TEPLIZUMAB FOR THE DELAY OF PROGRESSION TO CLINICAL STAGE 3 TYPE 1 DIABETES IN AT-RISK PATIENTS

SPONSOR BRIEFING DOCUMENT

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AbATE	Autoimmunity-blocking Antibody for Tolerance in Recently Diagnosed T1D
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	Biologics License Application
BMI	body mass index
BSA	body surface area
CAR	Chimeric antigen receptor
CD3ε	epsilon chain of the CD3 protein
CI	confidence interval
CMV	cytomegalovirus
CRS	cytokine release syndrome
DKA	diabetes ketoacidosis
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GAD	glutamic acid decarboxylase
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c, glycated hemoglobin
HLA	human leukocyte antigen
ICA	islet cell antibody
ICU	intensive care unit
IgG	immunoglobulin G
IL-6	Interleukin-6

Abbreviation	Definition
IND	Investigational New Drug Application
ITT	intent-to-treat
IV	Intravenous(ly)
mAb	monoclonal antibody
MAR	missing at random
mIAA	micro-insulin autoantibody
MMTT	mixed meal tolerance test
MNAR	missing not at random
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NPH	Neutral Protamine Hagedorn
OGTT	oral glucose tolerance test
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PMN	polymorphonuclear neutrophil
PPD	purified protein derivative
SAE	serious adverse event
SOC	System Organ Class
T1D	type 1 diabetes
T2D	type 2 diabetes
TCR	T cell receptor
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
ZnT8	zinc transporter 8

1 EXECUTIVE SUMMARY

Provention Bio, Inc is seeking approval of teplizumab for the delay of progression to clinical type 1 diabetes (T1D) (ie, symptomatic, Stage 3, insulin-dependent disease) in at-risk patients (ie, pre-symptomatic, Stage 2 disease as determined by the presence of 2 or more T1D-related autoantibodies and dysglycemia). If approved, teplizumab would be the first disease-modifying therapy in humans that preserves beta cell function in patients with early, Stage 2 disease who are at risk of developing Stage 3 clinical T1D.

In the pivotal TN-10 study – a randomized, double-blind, placebo-controlled study – a single 14-day course of teplizumab given to patients at risk for T1D (Stage 2) was well tolerated and resulted in a 2-year delay in the progression to Stage 3 insulin-dependent T1D. This pivotal study is supported by clinical evidence of teplizumab's preservation of beta cells from 5 additional supportive studies in newly diagnosed patients with Stage 3 clinical T1D with similar underlying autoimmune pathophysiology. The totality of the efficacy and safety data strongly supports the positive benefit/risk of teplizumab for the delay of progression to Stage 3 clinical T1D in at-risk patients with pre-symptomatic Stage 2 T1D.

Background and Unmet Need

T1D is an autoimmune disease that leads to beta cell destruction, loss of endogenous insulin production, and ultimately to life-long insulin dependence. There is an urgent need for treatment of T1D since the majority of patients are diagnosed as children and young adults who experience increased risk of serious acute and long-term micro- and macrovascular complications and decreased life expectancy.

T1D progresses through 3 stages:

- Stage 1: asymptomatic stage with emergence of 2 or more T1D-related autoantibodies and normoglycemia (44% risk of progression to Stage 3 in 5 years and lifetime risk approaches 100%).
- Stage 2: pre-symptomatic stage with persistence of 2 or more T1D-related autoantibodies and dysglycemia (75% risk of progression to Stage 3 in 5 years and lifetime risk approaches 100%).
- Stage 3: symptomatic or clinical T1D, when remaining beta cell capacity is insufficient to maintain glucose control and exogenous insulin is needed.

The emergence of T1D-related autoantibodies in Stage 1 reflects the initiation of the autoimmune process and thus the beginning of the disease. As the autoimmune process continues, destruction of beta cells and the appearance of dysglycemia signal entry into Stage 2. Further loss of beta cell function in Stage 2 ultimately leads to Stage 3 disease, when beta cell capacity is insufficient to maintain glucose homeostasis. Once individuals develop 2 or more T1D-related autoantibodies, the lifetime risk of progressing to Stage 3 T1D approaches 100% (Insel et al 2015). Beta cell function can be measured by

C-peptide levels, which reflect endogenous insulin production and are critical to describing beta cell reserve.

Currently, the only available therapies are directed at the time of diagnosis of Stage 3 T1D, treating the symptomatic metabolic consequences of the disease rather than the underlying autoimmune process. The majority of patients with asymptomatic Stage 2 T1D are undiagnosed until they become symptomatic and hyperglycemic and enter Stage 3 disease. Once diagnosed, lifelong insulin therapy, requiring multiple daily injections or administered via an insulin pump, is instituted along with intermittent or continuous glucose monitoring. In addition to a restricted dietary regimen, life becomes very different and often extremely difficult for these patients, especially those in the pediatric age group, and their caregivers.

A therapy to delay the progression to Stage 3 insulin-dependent disease by preserving beta cell function has not previously been demonstrated in humans and represents a major advance. Teplizumab is a disease-modifying therapy, which, if approved, would have a profound impact on the patients and families who otherwise must manage this lifelong condition once it is clinically manifested.

Overview of Teplizumab

Teplizumab is a 150-KD humanized monoclonal antibody (mAb) that binds to the epsilon chain of the CD3 protein (CD3ε), a cell surface antigen present on T lymphocytes that is a critical signaling component of the T cell receptor (TCR) complex. The FDA granted teplizumab breakthrough therapy designation for the indication of delay of progression to clinical T1D in patients at risk for Stage 3 clinical T1D (ie, patients with Stage 2 T1D).

The mechanism by which teplizumab prevents the decline in beta cell function in T1D is the result of its binding to CD3, resulting in partial T cell agonism and subsequent downstream immune modulation. This immune modulation leads to a number of effects on specific subpopulations of T cells integral to the initiation and propagation of the autoimmune process that causes beta cell destruction. These effects include reduction in effector function of T cells, including autoreactive T cells, and increase in the number and function of regulatory T cells (Ablamunits et al 2010; Bisikirska et al 2005; Long et al 2017; Waldron-Lynch and Herold 2011).

More recent studies indicate that teplizumab also induces immunologic “exhaustion” in a subset of effector CD8+ T cells previously believed to be autoreactive (Long et al 2016; Long et al 2017). Importantly, higher levels of exhausted CD8+ T cells have been associated with slower progression of T1D in the natural course of the disease (Wiedeman et al 2020), and teplizumab-mediated increases in the levels of these cells correlate with clinical response to teplizumab (Leighton et al 2017; Long et al 2016). Collectively, these mechanistic data suggest that the immunomodulatory effect of teplizumab involves not only the inhibition of the immune process leading to beta cell destruction but also facilitation of the rebalancing of effector and regulatory arms involved

in T1D autoimmunity, leading to the re-establishment of beta cell self-tolerance (Lebastchi et al 2013). The partial T cell agonism also leads to transient release of cytokines, which can result in self-limited mechanism-based adverse events (AEs) such as lymphopenia, rash, liver enzyme elevations, and fever.

The teplizumab clinical development program has been ongoing over 2 decades. The initial studies were focused on preserving remaining beta cell function in newly diagnosed patients with Stage 3 T1D and were conducted by academic investigators (Study 1, AbATE [Autoimmunity-blocking Antibody for Tolerance in Recently Diagnosed Type 1 Diabetes], Delay) and a prior sponsor, MacroGenics (Protégé and Encore). The majority of the Stage 3 patients in these studies received 2 treatment courses of teplizumab. While the registrational study (Protégé) in newly diagnosed Stage 3 T1D failed to meet its novel and unvalidated composite primary endpoint of hemoglobin A1c (HbA1c) and insulin use in 2010, it showed preservation of beta cell function consistent with prior studies, as measured by slower decline in C-peptide levels and lower exogenous insulin use in teplizumab-treated patients. Provention Bio acquired teplizumab in 2018 to continue the clinical development program and is currently conducting the Phase 3 PROTECT study in newly diagnosed patients with Stage 3 T1D (NCT03875729). The primary objective in PROTECT is to demonstrate preservation of beta cell function on C-peptide levels.

The pivotal TN-10 study, initiated in 2011, was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and conducted by TrialNet, which is an international network of leading academic institutions with primary focus on T1D research. The objective of the study was to evaluate the effect of a single 14-day treatment course of teplizumab to delay or prevent the onset of Stage 3 clinical T1D in patients with Stage 2 T1D (defined as those with at least 2 T1D-related autoantibodies and dysglycemia). The primary analysis of the TN-10 study was conducted in 2018, and results were available in 2019 and form the basis of this Biologics License Application (BLA) submission.

- Efficacy: The efficacy results from the TN-10 study support the proposed indication for teplizumab for the delay of progression to Stage 3 clinical T1D in patients with Stage 2 T1D. Efficacy is further supported by confirmatory evidence in the form of a meta-analysis of C-peptide levels, which demonstrates preservation of beta cell function in newly diagnosed Stage 3 patients, as requested by and agreed upon with Food and Drug Administration (FDA), signifying teplizumab's effect on the underlying pathophysiology of the disease.

- Safety: In the TN-10 study, a single treatment course of teplizumab showed no new safety signals beyond those observed in the prior Stage 3 studies. The most commonly reported AEs in the teplizumab group were transient lymphopenia, rash, and leukopenia. The safety findings from nearly 800 patients exposed to teplizumab with approximately 1,500 patient-years of follow-up in the Stage 2 and

Stage 3 T1D studies provide adequate population follow-up to support the safety profile of teplizumab for the proposed indication.

Efficacy Findings in Pivotal TN-10 Study

The TN-10 study was a multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of teplizumab in patients with Stage 2 T1D. Eligible patients were ages 8–45 years at the time of enrollment in the TrialNet Natural History Study (TN-01 study), which was the source of patients for the TN-10 Study (see Appendix 10.1), had a relative with Stage 3 T1D, and had 2 or more T1D-related autoantibodies and evidence of dysglycemia at baseline. Patients were randomized (1:1) to receive a single 14-day regimen of either teplizumab (with a total cumulative dose of 9.0 mg/m^2) or placebo, by intravenous (IV) infusion. Oral glucose tolerance tests (OGTTs) were performed at baseline, Month 3, Month 6, and every 6 months thereafter, or if indicated by symptoms or random screening glucose levels, until either clinical T1D diagnosis (ie, reaching Stage 3) or study termination.

The primary efficacy endpoint in TN-10 was the time to the diagnosis of Stage 3 clinical T1D. At least 71 patients were planned to be enrolled and followed until 40 patients were diagnosed with Stage 3 clinical T1D (refer to Section 6.1.1.2). The following signs, symptoms, and blood glucose levels were diagnostic of clinical T1D, but the primary endpoint needed to be confirmed by OGTT tests on 2 occasions at least 1 day apart:

- Symptoms of diabetes such as polyuria, polydipsia, or unexplained weight loss AND a casual plasma glucose concentration >200 mg/dL
- Fasting plasma glucose ≥126 mg/dL
- 2-hour plasma glucose ≥200 mg/dL

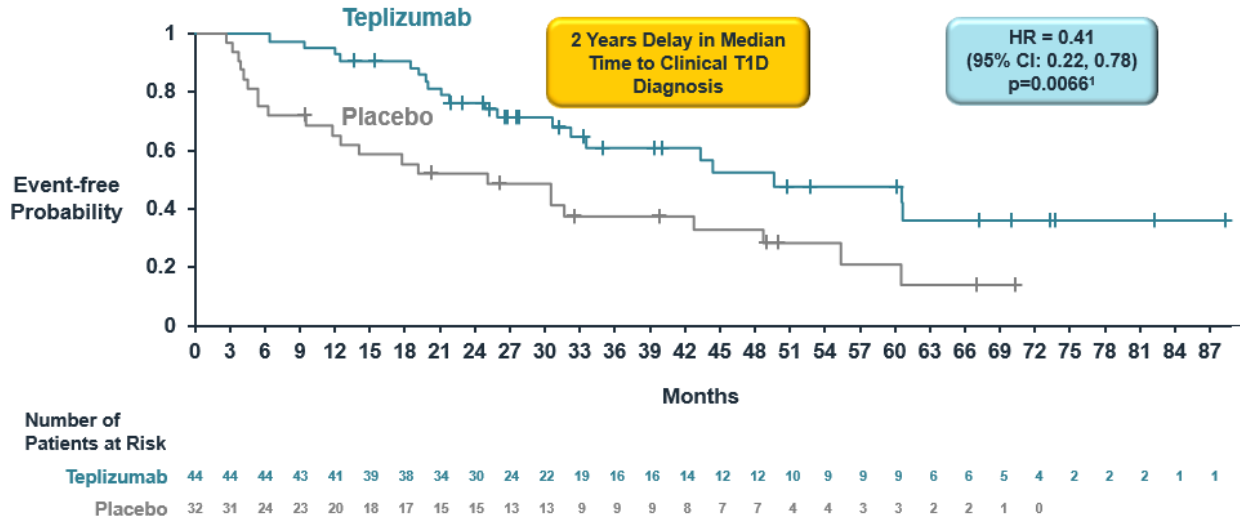
A total of 44 patients were randomized to the teplizumab group and 32 to the placebo group. Randomization was stratified by investigator's site (n=16) and age group (<18 vs ≥18 years) with block sizes of 4. The imbalance in number of patients between teplizumab and placebo was due to the low-enrolling sites. Nine of 16 sites randomized ≤3 patients. All 76 patients received treatment and were included in the Intent-to-Treat (ITT) and Safety Populations. Three patients in each treatment group terminated or discontinued the study early; however, 3 of these patients were diagnosed with Stage 3 clinical T1D (1 teplizumab, 2 placebo) and therefore met the primary endpoint. Of the remaining 3 patients, 2 withdrew consent (1 teplizumab, 1 placebo) and 1 was lost to follow-up (placebo); these 3 patients were censored from the primary analysis.

Baseline demographics were well balanced between treatment groups (details are provided in Section 6.1.2.2). The median age was 14 years in the teplizumab group and 13 years in the placebo group, with age ranging from 8.5 to 49.5 years. The 49.5-year-old patient was less than 45 years old at the time of enrollment in the TrialNet Natural History Study, which was the source of patients for the TN-10 study. Fifty-four percent of patients

were male, and the majority were White. The types and frequencies of T1D-related autoantibodies were generally comparable between groups at baseline. Baseline clinical characteristics were also well balanced. The mean non-fasting glucose level was 163 mg/dL in the teplizumab group and 155 mg/dL in the placebo group, and the mean HbA1c was approximately 5.2% in both groups.

The primary endpoint, time to Stage 3 clinical T1D diagnosis, was significantly delayed by a single 14-day course of teplizumab. The median time (95% confidence interval [CI]) to clinical T1D diagnosis was 49.5 months (32.2, Not Estimable) in the teplizumab group compared to 24.9 months (9.5, 48.6) in the placebo group, for a difference of 24.6 months (Figure 1). The primary analysis evaluated the hazard rate between treatment groups (ie, the hazard ratio) and was tested at the 0.025 level, one-sided, using the Cox Proportional Hazards model. The hazard ratio of clinical T1D onset between treatment arms obtained from the Cox model was 0.41 (95% CI: 0.22 to 0.78; p=0.0066), which represents a 59% reduction in risk of developing T1D.

Figure 1: TN-10: Time to Type 1 Diabetes Onset



[1] Cox Proportional Hazards model
Note: Tick marks indicate censored patients
Abbreviations: HR=hazard ratio, ITT=intent-to-treat, T1D=type 1 diabetes

At the time of the primary analysis, 54.5% (24/44) and 28.2% (9/32) of patients remained free of clinical T1D in the teplizumab and placebo groups, respectively.

The largest difference between groups was observed in the first year, and the benefit of teplizumab was preserved through Year 5. As shown in Figure 1, at the end of the study, there were more teplizumab-treated patients who did not progress to Stage 3 clinical T1D beyond the median of 48.4 months, suggesting that teplizumab may result in a prolonged delay of progression to Stage 3 clinical T1D in some individuals.

Pre-specified subgroup analyses of baseline characteristics were conducted. In general, the hazard ratio point estimates consistently favored teplizumab. The small numbers of

patients in most of the subgroups led to the overlap in the 95% CIs, and in conjunction with lack of adjustment for multiplicity of comparisons, it is difficult to draw definitive conclusions on the effect of teplizumab in specific subgroups. Overall, teplizumab demonstrated consistent benefit over placebo regardless of baseline factors.

As noted earlier, the underlying autoimmune process in T1D results in progressive destruction of pancreatic beta cells. C-peptide is a by-product of intracellular processing of pro-insulin to insulin and secreted by beta cells in equimolar amounts to insulin, and it is therefore a direct and standard measure of beta cell function and endogenous insulin production (Leighton et al 2017). Similar to the role of glomerular filtration rate as a clinical endpoint for the assessment of renal function, C-peptide values represent a clinical endpoint that is a surrogate for endogenous insulin production and thus can be used to monitor the status of T1D disease and its progression. Preservation of beta cell function is associated with more effective glycemic control and achievement of glycemic targets (HbA1c) (Dayan et al 2019).

In the TN-10 study, C-peptide was a pre-specified secondary outcome and showed that patients treated with teplizumab had significantly improved beta cell function compared to those treated with placebo. Figure 14 shows the change from baseline in C-peptide area under the concentration-time curve (AUC), a measurement of the total amount of C-peptide, following a 2-hour OGTT during the study. The analysis of C-peptide AUC over a 24-month period showed a statistically significant difference between treatment groups (Figure 15). These findings further support the effect of teplizumab in preserving beta cell function in this population.

Confirmatory Evidence: Meta-Analysis of C-peptide in Five Stage 3 T1D Studies

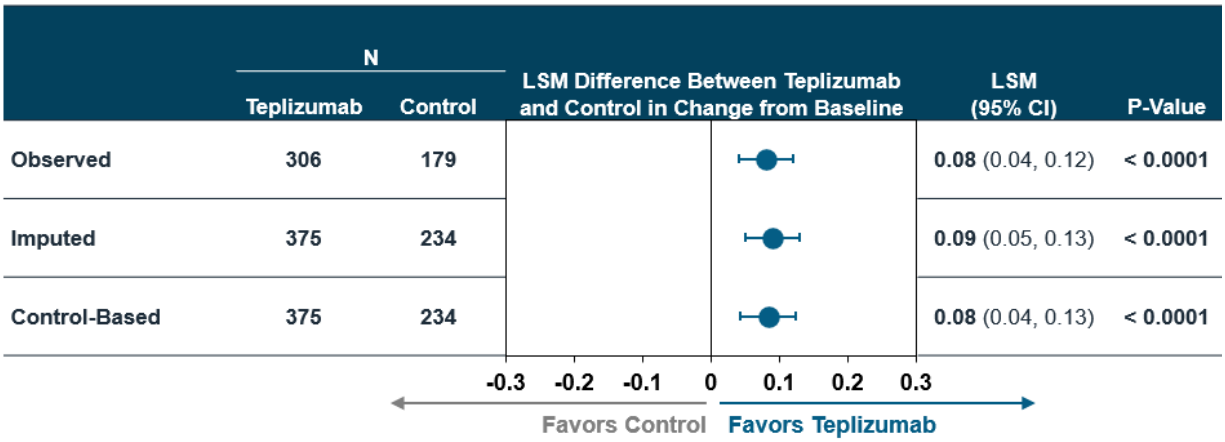
Confirmatory evidence in the form of a meta-analysis, which was recommended by and the design agreed upon with FDA, was conducted using pooled C-peptide data from 5 supportive studies, all of which were randomized clinical studies: Protégé, Encore, Study 1, AbATE, and Delay. These 5 studies compared teplizumab to either placebo or standard of care in newly diagnosed patients with Stage 3 clinical T1D and had similar designs that allowed for cross-study comparisons (Table 9).

The meta-analysis evaluated the change from baseline in C-peptide AUC in a 4-hour mixed meal tolerance test (MMTT). Analysis of covariance (ANCOVA) was used to predict mean C-peptide values (least square means) as well as respective treatment differences. The meta-analysis had 2 components: one analysis was performed on all 5 studies through 1 year of follow-up, and a second analysis was performed on the 3 studies that had 2 years of follow-up.

In the meta-analysis of the 1-year (Figure 2) and 2-year C-peptide data (Figure 3), patients treated with teplizumab showed significantly higher C-peptide levels compared to control ($p<0.001$ for both). This effect was consistent for observed and imputed data at

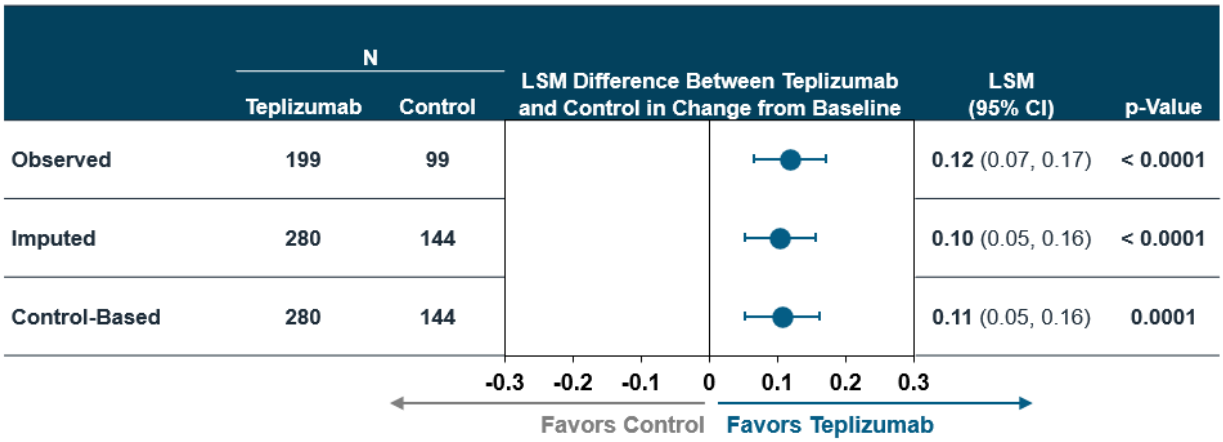
both 1 year and 2 years, as well as in sensitivity analyses that assigned control data to missing data in the teplizumab group.

Figure 2: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-Peptide AUC (nmol/L) at 1-Year Follow-up in Supportive Study Meta-Analysis



Note: Analysis conducted and results presented for ln(AUC+1)
Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, N=number with 1-year data included in the meta-analysis

Figure 3: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide AUC (nmol/L) at 2-Year Follow-up in Supportive Study Meta-Analysis



Note: Analysis conducted and results presented for ln(AUC+1)
Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, N=number with 2-year data included in the meta-analysis

Supportive Data: Summary of Insulin Use in Five Stage 3 T1D Studies

In the same 5 studies included in the C-peptide meta-analysis, exogenous insulin use was evaluated individually in each study. The mean insulin use over each timepoint in

each study was numerically lower in teplizumab-treated patients compared to placebo (Figure 20). In 2 of the studies (AbATE, Study 1) the difference was statistically significant.

Overall, these data support that teplizumab preserves beta cell function, as measured by C-peptide levels, and correspondingly, endogenous insulin production, resulting in a lower need for exogenous insulin.

Overview of Safety

Nearly 800 patients have been exposed to 1 or 2 courses of teplizumab dosing regimens, with approximately 1,500 patient-years of follow-up. The cumulative data demonstrate that teplizumab has an acceptable safety profile and given the experience to date, there has been no evidence of increased risk of serious infections or malignancies. Most of the AEs with teplizumab treatment were mechanism-based and predictable, and because teplizumab is given as a one or two-course regimen and not chronically, the events are transient and manageable.

Safety Results in TN-10 Study

In the TN-10 study, the overall median follow-up was 24.5 months (teplizumab 27.5 months [maximum 88.1 months], placebo 17.8 months [maximum 70.1 months]). A single treatment course of teplizumab showed no new safety signals beyond those observed in the earlier Stage 3 studies. The most commonly reported AEs in the teplizumab group were lymphopenia, rash, and leukopenia, all of which occurred more frequently in the teplizumab group compared to the placebo group.

Infection-related AEs occurred more frequently in the teplizumab group; however, most were Grade 1 or Grade 2 in severity and involved upper respiratory infections. Epstein-Barr virus (EBV) viremia was noted in 9 teplizumab patients with viral loads above 3,000 copies/mL. All patients were positive for immunoglobulin G (IgG) at baseline and subsequent visits, indicating a history of prior EBV infection. In all of these patients, viremia occurred between 3 and 6 weeks after dosing and resolved by Month 3 in 7 patients. The other 2 patients still had low levels (<1,000 copies/mL) at Month 12. In 1 patient, the viremia resolved at the 18-month visit, and decreased to 500 copies/mL at Month 48 in the other patient. Only 1 patient reported clinical symptoms of nasopharyngitis, which resolved in 3 weeks. The patient's EBV viral load peaked at 1 million copies/mL at Week 6 and resolved by Month 12. No other opportunistic infections were reported.

One patient in the teplizumab group had a Grade 2 AE of cytokine release syndrome (CRS), which resolved despite continued dosing. Seven patients (15.9%) in the teplizumab group and 1 (3.1%) in the placebo group experienced serious adverse events (SAEs).

No AEs of diabetic ketoacidosis (DKA), major hypoglycemia, malignancies, or deaths were observed in the TN-10 study.

Safety Results in the Pooled Analysis

Safety was integrated across 5 studies conducted in patients with Stage 2 or Stage 3 T1D (Protégé, Encore, AbATE, Delay, and TN-10). The safety data from these 5 studies were pooled based on their similar enrollment criteria and randomized controlled designs. In these studies, 773 patients were exposed to 1 or 2 courses of teplizumab, 220 to placebo, and 25 to standard of care. An additional 18 patients from the Delay study who were initially randomized to placebo, completed 1-year follow-up, and elected to receive open-label teplizumab at year 2 were included in the Pooled Safety Population, for a total of 791 patients exposed to teplizumab. In addition to the 5 studies in the pooled analysis, deaths and pregnancies were summarized from the Protégé Extension study.

A summary of the AEs in the Pooled Safety Population is shown in Table 1. The majority of patients in the teplizumab (99.5%) and control (95%) groups reported at least 1 AE. In the teplizumab group, 12% of patients experienced SAEs, and 14% experienced AEs leading to study treatment discontinuation. Two deaths occurred in the teplizumab group during the randomized controlled studies (9 and 15 months after the last teplizumab dose), and 1 additional death occurred in the Protégé Extension study (26 months after the last teplizumab dose; this event was not part of the pooled safety data). None of the deaths occurred during the dosing period (see Section 7.9 and Appendix 10.3 for details).

