ORIGINAL ARTICLE

Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes

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ABSTRACT

BACKGROUND

Teplizumab, a humanized monoclonal antibody to CD3 on T cells, is approved by the Food and Drug Administration to delay the onset of clinical type 1 diabetes (stage 3) in patients 8 years of age or older with preclinical (stage 2) disease. Whether treatment with intravenous teplizumab in patients with newly diagnosed type 1 diabetes can prevent disease progression is unknown.

METHODS

In this phase 3, randomized, placebo-controlled trial, we assessed β-cell preservation, clinical end points, and safety in children and adolescents who were assigned to receive teplizumab or placebo for two 12-day courses. The primary end point was the change from baseline in β-cell function, as measured by stimulated C-peptide levels at week 78. The key secondary end points were the insulin doses that were required to meet glycemic goals, glycated hemoglobin levels, time in the target glucose range, and clinically important hypoglycemic events.

RESULTS

Patients treated with teplizumab (217 patients) had significantly higher stimulated C-peptide levels than patients receiving placebo (111 patients) at week 78 (least-squares mean difference, 0.13 pmol per milliliter; 95% confidence interval [CI], 0.09 to 0.17; P<0.001), and 94.9% (95% CI, 89.5 to 97.6) of patients treated with teplizumab maintained a clinically meaningful peak C-peptide level of 0.2 pmol per milliliter or greater, as compared with 79.2% (95% CI, 67.7 to 87.4) of those receiving placebo. The groups did not differ significantly with regard to the key secondary end points. Adverse events occurred primarily in association with administration of teplizumab or placebo and included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome.

CONCLUSIONS

Two 12-day courses of teplizumab in children and adolescents with newly diagnosed type 1 diabetes showed benefit with respect to the primary end point of preservation of β-cell function, but no significant differences between the groups were observed with respect to the secondary end points. (Funded by Provention Bio and Sanofi; PROTECT ClinicalTrials.gov number, NCT03875729.)

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Type 1 diabetes is an autoimmune disease characterized by T-cell mediated destruction of insulin-producing pancreatic β-cells. The loss of endogenous β-cell function necessitates administration of exogenous insulin for metabolic control and survival.[1] Disease progression is most rapid in children. Despite advances in insulin analogues, insulin delivery systems, and glucose monitoring,[2,3] the burden of disease management is substantial,[4] and glycated hemoglobin levels fail to reach the targets recommended by the American Diabetes Association[5] in many patients[6,7] — especially in young people.[8] Glycemic control is particularly challenging in young people.[8,9] Therefore, treatment of the underlying pathophysiology is an important, unmet need.[2,10]

Therapies that block cytokine signaling[11,12] or target T or B cells[13-17] have been evaluated but involve continuous administration of medication or lead to long-term depletion of immune cells, which raises safety concerns, particularly in children. Before being studied in humans, anti-CD3 antibody administration was studied in nonobese diabetic mice and was shown to induce long-term disease remission without leading to chronic immunosuppression.[18] In 2022, teplizumab (an Fc receptor–nonbinding anti-CD3 monoclonal antibody) was approved by the Food and Drug Administration (FDA) to delay the onset of clinical (stage 3) type 1 diabetes in patients 8 years of age or older with preclinical (stage 2) type 1 diabetes.[19] However, the effects of teplizumab treatment may vary, depending on the stage of type 1 diabetes and the β-cell reserve when treatment is initiated.[19-25] One 14-day course of teplizumab delayed the median time to disease progression from stage 2 to stage 3 type 1 diabetes by 32.5 months and improved β-cell function.[20,25] Previous studies in patients with stage 3 type 1 diabetes indicated that a short course of teplizumab preserved β-cell function without long-term safety effects.[21-24] In the present phase 3 PROTECT trial (Provention Bio's Type 1 Diabetes Trial Evaluating C-Peptide with Teplizumab), we evaluated whether two courses of teplizumab would preserve β-cell function and improve clinical variables in children with newly diagnosed type 1 diabetes.

Methods

Trial Design and Oversight

We conducted this multicenter, double-blind, randomized, placebo-controlled trial at 61 sites (34 in the United States, 3 in Canada, and 24 in Europe) from March 2019 through May 2023. Eligible patients were randomly assigned, in a 2:1 ratio, to receive teplizumab or matching placebo, administered intravenously, for two 12-day courses. Randomization was stratified according to the peak C-peptide level (0.2 to 0.7 pmol per milliliter vs. >0.7 pmol per milliliter) and age (8 to 11 years vs. 12 to 17 years). An independent data monitoring committee reviewed clinical and safety data and provided trial oversight. A medical monitor, who was unaware of the group assignments, reviewed all safety data. The protocol, available with the full text of this article at NEJM.org, was reviewed by the FDA, individual European health authorities, and institutional review boards and ethics committees. The trial was conducted according to International Council for Harmonisation Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. Informed consent was obtained from patients' parents or caregivers, and assent was obtained from patients. Both Provention Bio and Sanofi participated in the collection of the data and writing the manuscript. The last author wrote the first draft of the manuscript. The first and last authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the authors participated in the interpretation of the results and in the drafting and approval of the manuscript.

