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# New Drug Evaluation: teplizumab-mzwv, injection

Date of Review: April 2023 Generic Name: teplizumab-mzwv End Date of Literature Search: 01/04/23 Brand Name (Manufacturer): Tzield<sup>™</sup> (Provention Bio, Inc)

Dossier Received: yes

## Plain Language Summary:

- This review evaluates a new medicine called teplizumab that the U.S. Food and Drug Administration (FDA) approved to delay onset of type 1 diabetes. The FDA approved teplizumab only for people that have a high chance of developing type 1 diabetes.
- Type 1 diabetes is a disease where the body's immune system mistakes its own healthy cells as foreign and attacks them. This destroys pancreas cells that make insulin and causes high blood sugar.
- In people who were at risk of getting type 1 diabetes, teplizumab delayed the occurrence of diabetes by approximately two years compared to placebo or no treatment.
- A study showed that teplizumab did not improve blood sugars for people who already have diabetes.
- Teplizumab side effects were rash, blood problems, headache and liver problems.
- We recommend that only diabetes specialists, called endocrinologists, prescribe teplizumab. We also recommend teplizumab be prescribed only to people who are at high risk of type 1 diabetes.

## **Research Questions:**

- 1. What is the evidence for efficacy for teplizumab in delaying the progression of type 1 diabetes (T1D) in people that are at high risk of developing the disease?
- 2. What is the harms evidence associated with the use of teplizumab?
- 3. Are there specific subpopulations that would be more likely to benefit from the use of teplizumab?

## **Conclusions:**

- The efficacy and safety of teplizumab was evaluated in two, phase 2, placebo-controlled trials and one phase 3 trial.<sup>1-3</sup>
- There is moderate quality of evidence that teplizumab delays the progression to T1D in people with stage 2 T1D at high risk of developing T1D (e.g., relative with diabetes, immunogenic markers and abnormal glucose tolerance) for approximately two years.<sup>1</sup>
- One phase 2 trial demonstrated preservation of c-peptide levels, which are indicative of endogenous insulin production, in those receiving teplizumab after 2 years of treatment compared to no treatment, based on low quality of evidence.<sup>2</sup>
- There is low quality evidence from a single phase 3 trial that teplizumab does not reduce insulin needs in people recently diagnosed with T1D.<sup>3</sup>

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- The most common adverse reactions associated with the use of teplizumab are rash, lymphopenia, leukopenia, headache and cytokine release syndrome (CRS).<sup>4</sup>
- There is insufficient long-term evidence for the use of teplizumab. Results are most applicable to those people that are White and under the age of 18 years of age who are at high risk of developing diabetes.

#### **Recommendations:**

• Implement prior authorization criteria to limit use to people with stage 2 T1D and high risk of progression to stage 3 T1D (Appendix 2).

## Background:

Diabetes is characterized by a hemoglobin A1c (HbA1c) of 6.5% or higher and associated with symptoms such as polydipsia, polyuria, weight loss, fatigue, and diabetic ketoacidosis (DKA).<sup>5</sup> People with diabetes have an increased risk of morbidity and mortality, and diabetes is the seventh leading cause of death in the United States (US).<sup>6</sup> There are two types of diabetes; T1D and type 2 diabetes. Type 1 diabetes is autoimmune mediated beta-cell destruction resulting in loss of insulin production while type 2 diabetes (T2D) is a non-autoimmune loss of beta-cell insulin secretion, often coinciding with insulin resistance and metabolic syndrome.<sup>5</sup> Type 2 diabetes more commonly occurs in adulthood and T1D often presents in childhood or adolescents. People with T1D often present with polydipsia, polyuria, weight loss and lower body mass index (BMI). Up to half of those with T1D are diagnosed after an episode of diabetic ketoacidosis (DKA).<sup>5</sup> People with T2D are often above their optimal BMI, are diagnosed at an older age and don't often present with DKA.

Type 1 diabetes accounts for approximately 10% of the diabetes diagnoses, with an estimated occurrence of 64,000 new cases annually in the US.<sup>7</sup> In some people with genetic predisposition to T1D, progression through stages of asymptomatic loss of insulin production occurs before overt hyperglycemia. Stages are defined based on different clinical and laboratory parameters (**Table 1**).<sup>5</sup> Development of autoantibodies occurs in Stage 1. Stage 2 is characterized by impaired metabolic response to glucose but normal levels of glycosylated hemoglobin; supplemental insulin is not required. In stage 3 T1D, people develop hyperglycemia with clinical symptoms leading to the need for life-long exogenous insulin.<sup>8</sup> People with characteristics of stage 2 disease, immunologic markers of T1D and abnormal glucose tolerance, are at high risk for progression to stage 3 and development of hyperglycemia symptoms over time. Development of stage 3 T1D to be 25% at 6 months, 60% at 2 years and 75% at 4 years in those individuals with dysglycemia and stage 2 T1D.<sup>8</sup> The lifetime risk for developing T1D is near 100% in high-risk individuals.<sup>8</sup> Caucasians have a higher prevalence of T1D with children, teens and young adults most commonly diagnosed. The most common ages of diagnosis is between 4 and 7 years of age. Family history is the most common risk factor.

	Stage 1	Stage 2	Stage 3
Characteristics	<ul> <li>Autoimmunity</li> </ul>	<ul> <li>Autoimmunity</li> </ul>	<ul> <li>Automimmunity</li> </ul>
	<ul> <li>Normoglycemia</li> </ul>	<ul> <li>Dysglycemia</li> </ul>	<ul> <li>Overt hyperglycemia</li> </ul>
	<ul> <li>Presymptomatic</li> </ul>	<ul> <li>Presymptomatic</li> </ul>	<ul> <li>Symptomatic</li> </ul>
Diagnostic Criteria	<ul> <li>Multiple islet cell autoantibodies</li> </ul>	<ul> <li>Islet cell autoantibodies (usually multiple)</li> </ul>	<ul> <li>Autoantibodies may become absent</li> </ul>
	<ul> <li>No IGT or IFG</li> </ul>	<ul> <li>Dysglycemia: IFG and/or IGT</li> <li>FPG 100-125 mg/dL</li> </ul>	<ul> <li>Diabetes by standard criteria</li> </ul>

## Table 1. Type 1 Diabetes Staging<sup>5</sup>

	<ul> <li>2-h PG 140-199 mg/dL</li> <li>HbA1c 5.7-6.4% or ≥10% increase in HbA1c</li> </ul>
Abbreviations: FPG = fasting plasma glucose: IFG = impaired fasting	$p_{r}$ glucose: IGT = impaired glucose tolerance: 2-h PG = 2 hour plasma glucose

Individuals that have the persistent presence of two or more islet autoantibodies are almost 100% likely to develop diabetes.<sup>5</sup> Determinants of progression include; age of first detection of autoantibody, number of autoantibodies, autoantibody specificity and autoantibody titers.<sup>5</sup> Several autoantibodies have been linked to the development of T1D. Exogenous insulin administration causes all individuals to develop insulin autoantibodies and should not be used to determine the presence of immune mediated diabetes. Glutamic acid decarboxylase (GAD) antibodies have been identified in approximately 70% of those with T1D.<sup>9</sup> Insulinoma-associated protein 2 (IA-2) is also commonly found in individuals with T1D and usually appears later than GAD or other autoantibodies to insulin. Zinc transporter (ZnT8) has been identified as a autoantigen in 60-80% of those with T1D, which appears later and is lost soon after the onset of T1D.<sup>9</sup> Islet cell antibodies (ICA) are present with insulin producing pancreatic beta cells are injured and are used to estimate the risk of T1D. Microinsulin autoantibodies (mIAA) are least commonly associated with other antibodies and rarely is indicative of the development of diabetes if it is the only antibody present.<sup>10</sup>