Table 1: Summary of Adverse Events (Pooled Safety Population)

	Teplizumab N=791[2] n (%)	Control N=245 n (%)
Patients with at least 1 type of event[1]		
AE	787 (99.5)	233 (95.1)
SAE	98 (12.4)	20 (8.2)
AE leading to study drug discontinuation	113 (14.3)	9 (3.7)
Death	2[3] (0.3)	0

[1] Patients who had more than 1 AE or SAE for a treatment were counted once.
[2] Delay patients initially randomized to the control arm, who were later also eligible for the open-label Course 2 administration of teplizumab, are counted once for each treatment arm.
[3] 1 additional death occurred in the Protégé Extension study
Abbreviations: AE=adverse event, SAE=serious adverse event.

The most common AEs were mechanism-based and related to T cell CD3 partial agonism, leading to transient lymphopenia (due to upregulation of adhesion molecules that results in accumulation and adhesion of lymphocytes to the blood vessel wall [lymphocyte margination]) and transient cytokine release. Lymphopenia was observed in approximately 80% of teplizumab patients and typically resolved despite continued dosing. In most patients, circulating lymphocytes returned to baseline values within 28 days, and there appears to be no associated increased risk of clinical infections with approximately 1,500 patient-years of follow-up. Other common AEs included leukopenia, neutropenia, decreased blood bicarbonate, and rash (Table 22). Most of these events were Grade 1 or Grade 2 (mild to moderate) in severity.

In the System Organ Class (SOC) of Infections and Infestations, comparable rates were reported in the 2 groups (53.0% teplizumab vs 52.7% control). The most common infections reported in more than 5% of patients included upper respiratory infection (19.0% teplizumab vs 17.6% control), nasopharyngitis (11.1% teplizumab vs 9.4% control), and pharyngitis (5.1% teplizumab vs 4.5% control).

The frequency of SAEs was 12% in the teplizumab group and 8% in the control group. Most of these events were associated with underlying T1D, including DKA (2.3% teplizumab, 0.4% control) and hyperglycemia (0.6% teplizumab, 1.2% control) (see Section 7.10). No other SAE occurred in more than 1% of patients.

AEs leading to study treatment discontinuation were more frequent in the teplizumab group (14%) compared to the control group (4%). More than half of these AEs were due to laboratory abnormalities that met protocol-defined discontinuation criteria. In both groups, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were the most common AEs leading to discontinuation and were considered to be due to transient cytokine release in the teplizumab group.

Adverse Events of Interest in the Pooled Analysis

Given the novel mechanism of action of teplizumab and the characteristics of the T1D population, certain AEs of interest were evaluated in the Pooled Safety Population. These AEs include infections, CRS, liver function abnormalities, DKA, major hypoglycemia, hypersensitivity reactions, serum sickness, and pregnancy. The risk of infection was monitored because of the immune modulatory mechanism of action of teplizumab. As noted earlier, consistent with teplizumab's mechanism of action via T cell CD3 partial agonism, mild cytokine release may occur in the initial days of teplizumab treatment until T cells become quiescent. Symptoms of CRS include rash, headache, nausea, vomiting, chills, and pyrexia. Transaminase elevations with or without bilirubin elevations can also occur with CRS. Events related to glycemic control such as DKA and "major" hypoglycemia (defined in the clinical program as ≥Grade 3 hypoglycemia alone, or ≥Grade 3 hypoglycemia associated with seizures, unconsciousness, or coma), which may be an adverse effect of insulin treatment, were investigated as AEs of interest.

In the pooled analysis, teplizumab was not associated with increased risk of serious infections, including opportunistic infections. With regard to EBV, the majority of patients were seropositive on study entry (teplizumab 76.6% and placebo 72.3%). New EBV infections were reported in 18 (2.3%) teplizumab patients and in 10 (4.1%) controls. Teplizumab does not appear to increase the likelihood of new EBV infection. Reactivation of EBV was reported in 40 (5.1%) teplizumab patients and 6 (2.4%) control patients. The viremia observed during reactivation was transient and typically occurred at a single study visit. Overall, teplizumab does not appear to increase the risk of primary EBV infection. Reactivation of EBV occurred more commonly in teplizumab patients, but these events were generally asymptomatic, and viremia, if present, was transient.

The majority of patients were seropositive for cytomegalovirus (CMV) on study entry (teplizumab 59.5% and placebo 59.2%). CMV infection was reported in 2 (0.3%) teplizumab patients and none in control. CMV test positive was reported in 8 (1.0%) teplizumab patients and 2 (0.8%) control patients, and all were asymptomatic. Of the 10 teplizumab patients with CMV infection or CMV test positive, 5 had asymptomatic new or primary infection (0.6%) and 4 (0.5%) had asymptomatic reactivation. The last patient was seropositive at baseline, which was reported erroneously as an AE. Of the 2 control patients, both were new or primary infections.

The incidence of CRS was higher in the teplizumab group (5.8%) compared to the control group (1%). Most events of CRS were observed during the first 3–5 days of dosing. The majority (88%) of these events were mild to moderate in severity and resolved within 2–3 days despite continued teplizumab dosing. Six cases were designated as SAEs due to the need for hospitalization (3 each of Grade 3 and Grade 2 events). CRS led to discontinuation in 9 of 46 patients in the teplizumab group, and all resolved without sequelae. No Grade 4 events of CRS or deaths due to CRS were reported. Elevated transaminase occurring concomitantly with elevated bilirubin was rare and occurred only in the setting of CRS (5 cases). Individual analyses of these cases support the hypothesis that the elevations were related to CRS, and no liver pathology was associated with these transient findings. More details on CRS are provided in Section 7.10.2.

SAEs of DKA and ketoacidosis occurred more frequently in the teplizumab group compared to the control group (Table 2). DKA was not observed in the TN-10 study; however, it should be noted that patients were not followed in the study after the diagnosis of Stage 3 clinical T1D. The 19 DKA events that were observed in the Stage 3 T1D population occurred approximately 10 months after the end of teplizumab or placebo treatment (mean 298.9 days, median 307, range 42–681). These events were associated with common triggering causes of DKA in diabetic patients, including infections and inappropriate insulin dose or lack of dietary adherence. These patients had a mean HbA1c of 11.9% (median 12.3%; range 7.1 to 17.3%) near the time of the DKA event, suggesting poor glycemic control, which was further evidenced by a mean blood glucose level of 439 mg/dL (median 422; range 290–726) for those available at the time of the DKA episode (n=9). In the teplizumab group, the observed cumulative incidence of DKA was 2.4% (19/791). Accounting for variation in the duration of follow-up, the incidence rate for DKA and ketoacidosis is 0.013 per patient-year (19 patients/1,464 patient-year experience). In the placebo group, the observed cumulative incidence of DKA is 0.4%, and after adjusting for the duration of follow up, the incidence rate for DKA is 0.002 per patient-year (1 patient/438 patient-year experience).

SAEs of hypoglycemia (Table 3) were observed in Stage 3 patients and none in Stage 2 TN-10 patients. In the Pooled Safety Population, the events are comparable between groups, with the exception of the 6 Stage 3 patients all in the teplizumab group (0.8%) who experienced hypoglycemic seizures. Review of these 6 patients identified multiple confounding factors; therefore, it is difficult to establish whether there is a causal

relationship with teplizumab. The observed cumulative incidence is 0.8% (6/791), and accounting for differences in duration of follow-up, the incidence rate for hypoglycemic seizure is 0.004 per patient-year (6 patients/1,464 patient-year experience).

Table 2: Serious Adverse Events of Diabetic Ketoacidosis and Hyperglycemia (Pooled Safety Population)

	Teplizumab N=791		Control N=245	
Preferred Term	**n**	**%**	**n**	**%**
Diabetic ketoacidosis	18	2.3%	1	0.4%
Ketoacidosis	1	0.1%	0	0
Diabetic ketosis	1	0.1%	0	0
Ketosis	0	0	1	0.4%
Hyperglycemia	5	0.6%	3	1.2%

Table 3: Serious Adverse Events of Hypoglycemia (Pooled Safety Population)

System Organ Class	Teplizumab N=791		Control N=245	
Preferred Term	**n**	**%**	**n**	**%**
Metabolism and Nutrition Disorders				
Hypoglycemia	5	0.6%	1	0.4%
Nervous System Disorders				
Hypoglycemic seizure	6	0.8%	0	0
Hypoglycemic unconsciousness	2	0.3%	1	0.4%
Hypoglycemic coma	1	0.1%	1	0.4%

Benefit-Risk Summary

Virtually all patients with Stage 2 T1D who do not receive intervention will progress to Stage 3 clinical T1D, resulting in lifelong insulin dependence. Current therapies for T1D are directed at Stage 3 disease; there are currently no treatments approved for Stage 2 T1D to address the underlying autoimmune process. A therapy that disrupts the causative mechanism of T1D preserves functioning beta cells, leading to the delay of progression to insulin dependence, would have a beneficial impact on the patients and families who manage this devastating disease.

In the TN-10 study, a single 14-day course of teplizumab resulted in a 2-year median delay in the progression to Stage 3 clinical T1D in patients with Stage 2 T1D. Due to the challenges of conducting the study, with an enrollment time of 6 years (2011-2017) and follow-up of an additional 1 year to reach the event rate, TN-10 enrolled a relatively small number of patients (n=76); nonetheless, the results were highly statistically significant. The delay of progression to clinical T1D is a clinical outcome that can be measured objectively and is therefore not susceptible to bias. Beyond 5 years, 9 teplizumab patients (compared to 3 placebo patients) have maintained freedom from Stage 3 clinical T1D

after a single course of teplizumab, suggesting that the persistence of efficacy may translate to a prolonged delay of Stage 3 T1D in some patients. Although not powered to detect differences across subgroups, the findings from the TN-10 study support the beneficial effects of teplizumab across the entire Stage 2 population studied.

The benefits of the observed minimum 2-year delay in the median time to diagnosis of clinical Stage 3 T1D and potential prevention of the onset of T1D in at-risk patients are clinically meaningful. Based on self-reported treatment preferences, families with children at high risk of developing Stage 3 T1D indicated their willingness to accept side effects of a novel treatment for a delay of 2 years before becoming insulin dependent (DiSantostefano et al 2020). A delay of 2 or more years lessens the amount of time that young people will experience the clinical implications and complications of Stage 3 T1D during their teenage or young adult years – a time in life when glycemic control is particularly difficult, likely due to reduced compliance with the complex demands of insulin therapy (Dayan et al 2019; Miller et al 2015; Wood et al 2013). It is now well established that exposure to hyperglycemia is the dominant factor in the etiology of microvascular complications in T1D and that an agent that reduces the level of glycemia will have long-term clinical benefits (Palmer et al 2004). Finally, it has been reported that patients diagnosed with clinical T1D early in life experience greater loss of life expectancy (Rawshani et al 2018). Thus, a treatment that delays the onset of clinical T1D beyond the childhood years could have important long-term impact.

The efficacy data from the TN-10 study is supported by the preservation of beta cell function as demonstrated by the statistically significant results of meta-analyses of C-peptide levels in Stage 3 patients. Lower mean insulin use over time from the individual studies further support the C-peptide findings. Together, these data provide evidence that teplizumab protects beta cells throughout the disease continuum.

Based on the experience to date in Stage 2 and Stage 3 T1D, the main risks with teplizumab are mechanism-based, predictable and transient with no evidence of increased risk of infections or malignancies. While not included in the pooled safety data, 7-year follow-up of teplizumab-treated Stage 3 or newly diagnosed patients in the AbATE study showed no increased risk of infections and no malignancies were observed (Perdigoto et al 2019).

It is not clear if there a causal relationship between teplizumab treatment and the observed higher incidence of DKA and major hypoglycemic events in the Stage 3 T1D population. It should be noted that blinded data (120-day safety update; median follow-up 208 days) from 161 patients in the ongoing Phase 3 PROTECT study in Stage 3 T1D (NCT03875729) has not shown any DKA or hypoglycemic clinical events (seizure, unconsciousness or coma). If approved, Provention Bio is committed to promoting education for patients, caregivers, and healthcare professionals on the need for ketone and blood glucose monitoring, dietary adherence, and adjustment of insulin dosing for those who progress to clinical Stage 3 disease. These events will continue to be

monitored in a post-marketing registry or surveillance program to determine if a causal relationship exists.

Teplizumab will be administered in outpatient settings staffed by healthcare providers who are experienced in the administration of biologics and the treatment of potential adverse reactions. Clinical symptoms and laboratory values should be monitored during infusions, and routine follow-up care should be provided as part of the standard of care for teplizumab.

T1D is associated with significant short-term and long-term morbidity and complications, leading to decreased survival, particularly in those who develop the disease at a younger age (Rawshani et al 2018). As there is currently no available therapy, the benefit of a delay of progression to clinical T1D with this novel therapy outweighs the risk that is predictable and characterized by transient and manageable symptoms. For the first time, there is a disease-modifying therapy that has the potential to improve short- and long-term outcomes of patients with this devastating, life-changing disease.

2 BACKGROUND ON TYPE 1 DIABETES

Summary

- T1D is a relentlessly insidious and progressive autoimmune disease in which T cell-mediated destruction of pancreatic beta cells eventually results in lifelong insulin dependence.
- T1D progresses through 3 stages: Stage 1 (2 or more T1D-related autoantibodies and normoglycemia), Stage 2 (persistence of 2 or more autoantibodies and dysglycemia), and Stage 3 (clinical T1D).
- Nearly all patients with Stage 2 disease, whether familial or from the general population, will progress to Stage 3 clinical T1D due to progressive destruction of beta cells; the majority progress within 5 years, leaving them to face a lifetime of insulin dependence for survival.
- T1D can reduce life expectancy by more than a decade, with a reduction of 16 years on average for patients diagnosed with T1D before the age of 10 years.
- Current FDA-approved therapies for T1D – insulin and amylin – are directed at the metabolic complications of Stage 3 disease rather than preventing progression to Stage 3.
- There are currently no treatments approved for Stage 2 T1D and no disease-modifying treatments that focus on the underlying cause.
- A therapy that protects beta cells and preserves their function to delay the progression to clinical T1D would have profound impact on the patients and families who manage this devastating disease.

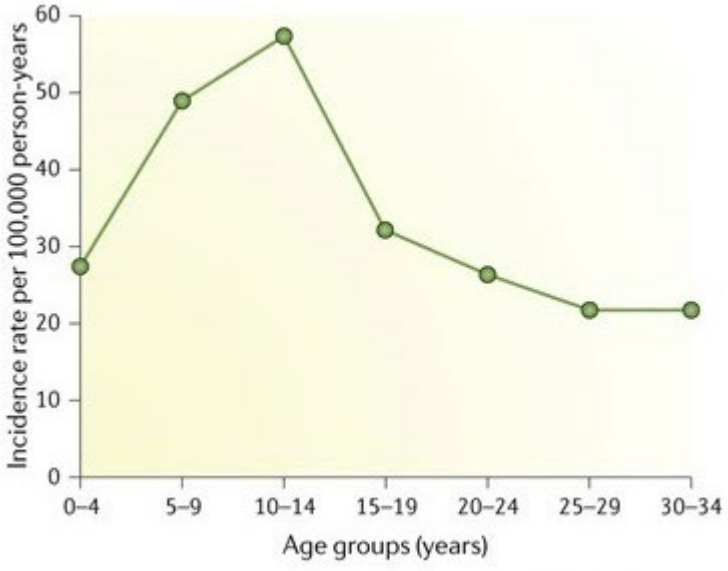
2.1 Overview of Type 1 Diabetes

T1D is an autoimmune disease in which T cell-mediated beta cell destruction results in lifelong dependence on exogenous insulin. T1D appears to be the result of an environmental trigger in genetically predisposed individuals (Akirav et al 2008; Bluestone et al 2010). While T1D is less common than type 2 diabetes (T2D), approximately 1.5 million Americans currently have T1D (CDC 2020), and it is the second-most common chronic disease of childhood (Menke et al 2013).

While the disease presents in both children and adults, the incidence rates are greater in children than adults, peaking at 10-14 years of age and remaining higher throughout adolescence (Figure 4). Those diagnosed between 11-15 years of age or 16-20 years of age have a decreased life expectancy of approximately 12 and 10 years, respectively, compared with non-diabetic age-matched controls. However, those with younger-onset disease (ie, before 10 years of age) have on average 16 years shorter life expectancy than that of non-diabetic individuals (Rawshani et al 2018). Patients diagnosed before the

age of 10 years have a 30-fold greater risk of serious cardiovascular outcomes than the general population, resulting in decreased life expectancy compared to healthy non-diabetic individuals. The cause of increased cardiovascular-related deaths is linked to lifelong increased glycemic load, which is intensified in younger-onset T1D due to more severe and rapid loss of beta cells.

Figure 4: Age-Specific Incidence Rates of Type 1 Diabetes



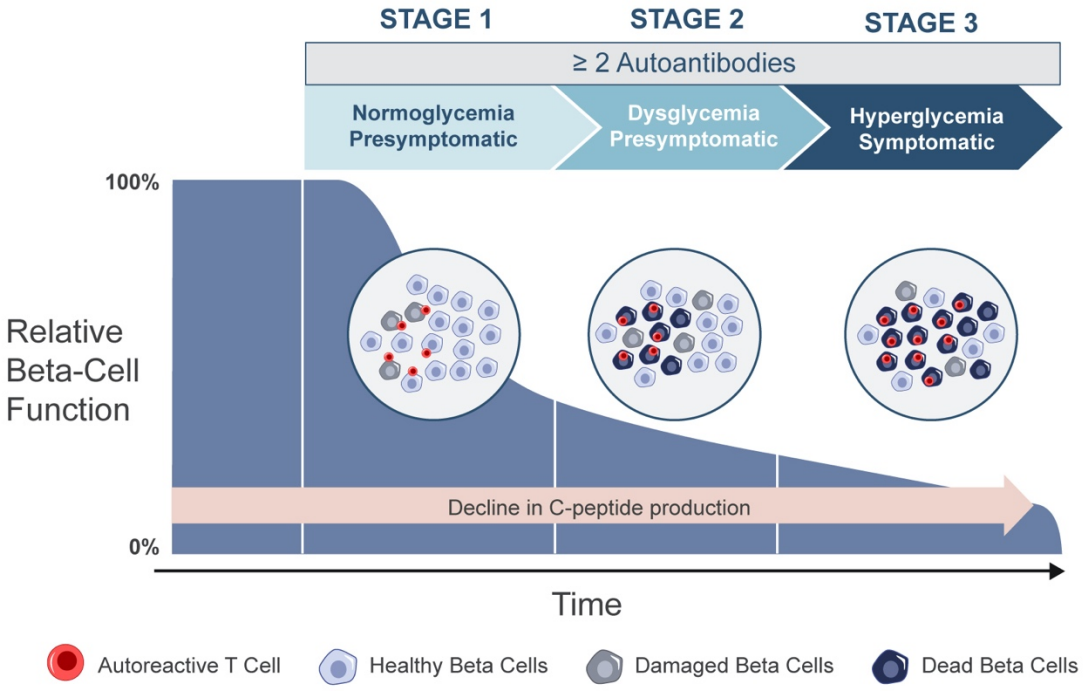
Source: Katsarou et al 2017; Rawshani et al 2014

2.1.1 Disease Progression

The clinical progression of T1D is relatively well understood as a predictable continuum marked by clinically relevant biomarkers that identify stages of the disease as shown in Figure 5 (Insel et al 2015). The natural history of T1D has been described in 3 stages:

- Stage 1: asymptomatic stage with emergence of 2 or more T1D-related autoantibodies, which reflect the initiation of the autoimmune process, and normoglycemia (44% risk of progression to Stage 3 in 5 years and lifetime risk approaches 100%).
- Stage 2: pre-symptomatic stage with persistence of 2 or more T1D-related autoantibodies with further loss of beta cell function and development of dysglycemia (75% risk of progression to Stage 3 in 5 years and lifetime risk approaches 100%).
- Stage 3: symptomatic or clinical T1D, when remaining beta cell capacity is insufficient to maintain glucose control and exogenous insulin is needed.

Figure 5: Stages of Type 1 Diabetes



Source: Insel et al 2015

Once an individual develops 2 or more T1D-related autoantibodies (ie, Stage 1), the disease is established, and progression to clinical Stage 3 T1D (symptomatic and requiring insulin) is almost inevitable. However, progression to clinical Stage 3 T1D occurs more rapidly for those whose beta cell function has deteriorated to an extent resulting in dysglycemia (ie, Stage 2 disease). The 5-year risk of developing symptomatic disease in Stage 2 is approximately 75% compared to approximately 44% with Stage 1 disease (Insel et al 2015). The progression from Stage 1 or Stage 2 to clinical Stage 3 disease is similar regardless of familial relationship or from the general population (Ziegler et al 2013).

2.1.2 C-Peptide as a Measure of Beta Cell Function

C-peptide is a short polypeptide that is cleaved from pro-insulin during the formation of insulin. C-peptide is released from the pancreas at the same time and in equal amounts as insulin (Jones and Hattersley 2013; Leighton et al 2017). Endogenous insulin production cannot be accurately measured directly in patients with T1D if they are receiving exogenous insulin, and therefore, C-peptide is used to reflect endogenous insulin production. Similar to the role of glomerular filtration rate as a clinical endpoint for the assessment of renal function, C-peptide is a clinical endpoint and thus can be used to monitor the status of T1D disease and its progression. Thus, C-peptide measurement is critical to describing the effect of treatment on preservation of beta cell function, which

could support the delay in the onset of clinical T1D and lifelong exogenous insulin dependence.

2.2 Current Treatment Options

Currently available therapies for T1D are indicated for treatment of patients with Stage 3 disease and only address the metabolic consequence of the disease (ie, hyperglycemia) rather than the underlying autoimmune process. These treatments, including insulin, approved in the 1920s, and amylin, approved in 2005, replace beta cell components. Despite improvements in care and technologies to manage the disease, the desired glycemic targets are not achieved in most patients with T1D (Miller et al 2015), and an increased risk of complications and death persists (Dabelea et al 2018; Rawshani et al 2018; Ziegler and Neu 2018).

There are no treatments approved for Stage 2 T1D. Additional challenges compound the lack of treatment options, including identifying Stage 2 patients who are not aware that they have the disease and the inadequacy of the screening process to detect T1D autoantibodies that signal that the disease is well under way. Early autoantibody screening with commercially available tests can identify those most at risk of developing T1D, reduce incidence of DKA at onset (Barker et al 2004; Elding Larsson et al 2011; Winkler et al 2012), and enable patients and families to prepare for the onset of clinical disease and lifetime of insulin administration and glucose monitoring. However, because there are no available treatment options for patients who are in Stage 2 or have no clinical symptoms, screening for T1D autoantibodies is not considered standard of care in the United States (US). Having a treatment option available will not only facilitate identification of patients eligible for treatment but also allow patients and doctors to make better informed decisions about Stage 2 T1D patient care.

2.3 Unmet Medical Need

Along with reduced life expectancy (Rawshani et al 2018), patients with T1D are at risk for secondary end-organ complications, including visual impairment and blindness, renal failure, vascular disease and limb amputation, peripheral neuropathy, and stroke. Patients with T1D also have an increased acute risk for severe hypoglycemia with potential life-threatening clinical sequelae. Moreover, at the time of diagnosis, many patients, particularly children, suffer significant morbidity frequently requiring intensive care unit admission.

In addition to the immediate and chronic medical morbidities, T1D imposes important psychosocial burden on patients, families, and caregivers. The diagnosis of T1D typically occurs suddenly in childhood and has been shown to have an immediate disrupting impact on physical, psychological, and social aspects of life (Due-Christensen et al 2018). Children with diabetes experience elevated levels of depression, anxiety, eating disorders, and psychological distress (Hanlan et al 2013; Reynolds and Helgeson 2011) and often have impaired physical growth (Santi et al 2019). Moreover, recent research

suggests that T1D may be linked to cognitive dysfunction, including persistent differences in total IQ and white matter volume, which are most pronounced when children are diagnosed at a younger age (Mauras et al 2021). Delaying clinical T1D to later in childhood or beyond is expected to reduce physical and neurocognitive deficits and may reduce diabetes-related psychological disorders.

Caregivers of pediatric patients with T1D experience high psychosocial burden due to the stress and anxiety of caring for a sick child (JDRF 2020). Patients and caregivers must incorporate insulin therapy as well as frequent monitoring and dietary and lifestyle changes. Parents report a preference for a treatment to delay onset of clinical Stage 3 T1D as opposed to only monitoring progression, understanding that such monitoring would likely reduce the risk of DKA at diagnosis (DiSantostefano et al 2020).

A therapy that could inhibit the autoimmune process leading to destruction of beta cells before they are rendered unrecoverable would delay the onset of clinical T1D and have profound impact in the management of this devastating disease.

3 TEPLIZUMAB PRODUCT DESCRIPTION

Summary

- Teplizumab is a first-in-class anti-CD3 mAb indicated for the delay of progression to clinical T1D in at-risk patients.
- Teplizumab is hypothesized to prevent the decline in beta cell function via inhibition of the immune process leading to beta cell destruction as well as re-establishment of beta cell self-tolerance.
- Teplizumab is administered by IV infusion in a single 14 consecutive day treatment course.