Patients

We enrolled male and female patients 8 to 17 years of age with stage 3 type 1 diabetes that had been diagnosed within 6 weeks before randomization according to the criteria of the American Diabetes Association. Eligible patients had at least one autoantibody associated with type 1 diabetes (antibodies against glutamic acid decarboxylase, zinc transporter 8, insulin, islet cells, or islet antigen 2) and a peak stimulated C-peptide level of 0.2 pmol per milliliter or greater.

Key exclusion criteria were major systemic illnesses, active infection, or a history of chronic infection. The trial was conducted during the coronavirus disease 2019 (Covid-19) pandemic; vaccination against severe acute respiratory syndrome coronavirus 2 was not required. Full inclusion and exclusion criteria can be found in the Supplementary Appendix (available at NEJM.org).

TRIAL PROCEDURES

Patients in the teplizumab group received the drug in two 12-day courses, 26 weeks apart; teplizumab was administered in an outpatient or inpatient setting by means of a daily intravenous infusion (106 μg per square meter of body surface area on day 1, 425 μg per square meter on day 2, and 850 μg per square meter on days 3 through 12) for a total cumulative dose of 9 mg per square meter. In the placebo group, placebo was administered intravenously in matching volumes and according to the same schedule. Patients received premedication with ibuprofen or acetaminophen, an antihistamine (e.g., diphenhydramine), an antiemetic (e.g., ondansetron), or all three for at least the first 5 days of each course. Because of Covid-19 pandemic restrictions, the protocol was amended, on the basis of safety and efficacy data from earlier studies,[21,23] to allow patients to delay the second 12-day course to approximately week 52, if necessary.

Trial investigators were instructed to maintain intensive glycemic control in patients by administering treatment to them to reach recommended target glucose levels.[26] All patients used a standard, unblinded continuous glucose monitoring device (Dexcom G6), with data captured at seven defined time points during the trial; continuous glucose monitoring was used for 14 days before clinical visits. Time in the target glucose range (70 to 180 mg per deciliter [3.9 to 10 mmol per liter]) and other continuous glucose monitoring metrics, including time above the target range (>180 mg per deciliter) and time below the target range (<70 mg per deciliter) were recorded. Patients and their parents or caregivers recorded their insulin doses and clinically important hypoglycemic events in an electronic diary (eDiary).

Patients and their parents or caregivers completed quality-of-life assessments, and the change from baseline was assessed at week 78. The measures included the Pediatric Quality of Life Inventory Diabetes Module and Family Module (scores range from 0 to 100, with higher scores indicating a better outcome), Hypoglycemia Fear Scale (scores range from 0 to 4, with lower scores indicating a better outcome), and Diabetes Treatment Satisfaction Questionnaire (scores range from 0 to 48, with higher scores indicating greater satisfaction).[27-29] Additional details can be found in the Supplementary Appendix. Adverse events were monitored and reported by investigators in electronic case-report forms.

END POINTS AND ASSESSMENTS

The primary end point was the change from baseline in C-peptide levels at week 78. C-peptide levels were determined from the area under the concentration-time curve (AUC) during a 4-hour mixed-meal tolerance test[24] and calculated with the use of the trapezoidal rule. The primary analysis tested the superiority of teplizumab to placebo, adjusted for age and the baseline C-peptide level. Unless otherwise specified, the C-peptide level from the AUC was analyzed with the use of the natural logarithm (ln[AUC+1]). The four key clinical secondary end points that were included in the prespecified plan to adjust for multiple testing and that were assessed at week 78 were the following: the mean of patients' daily insulin dose (units per kilogram per day), the mean daily percentage of time in the target glucose range, and the change from baseline in the mean glycated hemoglobin level, as well as clinically important hypoglycemic events (defined as a blood glucose level <54 mg per deciliter [3.0 mmol per liter]), severe cognitive impairment requiring assistance for recovery, or both) at week 78.

We also assessed the following composite exploratory end point as a measure of clinical remission: a glycated hemoglobin level of 6.5% or less and a daily insulin dose of 0.25 units per kilogram per day or less. This glycated hemoglobin level is the diagnostic threshold for diabetes, and this insulin dose was previously defined as the dose indicating remission.[30,31] The data from the quality-of-life questionnaires were analyzed as the change from the baseline score.

STATISTICAL ANALYSIS

Efficacy analyses were conducted in the intention-to-treat population, which comprised all patients who underwent randomization. The safety population included all patients who underwent randomization and received at least one dose of teplizumab or placebo.

The trial was designed to show a difference between the groups of 40% or more in C-peptide levels at week 78. We estimated that a sample size of 300 patients would provide 90% power, assuming a two-sided alpha error of 0.05, a 2:1 randomization ratio, and a 10% dropout rate. A pattern-mixture model was used to impute missing data for primary and secondary end points under the assumption that data were not missing at random. The trial was not powered to detect differences between teplizumab and placebo with regard to the secondary end points. The tertiary and exploratory end points were not adjusted for multiplicity; therefore, only point estimates and the associated 95% confidence intervals are presented and should not be used to infer definitive treatment effects.