There are several immunologic treatment options in development to prevent the progression to T1D by preserving beta-cell function.<sup>1</sup> Chronic immunosuppressive therapies, such as cyclosporin, have been studied as an option for delaying the loss of insulin secretion. Fc receptor non-binding anti-CD3 monoclonal antibodies, like teplizumab and otelixizumab (in development), target CD8+ lymphocytes that contribute to the destruction of beta-cells and have demonstrated the most promise.<sup>1</sup>

There is insufficient data on the most optimal outcome to measure the effectiveness of immunotherapy in people with T1D. The measurement of C-peptide is used in some studies to predict insulin levels and the progression to T1D.<sup>11</sup> C-peptide levels are an indication of endogenous insulin production. C-peptide is not metabolized by the liver, and therefore, is a better determinant of insulin production than glucose levels. Low levels of C-peptide are indicative of no or low insulin production by the pancreas and need for exogenous insulin. Important short-term outcomes of progression to T1D include risk of hyperglycemia and DKA and longer term outcomes are retinopathy, kidney disease, and cardiovascular disease.<sup>12</sup> Studies have shown that those who are diagnosed with T1D at an older age have higher C-peptide levels and lower risk of morbidity associated with clinical T1D.<sup>11, 13</sup>

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

## **Clinical Efficacy:**

Teplizumab was approved by the FDA in November of 2022.<sup>4</sup> Teplizumab is a CD-3 directed antibody indicated for use in adults and pediatric patients 8 years of age and older with Stage 2 T1D to delay the onset of Stage 3 T1D. Teplizumab should be used in people that have a confirmed diagnosis of Stage 2 T1D by documentation of at least two positive pancreatic islet autoantibodies (e.g., GAD autoantibodies, IAA, IA-2, ZnT8 and ICA) in those who have dysglycemia without overt hyperglycemia when using an oral glucose tolerance test (OGTT) or alternative method if OGTT is not available.<sup>4</sup> Teplizumab should not be used for T2D or gestational diabetes and patient clinical history should be reviewed prior to initiation to ensure the patient has not already developed clinical symptoms of diabetes indicative of stage 3 diabetes. Teplizumab is given as a one-time treatment course of an intravenous (IV) infusion over at least 30 minutes, once daily for 14 days. A complete blood count and liver enzyme tests should be performed prior to starting teplizumab. Teplizumab has been associated with Author: Sentena

cytokine release syndrome (CRS), and premedication before each teplizumab infusion, for the first five doses, is recommended. Pre-medications include oral nonsteroidal anti-inflammatory (NSAIDs) or acetaminophen, an antihistamine and and/or an antiemetic.

Teplizumab was evaluated in one good quality phase 2 trial, one poor quality phase 2 trial (AbATE) and one fair quality phase 3 trial (PROTÉGÉ) (**Table 5**).<sup>1-3</sup> Only one of these trials provided evidence for the approved indication of delaying the onset of Stage 3 T1D in those with stage 2 T1D.<sup>1</sup> Participants in this phase 2 trial were identified through the TrialNet Natural History Study. This study offers risk screening for relatives of people with T1D as well as clinical studies that test ways to slow down and prevent disease progression. Eligible participants had to be at high risk of developing diabetes, which was defined as people who have relatives with T1D and confirmed presence of autoantibodies (**Table 2**). Participants were also required to have a degree of dysglycemia on an OGTT (defined as a fasting glucose level of 110 to 125 mg per deciliter [6.1 to 6.9 mmol per liter], a 2-hour postprandial plasma glucose level of at least 140 mg per deciliter [7.8 mmol per liter] and less than 200 mg per deciliter [11.1 mmol per liter], or a postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter to nave a course of treatment over 14 days.<sup>1</sup> Dosing of teplizumab was the following in the phase 2 trials: 51 mcg/m<sup>2</sup> on day zero, 103 mcg/m<sup>2</sup> mcg on day one, 207 mcg/m<sup>2</sup> mcg area on day two, 413 mcg/m<sup>2</sup> on day three, 826 mcg/m<sup>2</sup> area on days four through 13. This regimen is comprised of slightly lower doses throughout taper and final dose compared to teplizumab labeling which recommends titration up to the highest dose of 1,030 mcg/m<sup>2</sup> for days 5 through 14.<sup>1</sup> Pre-medications were given to both the treatment and placebo group.

Participants in the Herold trial were followed for 745 days.<sup>1</sup> The median time to progression to T1D was longer in people treated with teplizumab compared to placebo, 48.4 months versus 24.4 months (hazard ratio [HR] 0.41; 95% CI, 0.22 to 0.78; p-value = 0.006).<sup>1</sup> The percentage of people that progressed to T1D was lower in people randomized to teplizumab compared to placebo, 43% versus 72%.<sup>1</sup> The progression to diabetes was highest in the first year after treatment compared to the second or third year following treatment. Diagnosis of T1D occurred in 7% of people taking teplizumab compared to 44% in the placebo group in the first year.<sup>1</sup> The FDA determined that the delay in the development of T1D by two years is clinically meaningful due to the benefits in quality of life, and a reduction in risk of complications.<sup>8</sup> Those diagnosed at an earlier age are more likely to develop diabetic ketoacidosis and DKA.

Autoantibodies	Teplizumab	Placebo					
Phase 2 Study <sup>1</sup>							
GAD65	40 (91%)	28 (88%)					
Micro insulin (mIAA)	20 (45%)	11 (34%)					
IA-2	27 (61%)	24 (75%)					
ICA	29 (66%)	28 (88%)					
ZnT8	32 (73%)	24 (75%)					
	Phase 2 Study (AbATE) <sup>14</sup>						
GAD-65	40 (76.5%)	24 (95.7%)					
IA-2	51 (98.0%)	24 (95.7%)					
Micro insulin (mIAA)	37 (70.6%)	18 (73.9%)					
ZnT8	45 (86.3%)	16 (65.2%)					
Phase 3 Study (PROTÉGÉ) <sup>3</sup>							

Table 2. Autoantibodies Present at Baseline in Participants in the Teplizumab Studies

GAD-65	375 (89%)	89 (91%)		
Human insulin	370 (88%)	88 (90%)		
Islet cell 512	231 (56%)	53 (54%)		
Abbreviations: GAD65 = glutamic acid decarboxylase 65: IA-2 = insulinoma-associated antigen 2 antibody: ICA = islet cell autoantibody: ZnT8 = zinc transporter 8				

In the second phase 2 trial (AbATE), participants were newly diagnosed with T1D (stage 3) and had positive autoantibodies.<sup>2</sup> The mean age of participants was 12 years and 59% were White.<sup>2</sup> Patients were followed for 2 years.<sup>2</sup> This open-label, phase 2 study evaluated the effect of teplizumab on C-peptide levels.<sup>2</sup> At 2 years, people receiving teplizumab had less reduction in C-peptide levels compared to no treatment, -0.28 mmol/L versus -0.46 mmol/L ; p=0.002), which suggests preservation of beta-cell function. However, there were no significant differences in HbA1c levels between the groups.<sup>2</sup>

In the phase 3 trial (PROTÉGÉ) eligible participants were diagnosed with T1D within the previous 12 weeks or less, were a mean age of 7 years and had a mean HbA1c of 8.25%.<sup>3</sup> Total insulin mean insulin dose was 0.65 U/kg per day at baseline.<sup>3</sup> During the study the investigators were advised to titrate insulin to an HbA1c of 6.5% or lower and an insulin dose of at least 0.25 U/kg per day. The dose of teplizumab was: teplizumab 14-day full dose (total dose of 9,034 mcg/m<sup>2</sup> over 14 days; repeated at week 26), teplizumab 14-day low dose (total dose of 2,985 mcg/m2 over 14 days; repeated at week 26), teplizumab 6-day full dose (total dose of 2,426 mcg/m2 over 6 days, followed by 8 days of placebo; repeated at week 26).<sup>3</sup> The composite outcome of the percentage of participants with insulin use of less than 0.5 units/kg per day and HbA1c less than 6.5% at one year.<sup>3</sup> Results were reported at one year as prespecified by the study protocol; however, the study duration was two years.<sup>3</sup> The results for the primary composite outcome were not significantly different between the teplizumab groups compared to placebo. The composite of patients with insulin use of less than 0.5% at 1 year, after 14 days of therapy, was 19.8% (n=41) for teplizumab full dose, 13.7% (n=14) for teplizumab low dose, 20.8% (n=22) for teplizumab 6-day full dose, and 20.4% (n=20) for placebo. Secondary outcome results were considered exploratory because the primary composite outcome did not reach statistical significance.