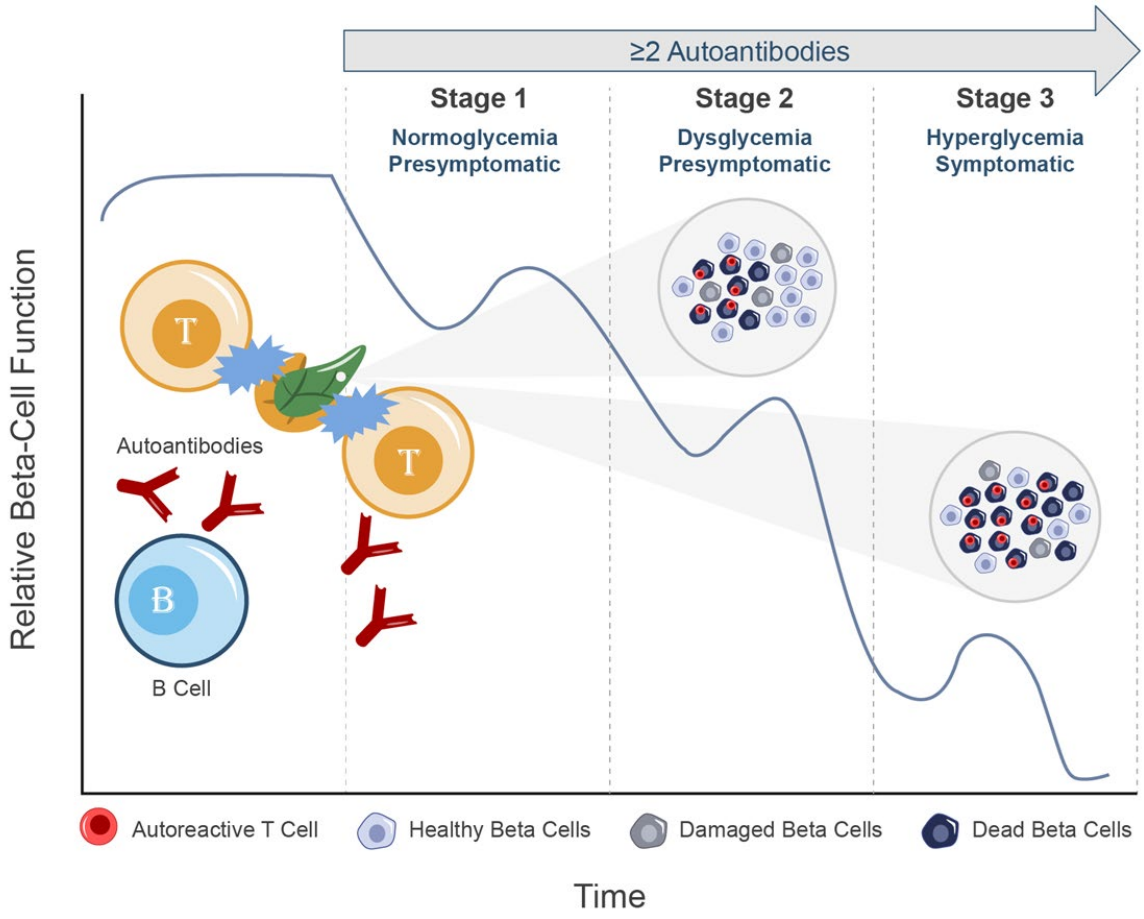
3.1 Product Overview

Teplizumab is a recombinant humanized anti-human CD3 mAb that binds with high specificity to the CD3ε chain of the TCR complex on human T cells. Teplizumab has a modified Fc region, which minimizes Fc receptor and complement binding, leading to reduced activation capacity, and thus reduced risk of CRS and improved safety and tolerability compared to the precursor anti-CD3 molecule. Furthermore, humanization of the antibody leads to decreased immunogenicity.

3.2 Mechanism of Action

While the pathophysiology of T1D is complex and multifactorial, a common denominator is the presence of autoreactive cells that react against beta cell antigens and lead to an imbalance in immune activation, which predominates and overwhelms immune regulation. This is evidenced by the presence of autoantibodies produced by B cells and by T cell infiltration of the pancreatic islets (insulitis). A current model suggests that infection of beta cells by viruses, such as coxsackievirus B, in genetically predisposed individuals would result in the generation of autoreactive T cells. These cells produce inflammatory cytokines and mediators that lead to beta cell dysfunction and eventually in beta cell destruction (van Belle et al 2011). As beta cell function declines, glycemic control is impaired. Two or more islet autoantibodies and dysglycemia define Stage 2 T1D. Stage 3, when most patients are diagnosed, is defined by overt hyperglycemia (Figure 6). Teplizumab intercepts the decline in beta cell mass and function by ‘deactivating’ the autoreactive T cells in the pancreas, which rebalances the immune system and leads to prolonged delay of the progression to Stage 3 clinical T1D.

Figure 6: Pathophysiology: Beta Cell Destruction Over the Disease Continuum

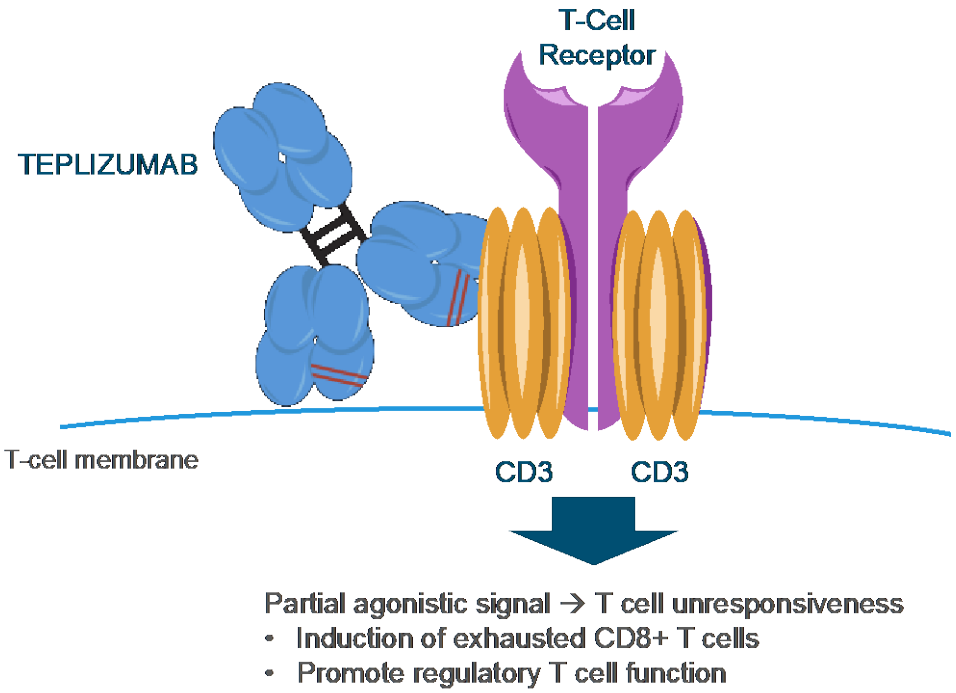


Adapted from van Belle et al 2011

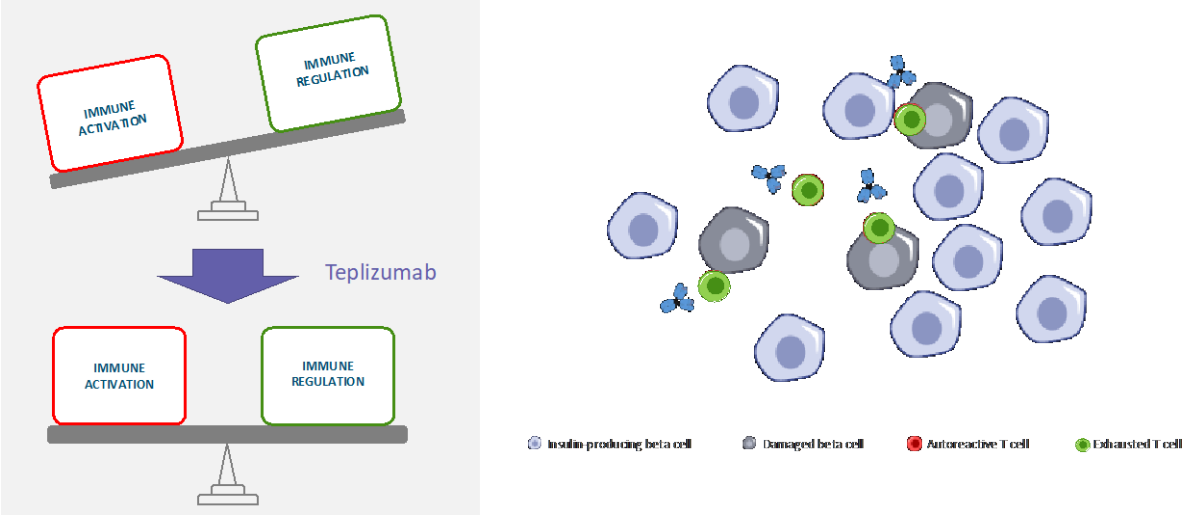
The molecular mechanism by which teplizumab deactivates the autoreactive T cells is by binding to CD3 a key component of the TCR on the surface of T lymphocytes (Figure 7). This binding does not lead to T cell depletion but rather results in partial or incomplete agonistic signaling of activated T cells leading to a state of unresponsiveness. This state of unresponsiveness is mediated by the induction of exhausted CD8+ T cells (Long et al 2016) and sparing and increasing the number and function of regulatory T cells (Ablamunits et al 2010; Bisikirska et al 2005; Long et al 2017; Waldron-Lynch and Herold 2011). The overall effect is to rebalance immune activation and immune regulation.

Figure 7: Mechanism of Action of Teplizumab

A.



B.



Adapted from Kuhn and Weiner 2016; Chen and Flies 2013

Exhaustion of T cells is a natural safeguard mechanism against excessive inflammatory damage in the context of immune responses. Exhausted T cells express inhibitory molecules on their cell surface, such as TIGIT, which has the capacity to modulate antigen-presenting cells (Yu et al 2009). It is believed that teplizumab triggers a conversion of autoreactive cells to exhausted CD8+ T cells. The increase correlates with clinical response to teplizumab in Stage 2 and Stage 3 T1D (Long et al 2016; Long et al

2017). Exhausted T cells also correlate with delayed progression to clinical T1D in the natural course of the disease in the absence of intervention (Wiedeman et al 2020).

Importantly, at the time teplizumab is administered to patients with T1D (Stage 2 or early Stage 3), the majority of the activated cells appear to be the autoreactive T cells. Since teplizumab targets activated effector cells and spares regulatory T cells and memory T cells against pathogens, the preservation of beta cells is achieved without long-term impact on immune competence (Perdigoto et al 2019). Therefore, while teplizumab is not specific for autoreactive T cells that target beta cells, preferential action on activated T cells confers a degree of selectivity.

Collectively, these mechanistic data suggest that the immunomodulatory effect of teplizumab involves not only the inhibition of the immune process leading to beta cell destruction but also facilitation of the rebalancing of effector and regulatory arms involved in T1D autoimmunity, leading to the re-establishment of beta cell self-tolerance (Lebastchi et al 2013) for extended periods of time in many treated patients, as illustrated by the results of the TN-10 study.

3.3 Dose Rationale

The early development of teplizumab focused on replacing OKT3 (muromonab, approved in 1986) for the treatment of acute renal transplant rejection. OKT3, a mouse mAb, was associated with frequent and severe CRS and immunogenicity. Teplizumab was derived from grafting the OKT3 complementarity-determining region onto a human IgG1 antibody background to minimize immunogenicity and mutating the Fc region to decrease FcR-binding activity.

While no formal dose-ranging studies have been conducted, the proposed dosing regimen has evolved from clinical testing over the past 2 decades, which has included absolute, weight-based, and body surface area (BSA)-based dosing. In the first human clinical study for the treatment of acute renal transplant rejection, the dosing regimen for teplizumab was modeled after the approved OKT3 regimen of daily IV administration of absolute daily doses for 10 to 14 days for a total cumulative dose of 76 mg (Woodle et al 1998; Woodle et al 1999). A subsequent study in patients with psoriatic arthritis given absolute daily doses with or without a ramp-up period for 12 to 14 days for a cumulative dose of approximately 40 mg suggested that a ramp-up regimen was important to decrease acute side effects of nausea, vomiting, and fever (Utset et al 2002).

From the late 1990s, teplizumab was administered in clinical studies in newly diagnosed patients with T1D as a single 12- or 14-day course that included a 2- or 4-day ramp-up period, respectively. Weight-based dosing was initially tested. However, in order to accommodate the pediatric population, whose body weight increases faster than BSA, a BSA-based dosing was adopted to minimize inter-patient variability in teplizumab exposure. The BSA-based dosing is designed to deliver a cumulative dose of approximately 9.0 mg/m^2. For reference, for a typical 10, 14, or ≥18-year-old individual

(with BSA of 1.2, 1.7, and 2.0 m^2, respectively), a 9.0 mg/m^2 dose would represent a total dose of 10.8 mg, 15.3 mg, and 18.0 mg for a treatment course, respectively.

Subsequently, 2 MacroGenics-sponsored Phase 3 clinical studies of teplizumab – Protégé and Encore – were conducted in newly diagnosed patients with T1D. In both studies, 3 teplizumab dosing regimens that included lower cumulative doses as well as a shorter regimen were evaluated:

- Full 14-day regimen: cumulative dose of ~9.0 mg/m^2 per course
    - 51, 103, 207, and 413 µg/m^2 on Days 1, 2, 3, and 4, respectively
    - 826 µg/m^2 daily on Days 5 through 14
- One-third 14-day regimen (1/3 of the dose on each day of the 14-day regimen): cumulative dose of ~3 mg/m^2 per course
- Full 6-day regimen (first 6 days of 14-day regimen): cumulative dose of ~2.4 mg/m^2 per course

Each of the treatment courses was administered twice with an interval of 6 months in between. The decision to administer 2 courses of treatment was predicated on the observation in newly diagnosed or Stage 3 T1D patients that the beneficial effects of teplizumab appear to peak 6 months after the initial course and then begin to decline slowly (Herold et al 2005).

While the novel and unvalidated composite primary endpoint (HbA1c <6.5% and insulin <0.5 U/kg/day at Week 52) was not met in the Protégé study, the full 14-day regimen that provided a cumulative dose of ~9.0 mg/m^2 was effective in preserving C-peptide levels in newly diagnosed patients with T1D at the 2-year follow-up. The benefit in C-peptide preservation was not observed in the one-third 14-day or the 6-day regimens.

In the pivotal TN-10 study in Stage 2 individuals at high risk of clinical T1D conducted by TrialNet, a single course of the full 14-day regimen (similar to full 14-day dosing regimen in the Protégé and Encore studies) was administered for a total cumulative dose of ~9.0 mg/m^2. As no prior study had been conducted in patients with Stage 2 T1D, only a single course of teplizumab was administered.

Based on the positive results of the TN-10 study, the full 14-day regimen with a 4-day ramp-up period and a cumulative dose of 9.0 mg/m^2 is recommended for the proposed indication.

3.4 Proposed Indication, Target Population, and Dosing

3.4.1 Proposed Indication and Target Population

Teplizumab is an anti-CD3 humanized mAb indicated for the delay of progression to clinical T1D in patients ≥8 years of age with at least 2 T1D autoantibodies and dysglycemia (ie, Stage 2 T1D).

While the pivotal TN-10 study enrolled relatives with T1D due to the focus of TrialNet on family members of T1D patients, and because the pathophysiology of the disease is the same and progression to clinical T1D is similar in both familial and general Stage 2 population (Ziegler et al 2020; Ziegler et al 2013), the target population is any individual with Stage 2 T1D who meets the above age criteria.

Dysglycemia is defined as an abnormal glucose tolerance in a 2-hour OGTT.

- Fasting plasma glucose ≥110 mg/dL and <125 mg/dL, or
- 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or
- 30, 60, or 90-minute value on OGTT ≥200 mg/dL

3.4.2 Dosing

Teplizumab is administered according to the following treatment course, with a cumulative dose of 9.0 mg/m^2 (also referred to as a full-dose 14-day regimen):

- Day 1: 51 µg/m^2
- Day 2: 103 µg/m^2
- Day 3: 207 µg/m^2
- Day 4: 413 µg/m^2
- Day 5–14: 826 µg/m^2

3.4.2.1 Infusion Procedure

Teplizumab must be prepared by a healthcare professional using aseptic technique. Teplizumab is administered as an IV infusion for a minimum period of 30 minutes. Teplizumab is supplied as a 2 mg/2 mL single dose vial. For preparation, 2 mL of teplizumab is added to 18 mL of 0.9% sodium chloride solution for a resulting 20 mL of 1:10 dilution (teplizumab:saline). The volume of teplizumab is calculated based on BSA-calculated dose.

Teplizumab infusion should be started within 2 hours of preparation, and the infusion must be completed within 6 hours of preparation. Patients should be monitored for signs or symptoms of adverse reactions. Should disabling symptoms occur, dosing can be temporarily paused for 1–2 days, and treatment can resume after improvement or resolution of symptoms.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The FDA granted breakthrough therapy designation for teplizumab in Stage 2 T1D.
- The teplizumab clinical development program includes the pivotal TN-10 study in patients at risk for development of clinical Stage 3 T1D and 5 studies with supportive data in newly diagnosed patients with T1D (Protégé, Encore, Study 1, AbATE, and Delay).
- At-risk patients in the Stage 2 TN-10 study were identified through TrialNet, an international network of academic institutions dedicated to prevention and early treatment of T1D.

4.1 Regulatory Milestones

The teplizumab clinical development program has been ongoing over 2 decades. The initial studies were focused on delaying disease progression (loss of beta cell function as measured by C-peptide levels) in the newly diagnosed Stage 3 population (Protégé, Encore, Study 1, AbATE, and Delay). While the registrational study in newly diagnosed Stage 3 T1D (Protégé) failed to meet the novel and unvalidated primary endpoint in 2010, the TN-10 study was initiated in 2011 to evaluate the effect of teplizumab in at-risk Stage 2 T1D patients (defined as those with at least 2 T1D-related autoantibodies and dysglycemia). All the Stage 2 (TN-10) and Stage 3 (Protégé, Encore, Study 1, AbATE, and Delay) clinical studies were conducted by academic investigators or MacroGenics before teplizumab was acquired by Provention Bio in May 2018. Provention Bio acquired teplizumab to continue the clinical development program in a newly diagnosed or Stage 3 T1D, which is a different indication from the current BLA. The Phase 3 PROTECT study in Stage 3 T1D indication was initiated by Provention Bio in April 2019 and is currently ongoing (NCT03875729).

The Investigational New Drug Application (IND) for teplizumab for the newly diagnosed (Stage 3) and at-risk indications (Stage 2) were submitted by MacroGenics in 2006 and 2009, respectively. Both INDs were subsequently acquired by Provention Bio in 2018.

The primary analysis of the TN-10 study was conducted by TrialNet in November 2018 and the results were announced by TrialNet in June 2019.

Based on the TN-10 results, Provention Bio applied for and was granted breakthrough therapy designation for teplizumab in Stage 2 T1D in August 2019. According to the FDA: "*Breakthrough therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical*

evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint."

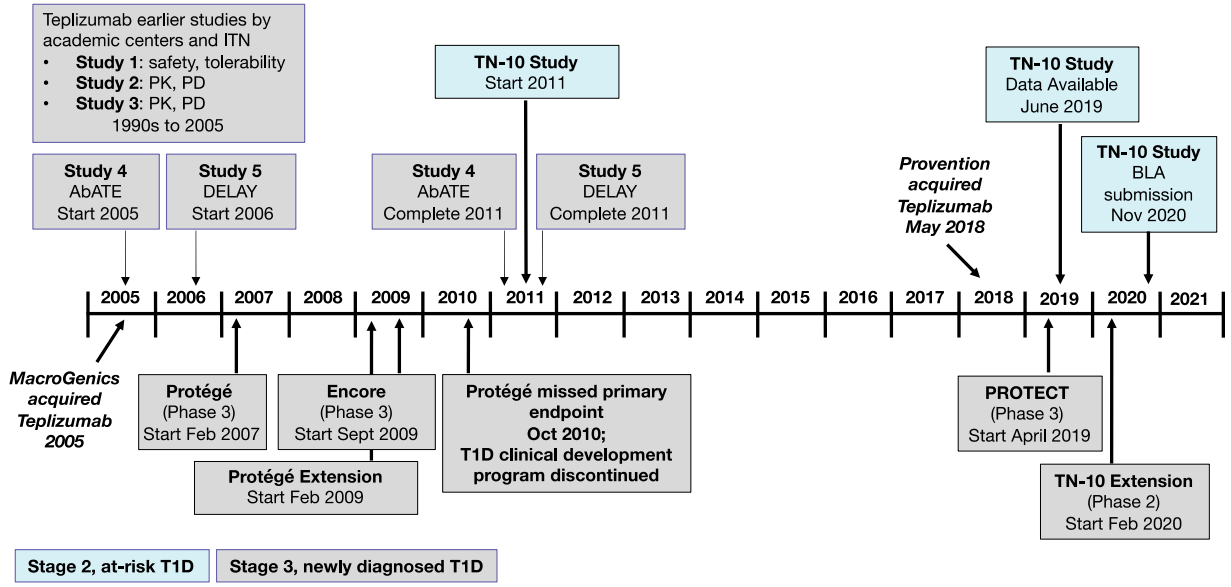
A final Statistical Analysis Plan for the supportive and confirmatory data from the C-peptide meta-analysis was approved by the FDA in June 2020.

The results of the TN-10 study form the basis of the BLA submission for teplizumab for the delay of progression to clinical T1D in at-risk (Stage 2) patients, which was completed in November 2020.

4.2 Clinical Development Program

The clinical development program is depicted in Figure 8.

Figure 8: Teplizumab Clinical Development Timeline



Abbreviations: BLA=Biologics License Application, ITN=Immune Tolerance Network, PD=pharmacodynamic, PK=pharmacokinetic, T1D=type 1 diabetes

Early studies conducted between the 1990s and 2005 in Stage 3 T1D consistently showed significant benefit in the preservation of beta cell function as measured by the clinical marker C-peptide. These studies were conducted by academic investigators and academic consortia, including the Immune Tolerance Network.

In 2005, based on the promising C-peptide preservation data, teplizumab was acquired by MacroGenics who, in collaboration with Eli Lilly, initiated a Phase 3 registrational program for teplizumab in patients with newly diagnosed Stage 3 T1D. This program consisted of 3 studies: Protégé, Protégé Extension, and Encore. As agreed with the FDA in 2006, the primary endpoint of the registrational program was a composite endpoint that measured a clinical metabolic response (insulin use and HbA1c), rather than a clinical marker of beta cell preservation (C-peptide level).

In 2010, the composite primary endpoint (insulin use and HbA1c) in the Protégé study was not met, leading to the termination of the Eli Lilly partnership and the discontinuation of the clinical development program by MacroGenics. It should be noted that the pre-specified secondary endpoint, preservation of C-peptide secretion, was met with the full 14-day teplizumab regimen, allowing glycemic control to be achieved at a lower insulin dose in the teplizumab group than in the placebo group.

In 2011, the TN-10 clinical study in Stage 2 at-risk patients was initiated. The study was sponsored by NIDDK and conducted by TrialNet, and patients were identified through the Type 1 Diabetes TrialNet Natural History Study (TN-01 study). TrialNet is an international network of academic institutions dedicated to prevention and early treatment of T1D.

In 2018, Provention Bio acquired teplizumab to continue the clinical development in patients with newly diagnosed Stage 3 T1D. As noted earlier, the composite primary endpoint (HbA1c and insulin use) in the Protégé study was not met; these metabolic endpoints, particularly insulin use, depended on patient and physician behavior (ie, how intensively they treat T1D), which may have influenced the outcome. On the other hand, promising data from the Protégé and earlier Phase 2 studies on C-peptide preservation, an objective clinical marker, led to the design of the Phase 3 PROTECT study, which was initiated in April 2019 with the intent to seek regulatory approval for the newly diagnosed Stage 3 T1D population. The PROTECT study is currently ongoing (NCT03875729).

In June 2019, the TN-10 study primary results became available, and these data form the basis of this BLA submission.

In addition, patients who develop Stage 3 T1D after the conclusion of the TN-10 study are eligible to receive open-label teplizumab within 12 months of T1D diagnosis in a Provention Bio-sponsored clinical study, the TN-10 Extension study (NCT04270942).

In discussions and agreement with the FDA, data from the Stage 3 T1D studies may be used to provide supportive efficacy (Protégé, Encore, Study 1, AbATE, Delay) and safety (Protégé, Encore, Delay, AbATE) information for the Stage 2 study (TN-10) in the at-risk population.

5 CLINICAL PHARMACOLOGY

Summary

- The terminal elimination half-life of teplizumab is approximately 4 days.
- Exposure to teplizumab is dependent on body weight and thus BSA-based dosing is appropriate to account for body-size dependence of pharmacokinetics (PK).
- A 14-day dosing regimen of teplizumab (cumulative dose of 9.0 mg/m^2) resulted in maximal CD3 receptor occupancy compared to regimens with lower cumulative dose.
- Teplizumab can lead to reversible lymphopenia and mild cytokine release due to downstream pharmacodynamic (PD) effects.
    - A decline in total lymphocyte count is generally observed over the first 5 days of dosing and begins to resolve on Day 6 despite continued dosing.

5.1 Pharmacokinetics

The PK profile of teplizumab following IV administration is described by a 2-compartment model, with saturable binding in central and peripheral compartments. The terminal elimination half-life for teplizumab is approximately 4 days. Age, sex, race, baseline immune parameters, disease state, or disease onset time do not appear to have clinically relevant effects on PK of teplizumab. Since exposure to teplizumab is dependent on body weight, BSA-based dosing is appropriate to account for the body-size dependence of teplizumab PK. Anti-drug antibodies were observed in approximately 60% of patients who received 1 course of treatment; however, there does not appear to be an effect of immunogenicity on efficacy or safety.

5.2 Pharmacodynamics

A number of biological markers have been identified that relate to the PD effects of teplizumab. The initial PD effect is occupancy (coating) of the CD3 receptor and subsequent modulation (clearance) of the CD3 receptor. Receptor occupancy and modulation were evaluated in the Protégé study, which enrolled newly diagnosed patients with Stage 3 T1D and tested 3 teplizumab dosing regimens: full-dose 14 days (9.0 mg/m^2 cumulative dose), one-third dose 14 days (~3.0 mg/m^2 cumulative dose), and truncated 6-days (~2.5 mg/m^2 cumulative dose). Data showed that in all treatment groups, teplizumab transiently bound to CD3 molecules on the surface of both CD4+ and CD8+ T cells during treatment. The full 14-day treatment regimen resulted in longer duration and higher intensity of receptor occupancy (ie, more teplizumab binding per cell). Binding of teplizumab to the CD3 receptor led to the modulation of the teplizumab/CD3 complex from the surface of the T cells, consistent with the level of receptor occupancy.

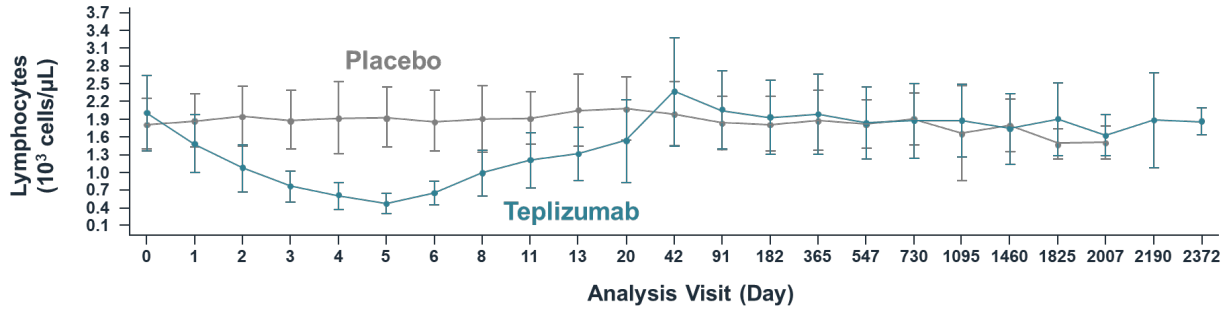
These results demonstrate a relationship between increased occupancy/modulation, increased exposure to teplizumab, and duration of dosing.