An analysis of covariance (ANCOVA) model was used to assess treatment differences in the C-peptide level (measured as ln[AUC+1]), the insulin dose, glycated hemoglobin levels, and the percentage of time in the target glucose range at week 78. Prespecified subgroup analyses of the change from baseline in C-peptide AUC levels at week 78 were analyzed according to age, sex, race, geographic region, insulin dose, baseline glycated hemoglobin level, and HLA type (DR3 or DR4). We determined that the four key clinical secondary end points would be assessed with the Hochberg method to adjust for multiplicity if the primary end point reached significance ($P<0.05$). Adverse events were summarized according to system organ class and preferred term with the use of the *Medical Dictionary for Regulatory Activities*, version 26.0. The severity of adverse events and their relationship to teplizumab or placebo were assessed by the investigators. All statistical analyses were performed with the use of SAS, version 9.4, in a secure environment that was validated as compliant with the Code of Federal Regulation, Part 11. Additional details can be found in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 328 children and adolescents were enrolled in the trial and were randomly assigned to receive teplizumab (217 patients) or placebo (111 patients). Demographics and baseline characteristics were generally balanced between the treatment groups (Table 1). The mean (±SD) time since patients received a diagnosis of type 1 diabetes was 5.3±0.8 weeks. Two patients assigned to the teplizumab group and 4 assigned to the placebo group had a history of ketoacidosis. In total, 32 patients withdrew from the trial (22 in the teplizumab group and 10 in the placebo group) and 45 patients suspended treatment but continued with follow-up (30 in the teplizumab group and 15 in the placebo group) (Fig. S1). Owing to Covid-19 pandemic restrictions, 16 patients taking teplizumab and 12 taking placebo received their second course of teplizumab or placebo at approximately week 52.

EFFICACY

Teplizumab treatment resulted in a significant difference from placebo at week 78 in the mean change from baseline in C-peptide AUC levels in the intention-to-treat population (least-squares mean difference, 0.13 pmol per milliliter; 95% confidence interval [CI], 0.09 to 0.17; $P<0.001$) (Table 2), which represents a 59.3% difference between the groups, favoring teplizumab. Mean C-peptide AUC levels from baseline to week 78 are shown in Figure 1A. A prespecified exploratory analysis showed that 94.9% (95% CI, 89.5 to 97.6) of patients who were treated with teplizumab had a clinically meaningful peak C-peptide level of 0.2 pmol per milliliter or greater at week 78 as compared with 79.2% (95% CI, 67.7 to 87.4) of those receiving placebo (Fig. S2). In prespecified subgroup analyses, the effect of teplizumab was generally consistent across subgroups (Fig. 2).

Significant differences were not shown with respect to the secondary end points, which were assessed to understand the effect of teplizumab treatment on clinical variables. The mean glycated hemoglobin level was rapidly controlled in both groups and did not differ between the groups through week 78 (Table 2 and Fig. S3).

Table 1. Demographic and Clinical Characteristics of Patients at Baseline.*

Characteristic	Teplizumab (N=217)	Placebo (N=111)	Total (N=328)
Mean age — yr	12.0±2.5	12.3±2.6	12.1±2.5
Age group — no. (%)			
8–11 yr	90 (41.5)	46 (41.4)	136 (41.5)
12–17 yr	127 (58.5)	65 (58.6)	192 (58.5)
Male sex — no. (%)	119 (54.8)	69 (62.2)	188 (57.3)
Race or ethnic group — no. (%)†			
White	189 (87.1)	94 (84.7)	283 (86.3)
Black	5 (2.3)	6 (5.4)	11 (3.4)
Asian	4 (1.8)	3 (2.7)	7 (2.1)
Other	19 (8.8)	8 (7.2)	27 (8.2)
Hispanic or Latino ethnic group — no. (%)†	14 (6.5)	4 (3.6)	18 (5.5)
Body-mass index‡			
Mean	18.9±3.5	19.1±3.6	18.9±3.5
Z score	0.063±1.072	0.056±1.096	0.060±1.079
Body weight — kg	46.7±15.0	49.2±15.9	47.5±15.3
Peak C-peptide level — no. (%)			
0.2–0.7 pmol/ml	91 (41.9)	47 (42.3)	138 (42.1)
>0.7 pmol/ml	126 (58.1)	64 (57.7)	190 (57.9)
C-peptide AUC — pmol/ml	0.745±0.365	0.724±0.319	0.738±0.350
Glycated hemoglobin level — %	8.90±1.73	9.18±1.92	9.00±1.80
Insulin dose — units/kg/day	0.447±0.309	0.383±0.254	0.426±0.293

* Plus–minus values are means ±SD. AUC denotes the area under the concentration–time curve.
† Race and ethnic group were reported by the patient. "Other" race categories include American Indian or Alaskan Native (1 patient in the teplizumab group), Native Hawaiian or Other Pacific Islander (1 patient in the placebo group), multiple (6 patients in the teplizumab group), other (4 in the teplizumab group and 1 in the placebo group), and not reported (8 in the teplizumab group and 6 in the placebo group).
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

The difference in the percentage of time in the target glucose range between the teplizumab and placebo groups was 4.71 percentage points (95% CI, –1.72 to 11.15) (Table 2); the percentage of patients who spent 70% or more time in the target glucose range is shown in Figure 1B.