Limitations to the studies are the small sample sizes, use in predominately White populations, and strict inclusion criteria. There is consistent evidence from two studies that teplizumab does not improve outcomes in participants that have been recently diagnosed with T1D. A phase 3 study for the treatment of early-onset T1D is underway (PROTECT, NCT03875729) and may inform additional indications for teplizumab. There is insufficient evidence for a second course of teplizumab; however this is being evaluated in ongoing studies.

## **Clinical Safety:**

Common adverse reactions experienced with teplizumab are presented in **Table 3**.<sup>4</sup> Teplizumab is associated with CRS which occurred in 2% of participants in trials compared to 0.0% of placebo treated participants.<sup>4</sup> Teplizumab should be discontinued in those people who have liver enzyme elevations 5 times of upper limit of normal. If severe CRS occurs, pausing dosing should be considered. Teplizumab should not be used in people with serious or chronic infection and teplizumab should be discontinued if a serious infection occurs. Serious infections (e.g. cellulitis, gastroenteritis, pneumonia, and wound infection) occurred in 9% in people taking teplizumab versus 0% in people taking placebo, during treatment and through 28 days after the last dose of study drug was given.<sup>4</sup> Lymphopenia has been associated with teplizumab use and should be discontinued in severe lymphopenia (<500 cells/µL) that persists for 1 week or longer. The average largest reductions in lymphocyte counts occurred at 5 days with return to baseline levels at week 6. Anemia has been associated with teplizumab compared to placebo, occurring in 27% and 23% of patients, respectively. Thrombocytopenia occurred in 13% of teplizumab treated patients and in 5% of those taking placebo.<sup>4</sup> Rash was a common, though generally not serious, adverse reaction and often would spontaneously resolve. Age-appropriate vaccines should be given to all people taking teplizumab before initiation of therapy. Teplizumab may cause fetal harm and patients should be advised to take appropriate precautions up to 30 days before becoming pregnant and during pregnancy.

#### Author: Sentena

Results from an open-label extension study of Protégé are available. However, the FDA determined that limited conclusions could be drawn from this data due to dramatic differences in follow up between teplizumab and placebo groups with a 1.4-fold longer median follow-up time in the teplizumab group.

 Table 3. Teplizumab Adverse Reactions in Adult and Pediatric Patients Occurring in 5% or more of Patients.<sup>4</sup>

Adverse Reaction	Placebo (n=32)	Teplizumab (n=44)
Lymphopenia	6%	73%
Rash	0%	36%
Leukopenia	0%	21%
Headache	6%	11%
Neutropenia	3%	5%
Increased alanine aminotransferase	3%	5%
Nausea	3%	5%
Diarrhea	0%	5%
Nasopharyngitis	0%	5%

## **Comparative Endpoints:**

- Clinically Meaningful Endpoints:
- 1) T1D diagnosis
- 2) Time to T1D diagnosis
- 3) HbA1c
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

## Primary Study Endpoint:

- 1) Median time to progression to clinical T1D
- 2) C-peptide levels
- 3) Composite outcome of daily insulin use and HbA1C levels below specified thresholds

## Table 4. Pharmacology and Pharmacokinetic Properties.<sup>4</sup>

Parameter	
Mechanism of Action	Binds to CD3 (a cell surface antigen on T-lymphocytes). Partial agonistic signaling and deactivation of pancreatic deactivation beta cell autoreactive T lymphocytes. Teplizumab increases the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.
Oral Bioavailability	NA
Distribution and Protein Binding	2.27 L
Elimination	Not described
Half-Life	4.5 days
Metabolism	Catabolic pathways into small peptides

Abbreviations: L – Liter; NA – not applicable

		Detient Deputation		Effice of Endersists		Cofety Outcome		
Ret./	Drug Regimens/	Patient Population	N	Efficacy Endpoints	AKK/	Safety Outcomes	ARR/	RISK OT BIAS/
Study Design			177		ININI		ININH	
1. Herold, et	1. Teplizumab 51	Demographics:	<u>    </u> :	Median time to progression		Dermatologic or skin	NA	RISK OT BIAS (IOW/ Nign/ unclear):
alt	mcg per square	Median age: 13.5 years	1.44	to clinical 11D based on		(rasn):	for	Selection Blas: (IOW) Randomized 1:1 and stratified
	meter of body	Male: 55%	2.32	<u>OGII</u> :		1. 16 (36%)	all	by those less than 18 years and those 18 and over.
DB, Phase 2,	surface area on day	Median HbA1c: 5.3%		1. 48.4 months		2.1(3%)		Randomization numbers and tables were done by
PC, RCT	zero, 103 mcg/m <sup>2</sup>	Median glucose: 160	<u>PP</u> :	2. 24.4 months				the trial coordinating center. All participants in the
	on day one, 207	mg/dL <sup>2</sup>	1.41	HR 0.41 (95% Cl, 0.22 to	NA	Blood or bone		teplizumab group were White compared to 93.8%
	mcg/m <sup>2</sup> on day two,	Sibling with T1D: 57%	2.28	0.78)		marrow		in the placebo group. There were 15% more
	413 mcg/m <sup>2</sup> on day	White: 97%		p-value = 0.006		<u>(lymphopenia)</u> :		participants in the placebo group that were under
	three, 826 mcg/m <sup>2</sup>		Attrition:			1. 33 (75%)		the age of 18 years.
	on days four	Key Inclusion Criteria:	1. 3 (7%)	Secondary Endpoint:		2. 2 (6%)		Performance Bias: (low) Double-masked.
	through 13. Doses	- Non-diabetic relatives	2.4	T1D Diagnosis at year 1:				Differences in adverse event rates could lead to
	given as an IV	of people with T1D	(12%)	1. 3 (7%)		Infection:		unblinding.
	infusion	- Ages 8 years to 45		2. 14 (44%)		1. 5 (11%)		Detection Bias: (low) Efficacy and safety analysis
		years		HR 0.13 (95% Cl, 0.05 to	37%/	2.3 (9%)		was done by an independent medical monitor.
	2. Saline IV infusion	- At high risk for		0.34)	3			Attrition Bias: (low) Attrition rates were low in
		development of		P-value not provided		Pain:		both groups. Results were measured via ITT
		diabetes				1.5 (11%)		analysis and missing data will be assumed to be
	Median follow-up:	- Two or more diabetes				2.3 (9%)		missing completely at random (MCAR) and no
	745 days (2 years)	related autoantibodies						method will be used to impute missing data.
	, , , , ,	detected in two				Cytokine Release		Reporting Bias: (high) Due to slower than expected
		samples obtained				Syndrome:		enrollment, the protocol was changed to detect a
		within 6 months before				1, 1 (2%)		60% lower risk of T1D in the teplizumab compared
		randomization				2, 0 (0%)		to placebo (instead of 50%) resulting in enrollment
		- Evidence of				2.0 (0/0)		of 71 participants compared to 144
		dysglycemia* during an				Discontinuations due		Other Bias: (high) Funded by industry
						to adverse events:		Other blas. (high) runded by modstry.
		oan				1 - 2 (7%)		Applicability
		Kow Evolution Critoria				1.3(7%)		Applicability:
		<u>Rev Exclusion Criteria</u> :				2.4 (13%)		<u>Patient</u> : Results are most applicable to young
		- Clinically important						adolescents that are white. The majority of
		medical histories				p-value not reported		patients were less than 18 years of age in the
		- Abnormal laboratory				for all		teplizumab and placebo groups, 66% and 81%,
		chemical values						respectively which is consistent with age of onset
		- Abnormal blood						for T1D.
		counts						Intervention: Teplizumab dose was appropriate
								based on previous studies.
		(n=76)						Comparator: Placebo comparison appropriate
								since there are no other therapies approved for
								delaying T1D.
								Outcomes: Time to development of T1D is an
								appropriate outcome for a therapy used for this
								purpose.
								Setting: Thirty one sites in the United States.
								Canada, Australia and Germany.