Downstream PD effects include transient and reversible lymphopenia (Section 5.2.1), ascribed to margination of T cells, and changes in T cell phenotype and subsets resulting from partial agonism of CD3.

5.2.1 Effect of Teplizumab on Lymphocyte Count

In the TN-10 study, a decline in total lymphocyte count was observed with teplizumab, with a nadir on the fifth day of dosing during a single 14-day course of treatment (Figure 9). The lymphopenia associated with teplizumab is not due to depletion (Herold et al 2009) but rather an upregulation of adhesion molecules that results in accumulation and adhesion of lymphocytes to the blood vessel wall (margination). Lymphocyte counts start to recover on the sixth day of the treatment course and generally recover to baseline levels within 28 days. The lymphocyte profile observed during dosing in the TN-10 study has been observed in all clinical studies and is considered a predictable PD marker for teplizumab effect. The Protégé and Encore studies, where a second course of treatment was administered at 6 months, showed a similar transient decrease in lymphocyte counts during the first and second courses of treatment.

Figure 9: TN-10: Total Lymphocyte Counts Over Time



Note: The first day of dosing is Day 0.

5.2.2 Effect of Teplizumab on Cytokine Levels

Mild cytokine release is likely due to partial CD3 agonism and is usually seen in the initial days of infusion until the activated T cells become quiescent. These cytokines are responsible for “mechanism-based” symptoms such as rash, headache, nausea, vomiting, and chills or pyrexia. Accordingly, CRS was monitored for in the teplizumab studies (details are provided in Section 7.10.2).

Cytokine profiles were not systematically measured in teplizumab clinical studies. However, limited cytokine measurements from early clinical studies and case narratives are available. In a study published by Herold and colleagues (Herold et al 2002) referred to as “Study 1,” newly diagnosed T1D patients received a 14-day course of teplizumab administered IV:

- Day 1: 1.42 µg/kg
- Day 2: 5.67 µg/kg
- Day 3: 11.3 µg/kg
- Day 4: 22.6 µg/kg
- Days 5–14: 45.4 µg/kg

This dosing regimen yields cumulative doses that are higher than the proposed regimen for at-risk patients. For a 14-year-old child weighing 50 kg, for example, the cumulative dose in Study 1 was ~24 mg: 71 µg on Day 1; 283 µg on Day 2; 550 µg on Day 3; 1,130 µg on Day 4; and 2,270 µg on days 5 through 14. For the proposed BSA-dose regimen of 9.0 mg/m^2, a 14-year-old child with BSA of 1.7 m^2 would receive a total dose of ~15 mg.

Cytokine levels were measured as part of Study 1. While cytokine levels generally increased from baseline and peaked after the second dose of teplizumab, the levels were lower than those typically seen in CRS associated with chimeric antigen receptor (CAR)-T cell therapy for hematological malignancies (Leisman et al 2020). Normal values for interleukin-6 (IL-6) and tumor necrosis factor (TNF) according to Mayo Clinic reference ranges are ≤1.8 pg/mL and ≤2.8 pg/mL, respectively. In Study 1, IL-6 levels increased in 8 of 12 patients and ranged from 14 to 225 pg/mL at peak, while TNF-α was detectable in all 12 patients at a range of 7 to 158 pg/mL. In CAR-T cell therapy, mean IL-6 levels are 3,110.5 pg/mL and TNF-α 52.2 pg/mL. The moderate cytokine increase observed with teplizumab is consistent with the mechanism of action of partial T cell CD3 agonism until the T cells are quiescent. The only consistent clinical manifestation reported was mild to moderate fever. No SAEs of CRS were reported in this study.

5.2.3 Biocomparability Study to Support Commercial Drug Product

Provention Bio conducted a single low-dose biocomparability study in healthy volunteers designed to evaluate teplizumab manufactured at Eli Lilly (TN-10 clinical study product) and AGC Biologics (commercial product). The products were biocomparable in terms of peak serum concentration (C_{max}), while the measurable AUCs were below the lower limit of the 80-125% biocomparability criteria. The lower drug exposure, however, did not have an impact on the pharmacodynamics (lymphocyte counts), immunogenicity, and safety, and these parameters were all found to be comparable. The Agency is actively working with Provention Bio to help resolve the PK comparability findings.

6 CLINICAL EFFICACY

Summary

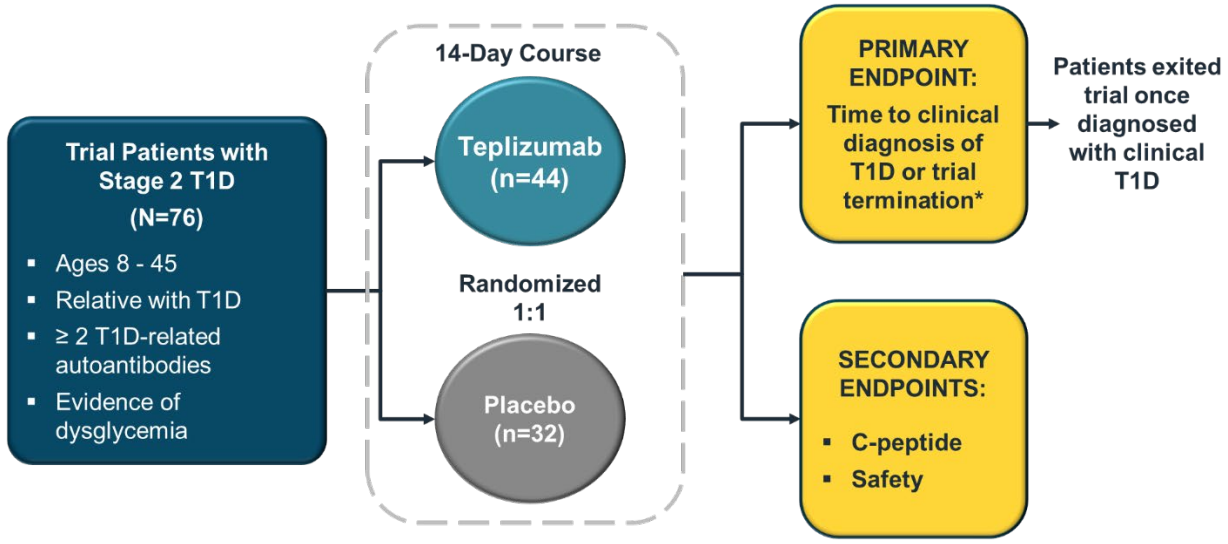
- Pivotal TN-10 study:
  - The primary endpoint was met in the randomized, placebo-controlled TN-10 study. A single 14-day course of teplizumab in patients with Stage 2 T1D significantly delayed the median onset of clinical Stage 3 T1D by a minimum of 2 years compared to placebo, with numerically more patients in the teplizumab group remaining free of clinical Stage 3 T1D beyond 5 years compared to placebo.
    - The median time to clinical T1D was doubled, from 24.9 months in placebo to 49.5 months in the teplizumab group, for a statistically significant difference of 24.6 months. The hazard ratio of clinical T1D onset between treatment arms was of 0.41 (95% CI: 0.22 to 0.78) which represents a 59% reduction in the risk of developing T1D (p=0.0066).
    - At the time of the primary analysis, 54.5% and 28.2% of patients remained free of clinical T1D in the teplizumab and placebo groups, respectively.
  - The analysis of the secondary endpoint in the TN-10 study showed that teplizumab had a statistically significant effect on preserving beta cell function as measured by C-peptide AUC levels, which were higher in the teplizumab group than the placebo group in all patients (p=0.021) and those who developed clinical T1D (p=0.030).
- Confirmatory evidence to support TN-10:
  - A meta-analysis from 5 additional randomized controlled clinical studies in newly diagnosed patients with Stage 3 T1D confirmed the effect of teplizumab on preservation of beta cell function as measured by C-peptide levels at 1 and 2 years compared to placebo or standard of care.
  - In all 5 studies, the mean exogenous insulin use over time was lower in the teplizumab group than placebo, reaching statistical significance in 3 of the studies.
  - Overall, these data support that a single 14-day course of treatment with teplizumab preserved beta cell function, resulting in the delay of Stage 3 clinical disease in patients with Stage 2 T1D.

6.1 Pivotal Data: TN-10 Study in Stage 2 T1D

6.1.1 Study Design

TN-10 was a multicenter, double-blind, randomized (1:1), placebo-controlled study to determine whether treatment with teplizumab in patients at high risk for diabetes resulted in delay or prevention of clinical T1D (Figure 10).

Figure 10: TN-10: Study Design



* The primary analysis was conducted when 40 patients were diagnosed with T1D.
Abbreviations: T1D=type 1 diabetes

Patients in the study were identified through TrialNet and were enrolled at 16 sites in the US, Canada, and Germany. TN-10 included patients 8–45 years of age who were at high risk of developing T1D based on several indicators, including the following:

- A relative who had been diagnosed with T1D. [Note that due to the focus of TrialNet on family members of T1D patients, enrollment in TN-10 comprised exclusively of Stage 2 patients with familial relationship.]
- Abnormal glucose tolerance at baseline defined as:
  - Fasting plasma glucose ≥110 mg/dL and <126 mg/dL, or
  - 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or
  - 30-, 60-, or 90-minute value on OGTT ≥200 mg/dL.
- Presence of ≥2 diabetes-related autoantibodies (anti-glutamic acid decarboxylase 65 [GAD65], anti-islet cell antibody 512 [ICA512], micro-insulin autoantibody [mIAA], zinc transporter 8 [ZnT8], and/or islet cell antibody [ICA]) on 2 occasions.

The randomization method was stratified at each TrialNet site by age at enrollment: <18 years or ≥18 years. Patients received a 14-day IV infusion of either teplizumab (as per the proposed dosing regimen described in Section 3.3) or placebo. Laboratory tests were conducted before each infusion, and vital signs were monitored for 2 hours after each

infusion. After the treatment course, patients had additional visits at Day 20, Week 6, Month 3, Month 6, and every 6 months thereafter until study termination or until clinical Stage 3 T1D was diagnosed. After the completion of the TN-10 study, patients who subsequently develop clinical Stage 3 T1D are eligible to enroll in a Provention Bio-sponsored clinical study, TN-10 Extension study, to receive open-label teplizumab treatment within 12 months of diagnosis (NCT04270942).

A Data and Safety Monitoring Board (DSMB) reviewed the efficacy and safety data twice per year throughout the course of the study. SAEs were reviewed by the TrialNet Medical Monitor, the TrialNet Safety Committee, and the DSMB, as appropriate.

6.1.1.1 Endpoint Definitions

The primary endpoint was the elapsed time from randomization to the clinical diagnosis of T1D or last contact.

Criteria for diabetes onset were based on glucose testing or the presence of unequivocal hyperglycemia with acute metabolic decompensation, such as DKA. One of the following had to be met on 2 occasions as soon as possible but ≥1 day apart (with 1 of the 2 testing occasions involving an OGTT):

- Symptoms of diabetes plus casual (ie, any time of day without regard to time since last meal) plasma glucose concentration >200 mg/dL (11.1 mmol/L). The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
- Fasting (ie, no caloric intake for ≥8 hours) plasma glucose ≥126 mg/dL (7 mmol/L).
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) from an OGTT. The test should be performed using a glucose load containing the equivalent of 1.75 g/kg body weight to a maximum of 75 g anhydrous glucose dissolved in water.

A pre-specified secondary endpoint was magnitude of beta cell preservation, as measured by C-peptide AUC responses to a 2-hour OGTT.

6.1.1.2 Statistical Analysis

Sample Size Calculation

Because of slower-than-expected rates of enrollment, the original protocol developed in 2010 (which called for the enrollment of 144 at-risk patients) was revised by TrialNet and agreed with the FDA in 2014 to reduce the sample size to 71 and to follow patients until 40 were diagnosed with T1D. This revision changed the statistical power calculation to detect a larger effect size of 60% versus the previous 50%, with 80% statistical power at a one-sided alpha level of 0.025. The Statistical Analysis Plan was finalized in March 2018 prior to unblinding to assess the primary efficacy endpoint in November 2018.

Primary Endpoint Analysis

The cumulative incidence of clinical Stage 3 T1D onset over time since randomization was estimated for each treatment group using the Kaplan-Meier method (proportion surviving diabetes-free as a function of time). The primary analysis evaluated the hazard rate between treatment groups (ie, the hazard ratio) and was tested at the 0.025 level, one-sided, using the Cox Proportional Hazards model with discrete time intervals at 3 months, 6 months, and the subsequent 6-month OGTT intervals. The primary test of treatment effect was adjusted for the design strata (≥18 years confirmed OGTT, <18 years confirmed OGTT, and <18 years unconfirmed OGTT).

The proportion of patients who were diagnosed with T1D was summarized by treatment.

Sensitivity Analyses

Time to event was evaluated by sensitivity analyses under 3 different scenarios:

- Placebo patients who were diagnosed with T1D during the first year (before 12 months) were set to 12 months
- Patients who withdrew consent or were lost to follow-up and thus censored were set to being diagnosed at their date of withdrawal or lost to follow-up
- Both of these scenarios were then combined

Subgroup Analysis

The effects of teplizumab were compared with placebo in subgroups based on baseline characteristics, including age, sex, body mass index (BMI) at baseline (<median and ≥median), autoantibodies (anti-GAD65, micro-insulin, anti-IA-2, ICA, anti-ZnT8), human leukocyte antigen (HLA) type (HLA DR3, HLA DR4), pre-treatment C-peptide (<median, ≥median), and glucose levels (<median, ≥median) during OGTT.

Results were presented in a forest plot as hazard ratios and 95% CIs of Stage 3 clinical T1D onset between teplizumab and placebo for each subgroup. The Cox model was adjusted for age, except for the interaction test for age (<18 years vs ≥18 years), but was not adjusted for multiple testing. Additionally, Kaplan-Meier graphs (over the first 24 months of the study) were presented for the 4 subgroups (anti-ZnT8 antibody status, HLA types [DR3 and DR4], pre-treatment C-peptide [<median and ≥median]) by treatment.

Secondary Endpoint Analysis

The 2-hour C-peptide AUC was calculated using the trapezoidal rule over the 2-hour period (0, 30, 60, 90, and 120 minutes) based on the time points available from the OGTT. Baseline was defined as time point 0. Results reported as less than the lower limit of detection were imputed as 0 for those time points. Once a patient was diagnosed with clinical Stage 3 T1D, no additional OGTTs were performed.

Missing Data

In general, missing values were assumed to be missing at random (MAR) unless empirical evidence to the contrary was established internal to the study. The methodology employed in analyzing time to clinical Stage 3 T1D utilized whatever follow-up had been recorded for each patient (ie, maximum utilization of follow-up time).

Presuming no evidence against MAR, and given the modest size of the study, no methods were employed to impute additional follow-up of patients who dropped out (ie, lost to follow-up). Secondary endpoints were analyzed using existing data. Imputation was used if MAR could not be justified and for any sensitivity analyses of secondary endpoints.

6.1.1.3 Key Enrollment Criteria

Key inclusion criteria included the following:

1. Patients in the TrialNet natural history study (TN-01) and thus a relative of a proband with T1D.
2. Between ages of 1–45 years at time of enrollment in TN-01 and age ≥8 at time of randomization in this study.
3. Patients <18 years of age at time of randomization must have had a TrialNet-conducted OGTT demonstrating abnormal glucose tolerance within 7 weeks (52 days) of baseline visit (Visit 0).
4. Patients ≥18 years of age at time of randomization must have had 2 consecutive TrialNet-conducted OGTTs demonstrating abnormal glucose tolerance, the most recent of which must have been within 7 weeks (52 days) of the baseline visit (Visit 0).
5. Patients must be positive for 2 or more diabetes-related autoantibodies on 2 occasions. The second occasion must occur within the 6 months prior to study drug administration but does not need to involve the same 2 autoantibodies as found on the first occasion. The autoantibodies that are to be confirmed are anti-GAD65, anti-ICA512, MIAA, ZnT8, and/or ICA.

Key exclusion criteria included the following:

1. If a patient was ≥18 years old, he or she had a diagnosis of diabetes or had a screening OGTT in which:
    a. Fasting plasma glucose ≥126 mg/dL, or
    b. 2-hour plasma glucose ≥200 mg/dL
2. If a patient was <18 years old, he or she had a diagnosis of diabetes or had a screening random glucose ≥200 mg/dL.
3. Lymphopenia (<1,000 lymphocytes/µL).
4. Neutropenia (<1,500 polymorphonuclear neutrophil [PMN]/µL).
5. Thrombocytopenia (<150,000 platelets/µL).

6. Anemia (hemoglobin <10 g/dL).
7. AST or ALT >1.5 x upper limit of normal (ULN).
8. Total bilirubin >1.5 × ULN, with the exception of patients with diagnosis of Gilbert's syndrome provided no other causes leading to hyperbilirubinemia.
9. International normalization ratio >0.1 above ULN at the participating center's laboratory.
10. A positive tuberculin purified protein derivative (PPD) test.
11. Serological evidence of current or past HIV, Hepatitis B, or Hepatitis C infection.
12. Current use of non-insulin pharmaceuticals that affect glycemic control.
13. Prior OKT3 or other anti-CD3 treatment.
14. Administration of a monoclonal antibody within the year before randomization.

A full list of inclusion and exclusion criteria is provided in Appendix 10.1.

6.1.2 Patient Disposition and Baseline Demographics

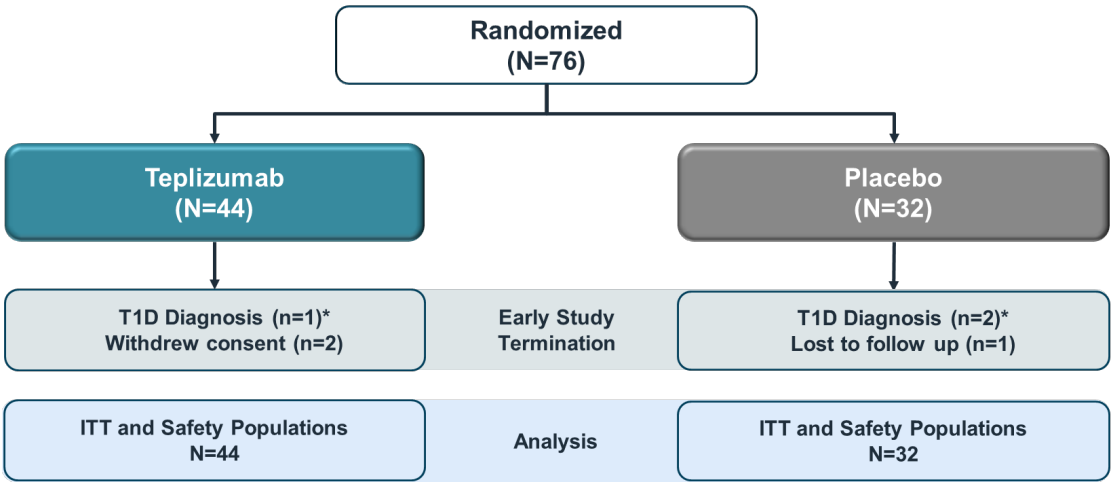
6.1.2.1 Patient Disposition

A total of 76 patients were randomized into the study: 44 were assigned to the teplizumab group and 32 were assigned to the placebo group. Randomization was stratified by investigator site (n=16) and age group (<18 vs ≥18) with block sizes of 4. The imbalance in number of patients between teplizumab and placebo was likely due to the low-enrolling sites. Nine of 16 sites randomized 3 or less patients. Randomization by study site is detailed in Appendix 10.2. Due to the low enrollment in many sites, the number of patients in each treatment group were not completely balanced. However, this imbalance did not cause incomparability in demographic and baseline characteristics between the treatment groups. To control for potential confounding effects, age and covariate strata (≥18 confirmed OGTT, <18 confirmed OGTT, and <18 unconfirmed OGTT) were included in the primary efficacy analysis. Both covariates were not significant.

All 76 patients received the study treatment and were included in the ITT and Safety Populations. Forty-three of 44 (97.7%) patients in the teplizumab group and 30 of 32 (93.8%) patients in the placebo group received all 14 doses of study drug.

As shown in Figure 11, 6 patients terminated or discontinued the study early (3 in each group). Of these 6 patients, 3 (2 placebo, 1 teplizumab) were diagnosed with T1D (ie, met the primary endpoint). The other 3 premature study discontinuations were due to lost to follow-up (1 placebo) and withdrawal of consent (1 placebo and 1 teplizumab). No patient discontinued the study prematurely due to AEs.

Figure 11: TN-10: Patient Disposition



*Patients counted as both early study termination and Stage 3 T1D diagnosis
Abbreviation: ITT=intent-to-treat

6.1.2.2 Baseline Demographics

Overall, the teplizumab and placebo groups were balanced with respect to demographic characteristics (Table 4). The median age was 14 years in the teplizumab group and 13 years in the placebo group, with a range of 8.5–49.5 years. Fifty-four percent of patients were male, and the majority were White and not Hispanic or Latino.

The teplizumab group had a lower proportion of patients less than 18 years of age compared with the placebo group (66% vs 81%, respectively) and a higher proportion of patients with BMI below median (59% vs 38%, respectively). These imbalances were likely caused by the small number of patients randomized at each site.

Table 4: TN-10: Baseline Demographics (ITT Population)

Characteristic	Teplizumab N=44	Placebo N=32
Age, year		
mean (SD)	19 (11.9)	18 (11.1)
median (min, max)	14 (8.5, 49.5)	13 (8.6, 45.0)
Age group, n (%)		
<18 years	29 (65.9)	26 (81.3)
≥18 years	15 (34.1)	6 (18.8)
Male, n (%)	25 (56.8)	17 (53.1)
Covariate strata, n (%)		
<18 years and confirmed OGTT	24 (54.5)	23 (71.9)
<18 years and unconfirmed OGTT	5 (11.4)	3 (9.4)
≥18 years and confirmed OGTT	15 (34.1)	6 (18.8)
Ethnicity, n (%)		
Hispanic or Latino	1 (2.3)	1 (3.1)
Not Hispanic or Latino	43 (97.7)	29 (90.6)
Unknown	0	2 (6.3)
Race, n (%)		
White	44 (100)	30 (93.8)
Asian	0	1 (3.1)
Multiple	0	1 (3.1)
Weight, kg		
mean (SD)	58 (24.7)	57 (19.5)
median (min, max)	52 (26.6, 143.5)	61 (27.2, 117.1)
BMI, kg/m^2		
mean (SD)	22.0 (6.38)	22.1 (4.39)
median (min, max)	20.0 (14.7, 43.7)	21.6 (16.0, 34.6)
BMI subgroup, n (%)		
<median	26 (59.1)	12 (37.5)
≥median	18 (40.9)	20 (62.5)
Relationship with person with T1D,[1] n (%)		
Sibling	30 (68.2)	19 (59.4)
Offspring	7 (15.9)	6 (18.8)
Parent	7 (15.9)	6 (18.8)
Sibling and another first-degree relative	3 (6.8)	3 (9.4)
Second-degree relative	5 (11.4)	7 (21.9)
Third-degree relative or further removed	1 (2.3)	2 (6.3)

[1] First-degree relative is defined as having at least 50% of shared genes (eg, full siblings, parents, offspring) with the patient; second-degree relative is defined as having 25% of shared genes (eg, grandparents, grandchildren, half-siblings, aunts, and uncles); third-degree relative is defined as having 12.5% of shared genes (eg, first cousins, great grandparents, and great grandchildren). A patient can have multiple relationships to persons with T1D; in such case, all relevant relationship groups are included in the calculation.
Abbreviations: BMI=body mass index, ITT=intent-to-treat, OGTT=oral glucose tolerance test, SD=standard deviation, T1D=type 1 diabetes.

6.1.2.3 Baseline Autoantibodies and HLA Status

The types and frequencies of T1D autoantibodies as well as HLA DR3 and DR4 status were generally comparable between the teplizumab and placebo groups (Table 5).

Table 5: TN-10: Baseline Type and Frequency of Autoantibodies and Presence of HLA Risk Alleles (ITT Population)

	Teplizumab N=44 n (%)	Placebo N=32 n (%)
Autoantibodies		
Anti-GAD65 (positive)	40 (90.9)	28 (87.5)
mIAA (positive)	19 (43.2)	11 (34.4)
Anti-IA-2 (positive)	26 (59.1)	24 (75.0)
ICA (positive)	29 (65.9)	28 (87.5)
Anti-ZnT8 (positive)	32 (72.7)	24 (75.0)
Number of positive autoantibodies		
1	1 (2.3)[1]	0
2	12 (27.3)	7 (21.9)
3	11 (25.0)	5 (15.6)
4	12 (27.3)	14 (43.8)
5	8 (18.2)	6 (18.8)
HLA risk alleles		
Neither DR3 nor DR4	5 (11.4)	3 (9.4)
DR3 only	10 (22.7)	8 (25.0)
DR4 only	16 (36.4)	14 (43.8)
Both DR3 and DR4	11 (25.0)	7 (21.9)
Missing	2 (4.5)	0
DR3 absent	21 (50.0)	17 (53.1)
DR3 present	21 (50.0)	15 (46.9)
DR absent	15 (35.7)	11 (34.4)
DR4 present	27 (64.3)	21 (65.6)

[1] This patient had 1 definite autoantibody detected, but the titer for the second autoantibody was borderline between positive and negative. This patient was permitted to enroll in the study at the Investigator's discretion.
Note: Autoantibody is counted positive by the following cut-off values: anti-GAD65 >20 units/mL, anti-IA-2 >5 units/mL, mIAA >0.010 units/mL, ICA ≥10 JDF units, anti-ZnT8 >0.020 units/mL.
Abbreviations: Anti-GAD65=anti-glutamic acid decarboxylase antibody, anti-IA-2=anti-islet antigen 2 antibody, anti-ZnT8=anti-zinc transporter 8 antibody, HLA=human leukocyte antigen, ICA=islet cell antibody, ITT=intent-to-treat, JDF=Juvenile Diabetes Foundation, mIAA=micro-insulin autoantibody.

6.1.2.4 Baseline Clinical Characteristics

The teplizumab and placebo groups were generally balanced in baseline glucose and HbA1c levels (Table 6).