At week 78, the estimated mean daily insulin dose was 0.46 units per kilogram per day in patients who were treated with teplizumab and 0.59 units per kilogram per day in those receiving placebo (difference, 0.13 units per kilogram per day [95% CI, –0.28 to 0.02], calculated with ANCOVA) (Table 2), and the mean insulin dose was lower in the teplizumab group than in the placebo group at all time points after week 12, as assessed in a prespecified analysis of mixed-effects model for repeated measures (Fig. 1C). The use of insulin pumps increased during the trial in both treatment groups.

The results of our exploratory analyses of the percentage of patients meeting the prespecified definition of clinical remission are shown in Figure S4. Although these results are consistent with those observed when a definition of remission that was based on insulin dose alone (≤0.25 units per kilogram per day) was used (Fig. S5),[30,31] no firm conclusion can be made from exploratory analyses. The percentages of patients who had clinically important hypoglycemic events were similar in the two groups (Ta-

Table 2. Efficacy (Intention-to-Treat Population).*

Efficacy End Point	Teplizumab (N=217)		Placebo (N=111)		Difference in Measure, Teplizumab vs. Placebo (95% CI)
	Measure	No. with Data	Measure	No. with Data	
Primary end point					
C-peptide level — pmol/ml					
Baseline	0.54±0.20	217	0.53±0.17	111	
Week 78†	0.46±0.20	188	0.34±0.21	88	
LS mean change from baseline	−0.09		−0.21		0.13 (0.09 to 0.17)‡ P<0.001
Key secondary end points§					
Glycated hemoglobin level					
Baseline	8.90+1.73	217	9.18±1.92	110	
Week 78†	6.97±1.26	192	7.07±1.45	100	
LS mean change from baseline	−1.98		−1.89		−0.09 (−0.42 to 0.24)¶
Percentage of time in the target glucose range‖					
Week 78†	68.7±19.6	140	64.6±22.4	63	
LS mean	67.4		62.7		4.71 (−1.72 to 11.15)
Insulin dose — units/kg/day					
Baseline	0.45±0.31	126	0.38±0.25	63	
Week 78†	0.45±0.27	98	0.60±0.33	50	
LS mean	0.46		0.59		−0.13 (−0.28 to 0.02)¶
Clinically important hypoglycemic events — no./patient-yr**	4.66±8.89	217	4.39±9.40	111	
Estimated rate (95% CI) ††	4.68 (3.70 to 5.91)		4.24 (3.06 to 5.89)		1.10 (0.74 to 1.64)‡‡

