

Abbreviations: ELISA, enzyme-linked immunoassay; FDA, United States Food and Drug Administration; IA-2, islet antigen-2; T1D, type 1 diabetes mellitus; ZnT8, zinc transporter 8.

APPENDIX C: FREQUENCY OF ORDERS FOR DIABETES-RELATED AUTOANTIBODIES BASED ON CPT CODE BY UTAH MEDICAID CLINICIANS

To visualize whether Utah Medicaid clinicians have previously ordered tests for diabetes-related autoantibodies, we pulled corresponding procedural codes (CPT) among fee for service Utah Medicaid members between January 1, 2018 and June 30, 2021. Table C1 shows the number of orders for a diabetic autoantibody test, and the number of unique patients with at least one order that year. In this timeframe, an estimated 396 orders were placed for a corresponding 228 unique patients. Note that there are multiple reasons why clinicians might order these tests, including as part of establishing a diagnosis of T1D.

Table C1. Orders for Diabetes-related Autoantibodies among Unique Utah Medicaid FFS Patients between January 1, 2018 and June 30, 2021

Year: / CPT:	2018		2019		2020		2021		TOTAL	
	Orders	Patients	Orders	Patients	Orders	Patients	Orders	Patients	Orders	Patients
86337[a]	23	11	18	16	18	12	4	4	63	43
86341[b]	58	28	76	62	88	55	21	17	243	160
TOTAL	81	32	94	64	106	57	25	19	306	170

[a]*Order for anti-insulin autoantibody testing.*[41]

[b]*Order for at least one of multiple possible other diabetes-related autoantibody testing; thought to include antibodies against pancreatic islet cell cytoplasm, zinc transporter 8, IA-2, and GAD-65.*[87]

Abbreviations: CPT, current procedural terminology code; FFS, fee-for-service; IA-2, islet antigen-2; GAD, glutamic acid decarboxylase; T1D, type 1 diabetes mellitus.

APPENDIX D: ELIGIBILITY CRITERIA FOR PIVOTAL TEPLIZUMAB PHASE 2 CLINICAL TRIAL (TN-10)

Table D1. Inclusion and Exclusion Criteria for Teplizumab Phase 2 TN-10 Trial[12,17]

Inclusion Criteria	Exclusion Criteria

• Related to a proband[a] T1D patient and:
  ○ Between ages 8 to 45 years[b] if proband is a first-degree relative (parent, child, or sibling), OR
  ○ Between the ages of 8 to 20 years[b] if the proband is a second- or third-degree relative (uncle, aunt, niece, nephew, grandchild, or cousin).
• Confirmed presence of ≥2 diabetes-related autoantibodies[c] (anti-GAD65, anti-ICA512, anti-insulin [mIAA], ZnT8[d] and/or ICA) on 2 occasions (second occasion must occur within 6 months prior to administration of drug).
• Confirmed (second) abnormal OGTT within 7 weeks of baseline visit[e]:
  ○ FBG[f] of 110 – 125 mg/dL, OR
  ○ 2-hour post-OGTT plasma glucose level of 140 – 199 mg/dL, OR
  ○ 30-, 60-, or 90-minute post-OGTT plasma glucose level ≥200mg/dL.
• Weight >26 kg (at randomization).
• Able/willing to provide informed consent (including parent/legal guardian for participants <18 years old.
• Both male and female participants must be willing to avoid pregnancy for at least 1 year after randomization; female participants with reproductive potential must have a negative pregnancy test on day 0.
• Study participants must be willing/able to postpone live vaccine immunizations for at least one year after treatment.
• Participants must be willing to not enroll in other experimental treatments during study.
	• Adults (>18 years) with diagnosed diabetes, OR with an OGTT of FBG ≥126 mg/dL, OR with a 2-hour plasma glucose ≥200 mg/dL at screening.
	• Children (<18 years) with diagnosed diabetes, OR have a random glucose ≥200 mg/dL at screening.
	• Abnormal blood counts including lymphopenia (<1000 lymphocytes/µL), neutropenia (< 1500 PMN/µL), thrombocytopenia (< 150,000 platelets/µL), or anemia (Hgb < 10 g/dL).
	• Abnormalities in liver enzymes (AST or ALT >1.5 x ULN).
	• Total bilirubin >1.5 x ULN (except in those with diagnosed Gilbert's syndrome, who may be eligible if there are no other causes for hyperbilirubinemia).
	• INR > 0.1 above the ULN.
	• Current infection or infection history meeting the following criteria:
	  ○ Chronic active infection aside from localized skin infections.
	  ○ Mononucleosis within the 3 months before enrollment.
	  ○ Evidence (laboratory or clinical) of EBV or CMV acute infection.
	  ○ Evidence (current or past) of HIV, HBV, or HCV infection based on serological tests.
	  ○ A positive PPD test.
	• Have a history of asthma or atopic disease that requires chronic treatment.
	• Immunized with a live vaccine within 8 weeks of randomization, OR with an inactive vaccine within 4 weeks of randomization.
	• Participation in vaccine or drug clinical trials within the 12 weeks before randomization.
	• Those who are currently pregnant or lactating, or who anticipate pregnancy.
	• Chronic use of immunosuppressive agents (eg, steroids), current use of non-insulin medications that affect glycemic control, OR prior use of OKT®3 or other anti-CD3 treatment.
	• Have had monoclonal antibody administration within the year before randomization.
	• Those with active Grave's disease or untreated hypothyroidism at randomization.
	• A condition that may interfere with the study or patient's safety based on investigator's opinion.