Table 6: TN-10: Baseline T1D-Related Clinical Characteristics (ITT Population)

	Teplizumab N=44	Placebo N=32	Normal Range
Glucose AUC in OGTT, mg/dL			<180 mg/dL
mean (SD)	162.5 (22.29)	155.3 (22.94)	
median (min, max)	164.6 (115, 207)	154.4 (103, 200)	
Glucose, fasting, mg/dL			<100 mg/dL
mean (SD)	97.4	109.5	
median (min, max)	94.5 (70, 168)	101 (79, 198)	
C-peptide AUC in OGTT, nmol/L			0.5 to 2.0 nmol/L
mean (SD)	1.98 (0.85)	1.89 (0.72)	
median (min, max)	1.77 (0.6, 4.4)	1.73 (0.7, 3.8)	
HbA1c, %			<5.7%
mean (SD)	5.16 (0.33)	5.21 (0.26)	
median (min, max)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)	

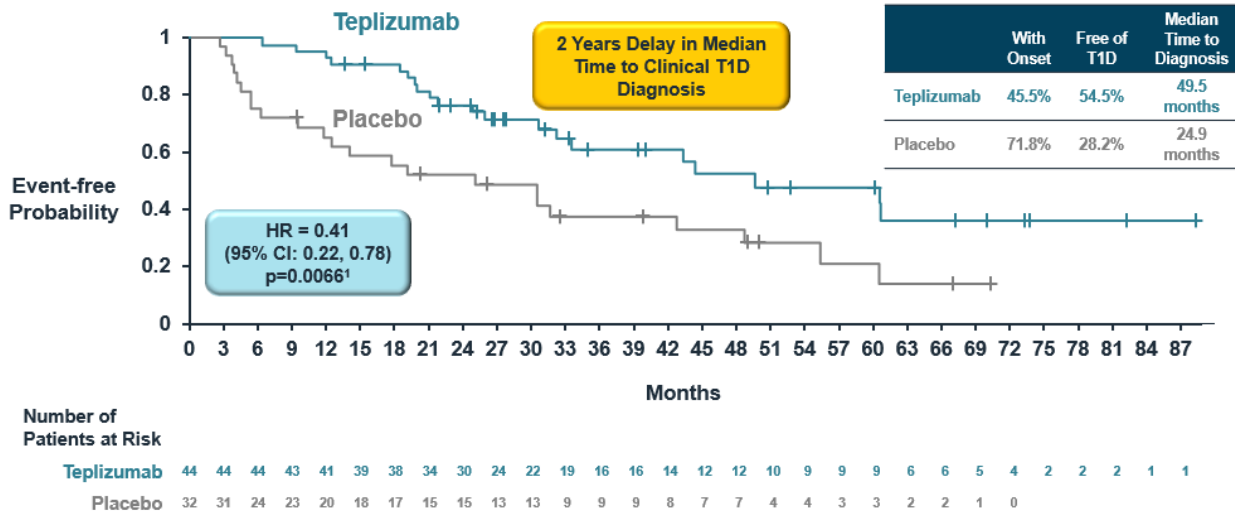
Abbreviations: AUC=area under the concentration-time curve, HbA1c=hemoglobin A1c, ITT=intent-to-treat, OGTT=oral glucose tolerance test, SD=standard deviation

6.1.3 Primary Endpoint Results: Time from Randomization to Clinical Stage 3 T1D Diagnosis

Treatment with a single 14-day course of teplizumab delayed the median time to Stage 3 clinical T1D by 24.6 months compared with placebo (24.9 months [95% CI: 9.5, 48.6] placebo vs 49.5 months [95% CI: 32.2, Not Estimable] teplizumab). The hazard ratio obtained from the Cox model was 0.41 (95% CI: 0.22, 0.78; p=0.0066). The diagnosis of clinical Stage 3 T1D were all confirmed by OGTT testing.

At the time of the primary analysis, 54.5% (24/44) and 28.2% (9/32) of patients remained free of clinical T1D in the teplizumab and placebo groups, respectively (Figure 12).

Figure 12: TN-10: Kaplan-Meier Curve of Time to T1D Diagnosis by Treatment Group (ITT Population)



[1]Cox Proportional Hazards model
Tick marks indicate censored patients
Abbreviations: CI=confidence interval, HR=hazard ratio, ITT=intent-to-treat, T1D=type 1 diabetes

The largest difference between the teplizumab and placebo group was observed in the first year, and the benefit of teplizumab was preserved through Year 5 (Table 7). Review of the distribution of the C-peptide levels at baseline indicated that there were similar percentages of patients in both teplizumab and control groups who were above and below the median at study entry, confirming similar representation of those with lower C-peptide levels in both groups.

Table 7: TN-10: Yearly Interval and Cumulative Hazard Ratios of Time to T1D Onset (ITT Population)

	n (%) T1D diagnosed			Hazard Ratio (95% CI)	
Year	Teplizumab	Placebo	Chi Square Test	Cumulative	Interval
1	4 (9.1)	13 (40.6)	9.16	0.18 (0.06, 0.54)	0.18 (0.06, 0.54)
2	8 (18.2)	3 (9.4)	5.92	0.39 (0.19, 0.83)	1.22 (0.32, 4.58)
3	3 (6.8)	3 (9.4)	6.58	0.41 (0.21, 0.81)	0.50 (0.10, 2.49)
4	3 (6.8)	2 (6.3)	6.09	0.45 (0.24, 0.85)	0.85 (0.14, 5.11)
5	2 (4.5)	2 (6.3)	7.16	0.44 (0.24, 0.80)	0.34 (0.05, 2.40)

Abbreviations: CI=confidence interval, ITT=intent-to-treat, T1D=type 1 diabetes

6.1.3.1 Sensitivity Analyses

Results of all 3 sensitivity analyses were consistent with the result of the primary efficacy analysis and showed that teplizumab significantly delayed the onset of clinical T1D compared to placebo (Table 8).

Table 8: TN-10: Sensitivity Analyses of the Primary Efficacy Endpoint

Sensitivity Analysis	Median time to T1D Diagnosis (Months)		Hazard Ratio (95% CI)	p-value
	Teplizumab	Placebo		
1. Placebo patients with T1D onset within first year delayed to T1D onset at 1 year	49.5	24.9	0.43 (0.22, 0.81)	p=0.0089
2. Patients who terminated early considered T1D onset at time of termination	44.3	22.0	0.42 (0.22, 0.78)	p=0.0065
3. Both 1 and 2 assumptions combined	44.3	22.0	0.43 (0.23, 0.81)	p=0.0086

Abbreviations: CI=confidence interval, T1D=type 1 diabetes

Analysis 1: Placebo Patients who Were Diagnosed with Clinical Stage 3 T1D During the First Year Were Set to the 12 Month Timepoint

Overall, 4 teplizumab and 14 placebo patients had follow-up durations less than 12 months. Of these patients, 3 teplizumab patients and 13 placebo patients were diagnosed with clinical Stage 3 T1D. To assess the possible impact of delaying the time to clinical T1D onset until 1 year after randomization for these placebo patients, the Kaplan-Meier and Cox model were used for a sensitivity analysis under this assumption.

The median time to clinical Stage 3 T1D diagnosis remained 49.5 months in the teplizumab group and 24.9 months in the placebo group. Teplizumab treatment was statistically significantly superior to placebo in delaying clinical T1D onset, with a hazard ratio of 0.43 (95% CI: 0.22, 0.81; p=0.0089).

Analysis 2: Patients Who Withdrew Consent or Were Lost to Follow-up Were Assumed to be Diagnosed with Clinical Stage 3 T1D at Their Last Evaluation

Six patients terminated the study early, 3 of whom were diagnosed with clinical Stage 3 T1D before early study termination and were already included in the primary endpoint. Of the remaining 3 patients, 2 withdrew consent (1 teplizumab, 1 placebo), and 1 was lost to follow-up (placebo). In this analysis, these remaining 3 patients were assumed to have been diagnosed with clinical Stage 3 T1D at their last evaluation.

The median time to clinical T1D was 22.0 months in the placebo group and 44.3 months in the teplizumab group, and the treatment difference was statistically significant with a hazard ratio of 0.42 (95% CI: 0.22, 0.78; p=0.0065).

Analysis 3: Both of the Above Assumptions Combined

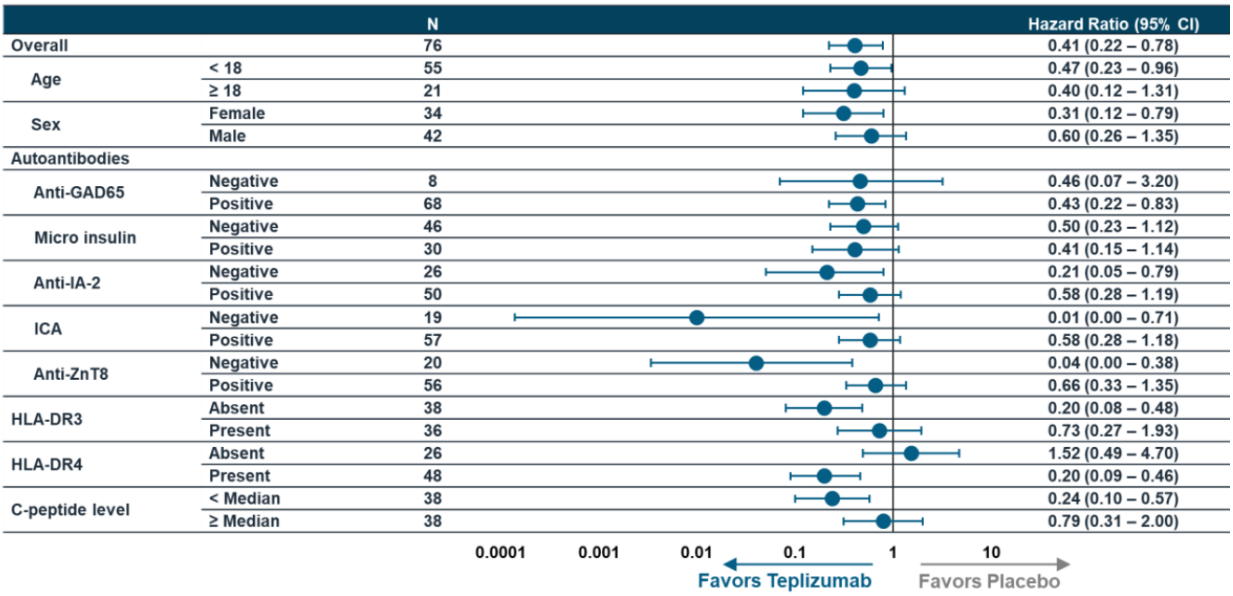
All placebo patients who were diagnosed with clinical Stage 3 T1D before 12 months were set to the 12-month timepoint after randomization, and the 3 early study terminations (withdrew consent or lost to follow-up) were assumed to have been diagnosed with clinical Stage 3 T1D at their last evaluation.

The median time to clinical Stage 3 T1D was 22.0 months in the placebo group and 44.3 months in the teplizumab group. Teplizumab treatment was statistically significantly superior to placebo in delaying clinical T1D onset, with a hazard ratio of 0.43 (95% CI: 0.23, 0.81; p=0.0086).

6.1.3.2 Subgroup Analyses

In general, as shown in the forest plot in Figure 13, the hazard ratio point estimates favored teplizumab in subgroup analyses. Teplizumab appeared to have a greater effect size in certain subgroups with the following baseline characteristics: negative anti-ZnT8 antibodies, HLA DR3 absent, HLA DR4 present, and C-peptide AUC level <median. It should be noted that the T1D autoantibody and HLA subgroups are not mutually exclusive and therefore patients are included in multiple subgroups, making it difficult to identify a specific baseline characteristic that would lead to a better response. In addition, further literature review suggest that these 4 subgroups have faster T1D progression, thus enhancing the greater effect of teplizumab (Ilonen et al 2013; Salonen et al 2013). Furthermore, the small numbers of patients in most of the subgroups led to the overlap in the 95% CIs, and in conjunction with lack of adjustment for multiplicity of comparisons, it is difficult to draw definitive conclusions on the effect of teplizumab in specific subgroups. Overall, teplizumab demonstrated benefit over placebo regardless of these baseline factors.

Figure 13: TN-10: Forest Plot of Subgroup Analyses on the Effect of Teplizumab Compared with Placebo on the Primary Endpoint (ITT Population)



Abbreviations: Anti-GAD65= anti-glutamic acid decarboxylase 65 antibody, Anti-IA-2=anti-islet antigen antibody, Anti-ZnT8=zinc transporter 8 antibody, CI=confidence interval, HLA=human leukocyte antigen, ICA=islet cell antibody, ITT=intent-to-treat

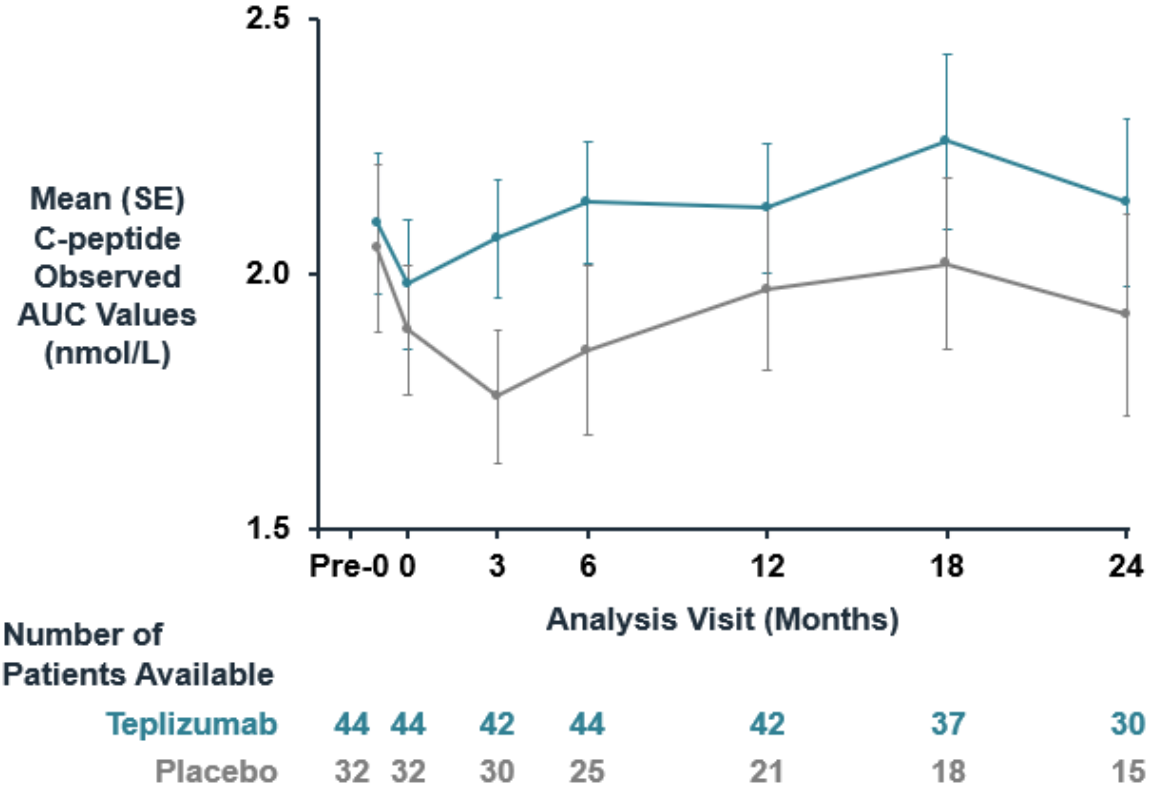
6.1.4 Secondary Endpoint: Magnitude of Beta Cell Preservation

Analyses of C-peptide AUC during 2-hour OGTT showed that teplizumab treatment significantly improved C-peptide levels upon initiation of treatment, while the placebo group had an overall decline (Figure 14 and Figure 15).

As expected, C-peptide levels in both groups showed declining levels prior to randomization (Pre-0 to 0 timepoint, Figure 14). Upon initiation of treatment, not only was the mean C-peptide level stabilized, but it increased upon initiation of teplizumab treatment, supporting the positive effect of teplizumab in preserving beta cell function. The increase in C-peptide was accompanied by increase in observed insulin production and improved blood glucose levels. Importantly, these findings suggest that not only does teplizumab stop the destruction of beta cells, but that it also rescues beta cells, which were previously not producing insulin.

After the diagnosis of clinical T1D, C-peptide levels were no longer measured in TN-10. Therefore, as more placebo patients exited the study compared to teplizumab (7/32 [22%] vs 0 at 6 months, respectively; 11/32 [34%] vs 2/44 [4.5%] at 12 months, respectively) due to clinical T1D diagnosis, the mean C-peptide levels increased in placebo patients over time as patients who converted to clinical T1D were excluded from the analysis of the mean C-peptide levels.

Figure 14: TN-10: Absolute Mean C-peptide AUC Values in 2-hour OGTT Including Pre-baseline Value (ITT Population)

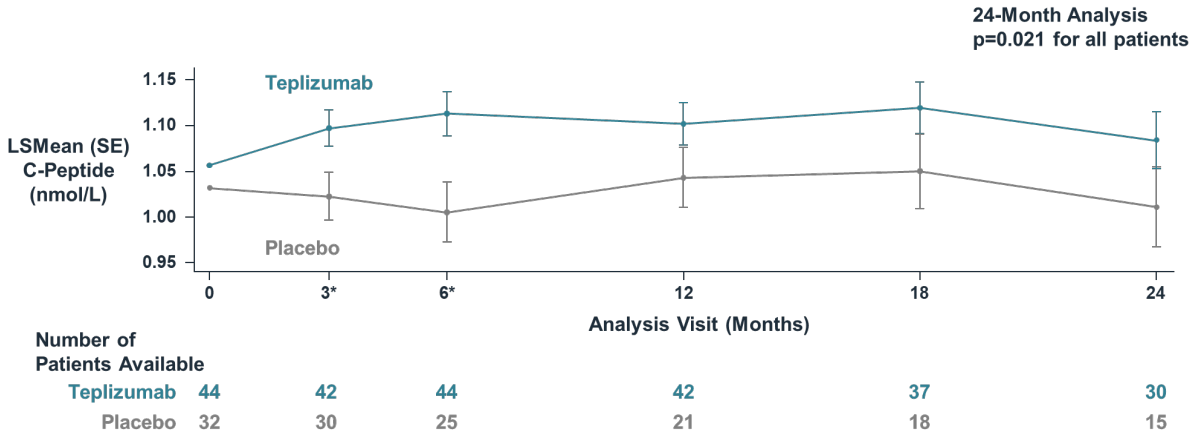


Note: If multiple data points were available within a study visit time window, the average value was used. Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, ITT=intent-to-treat, OGTT=oral glucose tolerance test, SE=standard error.

As shown in Figure 15, the treatment effect of teplizumab on C-peptide AUC for the 24-month analysis was statistically significant (p=0.021). The analysis was limited to 24 months because there were decreasing numbers of OGTTs beyond this timepoint: approximately 59% of patients had OGTTs at 24 months, and this declined to 46% at 30 months and continued to decline in the remainder of the study. Therefore, the C-peptide analyses up to and including 24 months post-randomization were conducted to avoid comparisons involving too few patients, particularly in the placebo group.

Taken together, these results further support the effect of teplizumab on preserving beta cell function in this population.

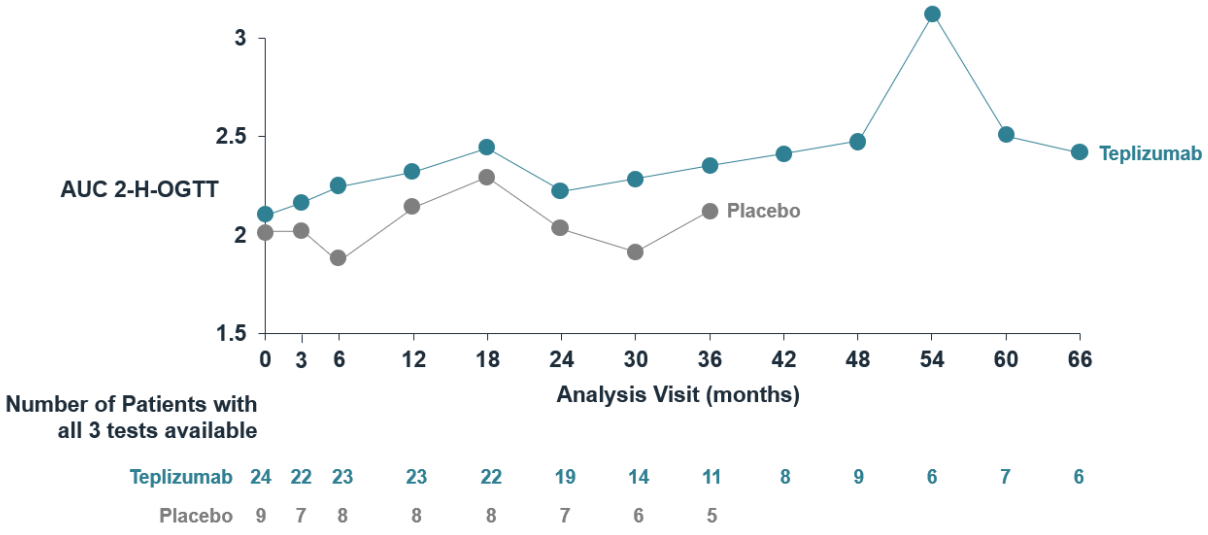
Figure 15: TN-10: C-peptide ln(AUC + 1) Least Squares Mean (± SE) by Treatment and Time Window from the 2-Year Model (ITT Population)



*Statistical significance between teplizumab and placebo was found at Month 3 and Month 6.
Abbreviations: AUC=area under the concentration-time curve, ITT=intent-to-treat, LSmean=least squares mean, SE=standard error.

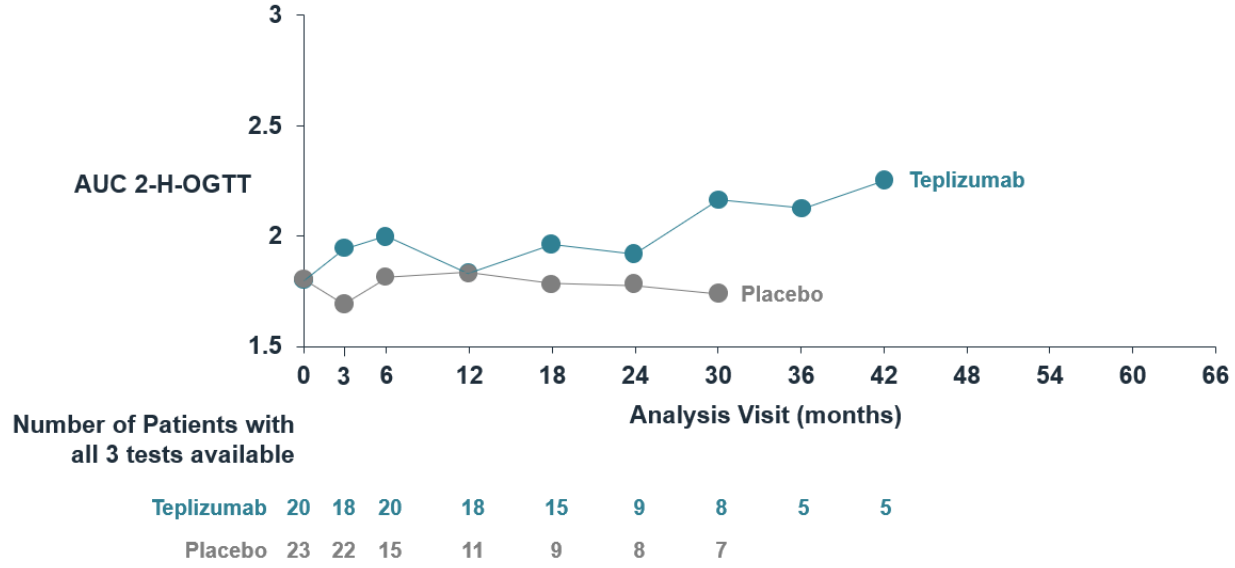
In order to assess whether C-peptide differed between those who were free of T1D and those who developed T1D, separate plots of mean C-peptide over time were developed (Figure 16 and Figure 17). As can be seen, those treated with teplizumab who remain free of T1D or ultimately develop T1D during the study had higher mean C-peptide values compared with their respective controls.

Figure 16: TN-10: C-Peptide AUCs (nmol/L) in Patients without T1D



Abbreviations: AUC=area under the concentration-time curve, T1D=type 1 diabetes, 2-H-OGTT= 2-hour oral glucose tolerance test

Figure 17: TN-10: C-Peptide AUCs (nmol/L) in Patients with T1D



Abbreviations: AUC=area under the concentration-time curve, T1D=type 1 diabetes, 2-H-OGTT= 2-hour oral glucose tolerance test

6.2 Confirmatory Evidence: Meta-Analysis of C-Peptide and Summary of Exogenous Insulin Use in Stage 3 T1D

6.2.1 Study Design

Confirmatory evidence in the form of a meta-analysis, which was recommended by and the design agreed upon with FDA, was conducted using pooled C-peptide data from 5 supportive randomized clinical studies: Protégé, Encore, Study 1, AbATE, and Delay. C-peptide AUC levels were obtained from a 4-hour MMTT.

Table 9 shows study design features across these 5 studies in Stage 3 T1D patients. These studies were chosen because they represented all the randomized studies conducted with teplizumab in Stage 3 T1D and used either placebo or standard of care as controls. A similar 14-day escalating dose regimen was used across the studies. In Study 1, a 14-day dosing regimen based on weight was subsequently modified to a 12-day dosing regimen based on BSA. However, due to apparently more AEs occurring during the early dosing period in the 12-day regimen with a 2-day ramp-up period, a 14-day regimen with a 4-day ramp-up period was adopted in subsequent clinical studies. Patients received two 14-day treatment courses in Protégé, Encore, and AbATE, and a single course of treatment at baseline in Delay and Study 1.

The Protégé and Encore studies enrolled newly diagnosed patients with Stage 3 T1D in 4 treatment arms: placebo and 3 teplizumab dosing regimens (full-dose 14 days [9.0 mg/m^2 cumulative dose], one-third dose 14 days [~3.0 mg/m^2 cumulative dose] and truncated 6-days (~2.5 mg/m^2 cumulative dose]). In the meta-analysis, C-peptide data

from the full-dose 14-day regimen was used. Study 1, AbATE, and Delay studies all used the full-dose 14-day regimen (9.0 mg/m^2 cumulative dose).