### Table 5. Comparative Evidence Table.

2. Herold, et	1. Teplizumab*: 51	Demographics:	mITT:	C-peptide levels at year 2:	NA	Dermatologic or skin	NA	Risk of Bias (low/high/unclear):
al <sup>2</sup>	mcg/m <sup>2</sup> on dav	Median age: 12 years	1.56	10.28 mmol/L (95% Cl	for all	(rash):	for	Selection Bias: (low) Randomized 2:1 within
	zero, 103 mcg/m <sup>2</sup>	Male: 59%	2.27	0.36 to -0.20)		1. 43 (83%)	all	randomly ordered blocks of six or three. More
AbATE	on day two. 206	Time since diagnosis:		20.46 mmol/L (95% Cl		2. 2 (8%)		people in the placebo group compared to
	mcg/m <sup>2</sup> on day	39 davs		0.57 to -0.35)				teplizumab were male, 64% vs. 53.8%.
Phase 2, OL,	three, 413 mcg/m <sup>2</sup>	Median HbA1c: 7.6%	PP:	HR not provided		Blood or bone		Performance Bias: (high) Trial was open-label.
RCT	on day four. 826	C-peptide AUC: 0.695	1.52	P=0.002		marrow		Laboratory personnel were masked to treatment
-	$mcg/m^2$ on days five	mmol/L	2.25			(lymphopenia):		assignments.
	thru 14. Doses given	- /	_	Secondary Endpoints:		1.1(2%)		Detection Bias: (unclear) Not described.
	as an IV infusion at	Key Inclusion Criteria:	Attrition:	HbA1C levels at year 2:		2.0(0%)		Attrition Bias: (low) Attrition rates were low in
	diagnosis and after	- Ages 8 years to 30	1.4(7%)	1. 7.5%				both groups. Results were measured via ITT
	1 year.	years	2.2(7%)	2. 7.7%		Upper respiratory		analysis and missing data for the primary endpoint
		- Diagnosed with T1D		(no CI provided)		tract infection:		was imputed as zero if previous value was zero and
	2. No infusion	within 8 weeks of study		P=0.093		1. 32 (62%)		if the value was more than zero then values among
	given/no treatment	enrollment				2. 14 (56%)		those in the same arm were regressed on AUC
		- Positive for anti-						values from the prior time point.
		GAD65, anti-ICA512 or				Abdominal Pain:		Reporting Bias: (high) Study was conducted per
	* Ibuprofen,	ICA.				1. 23 (44%)		protocol.
	diphenhydramine					2.6 (24%)		Other Bias: (high) Funded by industry.
	and acetaminophen	Key Exclusion Criteria:						
	premedication	- Not described				Cytokine Release		Applicability:
	given for infusion-					Syndrome:		Patient: Results applicable to patients with early
	related reactions					1.5 (10%)		stage 3 T1D.
						2.0(0%)		Intervention: Teplizumab dose was appropriate
								based on previous studies.
						Discontinuations due		Comparator: No comparator given. Lack of
						to Adverse Events:		comparator may bias results.
						1. 12 (21%)		Outcomes: C-peptide levels are an appropriate
						2.0(0%)		indicator of insulin production; however levels
								indicative of time to disease progression are
						p-value not reported		unknown.
						for all		Setting: Six study sites in North America.
			1					