[a] "A proband is an individual diagnosed with diabetes before age 40 and started on insulin therapy within one year of diagnosis." (page 18)[17] In cases where the proband did not meet this criterion but were considered to have T1D by their physician, the TrialNet Eligibility Committee could consider them for eligibility.

[b] Patients had to be between 1 to 45 years old at time of enrollment of in the precursor natural history study (TN-01). Patients were allowed to enter the TN-10 study if they were <45 at the time of starting TN-01. The original study protocol lists that age requirements differ according to the degree of relation to the relative with established T1D (ie, older participant ages were allowed if a fist-degree relative versus second- or third-degree relative.

[c] Investigators first evaluated for the presence of autoantibodies to mIAA, GAD and IA-2/ICA512. If at least one of these was positive, they additionally tested for both ICA and ZnT8. Radioimmunobinding assays (at one University) were used to measure antibodies to GAD-65, micro insulin, ICA-512 and ZnT8 while ICA was measured using indirect immunofluorescence at another University.

[d] ZnT8 autoantibody was added as an amendment (in 2012) to the initial study protocol (from 2010).

[e] "Fasting glucose levels of 110-126 qualify subjects as having abnormal glucose tolerance in this protocol as it reflects the criteria used for entry into the DPT-1 and the DPT-1 data was used for the calculation of diabetes risk for this trial." (page 18) [17]

[f] After 2014, the protocol was amended to allow patients <18 years old with a single abnormal OGTT result that meets other criteria to be included. This decision was "…because the rates of type 1 diabetes progression were similar with or without a confirmatory oral glucose-tolerance test in this age group." (page 4)[12] For those ≥ 18 years at time of randomization, 2 consecutive abnormal OGTTs were required with one completed within the prior 7 weeks.

Abbreviations: µL, microliter; CMV, cytomegalovirus; dL, deciliter; EBV, Epstein-Barr virus; FBG, fasting blood glucose; g, gram; GAD65, glutamic acid decarboxylase 65; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IA-2, islet antigen 2; ICA, islet-cell autoantibody; INR, international normalized ratio; kg, kilogram; mg, milligram; MIAA, micro insulin autoantibodies; OGTT, oral glucose tolerance test; PMN, polymorphonuclear leukocyte; PPD, purified protein derivative; T1D, type 1 diabetes; ULN, upper limit of normal; ZnT8, zinc transporter 8.