Table 9: Study Design Features Across Supportive Studies

	Protégé	Encore	Study 1	AbATE	Delay
Follow-up	Baseline, Day 140, Months 12, 18, 24	Baseline, Day 140, Months 12, 18, 24	Baseline, Months 6, 12, 18, 24	Baseline, Months 6, 12, 18, 24	Baseline, Months 6, 12
C-peptide endpoint status	Secondary, time not specified	Secondary, time not specified	Primary, at 2 years	Primary, at 2 years	Primary, at 1 year
Dosing schedule	14 days	14 days	12 or 14 days	14 days	14 days
Regimen	2 courses: Baseline, 6 months	2 courses: Baseline, 6 months	1 course: Baseline	2 courses: Baseline, 12 months	1 course: Baseline
Design	Randomized, double-blind	Randomized, double-blind	Randomized, open-label	Randomized, open-label	Randomized, double-blind
Control group	Placebo	Placebo	Standard care	Standard care	Placebo
Number of patients*	Placebo: 98 Teplizumab: 453	Placebo: 62 Teplizumab: 192	Control: 21 Teplizumab: 21	Control: 25 Teplizumab: 52	Placebo: 27 Teplizumab: 31

*Patients in the full 14-day teplizumab treatment regimen and placebo groups were included in the meta-analyses.

The patients enrolled in these studies (Table 10) were representative of the newly diagnosed T1D patient population, excluding those with significant medical history, clinical abnormalities, or active infection. Key inclusion criteria were similar across the studies. C-peptide level at study entry was ≥0.2 nmol/L in AbATE, Delay, and Study 1 and detectable levels for Protégé and Encore.

Table 10: Key Inclusion Criteria Across the Supportive Studies

	Protégé	Encore	Study 1	AbATE	Delay
Age at entry	8–35 years	8–35 years	7.5–30 years	8–30 years	8–30 years
Time of T1D diagnosis to treatment	≤ 12 weeks	≤ 12 weeks	≤ 6 weeks	≤ 8 weeks	4–12 months
Autoantibodies[1]	anti-ICA512, IA-2, anti-GAD65, IAA	anti-ICA512, IA-2, anti-GAD65, IAA	anti-GAD65, anti-ICA512, IAA	ICA, anti-GAD65, anti-ICA512	ICA, anti-GAD65, anti-ICA512
C-peptide level	detectable	detectable	≥0.2 nmol/L	≥0.2 nmol/L	≥0.2 nmol/L
Weight	≥36 kg	≥36 kg	N/A	≥25 kg	≥27.5 kg

[1] At least 2 of these antibodies were present at study entry.
Abbreviations: Anti-GAD65= anti-glutamic acid decarboxylase 65 antibody, IA-2=islet antigen, IAA=insulin autoantibodies, Anti-ZnT8=zinc transporter 8 antibody, CI=confidence interval, HLA=human leukocyte antigen, anti-ICA512=anti-islet cell antibody, N/A=not available, T1D=type 1 diabetes

The primary endpoint of the meta-analyses was the change from baseline in C-peptide AUC in a 4-hour MMTT. Each study used the same sample collection time points during the MMTTs to calculate C-peptide AUC (Table 11).

Table 11: Schedules of MMTTs and Sampling Time Points Across Supportive Studies

Study	Time Points in MMTT	Visits (Study Days)
Protégé	-10, 0, 15, 30, 60, 90, 120, 150, 180,210, 240	Baseline, D140, D365, D546, D728
Encore	-10, 0, 15, 30, 60, 90, 120, 150, 180,210, 240	Baseline, D140, D365
Study 1	-10, 0, 15, 30, 60, 90, 120, 150, 180,210, 240	Baseline, 183, D365, D546, D728
AbATE	-10, 0, 15, 30, 60, 90, 120, 150, 180, 210, 240	Baseline, D183, D364, D546, D728
Delay	-10, 0, 15, 30, 60, 90, 120, 150, 180, 210, 240	Baseline, D183, D365

Abbreviations: D=days, MMTT=mixed meal tolerance test

A one-stage meta-analysis using individual patient data was conducted on all 5 studies through 1 year of follow-up and on the 3 studies that had 2 years of follow-up, using both observed data and imputed data. Missing C-peptide data were imputed using 2 imputation approaches:

- Missing at random (MAR) approach for patients who missed MMTTs for reasons considered ignorable and non-informative.
- Missing not at random (MNAR) approach for patients who missed MMTTs due to an AE.

The change from baseline C-peptide ln(AUC+1) was analyzed using analysis of covariance, with treatment, age, baseline C-peptide ln(AUC+1), study, and study*treatment (interaction) as covariates. A sensitivity analysis was conducted using control-based imputation where missing data in teplizumab-treated patients were imputed based on data from the control group.

A secondary analysis was conducted on exogenous insulin use (U/kg/day) over the course of the study (24 months for Protégé, Study 1, and AbATE; 12 months for Delay). This analysis was included to provide additional supportive evidence, as lower exogenous insulin use is an index of greater endogenous insulin production, which is a correlate of improved preservation of C-peptide levels (Jones and Hattersley 2013; Leighton et al 2017).

6.2.2 Patient Disposition and Baseline Demographics Across Supportive Studies

6.2.2.1 Patient Disposition

A total of 609 patients (375 in the teplizumab group who received the full-dose 14-day regimen with a cumulative dose of 9.0 mg/m^2 and 234 in the control group) were included in the ITT Population for the pooled analysis. In the teplizumab group, 88% of patients completed their respective studies (Table 12). Three (0.8%) patients in the teplizumab group withdrew early due to an AE, and 17 (4.5%) were lost to follow-up.

Table 12: Pooled Supportive Studies: Patient Disposition (ITT Population)

	Teplizumab N=375 n (%)	Control N=234 n (%)
ITT by study		
Protégé	207 (55.2)	98 (41.9)
Encore	63 (16.8)	62 (26.5)
Study 1	21 (5.6)	21 (9.0)
AbATE	52 (13.9)	25 (10.7)
Delay	32 (8.5)	28 (12.0)
Completed planned treatment Course 1	337 (89.9)	229 (97.9)
Completed planned treatment Course 2	211 (65.5)	127 (68.6)
Completed study	330 (88.0)	212 (90.6)
Discontinued treatment Course 1	38 (10.1)	5 (2.1)
Discontinued treatment Course 2	16 (5.0)	6 (3.2)
Discontinued study	45 (12.0)	23 (9.4)
Reason for study discontinuation		
Lost to follow-up	17 (4.5)	6 (2.6)
Withdrawal by patient	16 (4.3)	6 (2.6)
Adverse events	3 (0.8)	0
Protocol violation	1 (0.3)	0
Other	8 (2.1)	10 (4.3)

Note: The teplizumab group includes those who received the full regimen with a cumulative dose of 9.0 mg/m^2
Abbreviation: ITT=intent-to-treat

6.2.2.2 Baseline Demographics

Baseline demographics across the 5 studies and pooled data are shown in Table 13. Patients in the Protégé and Encore studies were, on average, older than in those in Study 1, AbATE, and Delay. This was a result of a higher proportion of 18- to 35-year-old patients enrolled in these 2 studies. More than half of the patients in each study were male, ranging from 53.8% in AbATE to 62.8% in Protégé. Baseline C-peptide, HbA1c, and insulin were balanced between treatment and control groups within each study.

Table 13: Supportive Studies: Demographic and Baseline Characteristics by Study

	Protégé		Encore		AbATE		Delay		Study 1		Pooled	
	Tep N=207	Placebo N=98	Tep N=63	Placebo N=62	Tep N=52	Control N=25	Tep N=32	Placebo N=28	Tep N=21	Control N=21	Tep N=375	Placebo N=234
Age, years, mean (SD)	18.8 (7.4)	18.2 (7.3)	17.3 (6.4)	18.4 (7.9)	12.7 (4.9)	12.3 (4.1)	12.7 (4.1)	11.9 (4.0)	13.9 (5.4)	14.9 (6.0)	16.9 (7.1)	16.6 (7.2)
Male, %	62.8	62.2	60.3	66.1	53.8	64	56.3	60.7	61.9	61.9	60.5	63.2
HbA1c, %, mean (SD)	8.32 (2.01)	8.19 (2.03)	8.09 (2.0)	8.40 (2.0)	7.43 (0.99)	7.7 (1.23)	6.4 (0.8)[1]	7.14 (1.2)[1]	8.98 (1.7)	8.05 (1.1)	8.18 (1.90)	8.18 (1.86)
C-peptide AUC, nmol/L, mean (SD)	0.65 (0.53)	0.65 (0.44)	0.68 (0.56)	0.58 (0.35)	0.72 (0.29)	0.67 (0.28)	0.62 (0.30)	0.59 (0.42)	0.49 (0.2)	0.48 (0.2)	0.66 (0.48)	0.61 (0.38)
Insulin use, U/kg/day, mean (SD)	0.61 (0.40)	0.64 (0.31)	0.59 (0.29)	0.61 (0.33)	0.39 (0.26)	0.39 (0.17)	0.41 (0.14)	0.39 (0.20)	0.51 (0.25)	0.44 (0.21)	0.56 (0.36)	0.56 (0.30)
Time from T1D diagnosis, weeks, mean (SD)	8.5 (2.6)	8.5 (2.6)	9.1 (2.3)	8.6 (2.4)	5.8 (1.2)	5.4 (1.3)	30.9 (10.7)	30.7 (10.5)	<6[1]	<6[1]	10.0 (7.5)	10.6 (8.6)

[1]Data obtained from the publication.
Abbreviations: AUC=area under the concentration-time curve, HbA1c=hemoglobin A1c, SD=standard deviation, Tep=teplizumab, T1D=type 1 diabetes

6.2.3 Meta-Analysis of Change from Baseline in C-Peptide AUC in a 4-Hour MMTT

Patients in the teplizumab group had greater preservation of C-peptide (ie, smaller decreases from baseline) at 1 year (Table 14) and 2 years (Table 15) of follow-up. This effect was consistent for observed data and imputed data (p<0.0001 for both analyses). Furthermore, the conservative sensitivity analysis applying control-based imputation (assigning control data to missing teplizumab data) was also significant (p<0.0001).

Table 14: Supportive Studies: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide ln(AUC+1) (nmol/L) at 1-Year Follow-up

	Change from Baseline (nmol/L)		Difference in Change from Baseline (nmol/L)		
	Teplizumab LSM (SE)	Control LSM (SE)	LSM (SE)	95% CI	p-value
Observed data	-0.0569 (0.01386)	-0.1380 (0.01513)	0.0811 (0.02042)	0.041, 0.121	<0.0001
Imputed data	-0.0537 (0.01339)	-0.1433 (0.0149)	0.0896 (0.02026)	0.050, 0.129	<0.0001
Sensitivity: Control-based	-0.0626 (0.0152)	-0.1466 (0.01758)	0.0840 (0.02094)	0.043, 0.125	0.0001

Note: C-peptide AUC data at 1-year follow-up were obtained from all 5 studies: Protégé, Encore, Study 1, AbATE, and Delay.Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, SE=standard error.

Table 15: Supportive Studies: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide ln(AUC+1) (nmol/L) at 2-Years Follow-up

	Change from Baseline (nmol/L)		Difference in Change from Baseline (nmol/L)		
	Teplizumab LSM (SE)	Control LSM (SE)	LSM (SE)	95% CI	p-value
Observed data	-0.1334 (0.0168)	-0.2516 (0.02158)	0.1182 (0.02710)	0.065, 0.172	<0.0001
Imputed data	-0.1434 (0.0169)	-0.2476 (0.0211)	0.1042 (0.02660)	0.052, 0.156	<0.0001
Sensitivity: Control-based	-0.1471 (0.018)	-0.254 (0.023)	0.1069 (0.02793)	0.052, 0.162	<0.0001

Note: C-peptide AUC data at 2-year follow-up were obtained from 3 studies that had 2-year data: Protégé, Study 1, and AbATE. Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, SE=standard error.

The results for the 1-year and 2-year meta-analyses are shown in forest plots in Figure 18 and Figure 19, respectively. Both forest plots show that the observed (existing) and imputed analyses yielded consistent effects of teplizumab in preserving C-peptide AUC levels. In the 1-year forest plot, teplizumab treatment was consistently more effective than placebo in all studies, except Encore. The result in the Encore study was expected, as the study was modified before its completion due the companion Phase 3 study, Protégé, not meeting its 1-year primary endpoint, resulting in a large amount of missing data requiring the largest amount of imputation. Approximately 75% (93/125) of the MMTTs were missing. The primary endpoint of the Protégé study was a novel unvalidated composite endpoint focused on metabolic parameters (HbA1c and insulin use).

In the forest plot of 2-year data (Figure 19), teplizumab treatment significantly preserved C-peptide AUC levels compared with placebo in all 3 studies with 2-year data.

Figure 18: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-Peptide AUC (nmol/L) at 1 Year Follow-up in Supportive Study Meta-Analysis

	N		LSM Difference Between Teplizumab and Control in Change from Baseline	LSM (95% CI)
	Teplizumab	Control		
Overall Observed	306	179		**0.08** (0.04, 0.12)
Overall Imputed	375	234		**0.09** (0.05, 0.13)
Protégé Observed	188	91		**0.04** (-0.002, 0.08)
Protégé Imputed	207	98		**0.03** (-0.01, 0.08)
Encore Observed	17	17		**0.002** (-0.11, 0.12)
Encore Imputed	63	62		**0.05** (-0.06, 0.15)
AbATE Observed	50	22		**0.15** (0.06, 0.23)
AbATE Imputed	52	35		**0.15** (0.06, 0.24)
Delay Observed	30	28		**0.06** (-0.03, 0.15)
Delay Imputed	32	28		**0.06** (-0.03, 0.15)
Study 1 Observed	21	21		**0.16** (0.05, 0.26)
Study 1 Imputed	21	21		**0.16** (0.05, 0.26)

Note: Analysis conducted and results presented for ln(AUC+1)
Abbreviations: AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, N=number with 1-year data included in the meta-analysis

Figure 19: Predicted Mean Difference Between Teplizumab and Control in the Change from Baseline in C-peptide AUC (nmol/L) at 2 Year Follow-up in Supportive Study Meta-Analysis

	N		LSM Difference Between Teplizumab and Control in Change from Baseline	LSM (95% CI)
	Teplizumab	Control		
Observed	199	99		**0.12** (0.07, 0.17)
Imputed	280	144		**0.10** (0.05, 0.16)
Protégé Observed	131	64		**0.06** (0.004, 0.11)
Protégé Imputed	207	98		**0.06** (0.01, 0.10)
AbATE Observed	49	21		**0.14** (0.05, 0.23)
AbATE Imputed	52	25		**0.14** (0.05, 0.23)
Study 1 Observed	19	14		**0.16** (0.04, 0.28)
Study 1 Imputed	21	21		**0.12** (0.001, 0.24)

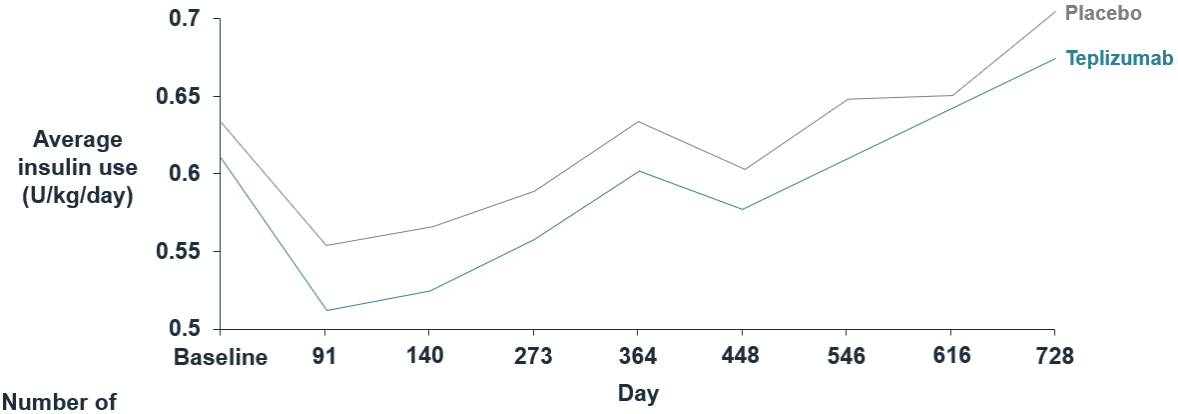
Note: Analysis conducted and results presented for ln(AUC+1)
AUC=area under the concentration-time curve, CI=confidence interval, LSM=least squares mean, N=number with 2-year data included in the meta-analysis

6.2.4 Summary of Exogenous Insulin Use

In all 5 studies, the mean insulin use over each timepoint was lower in teplizumab patients compared to placebo patients (Figure 20). Three studies (AbATE, Delay, and Study 1) showed that teplizumab treatment consistently led to statistically significantly lower levels of insulin requirement compared with placebo (Herold et al 2013a; Herold et al 2005; Herold et al 2013b). The insulin use in the teplizumab group was also lower compared to the placebo group but did not achieve statistical significance in the Protégé and Encore studies.

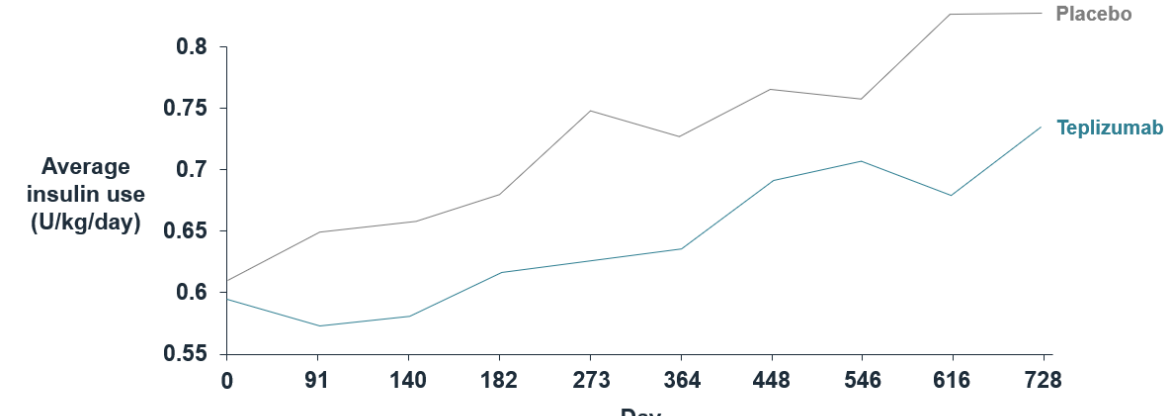
Figure 20: Supportive Studies: Average Insulin Use at Each Visit

a. Protégé



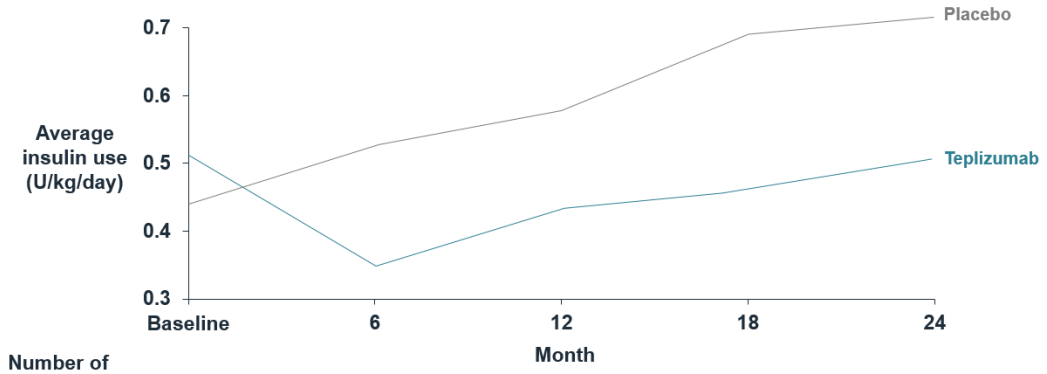
Number of Patients at Risk									
Teplizumab	205	199	199	186	195	176	179	163	171
Placebo	96	97	94	89	93	88	85	88	88

b. Encore



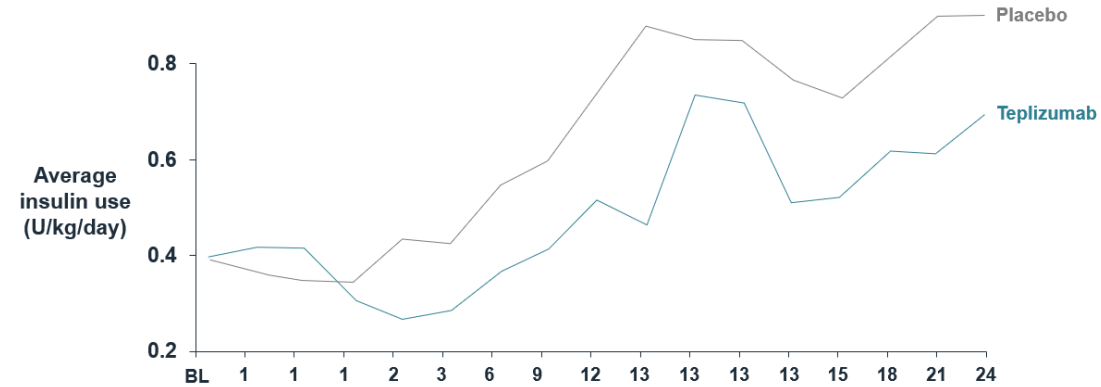
Number of Patients at Risk										
Teplizumab	60	56	53	52	51	51	49	46	13	14
Placebo	61	56	52	54	56	55	52	53	17	17

c. Study 1



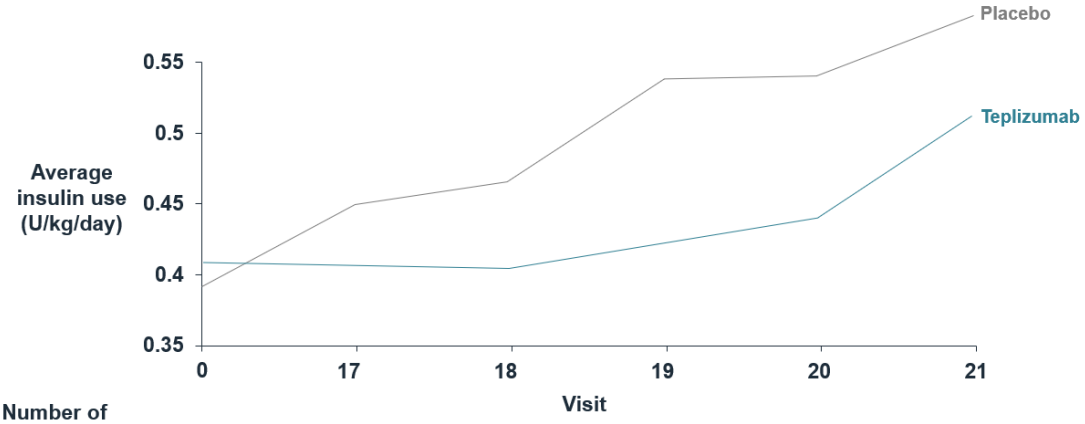
Number of Patients at Risk					
Teplizumab	20	21	21	21	20
Placebo	20	19	20	18	18

d. AbATE



Number of Patients at Risk																	
Teplizumab	49	25	18	26	28	43	49	47	50	26	24	17	33	45	47	39	48
Placebo	24	5	4	7	5	19	24	16	22	2	3	3	4	18	21	17	23

e. Delay



Number of Patients at Risk						
Teplizumab	32	30	30	30	30	29
Placebo	28	28	27	28	26	28

Taken together, these data support that teplizumab treatment preserves C-peptide levels as reflected by greater endogenous insulin production and less exogenous insulin requirement.

7 CLINICAL SAFETY

Summary

- Data from nearly 800 patients with Stage 2 and Stage 3 T1D treated with teplizumab represent approximately 1,500 patient-year follow-up.
  - The most common AEs were mechanism-based and related to T cell CD3 partial agonism and transient cytokine release.
- In TN-10, a single treatment course of teplizumab showed no new safety signals beyond those observed in the earlier Stage 3 studies.
  - The most common AEs observed with teplizumab treatment included transient lymphopenia, rash, and leukopenia.
  - 15.9% patients in teplizumab group and 3.1% in placebo had SAEs. No AEs of DKA or major hypoglycemia were observed.
- In the Pooled Safety Population (Protégé, Encore, Delay, AbATE, and TN-10), the majority of patients in both groups reported AEs.
  - Lymphopenia, leukopenia, neutropenia, blood bicarbonate decreased, and rash were the most commonly reported AEs occurring at a higher rate in the teplizumab group compared to the control group.
  - More patients in the teplizumab group (14%) experienced AEs leading to study drug discontinuation compared to the control group (4%), and most were due to laboratory abnormalities.
  - Across all studies, 3 deaths were reported (all in the teplizumab group). None of the deaths occurred during the dosing period, and all were assessed as not related to study drug by the clinical investigators.
  - 12% of patients in the teplizumab group and 8% in the control group experienced SAEs; the most common SAEs were associated with underlying T1D or its treatment, including DKA and major hypoglycemic events which were observed only in Stage 3 T1D studies and more frequently in teplizumab-treated patients.
  - Given the experience to date, there was no evidence of an increased risk of clinical infections, including EBV and CMV, or malignancies with teplizumab treatment.
  - CRS occurred in 5.8% of teplizumab-treated patients. The majority of these cases were mild to moderate in severity and resolved within 2–3 days despite continued teplizumab dosing.
  - Teplizumab can be associated with mild increases in liver enzymes that are commonly associated with CRS.

7.1 Safety Population

Stage 2 and Stage 3 T1D are contiguous phases in the continuum of T1D autoimmunity. These stages are similar in terms of disease pathophysiology and thus the impact of teplizumab on the autoimmune process is viewed to be comparable in this context. Therefore, safety findings from nearly 800 patients exposed to teplizumab in the Stage 2 and Stage 3 studies provide an adequate population exposure to support the safety profile of teplizumab for the proposed indication. These 5 studies (TN-10, Protégé, Encore, Delay, and AbATE) were chosen and pooled for the safety analysis because of shared design elements: (a) enrolled patients with T1D; (b) employed a randomized controlled design; and (c) studied the cumulative dose of 9,034 μg/m^2 (9.0 mg/m^2) per treatment course, which is applicable for the population that is the subject of the BLA.