2. Sterry, et al.     1. Leptumb 24- all wind Loss (Lev Machinger, Sam MA     NA     Reak of Bas (low Might/under): additional using additional using									
ali     day tui tose (total week 26     Mate : 63, 25, %     1.00 (state of 1, 0, 24) (state of 1, 0, 24) (state of 1, 0, 24)     Intry (sh) (state of 1, 0, 24) (state of 1, 0, 24)     Intry (sh) (state of 1, 0, 24)     Intry (sh) (state of 1, 0, 24)     Intry (sh) (state of 1, 0, 24)       PROTEGE (sh, MC, Phase 3, PC, RCT     Croit (sh)	3. Sherry, et	1. Teplizumab 14-	Demographics:	<u>ITT</u> :	Composite of percentage of	NA	Dermatologic or skin	NA	Risk of Bias (low/high/unclear):
PROTCÓC     PROTCÓC     Mean HALC: 5.25%     2.102     Hest stanto 5.20/Egner day and the 5.35%     21:11 12 y an interactive telephone system and the 5.25%       D6, MC, PADE 3P, CC, RCT     C. 2. Feplicumb 1- MALC: 5.25%     4.98     4.1 (19.98%)     2.55 (53%)     3.55 (53%)       D6, MC, RCT     C. 2. Teplicumb 1- MALC: 5.25%     2.79     3.2 (20.3%)     5.25 (53%)     3.55 (53%)       D6, MC, RCT     - Age 18 to 53 y ears mag/m 2 over 14 day low doe (total day low doe (total day low oet (total week 26     - Age 18 to 53 y ears mag/m 2 over 14 day low doe (total day low oet (total day low oet (total week 26     2.79     3.2 (20.3%)     1.12 (6%)     1.2 (6%)       110 and requirement week 26     - Age 18 to 52 y ears mag/m 2 over 14 day, Ropetad 2, expendic day low oet (total stimulate C. expendic day low set (bit day day low day low dat low day day low dat low set (bit day day low dat low dat low day dat low day low dat low dat low day dat low dat low low set (bit day dat low dat low dat low day dat low dat low dat low dat low dat low dat low dat dat low dat low dat low dat low dat dat low dat low dat low dat low dat low dat low dat dat low dat low dat low dat low dat dat low dat low dat low dat low dat low dat dat low dat low dat low dat low dat low dat low dat low dat low dat low dat low dat low	al <sup>3</sup>	day full dose (total	Mean age: 19 years	1. 207	patients with insulin use of	for all	(rash):	for	Selection Bias: (low) Patients were randomized
PROTEGE     mcg/m1 over 14 day Repeted at week 26     Multe: 71.5%     3.106     and HbALc of less than 5.5% at 1 year:     3.56 (5%)     according to a computer generated block base of year base of the participation. Baseline 5.5%       D6, MC, Phase 3, PC, RCT     2. Teplizumab 14     -Age 18 to 35 years     1.162     2.14 (13.7%)     2.2 (23%)     -Age 18 to 35 years       RCT     -Age 18 to 35 years     1.162     2.14 (13.7%)     -Age 18 to 35 years     3.82     -A 20 (20.4%)     -Age 18 to 35 years       RCT     -Age 18 to 35 years		dose of 9,034	Male: 63.5%	2. 102	less than 0.5 U/kg per day		1. 117 (56%)	all	2:1:1:1 by an interactive telephone system
days) Repeated at wrek 26     Write: 71%     9.98     af 1year:     3.56 (53%)     randomization by third party organization. Baseline characteristics were will matched.       D9, MC;     Phase 3, PC;     2. Teplizumab 14     -Age 18 to 38 years:     PI:     1.41 (19.8%)       RCT     day low doe (total     -Age 18 to 38 years:     2.79     3.22 (20.8%)     1.12 (20.4%)       BCT     day low doe (total     -Age 18 to 38 years:     2.79     3.22 (20.4%)     1.12 (20%)       day low doe (total     -10 day maxs 236 kg     2.79     3.22 (20.4%)     1.12 (20%)     1.12 (20%)       day low doe (total     TD and requirement     Scondary Endpoints:     2.2 (2%)     1.22 (20.4%)     1.22 (2%)       day low doe (total     TD and requirement     scondary Endpoints:     2.0 (0%)     1.22 (2%)     Detection Biss: (low) Patients in treatment groups. More patients in treatment groups.	PROTÉGÉ	mcg/m <sup>2</sup> over 14	Mean HbA1c: 8.25%	3. 106	and HbA1c of less than 6.5%		2. 58 (57%)		according to a computer-generated block
De, MC, Phase 3, PC, BCT     Ceptinumb 14- or you work of the second and the second a		days) Repeated at	White: 71%	4. 98	<u>at 1 year</u> :		3. 56 (53%)		randomization by third party organization. Baseline
DB, MC, RCT     C replicability: - Age 18 k0 35 years day low dose (total day) wo dose (total day) wo dose (total day) wo dose (total day) wo dose (total day) key each of trait days lexe each of day any key each of trait days lexe each of days lexe each of trait days lexe each of trait may any lexe each day each of trait days lexe each of		week 26					4. 21 (21%)		characteristics were well matched.
Phase 3, PC, C, Teplizumb 14-     -Age 18 to 35 years     1. 162     2.14 (13.7%)     Cytokine Release       RCT     day low dose (12,985     -512 weeks of diamont of equirement week 26     -3.82     4. 20 (20.4%)     -1.12 (6%)       1. Table 2000     -1.10 and requirement for exogenous insulin diagonity: tage 31     -4.70 (20.4%)     -1.12 (6%)     -1.12 (6%)       1. Table 2000     -1.10 and requirement for exogenous insulin diagonity: tage 31     -4.70 (20.4%)     -1.12 (6%)     -1.12 (6%)       1. Table 2000     -0 bettetable faiting or 2.426 mcg/m courses insulin diagonity: tage 31     -4.70 (20.4%)     -1.12 (6%)     -1.12 (6%)       1. Table 2000     -0 bettetable faiting or 2.426 mcg/m courses insulin diagonity: exogenous insulin diagonity: exogenous insulin diagonity exoses perspecified in the protocol     2.28     -2.73     -2.73     -2.73       1. 162     1.11 (11)     -1.121 (11)     -1.131 (17%)     -2.73     <	DB, MC,		Key Inclusion Criteria:	<u>PP</u> :	1. 41 (19.8%)				Performance Bias: (low) Medication were made
FCT     day low does (total lose of 2,987 mcg/m2 over 14 dys) Repeated requirement week 26     6 body mass 256 kg - 521 weeks of 110 and requirement week 26     2.92 (2.02,04%)     3.22 (2.03%) Cl and p-values not provided 3.8 (2.02,04%)     5 <u>syndrome;</u> 1.12 (6%)     double blind.       3. Teplizmab 6-day full dose (total dose of 2,425 mcg/m2     - Detectable fasting or 1.45 condary. Endopints: simulated C-peptide over 6 days, of placebol insulin 22 weeks of of placebol insulin 42 monthersing that conditions were considered exploratory because primary outcome was not significant, a prespecified in the protocol     Significant, a prespecified in the protocol     Significant, a prespecified in the protocol     Blood or bone marcoaw intersing bas: (too) Study conducted according to protocol     Blood or bone marcoaw intersing bas: (too) Study conducted according to protocol       4. Placebo     - Comorbid disorders that could affect trial outcomes or safety outcomes or safety in a clinical trial in a clinical trial or troratic protocol     - 1.131 (87%) 2.5 (52%)     - Diffect Blas: (too) Study conducted according to protocol.       7 Trial duration: 2 years     N=516     - Sing N- in A conducted incal vision dia conducted incal vision dincal conducted incal centers in North A conducted incal vi	Phase 3, PC,	2. Teplizumab 14-	- Age 18 to 35 years	1. 162	2. 14 (13.7%)		Cytokine Release		using a double-dummy design and dosing was
dose of 2,985     -512 weeks of mag/m2 over 14 days) Repeated at week 26     -512 weeks of mag/m2 over 120 over 6 days, followed by 8 days of 74,26 mg/m2     -512 weeks of mag/m2 over 6 or 74,26 mg/m2     4.87 over 6 days, followed by 8 days of placebol of placebol rotiol disorders: that could affect trial outcome so rasity     4.87 over 6 days, followed by 8 days of placebol rotiol disorders: that could affect trial outcome so rasity     1.42 (6%) (1.46 p-alues not provided and p-alues not provided and p-alues not provided and p-alues not provided exploratory because primary spreachfield in the protech     1.12 (6%) (1.26%)     Detection Bias; (low) Data analysis was done by an interiment groups. Normalitte. Attrition Bias; (low) Data analysis was done by an insting data compared to placebo. Participants with missing data compared to placebo. Participants with missing data compared to placebo. Participants with missing data were full was functioned by industry.       4. Placebo     -for the participants outcome sor asity were managed with exogenous insuli disorders or asity were managed with exogenous insuli disorders or asity years     5.112 - 112 (13%)     1.11 (13%)       * All participants were managed with exogenous insuli uses or asity years     - Nestore - State relaticipation - Repearing Bias; (low) Study conducted according to provide disorders; - Attrition Bias; (low) Study conducted according to protocol.     - Attrition Bias; (low) Study conducted according to placebo.       * All participants were managed with exogenous insuli uses or asity years     - Nestore - Study and the participants - Repearing Bias; (low) Study conducted according to provide to vaccination - Repearing Bias; (low) Study conducted according to provide to vaccination - Repearing Bias; (low) Study conducted according to pr	RCT	day low dose (total	- Body mass <u>&gt;</u> 36 kg	2. 79	3. 22 (20.8%)		Syndrome:		double blind.
Image: mage: m		dose of 2,985	- <u>&lt;</u> 12 weeks of	3. 82	4. 20 (20.4%)		1. 12 (6%)		Detection Bias: (low) Data analysis was done by an
days) Repeated at week 26     T10 and requirement (stage 3)     Attrition: (stage 3)     Secondary Endpoints: Endpoints were considered (22%)     3.8 (8%)     Attrition Bias; (unclear) Attrition was high in all teplizumab treatment groups had missing data compared to placeb. Participants with assing data compared to participants with assing data compared to placeb. Participants with missing data compared to placeb. Participants with assing data compared to placeb. Participants with assing data were designated as non-responders.           4. Placebo         S12/A-2, GAD 65 or startig insult network to participants were managed with exagenous inorid disorders that could affect trial outcomes or safety years         4. 11 (13%)         4. 51 (52%)         Applicability: Participants were managed with exagenous inorid disorders that could affect trial outcomes or safety years         5.56 (52%)         5.56 (52%)         5.56 (52%)         5.56 (52%)           Trial duration : years         N=516         N=516         N=516         N=516         N=516         N=516         N=516         Discontinuations due to adverse events: 1. 11 (5%)         Discontinuations due to adverse events: 2. 1 (1%)		mcg/m2 over 14	diagnosis for clinical	4. 87	CI and p-values not provided		2. 2 (2%)		independent data monitoring committee.