APPENDIX E: OVERVIEW OF PRIOR TEPLIZUMAB CLINICAL TRIALS AMONG PATIENTS WITH NEW-ONSET T1D

Table E1. Overview of Prior Phase 2/3 Trials of Teplizumab vs Control for the Treatment of New-onset T1D

First author; year (Trial name) Study design	Study comparison and study population	Teplizumab regimen	Primary endpoint and length of follow-up	C-peptide efficacy results	Adverse events[a]
Herold et al.; 2005[51] (Study 1) R, OL, controlled, phase 1/2 multicenter trial	TEP (n=21) vs control (n=21); control patients were monitored and received usual care without an additional intervention. • Ages 7.5-30 years. • New onset T1D (within 6 weeks of dx).	• Single course • 14-day regimen (first 12 patients); total dose ~536 µg/kg • 12-day regimen (last 9 patients); total dose ~19,500 /m²/course	C-peptide AUC (response) after 4-h MMTT; lymphocytes; and change in insulin secretion • 2-y	• Preservation (% of baseline) of average C-peptide response at -y: TEP (97± 9.6%) vs control (53 ± 7.6%), P=0.001. • Mean AUC of stimulated C-peptide: TEP > control at 12, 18 and 24 months (P<0.02). • Stimulated C-peptide response of ≥ 0.2 pmol/ml at 2-y (% meeting threshold, TEP vs control): 67% vs 26%, P = 0.014.	• TEP AE incidence > 10%: ○ Fever (36.4%), myalgia (22.7%), arthralgia (13.6%), and headache(72.7%); likely CRS related. ○ Rash (urticarial) (90.9%). • Less common mild AE (TEP): ○ Nausea, diarrhea, vomiting, rigors, fatigue. • SAE: ○ Grade 3 thrombocytopenia (TEP, n = 1). • Other events: ○ Anti-idiotype antibodies (50% at 6 mo.; 43% at 1-y; not detectable at >1:1000). • No evidence of long-term AE at 2-y.

[a] Details of AE reporting varied across the studies (for example, some did not report AE rates in the control group).

** Indicates a statistically significant difference from control (p<0.05).*

Abbreviations: Δ, change; Ab, antibodies; AE, adverse event; A1c, glycated hemoglobin; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CD4, cluster of differentiation 4 T cells; CI, confidence interval; CMV, cytomegalovirus; CRS, cytokine release syndrome; DB, double-blind; d/c, discontinued; dx, diagnosis; EBV, Epstein-Barr virus; IV, intravenous; ITT, intention to treat; h, hour; MMTT mixed-meal tolerance test; mo, months; mod, moderate; n, number; OL, open-label; OGTT, oral glucose tolerance test; PBO, placebo; Pts, patients; R, randomized; SAEs, serious adverse events; T1D, type 1 diabetes; y, year; TEP, teplizumab; U, units; WBC, white blood cell count.

Table E1. Overview of Prior Phase 2/3 Trials of Teplizumab vs Control for the Treatment of New-onset T1D