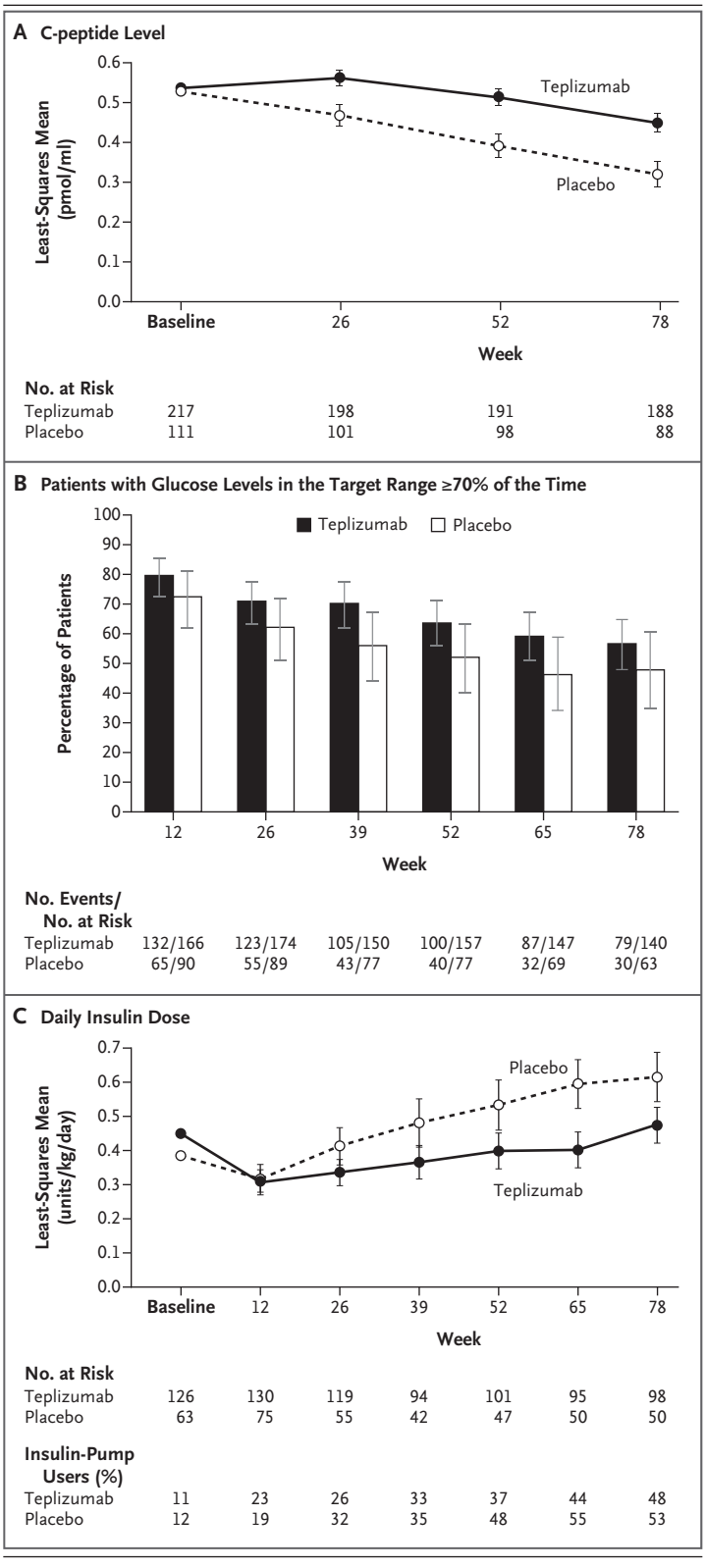
* Plus–minus values are means ±SD. LS denotes least-square.
† Missing data at week 78 were multiply imputed with the use of a pattern-mixture model under the assumption that data were not missing at random.
‡ Estimates and the P value were obtained with the use of an analysis of covariance (ANCOVA) model that included treatment, age group at randomization, and baseline C-peptide level measured as ln(AUC+1) as independent variables.
§ For the secondary end points, the widths of the confidence intervals have not been adjusted for multiplicity and may not imply treatment effects.
¶ Estimates were obtained with the use of an ANCOVA model that included treatment, age group at randomization, the peak C-peptide level at screening, and the glycated hemoglobin level at baseline as independent variables.
‖ Glucose levels were measured with the use of continuous glucose monitoring.
** Clinically important hypoglycemic events were defined as a glucose level less than 54 mg per deciliter (3.0 mmol per liter), severe cognitive impairment requiring assistance for recovery, or both. The event rate was calculated for each patient as the number of events divided by total trial follow-up time. More analysis of clinically important hypoglycemic events can be found in Table S1.
†† Estimates were obtained with the use of a negative binomial regression model with the rate of hypoglycemic episodes as a dependent variable and treatment, age group at randomization, and screening peak C-peptide level as independent variables.
‡‡ The data shown here are the estimated rate ratio (95% CI).

ble 2). The rate ratio for the comparison of the incidence per patient-year of severe hypoglycemic adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0), between the teplizumab and placebo groups was 0.29 (95% CI, 0.13 to 0.62) (Table S1).

Analyses of subjective quality-of-life question-

Figure 1. Efficacy End Point over the Course of the Study.

Panel A shows the area under the concentration-time curve (AUC, measured as ln[AUC+1]) for stimulated C-peptide levels over time. The data are presented as least-squares means; I bars represent 95% confidence intervals. Panel B shows the percentage of patients whose glucose levels were in the target glucose range for 70% or more of the time. Panel C shows the mean daily insulin dose over time. The data are presented as least-squares means; I bars represent 95% confidence intervals. Estimates were obtained from a mixed-effects model for repeated measures with treatment group, visit, and age group at randomization as fixed effects, and a treatment-by-visit interaction term. The widths of the confidence intervals have not been adjusted for multiplicity and may not imply treatment effects.



naires (Fig. S6) showed that teens in the teplizumab group had diabetes-control scores of 9.2 at baseline and 7.8 at week 78, and those in the placebo group had scores of 9.1 at baseline and 7.3 at week 78 (least-squares mean difference between the groups in the change from baseline, 1.1 [95% CI, 0.0 to 2.1]). Scores of parents' satisfaction with their teens' treatment (as measured by the Diabetes Treatment Satisfaction Questionnaire, parent version) were 35.7 at baseline and 38.5 at week 78 in the teplizumab group and 34.6 at baseline and 36.3 at week 78 in the placebo group (least-squares mean difference, 2.4 [95% CI, 0.3 to 4.5]).

SAFETY

Adverse events occurred in 99.5% of patients in the teplizumab group and in 97.3% of those in the placebo group (Table S2). Most events occurred in association with administration of teplizumab or placebo and were mild or moderate (grade 1 or 2) in severity, transient, and manageable. In the teplizumab group, 96.3% of patients had grade 1 events and 86.6% had grade 2 events; in the placebo group, 92.8% of patients had grade 1 events and 77.5% had grade 2 events. The percentage of patients who had adverse events that led to treatment discontinuation was 6.9% in the teplizumab group and 2.7% in the placebo group (Table 3). In the teplizumab group, most treatment discontinuations occurred because of results of protocol-specified laboratory investigations but were asymptomat-

ic. Most adverse events leading to treatment discontinuation were nonserious, except for two cytokine release syndrome events in the teplizumab group (both resolved within 7 days) and one device-related bacteremia event in the placebo group (which resolved in 12 days).