week 25     for exceptions insulin (stage 3)     for exceptions insulin (stage 3)     Secondary Endpoints: Endpoints were considered (22)     2.0 (0%)     teplizumab treatment groups. More patients in treatment groups. More patients in pacebo. Participants with missing data owner designated as non-responders.       0 4,245 mcg/m2     - Positive for antibiody 2,245 mcg/m2     - Positive for antibiody 2,236     2.23 a prespectified in the protocol     Biod or bone marrow.     Biod or bone marrow.     Reporting Bias; (low) Study conducted according to protocol       1 181 (87%)     - Positive for antibiody out on was not significant, insulin 5,2 weeks of starting insulin therapy 2, comorbid disorders that could affect trial out comes or safety for T1D     - Reporting Bias; (low) Study conducted according to protocol     - Reporting Bias; (low) Study conducted according to protocol       + All participants     - Comorbid disorders that could affect trial out comes or safety sever manage with exceent participation for T1D     - Recent participation - Recent vaccination - Pregnancy     - Reporting Bias; (low) Study conducted active weint accound affect trial out comes or safety - Recent vaccination for T1D     - Recent participation - Recent vaccination - Recent		days) Repeated at	T1D and requirement				3. 8 (8%)		Attrition Bias: (unclear) Attrition was high in all
Image: Stage 3)Attrition: exploratory bed missing data compared to exploratory bed missing data compared to placebo. Participants with marrowBiod or bone marrowBiod or bone marrowHereatment groups had missing data compared to placebo. Participants with missing data compared to placebo. Participants with marrowBiod or bone marrowBiod or bone marrowHereatment groups had missing data compared to designated as non-responders.0 cl 2426 mcg/n2 of placebo- Positive for antibody starting insulin therapy 262.236- Positive for antibody (2.2%)2.38- Positive for antibody as prespecified in the protocol- Reporting Biss (holy Study conducted according to protocol.0 cl pareboinsulin c2 weeks 61 (2.1%)- 1.145- Positive for antibody (2.2%)- Reporting Biss (holy Study conducted according to protocol.2 cl pareboinsulin c2 weeks 61 (2.1%)- 1.111 (1.1%)- Positive for antibody (2.5%)- Reporting Biss (holy Study conducted according to protocol.4. Placebo- Net exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety years- All participants - Repert participants - Recent varcingation in a clinical trial - Recent varcingation in a clinical trial - Recent varcingation in a clinical trial - Recent varcingation - Recent varcingation in a clinical trial - Recent varcingation - Recent varcingation - Recent varcingation - Recent varcingation - Recent varcingation - Recent varcingation - Recent varcingation <td></td> <td>week 26</td> <td>for exogenous insulin</td> <td></td> <td>Secondary Endpoints:</td> <td></td> <td>2.0 (0%)</td> <td></td> <td>teplizumab treatment groups. More patients in</td>		week 26	for exogenous insulin		Secondary Endpoints:		2.0 (0%)		teplizumab treatment groups. More patients in
3. Teplizumab 6-day, full dose (traited aces of 2,426 mcg/m2     - Detectable fasting or full dose (traited aces of 2,426 mcg/m2     1.45 outcome was not significant, as prespecified in the protocol <u>Blood or bone</u> <u>marrow</u> ( <u>Ivmphopenia</u> ): 1.181 (87%)     placebo. Participants with missing data were designed as non-responders.       A. Placebo     Key Exclusion Criteria: - Comorbid disorders that could affect trial outcome sor safety     3.24 insulin <u>C</u> 28%) (23%)     3.24 insulin <u>C</u> 28%) <u>C</u> 28% <u>C</u> 28%) <u>C</u> 28%) <t< td=""><td></td><td></td><td>(stage 3)</td><td>Attrition:</td><td>Endpoints were considered</td><td></td><td></td><td></td><td>treatment groups had missing data compared to</td></t<>			(stage 3)	Attrition:	Endpoints were considered				treatment groups had missing data compared to
full dose (total dose of 2,226 mositue for antibox over 6 days, of placebol insulin 52 weeks 26extitue (22%) as prespecified in the protocolmarrow as prespecified in the protocolmarrow (immphonenia): protocoldesignated as non-responders. Repeated at week 264. PlaceboKey Exclusion Criteria: - Comorbid disorders in a clinical trial outcomes or safety4.11 (13%)2.88 (86%)3.85 (80%)4.51 (52%)Applicability: Patient: Results are most applicable to young adults who are White with a recent diagnosis of T1D.4. PlaceboKey Exclusion Criteria: - Comorbid disorders in a clinical trial outcomes or safety1.51 (52%)Infection: 0.55 (52%)Applicability: Patient: Results are most applicable to young adults who are White with a recent diagnosis of T1D.7 rid duration: 2 yearsN=516Ferent participation - Recent vaccination -		3. Teplizumab 6-day	- Detectable fasting or	1. 45	exploratory because primary		Blood or bone		placebo. Participants with missing data were
of 2,426 mcg/m2     -Positive for antibody titers against ICA- followed by 8 day of placebol string insulin +2 queeks of 2.6     2.23 (23%) insulin +2, GAD-65 or insulin +2 queeks of 2.6     2.23 (23%) (23%) tatring insulin therapy (11%)     protocol     1.181 (87%) 2.58 (86%)     Beporting Bias: (low) Study conducted according to protocol.       4. Placebo     insulin +2 queeks of comorbid disorders that could affect trial outcomes or safety exogenous insulin for T1D     1.181 (87%) (11%)     2.53 (52%) 2.53 (52%)     Applicability: Patient: Results are most applicable to young adults who are White with a recent diagnosis of 1.94 (45%)       Trial duration: 2 years     - Recent participation in a clinical trial - Secent participation in a clinical trial - Pregnancy     - Recent participation in a clinical trial - Secent participation - Secent participation in a clinical trial - Secent participation in a clinical trial - Secent participation - Secent participation - Secent participation - Secent participation - Secent participation - Secent par		full dose (total dose	stimulated C-peptide	(22%)	outcome was not significant,		marrow		designated as non-responders.
over 6 days, followed by 8 days of placebol 26     titers against (Z- 512/IA-2, GAD-65 or starting insulin <2 veeks of starting insulin therapy 26     2.28 (23%)     1.181 (87%)     protocol.       4. Placebol     starting insulin therapy 26     4.11 (11%)     2.88 (86%)     4.51 (52%)     Patient: escults are most applicable to young adults who are White with a recent diagnosis of 1.94 (45%)       4. Placebol     Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety     7.53 (52%)     Intervention: Teplizumab dose was appropriate 3.55 (52%)       * All participants for T1D     - Recent vaccination - Pregnancy     - Recent vaccination - Pregnancy     - S16       Trial duration: 2 years     N=516     - N=516     - S16       Discontinuations due to adverse events: 1.11(5%)     2.4 (45%)     - 2.4 (45%)       2.1 (13%)     - 2(2%)     - 2.1 (13%)		of 2,426 mcg/m2	- Positive for antibody	2. 23	as prespecified in the		(lymphopenia):		Reporting Bias: (low) Study conducted according to
followed by 8 days of placebol Repeated at week 26     512/A-2, GAD-65 or insulin <2 weeks of starting insulin therapy 4. 11 (11%)     3. 24 (23%) 4. 11 (11%)     2. 88 (86%) 3. 85 (80%) 4. 51 (52%)     Other Bias: (high) Funded by industry.       4. Placebo     Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety - Recent participation in a clinical trial exogenous insulin for T1D     Key Exclusion Criteria: - Comorbid disorders that could affect trial in a clinical trial exogenous insulin for T1D     Infection: 1. 94 (45%) 2. 54 (55%)     Infection: 1. 94 (45%) 2. 54 (55%)       Trial duration: 2 years     - Recent participation in a clinical trial exogenous insulin for T1D     - Recent vaccination - Pregnancy     - Recent vaccination - Recent vaccination - Pregnancy     - Recent vaccination - Recent vaccination     - Recent vaccination - Recent vaccination     - Recent vaccination - Pregnancy     - Recent vaccination - Recent vaccination     - Recent vaccination     - Recent vaccination		over 6 days,	titers against ICA-	(23%)	protocol		1. 181 (87%)		protocol.
of placebo) Repeated at week 26       insulin 22 weeks of starting insulin therapy 26       (23%) 4.11 (1%)       3.85 (80%) 4.51 (52%) <b>Applicability:</b> Patient: Results are most applicable to young adults who are White with a recent diagnosis of T1D.         4. Placebo       Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety       2.53 (52%)       Intervention: Teplizumab dose was appropriate based on previous studies.         * All participants were managed with exogenous insulin for T1D       - Recent participation in a clinical trial - Pregnancy       - Recent vaccination - Pregnancy       - Sistorintestinal disorders: 1.11 (1%)       Discontinuations due to adverse events: 1.11 (5%) 2. 24 (42%)       Discontinuations due to adverse events: 1.11 (5%) 2. 24 (42%)         Vear       N=516       Intervention: - Recent participation - Pregnancy       N=516       Discontinuations due to adverse events: 1.11 (5%) 2. 24 (42%)       Setting: Eighty-three medical centers in North America, Europe, Israel and India.		followed by 8 days	512/IA-2, GAD-65 or	3. 24			2.88 (86%)		Other Bias: (high) Funded by industry.
Repeated at week 26       starting insulin therapy 26       4.11 (11%)       4.51 (52%)       Applicability: Patient: Results are most applicable to young adults who are White with a recent diagnosis of T1D.         4. Placebo       Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety       Infection: 1.94 (45%)       1.94 (45%)       T1D.         * All participants were managed with exogenous insulin for T1D       - Recent participation in a clinical trial - Pregnancy       - Recent participation - Pregnancy       - Recent clinical trial - Pregnancy       - Recent participation in a clinical trial - Pregnancy       - Recent participation - Recent participation - Pregnancy       - Recent participation - Pregnancy       - Recent participation - Recent participation - Pregnancy       - Recent participation - Recent participation - Recent participation - Recent participation - Recent participation - Pregnancy       - Recent participation - Recent participation - Recent participation - Recent participation - Recent participation - Recent participation - Recent pa		of placebo)	insulin <u>&lt;</u> 2 weeks of	(23%)			3. 85 (80%)		