7.2 Treatment Exposure

The pooled safety database includes 1,018 patients who were randomized in these 5 studies (Table 16), with study durations ranging from 1 to over 2 years. A total of 791 patients were exposed to teplizumab, which includes 18 patients in the Delay study who were initially randomized to the placebo group, completed 1 year of follow-up, and elected to receive teplizumab open-label at year 2; 245 patients received placebo or standard of care. In addition to the 5 studies in the pooled analysis, deaths and pregnancy were summarized from the Protégé Extension study.

Table 16: Teplizumab Exposure by Study

Study	Study Duration	Exposed to Teplizumab Alone (n)	Exposed to Placebo (n)	Exposed to Other[1] (n)	Total
Protégé	2 years	453	98	0	551
Encore	2 years[3]	192	62	0	254
Delay[2]	1 year	32	28	0	60
AbATE	2 years	52	0	25	77
TN-10	Time to event study: median follow-up: 24.5 months (maximum 88.1 months)	44	32	0	76
Total		**773**	**220**	**25**	**1,018**

[1] 'Other' refers to standard of care, no placebo infusion. In the safety discussion "controls" will represent both placebo and those who received standard of care.
[2] Patients in placebo group who completed 12 months of follow-up received 14-day course of open-label teplizumab treatment (n=18)
[3] Of the 254 patients, 89.8% and 29.1% of patients completed 1 and 2 years of follow-up, respectively, due to early study termination by study sponsor

Table 17 presents teplizumab drug exposure in the pooled safety database based on BSA dosing (μg/m^2). The total cumulative treatment exposure is the sum of the daily dose

delivered in the total duration of treatment. While TN-10 patients received only 1 course of treatment, the majority of the Safety Population received 2 courses of the full 14-day dosing regimen (Protégé, Encore, AbATE), with a total cumulative dose of 9.0 mg/m^2 per course.

Table 17: Drug Exposure by Study, Total Dose, and Duration of Exposure

Study	Total Dose (per course) µg/m^2	Duration (Days)	Courses of Treatment	Number of Patients
Protégé	9,034	14	2	245
	2,985	14	2	102
	2,426	6	2	106
Encore	9,034	14	2	63
	2,985	14	2	66
	426	6	2	63
Delay	9,034	14	1[1]	32
AbATE	9,034	14	2	52
TN-10	9,034	14	1	44

[1] Patients in the placebo group who completed 12-months of follow-up received 14-day course of open-label teplizumab treatment (n=18).

7.3 Safety in Stage 2 T1D (TN-10 Study)

The safety profile of teplizumab in TN-10 patients was comparable to that in the Stage 3 population (Protégé, Encore, Delay, AbATE).

In the TN-10 study, 43 (97.7%) patients in the teplizumab group and 22 (68.8%) in the placebo group had at least 1 AE (Table 18). Higher rates of SAEs and Grade 2/Grade 3 AEs were reported in the teplizumab group.

Table 18: TN-10: Summary of Adverse Events (Safety Population)

	Teplizumab N=44 n (%)	Placebo N=32 n (%)
Patients with at least 1 type of event[1]		
AE	43 (97.7)	22 (68.8)
SAE	7 (15.9)[2]	1 (3.1)
AE leading to treatment withdrawal	1 (2.3)	2 (6.3)
AE by grade		
Grade 1	5 (11.4)	3 (9.4)
Grade 2	42 (95.5)	22 (68.8)
Grade 3	26 (59.1)	3 (9.4)
Grade 4	0	0
Death	0	0

[1] Patients who had more than 1 AE or SAE for a treatment were counted once.
[2] A total of 8 SAEs occurred in 7 patients in the teplizumab group.
Abbreviations: AE=adverse event, SAE=serious adverse event.

The most common AEs in the teplizumab group were lymphopenia, leukopenia, and rash, all of which occurred more frequently in the teplizumab group compared to the placebo group (Table 19). Other common AEs include nasopharyngitis and headache. One AE of CRS (Grade 2) occurred in a teplizumab patient and resolved while the entire 14-day treatment course was completed.

There were no AEs of DKA or major hypoglycemia events (≥Grade 3 severity); however, it should be noted that patients were not followed in the study after development of clinical Stage 3 T1D.

Table 19: TN-10: Adverse Events Occurring in >5% of Patients in Any Treatment Group by Preferred Term (Safety Population)

Preferred Term	Teplizumab N=44 n (%)	Placebo N=32 n (%)
Patients with at least 1 AE	43 (97.7)	22 (68.8)
Lymphopenia	32 (72.7)	2 (6.3)
Leukopenia	9 (20.5)	0
Nasopharyngitis	7 (15.9)	2 (6.3)
Rash pruritic	7 (15.9)	0
Rash	6 (13.6)	0
Headache	5 (11.4)	3 (9.4)
Hypertension	4 (9.1)	1 (3.1)
Pneumonia	4 (9.1)	1 (3.1)
Sinusitis	4 (9.1)	1 (3.1)
Upper respiratory tract infection	4 (9.1)	1 (3.1)
Bronchospasm	3 (6.8)	0
Cough	3 (6.8)	0
Neutropenia	3 (6.8)	1 (3.1)
Vomiting	2 (4.5)	2 (6.3)
Hyperbilirubinemia	0	2 (6.3)

Abbreviation: AE=adverse event

Infection-related AEs occurred more frequently in the teplizumab group but were mostly Grade 1 and Grade 2 in severity and involved the upper respiratory tract. Four infections were Grade 3, and all were categorized as SAEs, but only 1 event (pneumonia) was considered by the investigators to be related to treatment. EBV viremia was noted in 9 teplizumab patients with viral loads above 3,000 copies/mL. All patients were positive for IgG at baseline and subsequent visits, indicating a history of prior EBV infection. In all of these patients, viremia occurred between 3 and 6 weeks after dosing, and, resolved by Month 3 in 7 patients. The other 2 patients still had low levels (<1,000 copies/mL) at Month 12. One patient (342–455 copies/mL) resolved at the 18-month visit, and the other decreased to 500 copies/mL (lower limit of quantification) at Month 48. Only one patient reported clinical symptoms of nasopharyngitis which resolved in 3 weeks; the EBV viral

load peaked at 1 million copies/mL at Week 6 and resolved by Month 12. No other opportunistic infections were reported.

Eight (18.2%) patients had a total of 9 SAEs during the study, including 7 (15.9%) patients in the teplizumab group and 1 (3.1%) in the placebo group (Table 20). Of the 8 SAEs reported in teplizumab patients, 4 were infections (pneumonia, cellulitis, wound infection, and gastroenteritis). Two SAEs were considered by the investigators to be related to study treatment and included serum sickness and pneumonia. These events were all considered SAEs due to the need for hospitalization or prolongation of hospitalization. No deaths were observed.

Table 20: TN-10: List of Serious Adverse Events in Teplizumab Patients (Safety Population)

Preferred Term/System Organ Class	Verbatim Term	Severity Grade	Investigator Assessed Causality	Outcome
Pneumonia/Infections and infestations	Infection with normal ANC or Grade 1 or 2 neutrophils	3	Probably related	Recovered/ resolved
Dizziness/Nervous system disorders	Dizziness	2	Definitely not related	Recovered/ resolved
Ankle fracture/Injury, poisoning and procedural complications	Fracture	3	Definitely not related	Recovering/ resolving
Serum sickness/Immune disorders	Pain	3	Possibly related	Recovered/ resolved
Musculoskeletal chest pain/Musculoskeletal and connective tissue disorders	Musculoskeletal/ Soft Tissue – Other (specify in event details)	2	Definitely not related	Recovered/ resolved
Cellulitis/Infections and infestations	Infection with unknown ANC	3	Probably not related	Recovered/ resolved
Wound infection/Infections and infestations	Infection – Other (specify in event details)	3	Definitely not related	Recovered/ resolved
Gastroenteritis/Infections and infestations	Gastrointestinal – Other (specify in event details)	3	Probably not related	Recovered/ resolved

Abbreviations: ANC=absolute neutrophil count

Three patients (1 teplizumab and 2 placebo) discontinued study treatment due to AEs. The patient in the teplizumab group discontinued treatment due to increased ALT. The 2 placebo patients discontinued study drug treatment due to hyperbilirubinemia.

Twenty-six (59.1%) patients in the teplizumab group and 3 (9.4%) in the placebo group experienced Grade 3 AEs. Lymphopenia was the most common Grade 3 AE in the teplizumab group. There were no Grade 4 AEs observed in the study.

The most common laboratory-related AE was lymphopenia, observed in 72.7% of patients in the teplizumab group and 6.3% in placebo. As discussed in Section 5.2.1, declines in absolute lymphocyte count are mechanism-based and transient.

Overall, teplizumab was well tolerated in the TN-10 study, and no new safety signals were identified.

7.4 Safety in Pooled Analyses

In the Pooled Safety Population, 99.5% of patients in the teplizumab group and 95.1% in the control group reported AEs (Table 21). More patients in the teplizumab group experienced SAEs and AEs leading to treatment interruption or withdrawal compared to the placebo group. There were 3 deaths in the teplizumab group: 2 in the Protégé study that are included in the pooled analysis and 1 in the Protégé Extension study. No deaths were considered to be related to study drug (details are provided in Section 7.9).

Table 21: Summary of Adverse Events (Pooled Safety Population)

	Teplizumab N=791[2] n (%)	Control N=245 n (%)
Patients with at least 1 type of event[1]		
AE	787 (99.5)	233 (95.1)
SAE	98 (12.4)	20 (8.2)
AE leading to treatment interruption	88 (11.1)	7 (2.9)
AE leading to treatment withdrawal	113 (14.3)	9 (3.7)
AE by CTCAE grade[3]		
Grade 1	749 (94.7)	214 (87.3)
Grade 2	695 (87.9)	146 (59.6)
Grade 3	467 (59.0)	56 (22.9)
Grade 4	65 (8.2)	5 (2.0)
Grade 5	2 (0.3)	0
Death	2[4] (0.3)	0

[1] Patients who had more than 1 AE or SAE for a treatment were counted once.
[2] Delay patients initially randomized to the control arm, who were later also eligible for the open-label administration of teplizumab, are counted once for each treatment arm.
[3] Grading is unified based on existing grading –studies with CTCAE grading remain as coded for Protégé, Encore and TN-10; grading in other studies (AbATE and Delay) was converted: mild to Grade 1, moderate to Grade 2, severe to Grade 3, SAE to Grade 4 and death to Grade 5.
[4] Both deaths occurred in the Protégé Study. There was one additional death in the Protégé Extension study.
Abbreviations: AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events, SAE=serious adverse event.

7.5 Common Adverse Events

AEs by preferred term occurring in ≥5% of patients are shown in Table 22. Lymphopenia, leukopenia, neutropenia, blood bicarbonate decreased, and rash were the most commonly reported AEs and occurred at a higher rate in the teplizumab group compared to the control group. These events are mechanism-based and related to the T cell CD3 partial agonism and transient mild cytokine release caused by teplizumab. Most of these events were Grade 1 or Grade 2 in severity.

Table 22: Adverse Events >5% by Preferred Term (Pooled Safety Population)

System Organ Class[1] Preferred Term	Teplizumab N=791[2] n (%)	Control N=245 n (%)
Patients with at least 1 adverse event[3]	787 (99.5)	233 (95.1)
Lymphopenia	632 (79.9)	41 (16.7)
Leukopenia	501 (63.3)	65 (26.5)
Neutropenia	313 (39.6)	53 (21.6)
Blood bicarbonate decreased	303 (38.3)	67 (27.3)
Rash	273 (34.5)	25 (10.2)
Hemoglobin decreased	228 (28.8)	55 (22.4)
Aspartate aminotransferase increased	222 (28.1)	50 (20.4)
Headache	215 (27.2)	61 (24.9)
Alanine aminotransferase increased	210 (26.5)	28 (11.4)
Pyrexia	188 (23.8)	41 (16.7)
Thrombocytopenia	172 (21.7)	24 (9.8)
Hyponatremia	170 (21.5)	49 (20.0)
Nausea	155 (19.6)	34 (13.9)
Upper respiratory tract infection	150 (19.0)	43 (17.6)
Hypocalcemia	137 (17.3)	36 (14.7)
Blood sodium decreased	129 (16.3)	36 (14.7)
Pruritus	118 (14.9)	14 (5.7)
Vomiting	110 (13.9)	25 (10.2)
Blood alkaline phosphatase increased	107 (13.5)	34 (13.9)
Blood calcium decreased	100 (12.6)	20 (8.2)
Nasopharyngitis	88 (11.1)	23 (9.4)
Fatigue	80 (10.1)	14 (5.7)
Oropharyngeal pain	78 (9.9)	21 (8.6)
Hyperkalemia	77 (9.7)	16 (6.5)
Proteinuria	76 (9.6)	15 (6.1)
Cough	68 (8.6)	12 (4.9)
Anemia	66 (8.3)	17 (6.9)
Blood albumin decreased	66 (8.3)	11 (4.5)
Blood potassium increased	66 (8.3)	17 (6.9)
Chills	61 (7.7)	8 (3.3)
Diarrhea	59 (7.5)	15 (6.1)
Hyperbilirubinemia	59 (7.5)	14 (5.7)
Blood bilirubin increased	58 (7.3)	8 (3.3)
Hypoalbuminemia	56 (7.1)	14 (5.7)
Hypoglycemia	55 (7.0)	14 (5.7)
Abdominal pain	50 (6.3)	13 (5.3)
Abdominal pain upper	47 (5.9)	16 (6.5)
Cytokine release syndrome	46 (5.8)	3 (1.2)
Eosinophilia	44 (5.6)	4 (1.6)
Blood potassium decreased	43 (5.4)	6 (2.4)
Gamma-glutamyltransferase increased	42 (5.3)	13 (5.3)
Hypokalemia	42 (5.3)	12 (4.9)
Blood creatinine increased	41 (5.2)	8 (3.3)

System Organ Class[1] Preferred Term	Teplizumab N=791[2] n (%)	Control N=245 n (%)
Hypercalcemia	41 (5.2)	7 (2.9)
Pharyngitis	40 (5.1)	11 (4.5)

[1] Only System Organ Classes with patient count meeting threshold are included.
[2] Delay patients initially randomized to the control arm, who were later also eligible for the open-label administration of teplizumab, are counted once for each treatment arm.
[3] Patients who had more than 1 AE or SAE for a treatment were counted once.
System Organ Classes and preferred terms are based on MedDRA version 23.0
Abbreviations: AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, SAE=serious adverse event

In the SOC of Infections and Infestations, comparable rates were reported in the 2 groups: (53.0% teplizumab vs 52.7% in control). The most common infections reported in more than 5% of patients were also reported at similar rates between the teplizumab and control groups and included upper respiratory infection, nasopharyngitis, and pharyngitis.

7.6 Adverse Events Leading to Study Drug Discontinuation

A greater percentage of patients in the teplizumab group (14.3%) experienced AEs leading to permanent discontinuation of study drug compared with the control group (3.7%; Table 23). The majority of AEs leading to discontinuation of study drug in the teplizumab group were due to laboratory abnormalities such as elevated liver enzymes (ALT and AST) and cytopenias, including neutropenia, thrombocytopenia, lymphopenia, and anemia/hemoglobin decreased. These were predominantly due to protocol-defined discontinuation criteria. The only other AE leading to discontinuation in >1% of patients in either group was CRS (1.1% in the teplizumab group).

Table 23: Adverse Events Leading to Permanent Discontinuation of Study Drug by Preferred Term in >1 Patient (Pooled Safety Population)

Preferred Term	Teplizumab N=791[1] n (%)	Control N=245 n (%)
Patients with at least 1 AE leading to discontinuation[2]	113 (14.3)	9 (3.7)
Alanine aminotransferase increased	36 (4.6)	1 (0.4)
Aspartate aminotransferase increased	17 (2.1)	1 (0.4)
Hemoglobin decreased	12 (1.5)	0
Neutropenia	11 (1.4)	0
Cytokine release syndrome	9 (1.1)	0
Thrombocytopenia	9 (1.1)	0
Hyperbilirubinemia	6 (0.8)	2 (0.8)
Lymphopenia	4 (0.5)	1 (0.4)
Pyrexia	4 (0.5)	0
Blood bilirubin increased	3 (0.4)	0
CD4 lymphocytes decreased	3 (0.4)	0
Herpes zoster	3 (0.4)	1 (0.4)
Anemia	2 (0.3)	0
Epstein-Barr virus	2 (0.3)	1 (0.4)
Gamma-glutamyltransferase increased	2 (0.3)	0
International normalized ration increased	2 (0.3)	0
Nasopharyngitis	2 (0.3)	0

[1] Delay patients initially randomized to the control arm, who were later also eligible for the open-label administration of teplizumab, are counted once for each treatment arm.
[2] Patients who had more than 1 AE for a treatment were counted once.
Preferred Terms are based on MedDRA version 23.0
Abbreviations: AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities

7.7 Serious Adverse Events

SAEs occurring in more than 1 patient are shown in Table 24. Ninety-eight (12.4%) patients in the teplizumab group and 20 (8.2%) in the control group experienced 1 or more SAEs. SAEs associated with the underlying disease of T1D or its treatment, including DKA (Section 7.10.3), hyperglycemia, hypoglycemia, hypoglycemic seizure, and hypoglycemic unconsciousness were among the most commonly reported. Of these events, DKA and hypoglycemic seizure occurred in higher frequency in teplizumab patients compared to control.

Table 24: Serious Adverse Events by Preferred Term in >1 Patient (Pooled Safety Population)

Preferred Term	Teplizumab N=791[1] n (%)	Control N=245 n (%)
Patients with at least 1 SAE[2]	98 (12.4)	20 (8.2)
Diabetic ketoacidosis	18 (2.3)	1 (0.4)
Cytokine release syndrome	6 (0.8)	0
Hypoglycemic seizure	6 (0.8)	0
Hyperglycemia	5 (0.6)	3 (1.2)
Hypoglycemia	5 (0.6)	1 (0.4)
Diabetes mellitus inadequate control	3 (0.4)	0
Gastritis	3 (0.4)	0
Gastroenteritis	3 (0.4)	2 (0.8)
Alanine aminotransferase increased	2 (0.3)	0
Aspartate aminotransferase increased	2 (0.3)	0
Cataract subcapsular	2 (0.3)	0
Cellulitis	2 (0.3)	2 (0.8)
Gastroenteritis viral	2 (0.3)	0
Hypoglycemic unconsciousness	2 (0.3)	1 (0.4)
Infection	2 (0.3)	0
Lymphopenia	2 (0.3)	0
Neutropenia	2 (0.3)	1 (0.4)
Non-cardiac chest pain	0	2 (0.8)
Pneumonia	2 (0.3)	0
Pyrexia	2 (0.3)	0
Rash	2 (0.3)	0
Suicide attempt	2 (0.3)	0
Splenic rupture	2 (0.3)	0

[1] Delay patients initially randomized to the control arm, who were later also eligible for the open-label administration of teplizumab, are counted once for each treatment arm.
[2] Patients who had more than 1 AE for a treatment were counted once.
Preferred terms are based on MedDRA version 23.0
Abbreviations: AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, SAE=serious adverse event.

7.8 Malignancies

In the 5 studies included in the pooled analysis, one case of metastatic melanoma (Protégé 0052001) was reported. This was a case of metastatic melanoma in a pre-existing lesion that was not diagnosed until after entering the study in a subject who had a history of dysplastic nevi. The subject underwent excision of the lesion and was in full remission 2 years post-excision, and there has been no recurrence of metastatic malignant melanoma (see Appendix 10.3).

There were 2 additional cases in studies not included in the pooled safety analysis because they were not T1D patients.

1. An islet transplant recipient in an investigator-initiated study was reported to experience a nonmalignant lymphoproliferative syndrome associated with reactivation of EBV infection. The subject received a cumulative dose of 43 mg of hOK3γ1(Ala-Ala) (pre-cursor product of teplizumab) and 3 additional immunosuppressive agents including tacrolimus (calcineurin inhibitor), sirolimus (mTOR inhibitor) and etanercept (anti-TNF). The patient developed lymphadenopathy and tonsillar swelling felt to be a manifestation of nonmalignant lymphoproliferative syndrome associated with an increase in EBV viral loads. The symptoms resolved after discontinuation of immunosuppression and treatment with anti-viral therapy.

2. A renal transplant recipient developed Grade 2 squamous cell carcinoma 6 months after dosing with teplizumab and was treated with non-drug therapies. The investigator indicated that this event was a recurrence and did not consider the squamous cell carcinoma related to teplizumab.

7.9 Deaths

Three deaths have been reported across the teplizumab studies (Table 25). Two deaths occurred in patients in the Protégé study and are included in the pooled analysis; 1 death occurred in the Protégé Extension study. All deaths occurred in patients randomized to teplizumab, and the investigator's causality assessments indicated that the deaths were not related to study drug. Detailed narratives of these events are provided in Appendix 10.3.

Table 25: List of All Patient Deaths in Teplizumab Clinical Studies

Study	Age at Enrolment/Sex	Adverse Event/Time to Onset Post-last Dose	Cause of Death	Relationship to Study Drug
Protégé	19/Female	Diabetic ketoacidosis 9 months	Diabetic ketoacidosis	Unlikely
Protégé	27/Male	Anterior Myocardial Infarction 15 months	Anterior Myocardial Infarction; Ventricular tachycardia; cardiopulmonary arrest	Not related
Protégé extension[1]	24/Female	Death 26 months	Unknown; Death preceded by abdominal pain, vomiting and loose stools; Admitted due to vomiting; Records were unable to be obtained from clinical site	Not related

[1] Study not included in pooled analysis.

7.10 Additional Adverse Events of Interest

7.10.1 Infections

Based on teplizumab's immune modulatory mechanism of action, the key aspect of the safety evaluation plan was to monitor for complications associated with infections. In addition, while teplizumab has a modified Fc region to minimize immune activation, safety evaluations were designed to monitor for occurrence of the signs, symptoms, and sequelae of immune activation.

Overall, AEs in the SOC of Infections and Infestations occurred in 53.0% of patients in the teplizumab group and 52.7% in the control group. The most common AEs, upper respiratory infection, nasopharyngitis, and pharyngitis, occurred at similar rates between the 2 groups (Table 26).

SAEs of Infections and Infestations occurred in 28 (3.5%) teplizumab-treated patients and 5 (2.0%) control patients. The most common infection-related SAE was gastroenteritis, which occurred more frequently in the control group (3 [0.4%] teplizumab-treated patients and 2 [0.8%] control patients). Only 4 other infection-related SAEs occurred in more than 1 patient overall. These SAEs (gastroenteritis viral, infection, and pneumonia) occurred in 2 teplizumab-treated patients each but none of the control patients. Cellulitis occurred in 2 patients each in the teplizumab and control groups.

Table 26: Adverse Events of Infections and Infestations Occurring in ≥5% (Safety Population)

Preferred Term	Teplizumab N=791[1] n (%)	Control N=245 n (%)
Infections and Infestations	419 (53.0)	129 (52.7)
Upper Respiratory Tract Infection	150 (19.0)	43 (17.6)
Nasopharyngitis	88 (11.1)	23 (9.4)
Pharyngitis	40 (5.1)	11 (4.5)

[1] Delay patients initially randomized to the control arm, who were later also eligible for the open-label administration of teplizumab, are counted once for each treatment arm.

7.10.1.1 Herpes Viruses

Viral infections are important safety events to monitor with immunomodulatory therapy, particularly reactivation of latent DNA viruses, such as EBV, CMV, herpes simplex virus, and varicella zoster virus. The AEs related to these infections are shown in Table 27.

Table 27: Adverse Events Related to Herpes Viruses (Safety Population)

System Organ Class Preferred Term	Teplizumab N=791 n (%)	Control N=245 n (%)
Infections and Infestations		
EBV viraemia	25 (3.2)	3 (1.2)
EBV infection	18 (2.3)	5 (2.0)
Herpes zoster	10 (1.3)	1 (0.4)
Oral herpes	8 (1.0)	0
Herpes simplex	2 (0.3)	1 (0.4)
Varicella	5 (0.6)	1 (0.4)
Infectious mononucleosis	3 (0.4)	1 (0.4)
CMV infection	2 (0.3)	0
Mononucleosis syndrome	1 (0.1)	0
Herpes virus infection*	1 (0.1)	0
Investigations		
EBV antibody positive	17 (2.1)	8 (3.3)
CMV test positive	8 (1.0)	2 (0.8)
EBV test positive	3 (0.4)	0
EBV antigen positive	1 (0.1)	0

*This event was a result of a cat scratch and was considered definitely not related to study drug.
Abbreviations: CMV=cytomegalovirus, EBV=Epstein-Barr virus

Epstein-Barr Virus

The majority of patients were seropositive for EBV on study entry (76.6% teplizumab and 72.3% placebo).

EBV viremia was reported in a total of 28 patients (25 [3.2%] teplizumab and 3 [1.2%] control). The detectable viral DNA was minimally elevated, occurring typically 4 to 6 weeks after the start of dosing, and was transient. These transient viral DNA elevations were generally asymptomatic EBV reactivations.

EBV infection was reported in a total of 23 patients (18 [2.3%] teplizumab and 5 [2.0%] control). There were 2 infections during screening and 7 new or primary EBV infections (5 teplizumab and 2 control). Of the remaining 14 patients, all were seropositive at baseline and developed detectable EBV IgM during the study (11 teplizumab and 3 control), consistent with reactivation without evidence of viremia.

EBV antibody positive was reported in a total of 25 patients (17 [2.1%] teplizumab and 8 [3.3% control). This represented new or primary EBV infection in 11 teplizumab and 8 controls. Of the remaining 6 patients, 2 teplizumab cases represented reactivation. The others were laboratory errors (2) or reporting errors (2).

EBV test positive were reported in a total of 3 patients, all on teplizumab; 2 were asymptomatic new or primary infections and 1 was asymptomatic reactivation.

EBV antigen positive was reported in 1 seropositive teplizumab patient with asymptomatic viremia noted on Day 12 up to 172, consistent with EBV reactivation.

In summary, new or primary EBV infections were reported in 18 (2.3%) teplizumab patients and in 10 (4.1%) controls. Reactivation of EBV was reported in 40 (5.1%) teplizumab patients and 6 (2.4%) control patients. The viremia observed during reactivation was transient and typically occurred at a single study visit. Overall, teplizumab does not appear to increase the risk of primary EBV infection. Reactivation of EBV occurred more commonly in teplizumab patients, but these events were generally asymptomatic, and viremia, if present, was transient.

EBV and Mononucleosis

AEs of infectious mononucleosis (3 [0.4%] teplizumab patients and 1 [0.4%] control patient) and mononucleosis syndrome (1 [0.1%] teplizumab patient and 0 control patients) were uncommonly reported and comparable between groups. Of the 4 teplizumab patients, 3 cases were consistent with EBV reactivation mononucleosis and 1 was consistent with new EBV infection. The one control case was consistent with a new infection.