Adverse events of special interest were prespecified and occurred in 29% of patients treated with teplizumab and in 21.6% of patients receiving placebo (Table S2). The most common adverse event of special interest was severe hypoglycemia, which occurred in 13.4% of patients in the teplizumab group and in 16.2% of those in the placebo group.

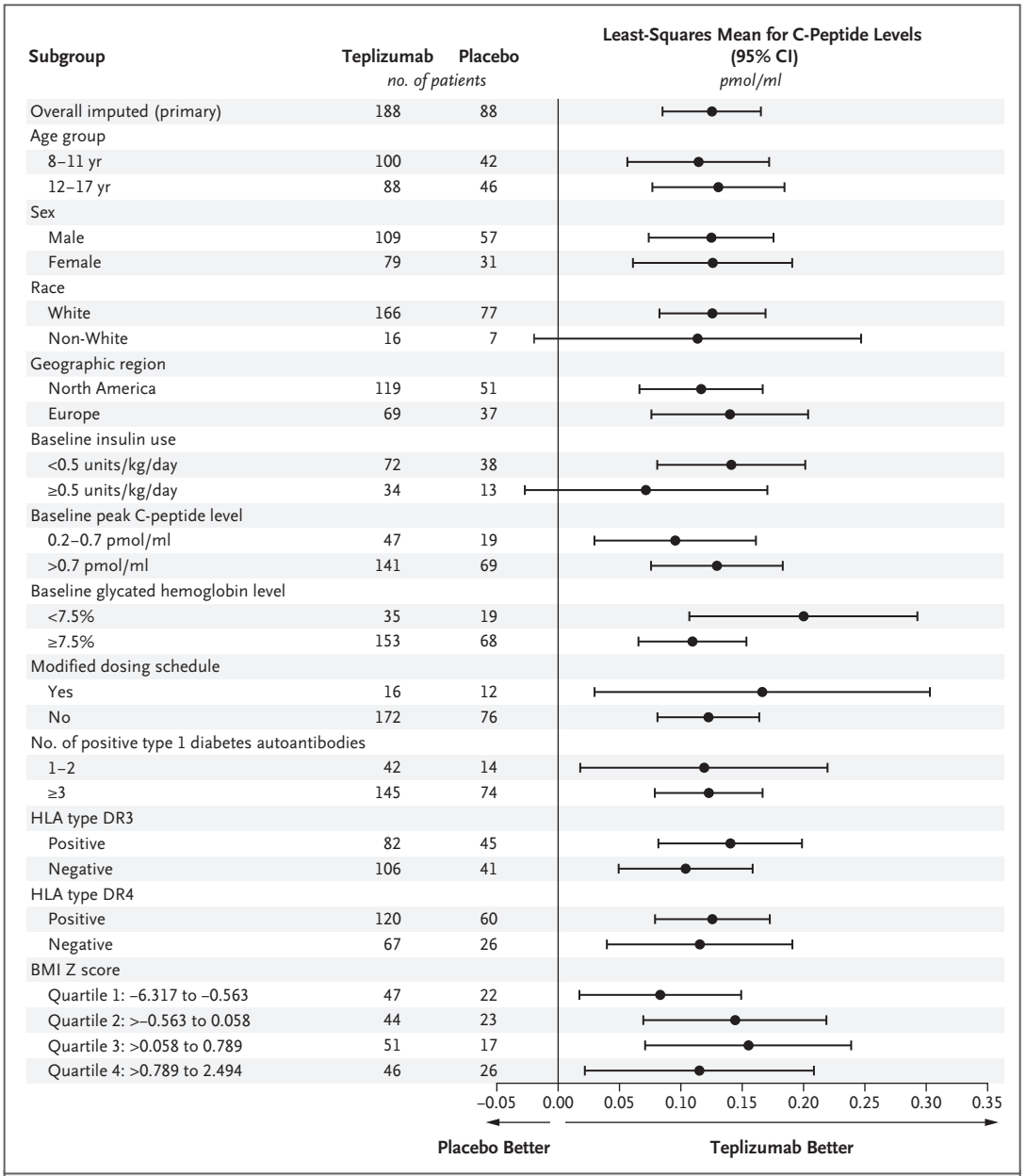


Figure 2. C-Peptide AUC Responses to Teplizumab in Subgroups (Intention-to-Treat Population).

Patient numbers do not add up to the total number because of missing data. Missing data at week 78 were multiply imputed with the use of a pattern-mixture model under the assumption that data were not missing at random. The widths of the confidence intervals have not been adjusted for multiplicity and may not imply treatment effects.

Transient lymphopenia was observed in the teplizumab group, a finding that was consistent with previous experience with teplizumab (Fig. S7). Epstein–Barr virus (EBV) reactivation was detected in eight patients treated with teplizumab and was asymptomatic in six of these patients. There was one new case of EBV infection in each treatment group. All events resolved without antiviral treatment. Covid-19 was reported in 49 patients (22.6%) in the teplizumab group and in 26 patients (23.4%) in the placebo group. None of these patients received antiviral treatment or were hospitalized. There were no events of diabetic ketoacidosis. Additional details about adverse events can be found in Table S2.