26       (11%)       Infection: - Comorbid disorders that could affect trial outcomes or safety * All participants were managed with exogenous insulin for T1D        Infection: 1.94 (45%) 2.53 (52%)        Intervention: Teplizumab dose was appropriate based on previous studies. 2.54 (55%)          Trial duration: 2 years        Personancy        Present vaccination - Recent participation in a clinical trial - Recent vaccination - Pregnancy        Setting: Eighty-three medical centers in North 4. 26 (26%)          Trial duration: 2 years        N=516        N=516        Intervention: reported for T10,          Discontinuations due to adverse events: 1.11 (5%) 2.1 (1%)        Discontinuations due to adverse events: 1.11 (5%) 2.1 (1%)        Setting: Eighty-three medical centers in North America, Europe, Israel and India.		Repeated at week	starting insulin therapy	4. 11			4. 51 (52%)		Applicability:
4. Placebo       Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety       1.94 (45%)       adults who are White with a recent diagnosis of T1D.         * All participants were managed with exogenous insulin for T1D       - Recent participation in a clinical trial - Recent vaccination for T1D       - Recent participation in a clinical trial - Recent vaccination - Pregnancy       2.54 (55%)       Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D.         Trial duration: 2 years       - Pregnancy       2.31 (30%)       progression.         Setting: Eighty-three medical centers in North A 2.6 (26%)       3.44 (42%)       Setting: Eighty-three medical centers in North A merica, Europe, Israel and India.         Discontinuations due to adverse events: 1.11 (5%)       2.1 (1%)       2.1 (1%)       Prevalue not reported for all		26		(11%)					Patient: Results are most applicable to young
4. Placebo       - Comorbid disorders that could affect trial outcomes or safety       1. 94 (45%)       T1D.         * All participants       - Recent participation in a clinical trial       3. 55 (52%)       Lintervention: Teplizumab dose was appropriate based on previous studies.         • All participants       - Recent participation in a clinical trial       2. 54 (55%)       Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D.         • Pregnancy       - Pregnancy       disorders: 1. 71 (34%)       0utcomes: Composite of insulin use and A1c appropriate to evaluate clinically significant disease progression.         Years       N=516       3. 44 (42%)       Setting: Eighty-three medical centers in North 4. 26 (26%)         Discontinuations due to adverse events:       1. 11 (5%)       2. 4 (4%)         2. 2 (2%)       2. 1 (1%)       p-value not reported for all.			Key Exclusion Criteria:				Infection:		adults who are White with a recent diagnosis of
* All participants were managed with exogenous insulin for T1D       that could affect trial outcomes or safety - Recent participation in a clinical trial - Recent vaccination - Pregnancy       2. 53 (52%)       Intervention: Teplizumab dose was appropriate based on previous studies. 2. 54 (55%)         Trial duration: 2 years       - Recent vaccination - Pregnancy       - Recent vaccination - Recent vaccination       - Recent vaccination - Pregnancy       0utcomes: Composite of insulin use and A1c 1.71 (34%)       0utcomes: Composite of insulin use and A1c 0utcomes: Composite of insulin use and A1c 1.71 (34%)         Years       N=516       3. 44 (42%)       Setting: Eighty-three medical centers in North 4. 26 (26%)         Discontinuations due to adverse events: 1. 11 (5%)       Discontinuations due to adverse events: 1. 11 (5%)       P-value not reported for all		4. Placebo	- Comorbid disorders				1. 94 (45%)		T1D.
* All participants were managed with exogenous insulin for T1D       - Recent participation in a clinical trial - Recent vaccination - Pregnancy       3.55 (52%)       based on previous studies. Comparter: Placebo comparison appropriate since there are no other therapies approved for delaying T1D.         Trial duration: 2 years       - Recent yaccination - Pregnancy       - Recent yaccination - Pregnancy       0utcomes: - Recent vaccination - Pregnancy       0utcomes: Composite of insulin use and A1c appropriate to evaluate clinically significant disease progression         years       N=516       - S16       - S16       - S16         Discontinuations due to adverse events: 1.11 (5%) 2.1 (1%)       - S2(2%) 2.1 (1%)       - Recent yaccination - Pregnancy       - Recent yaccination - Pregnancy			that could affect trial				2. 53 (52%)		Intervention: Teplizumab dose was appropriate
* All participants were managed with exogenous insulin for T1D       - Recent participation in a clinical trial - Recent vaccination - Pregnancy       2. 54 (55%)       Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D.         Tial duration: 2 years       - Pregnancy       - Recent vaccination - Pregnancy       - Recent vaccination - Pregnancy       - Other therapies approved for delaying T1D.         Trial duration: 2 years       years       N=516       - Setting: Eighty-three medical centers in North 4. 26 (26%)       - Setting: Eighty-three medical centers in North 4. 26 (26%)         Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (4%) 3. 2 (2%) 2. 1 (1%)       Discontinuations due to adverse events: 1. 11 (5%) 2. 1 (1%)       - Pregnancy			outcomes or safety				3. 55 (52%)		based on previous studies.
were managed with exogenous insulin for T1D       in a clinical trial - Recent vaccination - Pregnancy       Recent vaccination - Pregnancy       Gastrointestinal disorders: 1. 71 (34%)       Since there are no other therapies approved for delaying T1D.         Trial duration: 2 years       N=516       N=516       3. 44 (42%)       appropriat to evaluate clinically significant disease progression.         Setting: Eighty-three medical centers in North A. 26 (26%)       Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (42%)       Setting: Eighty-three medical centers in North America, Europe, Israel and India.         Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (42%)       3. 2 (2%) 2. 1 (1%)       P-value not reported for all		* All participants	- Recent participation				2. 54 (55%)		Comparator: Placebo comparison appropriate
exogenous insulin for T1D       - Recent vaccination - Pregnancy       - Recent vaccination - Discontinuations due to adverse events: 1. 11 (5%)       - Pregnancy		were managed with	in a clinical trial						since there are no other therapies approved for
for T1D       - Pregnancy       disorders:       Outcomes: Composite of insulin use and A1c         Trial duration: 2       years       N=516       2.31 (30%)       3.44 (42%)       Setting: Eighty-three medical centers in North A. 26 (26%)         Discontinuations due to adverse events:       1.11 (5%)       2.4 (4%)       Setting: Eighty-three medical and India.         Discontinuations due to adverse events:       1.11 (5%)       2.4 (4%)       3.2 (2%)       2.1 (1%)         P-value not reported for all		exogenous insulin	- Recent vaccination				Gastrointestinal		delaying T1D.
Trial duration: 2 years       N=516       1. 71 (34%)       appropriate to evaluate clinically significant disease progression.         Setting: Eighty-three medical centers in North A. 26 (26%)       3. 44 (42%)       Setting: Eighty-three medical centers in North America, Europe, Israel and India.         Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (4%) 3. 2 (2%) 2. 1 (1%)       Discontinue not reported for all		for T1D	- Pregnancy				disorders:		Outcomes: Composite of insulin use and A1c
Trial duration: 2 years       N=516       2. 31 (30%)       3. 44 (42%)       3. 44 (42%)         4. 26 (26%)       4. 26 (26%)       America, Europe, Israel and India.         Discontinuations due to adverse events: 1. 11 (5%)       1. 11 (5%)       2. 4 (4%)         3. 2 (2%)       2. 1 (1%)       p-value not reported for all       p-value not reported			<i>c</i> ,				1. 71 (34%)		appropriate to evaluate clinically significant disease
years       N=516       3. 44 (42%)       Setting: Eighty-three medical centers in North         1       26 (26%)       1       Discontinuations due to adverse events:       America, Europe, Israel and India.         1       1.11 (5%)       2. 4 (4%)       3. 2 (2%)       2. 1 (1%)         1       1.1%)       1.1%)       1.1%		Trial duration: 2					2. 31 (30%)		progression.
4. 26 (26%)       America, Europe, Israel and India.         Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (4%) 3. 2 (2%) 2. 1 (1%)       America, Europe, Israel and India.         p-value not reported for all       p-value not reported for all       Postale not reported		years	N=516				3. 44 (42%)		Setting: Eighty-three medical centers in North
Discontinuations due to adverse events:       1. 11 (5%)       2. 4 (4%)       3. 2 (2%)       2. 1 (1%)       p-value not reported for all		·					4. 26 (26%)		America, Europe, Israel and India.
Discontinuations due         to adverse events:         1. 11 (5%)         2. 4 (4%)         3. 2 (2%)         2. 1 (1%)         p-value not reported         for all									
to adverse events:         1. 11 (5%)         2. 4 (4%)         3. 2 (2%)         2. 1 (1%)         p-value not reported         for all							Discontinuations due		
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2. 4 (4%) 3. 2 (2%) 2. 1 (1%) p-value not reported for all							1. 11 (5%)		
3. 2 (2%) 2. 1 (1%) p-value not reported for all							2.4 (4%)		
2. 1 (1%) p-value not reported for all							3.2 (2%)		
p-value not reported for all							2.1(1%)		
p-value not reported for all							()		
for all							p-value not reported		
							for all		