First author; year (Trial name) Study design	Study comparison and study population	Teplizumab regimen	Primary endpoint and length of follow-up	C-peptide efficacy results	Adverse events[a]
Herold et al.; 2009[52] (n/a) R, OL, controlled, phase 2b trial	TEP (n =6) vs control (n = 4); details of control group not reported. • Ad-hoc analysis matched control (n = 12). • Ages 7-30 years. • New onset T1D (within 6 weeks of dx).	• 3 courses planned but stopped after 1 course • 12-day regimen; total dose ~19,500 µg/m²/course	Change in C-peptide AUC in response to 4-hr MMTT; Insulin use and A1c • 2-y • Study stopped prematurely, in part due to accidental higher exposure to TEP and higher incidence of mild-mod CRS and higher grade AE	• Difference in change in C-peptide AUC from baseline at 1-y: Numerical increase in C-peptide response with TEP vs decrease with control, but difference was not statistically significant between TEP vs control (P = 0.2). • Change in C-peptide AUC at 2-y in ad-hoc analysis: Lower decline with TEP > control (P = 0.008).	• Overall AE (n, TEP vs control): 202 vs 50: ○ Mild AE (grade 1) (72%) ○ Moderate AE (grade 2) (24%) ○ Severe AE (grade 3) (4%) • SAE: ○ 7 events; TEP n = 2, control n = 1 • TEP AE incidence >10%: ○ GI disorder, fever, nausea, infections, infections, pharyngitis or URI (100% each) ○ Rigors or rash (83% each) ○ Vomiting or headache (67% each) ○ Myalgia, pharyngitis, or thrombocytopenia (33% each) ○ Chest pain or lymphadenopathy (17%) ○ Mild to mod CRS (100%) ○ Grade 2 or grade 3 lymphopenia (100%) • Other TEP AE: ○ Grade 3 CD4 cytopenia (n = 1, 17%)

[a] *Details of AE reporting varied across the studies (for example, some did not report AE rates in the control group).*

** Indicates a statistically significant difference from control (p<0.05).*

Abbreviations: Δ, change; Ab, antibodies; AE, adverse event; A1c, glycated hemoglobin; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CD4, cluster of differentiation 4 T cells; CI, confidence interval; CMV, cytomegalovirus; CRS, cytokine release syndrome; DB, double-blind; d/c, discontinued; dx, diagnosis; EBV, Epstein-Barr virus; IV, intravenous; ITT, intention to treat; h, hour; MMTT mixed-meal tolerance test; mo, months; mod, moderate; n, number; OL, open-label; OGTT, oral glucose tolerance test; PBO, placebo; Pts, patients; R, randomized; SAEs, serious adverse events; T1D, type 1 diabetes; y, year; TEP, teplizumab; U, units; WBC, white blood cell count.

Table E1. Overview of Prior Phase 2/3 Trials of Teplizumab vs Control for the Treatment of New-onset T1D