Table 3. Adverse Events.*

Event	Teplizumab (N=217)	Placebo (N=111)
	no. of patients (%)	
Adverse events leading to discontinuation of teplizumab or placebo	15 (6.9)	3 (2.7)
Elevations in protocol-specified liver-function tests	9 (4.1)	1 (0.9)
Cytokine release syndrome	4 (1.8)	0
Hypersensitivity	1 (0.5)	0
Coronavirus disease 2019	1 (0.5)	1 (0.9)
Cellulitis	0	1 (0.9)
Device-related bacteremia	0	1 (0.9)
Phlebitis	1 (0.5)	0
Adverse events leading to trial withdrawal	5 (2.3)	0
Serious adverse events	12 (5.5)	6 (5.4)
Cytokine release syndrome	3 (1.4)†	0
Hyperglycemia	1 (0.5)	0
Hypoglycemia	1 (0.5)	1 (0.9)
Psychiatric disorders‡	2 (0.9)	1 (0.9)
Palpitations	1 (0.5)	0
Gastrointestinal disorders§	1 (0.5)	1 (0.9)
Concussion	1 (0.5)	0
Nephrolithiasis	1 (0.5)	0
Atopic dermatitis	1 (0.5)	0
Infections and infestations¶	0	3 (2.7)†
Syncope	0	1 (0.9)

* Shown are adverse events that occurred after the administration of the first dose of teplizumab or placebo through the end of the trial. A full list of adverse events is shown in Table S2.
† These serious adverse events were deemed possibly or probably related to teplizumab or placebo administration by investigators.
‡ This category includes suicidal ideation, suicide attempt, and anxiety.
§ This category includes vomiting and constipation.
¶ This category includes device-related bacteremia and gastroenteritis.

DISCUSSION

The present trial showed that two 12-day courses of intravenous teplizumab significantly improved stimulated C-peptide levels, as compared with placebo, at week 78 in patients with stage 3 type 1 diabetes who had enrolled in the trial within 6 weeks after diagnosis. There were no significant differences between the groups in the key secondary clinical end points — insulin dose, change in glycated hemoglobin, percentage of time in the target glucose range, and clinically important hypoglycemic events.[32-34]

The side effects of teplizumab observed in the present trial included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome. These findings were consistent with previous experience,[21,24] and the events resolved spontaneously. Reports of EBV reactivation were low, as was the rate of drug discontinuation due to adverse events. The incidence of Covid-19 was similar in the two groups, and the illnesses resolved without additional therapies, which further supports the notion that teplizumab is immunomodulatory and not immunosuppressive.

There are several important features that distinguish teplizumab from other therapies previously tested in patients with type 1 diabetes. First, teplizumab was administered in two defined intravenous courses (12 days each), and a more rapid recovery of circulating immune cells occurred after treatment than has been shown to occur with therapies given continuously or with those that result in prolonged cell depletion. The long-term effects of teplizumab do not appear to entail chronic immunosuppression.[15,35,36] The clinical evidence for recovery of immune function was apparent in this trial from the resolution of EBV reactivation and Covid-19 in patients treated with teplizumab. Second, the effects of teplizumab appeared to be prolonged. Teplizumab is thought to induce partial CD8+ T-cell exhaustion that impedes T-cell function.[37] Such a mechanism may affect certain T cells, which have relatively weak engagement with their targets, such as autoreactive cells, and thus, we speculate, may be more easily modulated. These features appeared to be consistent with func-

tional immune tolerance (i.e., the restoration of unresponsiveness to one's own tissues [or self-antigens] while maintaining defensive immune responses). A recently published integrated analysis of five trials in patients with stage 3 type 1 diabetes (609 patients) showed that one or two courses of teplizumab significantly preserved β-cell function as compared with placebo at 1 and 2 years of follow-up (P<0.0001).[38] Finally, our trial focused on children and adolescents, who represent the age groups most affected by type 1 diabetes and who are considered to have the greatest need for improved treatment. We also report the outcomes of quality-of-life questionnaires in this trial of immune therapy. These results are consistent with those in other exploratory investigations.

Our trial had certain limitations. The Covid-19 pandemic complicated the way the trial was conducted, including our having to account for missed patient visits and disrupted data collection. However, the dropout rate was not higher than anticipated and affected both treatment groups equally. The patient population was similar to populations in other clinical trials of type 1 diabetes (Table S3). However, most of the participants in our trial were White, which is not representative of persons who report new-onset disease in the general population, and our trial showed lower rates of diabetic ketoacidosis than those seen in other new-onset cohorts.[2,15,23,24] Complete blinding with this type of biologic agent is challenging, but our primary end point was objective and was probably unaffected by the possible unblinding of the trial data to the investigators.[14,16,35,36] Finally, the secondary end points did not meet thresholds for statistical significance, and the trial was probably underpowered to address them.