<u>Key:</u>\* Dysglycemia defined as fasting glucose level of 110 to 125 mg/dL, 2-hour post-prandial plasma glucose level of at least 140 mg per dL and less than 200 mg per dL or an intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per dL on two occasions, within 52 days before enrollment. The protocol was amended to include participants younger than 18 who had a single abnormal OGTT because rates of progression to T1D was similar with or without a confirmatory OGTT.

<u>Abbreviations</u>: AUC = area under the curve; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; GAD = glutamic acid decarboxylase; ITT = intention to treat; ICA = islet-cell antigen; IV = intravenous; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OGTT = oral glucose tolerance test; PC = placebo-controlled; PP = per protocol; T1D = type 1 diabetes.

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#### Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use TZIELD safely and effectively. See full prescribing information for TZIELD.

#### TZIELD<sup>™</sup> (teplizumab-mzwv) injection, for intravenous use Initial U.S. Approval: 2022

TZIELD is a CD3-directed antibody indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D (1).

#### -----DOSAGE AND ADMINISTRATION -----

- Confirm Stage 2 T1D by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available (2.1).
- In patients who meet criteria for a diagnosis of Stage 2 type 1 diabetes, ensure the clinical history of the patient does not suggest type 2 diabetes (2.1).
- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests. Use of TZIELD is not recommended in patients with certain laboratory abnormalities (2.2).
- Must dilute TZIELD in 0.9% Sodium Chloride Injection, USP. See full prescribing information for detailed preparation and administration instructions (2.3, 2.4, 2.5).
- Premedicate with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic before each TZIELD dose for at least the first 5 days of the 14-day treatment course (2.3).
- Administer TZIELD by intravenous infusion (over a minimum of 30 minutes) once daily for 14 days. See full prescribing information for the dosing schedule (2.4).

#### ----- DOSAGE FORMS AND STRENGTHS-----

Injection: 2 mg per 2 mL (1 mg/mL) single-dose vial (3).

## ----- CONTRAINDICATIONS ------

None. (4).

#### ----- WARNINGS AND PRECAUTIONS -----

- Cytokine Release Syndrome (CRS): Premedicate, monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal, and if severe CRS develops consider temporarily pausing dosing (5.1).
- Serious Infections: Use of TZIELD is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after TZIELD treatment. If a serious infection develops, discontinue TZIELD (5.2).
- Lymphopenia: Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD (5.3).
- Hypersensitivity Reactions: If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly (5.4).
- Vaccinations: Administer all age-appropriate vaccinations prior to starting TZIELD. See recommendations regarding live-attenuated, inactivated, and mRNA vaccines (2.2, 5.5).

#### ----- ADVERSE REACTIONS ------

Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache (6.1).

#### ----- USE IN SPECIFIC POPULATIONS ------

- Pregnancy: May cause fetal harm (8.1).
- Lactation: A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration (8.2).

#### To report SUSPECTED ADVERSE REACTIONS, contact Provention Bio at 1-844-778-2246 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

## See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

## Appendix 2: Prior Authorization Criteria

# Teplizumab

# Goal(s):

• To optimize the safe and effective use of teplizumab for *prevention* of type 1 diabetes mellitus (T1DM).

## Length of Authorization:

• One 14-day treatment course.

## **Requires PA:**

• All provider-administered and pharmacy point-of-sale claims for teplizumab

# **Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at
- Searchable site for Oregon FFS Drug Class listed at <u>www.orpdl.org/drugs/</u>

Approval Criteria						
1. Is the request for an FDA approved age (e.g. 8 years of age or older)?	Yes: Go to #2	<b>No:</b> Pass to RPh. Deny; medical appropriateness.				
2. Has the patient previously been treated with teplizumab (use beyond the original 14 day infusion)?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness. No evidence to support additional doses.	No: Go to #3				
3. Is the medication prescribed by or in consultation with an endocrinologist?	Yes: Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness.				

A	oproval Criteria		
4.	<ul> <li>Does the patient meet the standard criteria for the diagnosis of type 1 diabetes as determined as having one of the following:</li> <li>HbA1c of 6.5% or higher <b>OR</b></li> <li>Fasting plasma glucose (FPG) of 126 mg/dL or higher <b>OR</b></li> <li>Oral glucose tolerance test (OGTT) of 200 mg/dL or higher?</li> </ul>	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	No: Go to #5
5.	Have baseline liver function tests and complete blood panel been evaluated in the past 2 months?	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness
6.	<ul> <li>Has the patient received, or have contraindications to, all routine immunizations recommended for their age based on provider attestation of immunization history?</li> <li>Note: <ul> <li>Teplizumab labeling recommends administration of liveattenuated vaccines at least 8 weeks prior to treatment and inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment.</li> <li>Routine vaccinations for patients at least 8 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.</li> </ul> </li> </ul>	Yes: Go to #7 Document provider attestation of immunization history.	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Approval Criteria		
<ul> <li>7. Is the person at high risk of developing T1DM (e.g. Stage 2 diabetes) as determined by having the following: <ul> <li>Presence of two or more diabetes-related autoantibodies (e.g. insulin autoantibodies (IAA), islet cell antibodies (ICA), glutamic acid decarboxylase 65 (GAD) autoantibodies, insulinoma-associated antigen 2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A)) AND</li> <li>Abnormal glucose confirmed within the last 2 months as determined by one of the following: <ul> <li>An abnormal glucose during an OGTT (140-199 mg/dL) OR</li> <li>FPG 100-125 mg/dL OR</li> <li>HbA1c 5.7-6.4% or ≥10% increase in HbA1c OR</li> <li>2-hour plasma glucose dwith symptomatic T1DM (e.g. Stage 3)</li> </ul> </li> </ul></li></ul>	Yes: Approve for one 14-day course.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 4/23 (KS) Implementation: 5/1/23