First author; year (Trial name) Study design	Study comparison and study population	Teplizumab regimen	Primary endpoint and length of follow-up	C-peptide efficacy results	Adverse events[a]
Sherry et al.; 2011[23] and Hagopian et al.; 2013[24] (Protégé) R, DB, DD, PBO controlled, multicenter, multinational, 4-arm, phase 2/3 trial	TEP 14-day full dose (n=209) vs TEP 14-day low-dose (n=102) vs TEP 6-day full-dose (n=106) vs PBO [matching intravenous] (n=99). • Ages 8-35 years • New onset T1D (within 12 weeks of dx).	2 identical courses 26 weeks apart: • Arm 1: TEP 14-day full dose; total dose ~9034 µg/m²/course • Arm 2: TEP 14-day low dose; total dose ~2985 µg/m²/course • Arm 3: TEP 6-day full dose + 8 days PBO; total dose ~2426 µg/m²/course	Composite of A1c <6·5% and insulin dose <0·5 U/kg per day; mean A1c change from baseline • Secondary endpoint: Mean change from baseline in AUC of stimulated C-peptide after 4-h MMTT • 2-y (initial 1-y analysis was pre-planned) • Follow-up: 90% completed 2-y, but only 64% with 2-y C-peptide AUC data	• Sherry et al. (1-y): ○ Change from baseline in AUC of C-peptide: TEP 14-day full dose vs PBO: (-0.06 vs -0.09 nmol/L/min, P = 0.382). ○ Median change from baseline in AUC of C-peptide (exploratory analysis): TEP 14-day full dose vs PBO: (-0.06 vs -0.14 nmol/L/min, P = 0.046). • Hagopian et al. (2-y): ○ Adjusted mean change from baseline in mean AUC of C-peptide: TEP 14-day full dose vs PBO: less decrease with TEP (-0.136 vs -0.191P = 0.027; in US only, P = 0.010). ○ Significant differences vs PBO not observed with other (lower dose) TEP regimens.	• SAE at 1-y (14-day full-dose TEP vs PBO): 9% in each; DKA observed in TEP groups (1-3%) vs 0% PBO. • AE >10% at 1-y (14-day full-dose TEP vs PBO). ○ Blood disorders (87% vs 52%): Lymphopenia* (73% vs 19%), leukopenia* (47% vs 23%), neutropenia* (36% vs 20%), anemia (14% vs 13%) ○ GI disorders: nausea (20% vs 11%), vomiting* (14% vs 5%) ○ General: pyrexia (21% vs 20%), fatigue (11 vs 5%), chills (10% vs 2%) ○ CRS (6% vs 0%) ○ Hepatobiliary disorders (12% vs 9%) ○ Infections: URI (12% vs 15%), mono-like syndrome (7% vs 8%) ○ Skin disorders: rash* (52% vs 20%), pruritus* (15% vs 4%) ○ Headache* (25% vs 15%) ○ MSK disorders (14% vs 8%) ○ Proteinuria (12% vs 9%) ○ Respiratory/thoracic disorders (21% vs 20%) • Laboratory AE >10% and statistically significantly higher with any TEP vs PBO at 1-y: ○ Blood carbonate decrease, WBC decrease, ALT increase, lymphocyte count decrease • Other AE at 1-y (any TEP vs PBO): ○ Anti-EBV IgG or IGM (5% vs 7%); transient increase in EBV viral load, TEP (n =1) ○ Anti-TEP Ab with titer >1:100 at day 28 or 56 (77% vs 13%) • AE at 2-y (14-day full-dose TEP vs PBO): ○ Grade 3 SAE: 65.2% vs 28.6%, primarily due to lymphopenia ○ SAE (11.1% vs 12.2%): ○ All infections (48.3% vs 58.2%); Herpes zoster: 3.4% vs 0%, acute mono-like illness (7.7% vs 8.2%), mono (1.4 vs 1%), TB (0% vs 1%), URTI (16.3% vs 15.5%) ○ Deaths (any TEP vs PBO): 2 (1.5%) vs 0 (0%) • Pt withdrawal due to AE: ○ At 1-y, any TEP vs PBO: 39 (9%) vs 2 (2%) ○ At 2-y, any TEP vs PBO: 64 (34.7%) vs 5 (5.1%) • Anti-TEP Ab (with titer >1:100) was observed; 14-day full-dose course: more after cycle 2 (60%) than cycle 1 (56%). For some patients, the anti-TEP Ab was associated with faster clearance of teplizumab, but did not seem to affect efficacy

[a] *Details of AE reporting varied across the studies (for example, some did not report AE rates in the control group).*

** Indicates a statistically significant difference from control (p<0.05).*

Abbreviations: Δ, change; Ab, antibodies; AE, adverse event; A1c, glycated hemoglobin; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CD4, cluster of differentiation 4 T cells; CI, confidence interval; CMV, cytomegalovirus; CRS, cytokine release syndrome; DB, double-blind; d/c, discontinued; dx, diagnosis; EBV, Epstein-Barr virus; IV, intravenous; ITT, intention to treat; h, hour; MMTT mixed-meal tolerance test; mo, months; mod, moderate; n, number; OL, open-label; OGTT, oral glucose tolerance test; PBO, placebo; Pts, patients; R, randomized; SAEs, serious adverse events; T1D, type 1 diabetes; y, year; TEP, teplizumab; U, units; WBC, white blood cell count.