In this trial involving patients with type 1 diabetes, treatment with teplizumab administered intravenously every day for two 12-day courses resulted in benefits with respect to the primary end point of maintenance of β-cell function. However, it did not result in significant differences with respect to the key secondary end points.

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REFERENCES

1. Bluestone JA, Buckner JH, Herold KC. Immunotherapy: building a bridge to a cure for type 1 diabetes. Science 2021;373:510-6.
2. McVean J, Forlenza GP, Beck RW, et al. Effect of tight glycemic control on pancreatic beta cell function in newly diagnosed pediatric type 1 diabetes: a randomized clinical trial. JAMA 2023;329:980-9.
3. Beck RW, Bergenstal RM, Laffel LM, Pickup JC. Advances in technology for management of type 1 diabetes. Lancet 2019;394:1265-73.
4. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. Diabetes Technol Ther 2019;21:66-72.
5. American Diabetes Association Professional Practice Committee. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes — 2022. Diabetes Care 2022;45:Suppl 1:S125-S143.
6. Demeterco-Berggren C, Ebekozien O, Noor N, et al. Factors associated with achieving target A1C in children and adolescents with type 1 diabetes: findings from the T1D exchange quality improvement collaborative. Clin Diabetes 2022;41:68-75.
7. Cardona-Hernandez R, Schwandt A, Alkandari H, et al. Glycemic outcome associated with insulin pump and glucose sensor use in children and adolescents with type 1 diabetes: data from the international pediatric registry SWEET. Diabetes Care 2021;44:1176-84.
8. Holman N, Woch E, Dayan C, et al. National trends in hyperglycemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a challenge due to age or stage of development, or is new thinking about service provision needed? Diabetes Care 2023;46:1404-8.
9. van den Boom L, Karges B, Auzanneau M, et al. Temporal trends and contemporary use of insulin pump therapy and glucose monitoring among children, adolescents, and adults with type 1 diabetes between 1995 and 2017. Diabetes Care 2019;42:2050-6.
10. Boughton CK, Allen JM, Ware J, et al. Closed-loop therapy and preservation of C-peptide secretion in type 1 diabetes. N Engl J Med 2022;387:882-93.
11. 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;383:2007-17.
12. 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 diabe-

tes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:212-24.
13. Gitelman SE, Bundy BN, Ferrannini E, et al. Imatinib therapy for patients with recent-onset type 1 diabetes: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:502-14.
14. Haller MJ, Schatz DA, Skyler JS, et al. Low-dose anti-thymocyte globulin (ATG) preserves β-cell function and improves HbA_{1c} in new-onset type 1 diabetes. Diabetes Care 2018;41:1917-25.
15. 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;378:412-9.
16. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med 2009;361:2143-52.
17. Rigby MR, DiMeglio LA, Rendell MS, et al. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol 2013;1:284-94.
18. Chatenoud L, Thervet E, Primo J, Bach JF. Anti-CD3 antibody induc)Oes long-term remission of overt autoimmunity in nonobese diabetic mice. Proc Natl Acad Sci U S A 1994;91:123-7.
19. Highlights of prescribing information: TZIELD (teplizumab-mzwv). Silver Spring, MD: Food and Drug Administration, November 2022 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf).
20. 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;381:603-13.
21. 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;62:3766-74.
22. 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;56:391-400.
23. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 2002;346:1692-8.
24. 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;378:487-97.
25. 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):eabc8980.
26. American Diabetes Association Professional Practice Committee. Glycemic targets: standards of medical care in diabetes — 2022. Diabetes Care 2022;45:Suppl 1:S83-S96.
27. Glocker V, Bachmann S, Hess M, Szinnai G, Burckhardt MA. Fear of hypoglycemia and quality of life in young people with type 1 diabetes and their parents in the era of sensor glucose monitoring. Front Endocrinol (Lausanne) 2022;13:958671.
28. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL. The PedsQL in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and Type 1 Diabetes Module. Diabetes Care 2003;26:631-7.
29. Varni JW, Sherman SA, Burwinkle TM, Dickinson PE, Dixon P. The PedsQL Family Impact Module: preliminary reliability and validity. Health Qual Life Outcomes 2004;2:55.
30. Feutren G, Papoz L, Assan R, et al. Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset: results of a multicentre double-blind trial. Lancet 1986;2:119-24.
31. Diabetes Prevention Trial–Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med 2002;346:1685-91.
32. Mortensen HB, Swift PG, Holl RW, et al. Multinational study in children and adolescents with newly diagnosed type 1 diabetes: association of age, ketoacidosis, HLA status, and autoantibodies on residual beta-cell function and glycemic control 12 months after diagnosis. Pediatr Diabetes 2010;11:218-26.
33. Sørensen JS, Johannesen J, Pociot F, et al. Residual β-cell function 3-6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. Diabetes Care 2013;36:3454-9.
34. Steffes MW, Sibley S, Jackson M, Thomas W. β-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832-6.
35. 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;68:1267-76.
36. 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;125:3285-96.
37. 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):eaai7793.
38. Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: a disease-modifying therapy for type 1 diabetes that preserves β-cell function. Diabetes Care 2023;46:1848-56.