Table E1. Overview of Prior Phase 2/3 Trials of Teplizumab vs Control for the Treatment of New-onset T1D

First author; year (Trial name) Study design	Study comparison and study population	Teplizumab regimen	Primary endpoint and length of follow-up	C-peptide efficacy results	Adverse events[a]
Herold et al.; 2012[54] (Delay) R, DB, PBO-controlled, 2-arm, phase 2, multicenter trial	Number in analysis: TEP (n=31) vs PBO [matching normal saline] (n=27). • Age 8-30 years • Recent T1D (within 4-12 months of dx)	• Single course • 14-day regimen; total dose ~ 9033 μg/m²/course	C-peptide AUC in response to 4-h MMTT. • 1-y	Mean AUC of C-peptide response at 1-y, TEP vs PBO: 0.45 (95%CI 0.40 - 0.51) nmol/l vs 0.37 (95% CI 0.32 - 0.42) nmol/l, P=0.03.	• SAE (TEP vs PBO): 1 (3%) vs 4 (14.8%) • Overall AE (TEP vs PBO): ○ grade 1: (82.8% vs 82.8%) ○ grade 2: (12% vs. 12.1%) ○ grade 3: (3.0% vs 3.9%) ○ grade 4: (0.1% vs. 0%) • AE ≥40% and more with TEP vs PBO: ○ Rash, lymphopenia • Other AE ○ EBV infection (TEP, n = 1) ○ CRS (TEP, n = 2; PBO, n = 1) • Pt withdrawal from drug due to AE: TEP: 1 (3%), due to grade 3 neutropenia; PBO: 2 (7.4%)
Daifotis et al.; 2013[50] FDA advisory committee brief; 2021[2] (Protégé Encore [unpublished]) R, DB, PBO-controlled, multinational, 4-arm, phase 3 trial	TEP 14-day full dose (n=63) vs TEP 14-day low-dose (n=66) vs TEP 6-day full-dose (n=63) vs PBO (n=62). • Age 8-35 years • New onset T1D (within 12 weeks of dx)	Same as Protégé trial[23,24] (see above)	Composite of A1c (<7.0% and insulin; <0.25 U/kg/day) • 2-y • Trial stopped early due to "failure" of Protégé trial • 89.8% completed 1-y, 29.1% completed 2-y[2]	Fasting C-peptide at 1-y TEP 14-day full-dose (~9034 μg/m²/course) vs PBO: Numeric improvement with TEP (P = 0.090).	AE (% of patients): Neutropenia (37%), increased AST and ALT (33%), thrombocytopenia (30%), rash (60%), EBV viremia (21%), fever (22%).

[a] *Details of AE reporting varied across the studies (for example, some did not report AE rates in the control group).*

** Indicates a statistically significant difference from control (p<0.05).*

Abbreviations: Δ, change; Ab, antibodies; AE, adverse event; A1c, glycated hemoglobin; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CD4, cluster of differentiation 4 T cells; CI, confidence interval; CMV, cytomegalovirus; CRS, cytokine release syndrome; DB, double-blind; d/c, discontinued; dx, diagnosis; EBV, Epstein-Barr virus; IV, intravenous; ITT, intention to treat; h, hour; MMTT mixed-meal tolerance test; mo, months; mod, moderate; n, number; OL, open-label; OGTT, oral glucose tolerance test; PBO, placebo; Pts, patients; R, randomized; SAEs, serious adverse events; T1D, type 1 diabetes; y, year; TEP, teplizumab; U, units; WBC, white blood cell count.

Table E1. Overview of Prior Phase 2/3 Trials of Teplizumab vs Control for the Treatment of New-onset T1D

First author; year (Trial name) Study design	Study comparison and study population	Teplizumab regimen	Primary endpoint and length of follow-up	C-peptide efficacy results	Adverse events[a]
Herold et al., 2013[53] (AbATE) R, OL, controlled, 2-arm, multicenter, phase 2 trial	Number in analysis: TEP (n=52) vs control (n=25) [normal care, no infusion] Age 8-30 years New onset T1D (within 8 weeks of dx)	• 2 courses 1 year apart (n = 40 received second course) • 14-day regimen; total dose ~ 9034 µg/m²/course	Change in mean C-peptide AUC from baseline after 4-hr MMTT. • 2-y	• Change in mean C-peptide AUC after adjustment for baseline C-peptide AUC in ITT analysis (TEP vs control): –0.28 vs –0.46 nmol/L, P = 0.002 • Mean percent change in mean C-peptide AUC after adjustment for baseline C-peptide AUC in ITT analysis (TEP vs control): –45.1% vs –72.2%, P <0.001	• SAE (TEP vs control): 11 (21.1%) vs 2 (8%) ○ TEP: DKA (n=1), diarrhea (n=1), CRS (n =5), infection (n=2), hypoglycemia (n = 2) ○ Control: hypoglycemia (n =1) • Overall AE: ○ Grade 1: 11.5% vs 28%; grade 2: 42.3% vs. 48%; grade 3 (40.4% vs. 16%); grade 4 (5.8% vs. 0%) • AE >15% (TEP vs control): ○ URI (61.5% vs 56%), flu (19.2% vs 20%), pharyngitis (21.2% vs 12%), nausea (48.1% vs 20%), abdominal pain (44.2% vs 24%), vomiting (36.5% vs 12%), rash (82.7% vs 8%), pruritus (28.8% vs 4%), headache (57.7% vs 40%), pyrexia (38.5% vs 20%), cough (32.7% vs 12%), nasal congestion (15.4% vs 20%), oropharyngeal pain (23.1% vs 4%), hypoglycemia (40.4% vs 24%), hypotension (23.1% vs. 0%) • Laboratory AE (TEP vs control): ○ Increased ALT (9.6% vs 0%), increased AST (7.7% vs 0%), increased total bilirubin (3.8% vs 4%), increased direct bilirubin (3.8% vs 0%), neutropenia (71.2% vs 0%), anemia, lymphopenia >30-days after TEP (1.9% vs 0%), thrombocytopenia (1.9% vs 0%) • Other AE (TEP vs control): ○ EBV and CMV reactivation with TEP: transient increase in viral load; after first course: (EBV: 9 of 21, CMV: 2 of 16); after second course: EBV: 3 of 21, CMV: 1 of 16). 5 patients with possible EBV infection symptoms. ○ Neoplasm [benign and malignant] (5.8% vs. 0%), hepatobiliary disorders (5.8% vs 4%), cardiac disorders (5.8% vs 0%), CRS (9.6% vs 0%) • Pt withdrawal due to AE: • TEP: n = 15 overall d/c, 13 related to AE
Perdigoto et al., 2019[55] AbATE trial extended follow-up	This was a 7-year follow-up trial to the AbATE trial (above). Only 56% of the original participants, including 31 from TEP and 12 from the control group (only those with detectable C-peptide at year 2 of AbATE trial) were eligible; median follow-up 7.3-y, range 6.3- to 8.8-y: • No significant difference in C-peptide response after 4-h MMTT between TEP and control groups; significant differences in C-peptide response for responders vs non-responders + control group (P=0.01). • AE similar between groups including infections; non-significant numerical increase in hypoglycemic events among TEP non-responders and control patients vs TEP responders.				

[a] *Details of AE reporting varied across the studies (for example, some did not report AE rates in the control group).*

** Indicates a statistically significant difference from control (p<0.05).*

Abbreviations: Δ, change; Ab, antibodies; AE, adverse event; A1c, glycated hemoglobin; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AUC, area under the curve; CD4, cluster of differentiation 4 T cells; CI, confidence interval; CMV, cytomegalovirus; CRS, cytokine release syndrome; DB, double-blind; d/c, discontinued; dx, diagnosis; EBV, Epstein-Barr virus; IV, intravenous; ITT, intention to treat; h, hour; MMTT mixed-meal tolerance test; mo, months; mod, moderate; n, number; OL, open-label; OGTT, oral glucose tolerance test; PBO, placebo; Pts, patients; R, randomized; SAEs, serious adverse events; T1D, type 1 diabetes; y, year; TEP, teplizumab; U, units; WBC, white blood cell count.