Cytomegalovirus

The majority of patients were seropositive for CMV on study entry (teplizumab 59.5% and placebo 59.2%). CMV infection was reported in 2 (0.3%) teplizumab patients and no control patients. CMV test positive was reported in 8 (1.0%) teplizumab patients and 2 (0.8%) control patients; all were asymptomatic. Of the 10 teplizumab patients with CMV infection or CMV test positive, 5 had asymptomatic new or primary infection (0.6%) and 4 (0.5%) had asymptomatic reactivation. The last patient (0.1%) was seropositive at baseline, which was reported erroneously as an AE. Of the 2 control patients, both were new or primary infections.

Herpes Zoster and Herpes Simplex

Herpes zoster was reported 10 (1.3%) teplizumab patients and 1 (0.4%) control patient. All events resolved with antiviral treatment. The onset was highly variable, with 3 events occurring within the first 3 weeks of Course 1 dosing, 5 between 3 weeks and 1 year, and 2 patients had onset beyond 1 year. Eight of the 10 teplizumab patients had Grade 1 or Grade 2 events and 2 had Grade 3. The control patient experienced a Grade 3 event that occurred in Month 7 and resolved with antiviral treatment.

Varicella infections (chicken pox) were reported in 5 (0.6%) teplizumab patients and 1 (0.4%) control patient.

Herpes simplex (2 [0.3%] teplizumab, 1 [0.4%] control) or oral herpes (8 [1.0%] teplizumab, 0 control) was infrequently reported in both groups and resolved without sequelae.

7.10.2 Cytokine Release Syndrome

Mild cytokine release is likely due to partial CD3 agonism and is usually seen in the initial days of infusion until the activated T cells become quiescent. These cytokines are believed to be responsible for the transient rash and along with upregulation of adhesion molecules that results in accumulation and adhesion of lymphocytes to the blood vessel wall (margination), lymphopenia is also commonly observed.

As previously mentioned, 46 (5.8%) patients in the teplizumab group experienced AEs of CRS, and this was most often observed during the first 3–5 days of dosing. Increased transaminase AEs occurred in more than half of the patients with CRS, and additional patients experienced AEs of increased gamma-glutamyl transferase (GGT) or total bilirubin (more details are in Section 7.10.2.1).

Most CRS events were Grade 1 (40%) or Grade 2 (48%) in severity. CRS led to discontinuation in 9 patients in the teplizumab group. Six teplizumab patients experienced SAEs of CRS; all resolved without sequelae.

7.10.2.1 Liver Function Abnormalities

Increased aminotransferases have been reported to be associated with CRS and likely related to cytokine effects on the liver (Lee et al 2014; Shimabukuro-Vornhagen et al 2018). Another anti-CD3, visilizumab, in the treatment of Crohn's disease patients led to typical symptoms of CRS and cytokine release within an hour of the infusion (Baumgart et al 2009). After infusion, transient modest elevations (<2× ULN) in hepatic enzymes were noted and resolved rapidly, with complete resolution in 7 to 14 days. These authors postulate that the hepatic injury was not a direct result of visilizumab since the elevations did not continue to increase with repeated dosing. The ALT and AST changes all point to cytokine release, which occurred within 15 minutes of dosing. Activated T cells are the primary target of the drug, which induces cytokine release. The intestines and abdominal organs send all cytokines into the portal circulation to the liver. Endothelial cells quickly become involved, releasing cytokines and chemokines. The liver therefore receives a rapid but transient insult from cytokines both released in the liver or into the portal system. In summary, these liver enzyme elevations are related to cytokine release and typically resolve with continued therapy.

As expected, the teplizumab group showed transient increases in ALT, AST, and GGT and transient decreases in alkaline phosphatase (ALP) and bilirubin in the pooled analysis.

Elevations of ALT/AST above the ULN occurred commonly, and the majority of elevations were minor and did not exceed 3 × ULN. Peak ALT >ULN but <3 × ULN was noted in 408 (51.6%) teplizumab-treated patients and 70 (28.6%) control patients. Most studies set the exclusion criteria at 1.5 × ULN; therefore, some patients could already have had minor elevations at baseline.

One hundred and twelve (14.2%) teplizumab patients had peak ALT >3 × ULN compared to 7 (2.9%) control patients. Additionally, 39 (5.0%) teplizumab patients and 2 (0.8%) control patients had peak ALT >5 × ULN, and 11 (1.4%) teplizumab patients and 1 (0.4%) control patient with ALT >10 × ULN (Table 28).

Of these 11 cases with ALT >10 × ULN, several had etiologies such as Hepatitis A, malaria, and probable CMV, or the timing occurred remote from dosing, making the relationship unlikely related. Of the remaining patients, 1 had definite CRS, and the remaining 4 were probably due to CRS based on the proximity to dosing and associated symptoms.

Table 28: Teplizumab Patients with ALT >10 × ULN

Study	Onset	Peak ALT (NR: 0-35 U/L)	Peak AST (NR: 0-35 U/L)	Total Bili (NR: 0.3-1.0 mg/dL)	Cause	Comments
AbATE	Course 1 Day 4	641	346	0.7	CRS	Full 14-day dose regimen
Encore	Course 1 Day 5	482	275	0.7	Cytopenia (signs/symptoms consistent with CRS)	Full 14-day dose regimen
Encore	Course 1 Day 14	276	184	0.4	Fever (signs/symptoms consistent with CRS)	1/3 dose dose regimen
Encore	Course 1 Week 6	296	124	0.7	Treatment discontinued	1/3 dose Dose regimen
	Course 2 Not dosed Day 217	408	183	1.8	New CMV IgG	
Encore	Course 1 Day 23	702	362	0.5	Rash, lymphopenia (signs/symptoms consistent with CRS)	6-day dose regimen
Encore	Course 1 Day 6	454	211	0.47	Cytopenia, headache; (signs/symptoms consistent with CRS)	Full 14-day dose regimen
Protégé	Day 98	654	318	0.8	Remote from treatment	Full 14-day dose regimen
Protégé	Day 22	833	195	0.4	Malaria	Full 14-day dose regimen
Protégé	Course 2 Day 3 (185)	127	257	0.4	Remote from treatment	1/3 dose dose regimen dosing stopped after 3 doses
	Day 273	435	399	0.7		
Protégé Seg 1	Course 1 Day 6	488	358	0.4	Cytopenia, anemia (signs/symptoms consistent with CRS)	Full 14-day dose regimen
Protégé Seg1	Course 1 Week 6	447	76	0.5	Hepatitis A	Full 14-day dose regimen ALP 644

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMC=cytomegalovirus, CRS=cytokine release syndrome, IgG=immunoglobulin G, NR=normal range, ULN=upper limit of normal; Bili=bilirubin

Half of the patients treated with teplizumab who experienced CRS also had AEs of increased ALT, AST, or ALP, and additional patients had AEs of increased GGT or total bilirubin.

In all teplizumab studies, including those for other indications, 7 cases have been identified with ALT/AST >3 × ULN and total bilirubin >2 × ULN. In 2 cases, the etiologies were biloma and Hepatitis A, and the remaining 5 cases were cytokine induced.

The 5 cases of CRS associated with elevations of transaminases concomitant with elevated bilirubin (ALT/AST >3× ULN and total bilirubin >2× ULN) are described below and in Table 29.

- 1 patient in an early T1D study (Study 3 [ITN017AI]; not included in the Integrated Safety Database)
- 1 patient in a psoriatic arthritis study ([ITN011AI]; not included in the Integrated Safety Database)
- 1 patient in the T1D Phase 3 study Protégé (included in the Integrated Safety Database)
- 2 patients, one each from 2 ongoing blinded studies
    - 1 patient in AG019-T1D-101 (not included in the Integrated Safety Database)
    - 1 patient in PRV-031-001 (PROTECT study [NCT03875729]) (not included in the Integrated Safety Database)

In 2 of these studies (Study 3 ITN017AI [T1D] and ITN011A1 [psoriatic arthritis]), higher initial doses than the proposed dose regimen for teplizumab were administered and were the only cases reported as SAEs.

The onset of increased aminotransferases varied between Day 2 and Day 4 of dosing, with one of the earlier cases preceded by hyperbilirubinemia associated with hemolysis. In all cases, the increases in ALT and AST improved rapidly with drug discontinuation and were normal within 2 to 4 weeks. Bilirubin elevations were typically <3× ULN, except when associated with coagulopathy or hemolysis. ALP, where available, was typically normal or minimally increased. GGT was elevated in the 2 patients where it was available and mirrored the ALT and AST elevations.

In the patient with psoriatic arthritis who received the first and only dose of 1 mg (~482 ug/m^2), cytokine measurements (IL-10, IL-6, and TNF-α) were available before and after treatment. IL-6 and TNF-α increased >2024 pg/mL and 407.3 pg/mL, respectively, on Day 2. Approximately 3 weeks later, in consideration for continued methotrexate therapy in the setting of psoriatic arthritis, a hepatic ultrasound and liver biopsy were performed. The ultrasound revealed mild fatty liver. The liver biopsy revealed mild hepatocyte unrest and mild macro-vesicular steatosis, but no inflammation or fibrosis (see liver function test Narratives in Appendix 10.3). These results support the hypothesis that the elevations in hepatic enzymes are related to CRS and no significant hepatic pathology is associated with these transient findings.

Thus, of these 5 CRS-related cases, 2 patients received much higher first and second teplizumab ramp-up doses compared to the proposed dosing regimen. Of the 3 cases identified with the proposed dosing regimen, none were SAEs. All cases of CRS-induced transaminase and bilirubin elevations promptly resolved upon discontinuation of teplizumab.

Table 29: Cases of Cytokine Release Syndrome Associated with Transaminase Elevations Concomitant with Elevated Bilirubin (ALT/AST >3× ULN and Total Bilirubin >2× ULN)

Study	AE/ SAE	Preferred Term	Dose Regimen	Dosing Day	Total Bilirubin (NR: 0.3-1.0 mg/dL)	Direct Bilirubin (NR: 0.1-0.3 mg/dL)	ALT (NR: 0-35 U/L)	AST (NR: 0-35 U/L)	ALP (NR: 30-120 U/L)	GGT (NR: 1-94 U/L)	Last Dose
Study 3 ITN017AI	SAE	Hyper-bilirubinemia	~12 mg/m^2 D1: 284 μg/m^2 [=531 μg] D2: 574 μg/m^2 [=1,073 μg] D3–12: 1,149 μg /m^2	Screening Day 2 Day 3 Day 3 Day 4 Day 7 Day 12	0.7 3.3 11.3 9.0 6.5 2.8 1.0	0.1 1.3 6.6 5.8 4.2 1.3 0.4	11 56 52 52 46 167 18	15 66 61 61 35 235 18	 121 	 	 Day 2
ITN011AI (psoriatic arthritis)	SAE	CRS with LFTs	D1: 1 mg (~481 μg/m^2) D2: 2 mg D3-D5: 4 mg	Screening Day 1 Day 2 Day 2 Day 3 Day 4 Week 6	0.3 0.3 1.8 2.8 3.7 3.4 0.6	 1.6 2.6 	97 69 332 331 207 - 33	38 32 234 209 104 - 22	124 100 115 	 	 Day 1
Protégé	AE AE AE	Increased ALT Increased AST Increased GGT	~9 mg/m^2 D1: 51 μg/m^2 D2: 103 μg/m^2 D3: 207 μg/m^2 D4: 413 μg/m^2 D5–14: 826 μg/m^2	Screening Day 1 Day 2 Day 3 Day 4 Day 5 Day 8 Day 182	0.3 0.4 0.6 2.8 0.5 0.3 0.4 0.5	 - 	12 23 22 118 85 61 88 15	17 21 29 148 56 28 65 23	 	11 14 14 145 130 103 91 14	 Day 2
AG019-T1D-101 (ongoing; blinded)	AE	Increased LFTs	~9 mg/m^2 D1: 106 μg/m^2 D2: 425 μg/m^2 D3–12: 850 μg/m^2	Screening Day 1 Day 2 Day 3 Day 4 Day 7 Day 12	0.6 0.9 0.8 2.7 1.2 0.7 0.9	 - 	13 15 13 123 133 64 22	33 29 21 214 142 40 25	107 92 - - 196 117 107	 	 Day 2
PRV-031-001 PROTECT (ongoing; blinded)	AE	CRS with LFTs	~9 mg/m^2 D1: 106 μg/m^2 D2: 425 μg/m^2 D3–12: 850 μg/m^2	Screening Day 1 Day 2 Day 4 Day 4 Day 5 Day 6 Day 8 Day 11 Day 26	0.7 0.5 1.0 3.0 2.6 1.3 1.1 0.8 0.8 0.8	- 0.3 0.4 2.1 - 0.8 0.7 0.4 0.4 -	24 10 36 372 364 231 276 260 125 16	35 17 52 182 163 54 175 118 33 17	- 119 119 277 296 254 265 214 185 145	 	 Day 3

Abbreviations: AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRS=cytokine release syndrome, D=day, GGT=gamma-glutamyl transferase, LFTs=liver function tests, NR=normal range, SAE=serious adverse event, ULN=upper limit of normal

7.10.3 Metabolic Disorders

7.10.3.1 Diabetic Ketoacidosis and Hyperglycemia

SAEs of DKA occurred more frequently in the teplizumab group compared to the control group (Table 30). SAEs related to DKA and ketoacidosis were reported in 18 (2.3%) patients in the teplizumab group and 1 (0.4%) in the control group. DKA was not observed in the TN-10 study; however, it is important to note that patients were not followed in the study after the diagnosis of Stage 3 clinical T1D.

Table 30: Serious Adverse Events of Diabetic Ketoacidosis and Hyperglycemia (Pooled Safety Population)

	Teplizumab N=791		Control N=245	
Preferred Term	**n**	**%**	**n**	**%**
Diabetic ketoacidosis	18	2.3%	1	0.4%
Ketoacidosis	1	0.1%	0	0
Diabetic ketosis	1	0.1%	0	0
Ketosis	0	0	1	0.4%
Hyperglycemia	5	0.6%	3	1.2%

The 19 patients with DKA that were all observed in the Stage 3 T1D population did not occur during the time of study drug treatment but at an average of 10 months after the end of teplizumab treatment (mean 298.9 days, median 307, range 42–681). The events were associated with common triggering causes of DKA in diabetic patients, including infections (urinary tract infection, kidney infection, viral infection, pneumonia, and Dengue fever) and cases related to inappropriate insulin dose or lack of dietary adherence (missed doses of insulin, insulin pump malfunction, noncompliance with diabetic diet, and uncontrolled diabetes).

- These patients had a mean HbA1c of 11.9% (median 12.3%; range 7.1 to 17.3%) near the time of the DKA event, suggesting poor glycemic control, also evidenced by blood glucose levels of mean glucose 439 mg/dL (median 422; range 290–726) for those available at the time of the DKA episode (n=9, 3 additional patient glucose levels were recorded as high without numerical value given).
- Near the time of the DKA event, the mean C-peptide AUC was 0.131 nmol/L (median 0.106; range 0.032–0.391), which declined from baseline with mean AUC of 0.474 nmol/L (median 0.439, range 0.058–1.366 nmol/L).

While the observed cumulative incidence of DKA is 2.4% (19/791), as there were differences in duration of follow-up, the incidence rate adjusted for duration of follow-up for DKA is 0.013 per patient-year (19 patients/1,464 patient-year experience). In the placebo group, the observed cumulative incidence of DKA is 0.4%; the incidence rate

adjusted for duration of follow up is 0.002 per patient-year (1 patient/438 patient-year experience).

Given multiple confounding factors, it is not clear if there a causal relationship between teplizumab treatment and the observed higher incidence of DKA in the Stage 3 T1D population. It should be noted that blinded data (120-day safety update; median follow-up 208 days) from 161 patients in the ongoing Phase 3 PROTECT study in Stage 3 T1D (NCT03875729) has not shown any DKA events.

7.10.3.2 Hypoglycemia

AEs of hypoglycemia occurred in 55 (7.0%) teplizumab patients and 14 (5.7%) control patients. Most events of hypoglycemia were Grade 1 or Grade 2 in severity and generally considered unrelated to study drug.

With respect to SAEs of hypoglycemic events (hypoglycemia, hypoglycemic seizures, hypoglycemic unconsciousness, and hypoglycemic coma) (Table 31), all were observed in Stage 3 patients and none in Stage 2 TN-10 patients. In the Pooled Safety Population, 6 Stage 3 patients in the teplizumab group (0.8%) experienced hypoglycemic seizures, compared with no patients in the control group. The rates of hypoglycemic unconsciousness and hypoglycemic coma were comparable in both groups.

Table 31: Serious Adverse Events of Hypoglycemia (Pooled Safety Population)

System Organ Class Preferred Term	Teplizumab N=791		Control N=245	
	n	%	n	%
Metabolism and Nutrition Disorders				
Hypoglycemia	5	0.6%	1	0.4%
Nervous System Disorders				
Hypoglycemic seizure	6	0.8%	0	0
Hypoglycemic unconsciousness	2	0.3%	1	0.4%
Hypoglycemic coma	1	0.1%	1	0.4%

Review of the 6 patients with hypoglycemic seizures indicate over-treatment with insulin in 4 of the 6 patients (narratives are provided in Appendix 10.3). Of these 4 patients, 2 had additional contributing factors, including noncompliance with diet and glucose monitoring in one patient and increase in activity/exercise with decreased food intake without adjustment of exogenous insulin in the other patient. Of the 2 patients who did not have documentation of over-treatment with insulin, one had symptoms of “shaking” with transient loss of consciousness that responded to oral glucose (no blood sugar recorded) and the other had “convulsions” at home, which resolved spontaneously without treatment, and upon presentation to the emergency room the blood glucose was documented to be 81 mg/dL.

Although the observed cumulative incidence is 0.8% (6/791), to account for differences in duration of follow-up, the incidence rate for hypoglycemic seizure is 0.004 per patient-year (6 patients/1464 patient-year experience).

It should be noted that blinded data (120-day safety update; median follow-up 208 days) from 161 patients in the ongoing Phase 3 PROTECT study in Stage 3 T1D (NCT03875729) has not shown any hypoglycemic clinical events (seizure, unconsciousness or coma).

7.10.3.3 Post-Approval Plans for Monitoring Glycemic Events

If approved, Provention Bio is committed to promoting education for patients, caregivers, and healthcare professionals on the need for ketone and blood glucose monitoring, dietary adherence, and adjustment of insulin dosing for those who progress to clinical Stage 3 disease. DKA and hypoglycemic events will continue to be monitored in a post-marketing registry study or surveillance program to determine if a causal relationship exists.

7.10.4 Hypersensitivity Reactions

Hypersensitivity or drug hypersensitivity occurred in 13 (1.6%) teplizumab patients and 2 (0.8%) controls. The majority (in 9 of 13 patients) were considered unrelated to study drug and included reactions to other drugs and environmental allergens. Of the 4 cases related to teplizumab, the patients had signs and symptoms related to cytokine release. All were Grade 1 (n=5) or Grade 2 (n=7), with the exception of 1 patient who developed a Grade 3 drug hypersensitivity to an allergy immunization injection, which was reported as an SAE and considered definitely not related to study treatment.

7.10.5 Serum Sickness

One patient experienced an SAE of immune complex disorder (possible serum sickness), which resulted in hospitalization and was considered possibly related to teplizumab. The patient, a 12-year-old male, received all 14 teplizumab infusions. During the treatment course, he experienced fever, vomiting, and rash. Approximately 5 days after the last dose of the teplizumab, he developed arthralgias of the shoulders, hips, wrists, and knees. The cause of the arthralgias was most likely serum sickness based on elevated C-reactive protein, erythrocyte sedimentation rate, and reduced level of C4 complement. Due to the presence of low positive (1:80) antinuclear antibody titer prior to the initiation of study drug treatment, a possible underlying immune process may have contributed to the clinical outcome. The event resolved after approximately 2.5 months.

7.10.6 Pregnancy

Seventeen pregnancies were reported during teplizumab clinical development. Two pregnancies occurred in female partners of male patients enrolled in the studies, 1 each in teplizumab and control groups. Outcomes for the 17 pregnancies include 12 normal neonates, 3 elective terminations, 1 spontaneous abortion, and 1 unknown lost to

follow-up (Table 32). In the patient with the spontaneous abortion, the time from last dose of teplizumab to time of conception was approximately 20 months. The investigator assessed the event of spontaneous abortion as unlikely related to the study drug and suggested the patient's T1D and Graves' disease as an alternate cause of the event.

Table 32: Pregnancies in the Teplizumab Clinical Program

Study	Teplizumab vs control or placebo	Outcome	Last Dosing to conception (approximate)
Protégé	Control	Pregnancy medically terminated (voluntary)	NA
	Control	No complications	2 months
	Full 14-day	No complications	9 months
	Full 14-day	No complications	9 months
	Full 14-day	No complications	5 months
	Full 14-day	Pregnancy medically terminated	Before treatment end
	Full 14-day	No complications	>11 months
	Full 14-day	Pregnancy medically terminated	>11 months
	1/3 14-day	No complications	<1 month
	Full 6-day	No complications	12 months
Encore	Control[2]	No complications; 35 weeks female infant normal	<1 month
	Control	No complications	3 months
	Full 14-day	No complications; 34 weeks male infant normal	2 months
	Full 6-day[2]	No complications	2 months
	Full 14-day	Lost to follow-up	4 months
Study 1[1]	Control	No complication	17 months
Protégé Extension[1]	Full 14-day	Abortion spontaneous	20 months

[1] Studies not included in pooled analysis.
[2] Female partners of male patients.
Abbreviation: NA=not applicable.

7.11 Safety in Subgroups

AEs were summarized by intrinsic factors of sex, age groups (<18 vs ≥18 and ≥12 to <18 years), race, dose regimen, number of courses of treatment received, and follow-up time. No clinically meaningful differences in AEs were observed between subgroups. Pediatric patients (<18 years old) reported slightly more frequent rash and vomiting, which were also more common in children <12 years old compared to adolescents. There were too few non-White patients for a meaningful comparison by race in these small populations.

7.12 Risk Management Plan

Provention Bio is committed to promoting the safe use of teplizumab for prescribers and patients. Risk mitigation measures are outlined below. These measures are similar to

those employed during clinical development and are proposed for implementation in the post-marketing setting for teplizumab.

Target Group: Prescribers	
Proposed Measures	**Key Recommendations**
Prescribing Information	Pre-medicate with anti-pyretics (eg, nonsteroidal anti-inflammatory drugs or acetaminophen), antihistamines and anti-nausea medications, before each dose for at least the first 5 days of the 14-day treatment course.
	Administer by IV infusion for a minimum of 30 minutes. Do not administer by IV push or bolus. If AEs develop during infusion, the infusion may be slowed or interrupted. If interrupted, the infusion may be restarted, preferably at a slower rate. If any dose is missed, resume dosing to complete the 14-day regimen but 2 doses must not be given on the same day.
	On each infusion day, monitor for CRS. If disabling signs and symptoms occur, consider temporary pause of dosing for 1–2 days. Treatment can resume after improvement or resolution of symptoms. CRS symptoms may include fever, chills, fatigue, weakness, loss of appetite, nausea, vomiting, diarrhea, headache, rash, joint or muscle aches
	Complete blood count with differential and liver function tests (AST, ALT, bilirubin) should be monitored prior to the first dose and prior to the third day and last day (Day 14) of the treatment course. Further testing can be conducted as needed. Discontinue dosing in individuals who develop ALT or AST abnormalities >5× ULN or bilirubin >3× ULN. Lymphopenia is common with dosing. Maximum lymphopenia is typically observed on Day 5 of treatment and begins to recover even during the completion of the treatment course, with most patients returning to baseline values by Day 28
	Closely monitor for signs and symptoms of infection during and after the 14-day dosing course.
	Do not administer to individuals with an active infection.
	Do not administer to individuals with pre-existing lymphopenia (<1,000 lymphocytes/μL)
	Do not administer to individuals with pre-existing ALT or AST abnormalities >2.0× ULN or bilirubin >1.5× ULN.
Medication Guide	Advise patients to read the FDA-approved Medication Guide
Clinical T1D Counseling and Monitoring	For individuals who develop clinical T1D, provide education and counseling for appropriate diabetes control. Monitor for signs and symptoms of major hypoglycemia events (seizure, coma, unconsciousness) or major hyperglycemia events (DKA).

Target Group: Patients	
Proposed Measures	**Key Recommendations**
Medication Guide	Before starting dosing, tell your healthcare provider if you have any kind of infection or symptoms of infection (fever, sweating, chills, cough, or other flu-like symptoms).
	Before starting dosing, tell your healthcare provider if you have recently received a vaccination or are scheduled to receive a vaccination.
	After starting dosing, tell your healthcare provider about any symptoms that may be related to your treatment (fever, chills, rash, nausea, vomiting or fatigue).
Clinical T1D Monitoring	For individuals who develop clinical T1D, follow your healthcare provider's directions for managing T1D.

Target Group: Emergency Care Providers	
Proposed Measures	**Key Recommendations**
Major Hypoglycemia	In the event of a major hypoglycemic event (seizure, coma, unconsciousness), treat promptly (glucagon, IV dextrose, or oral glucose gel).
DKA	Measure glucose, serum/urine ketones, and serum bicarbonate in case of symptoms indicative of DKA, even if blood glucose levels are below those typically expected for DKA. If DKA is suspected, treat promptly.

8 BENEFIT-RISK CONCLUSIONS

Virtually all patients with Stage 2 T1D who do not receive intervention will progress to Stage 3 clinical T1D, resulting in lifelong insulin dependence. Current therapies for T1D are directed at Stage 3 disease; there are currently no treatments approved for Stage 2 T1D to address the underlying autoimmune process. A therapy that disrupts the causative mechanism of T1D preserves functioning beta cells, leading to the delay of progression to insulin dependence, would have a beneficial impact on the patients and families who manage this devastating disease.

In the TN-10 study, a single 14-day course of teplizumab, resulted in a 2-year median delay in the progression to Stage 3 clinical T1D in patients with Stage 2 T1D. Due to the challenges of conducting the study, with an enrollment time of 6 years (2011-2017) and follow-up of an additional 1 year to reach the event rate, TN-10 enrolled a relatively small number of patients (n=76); nonetheless, the results were highly statistically significant. The delay of progression to clinical T1D is a clinical outcome that can be measured objectively and is therefore not susceptible to bias. Beyond 5 years, 9 teplizumab patients (compared to 3 placebo patients) have maintained freedom from Stage 3 clinical T1D after a single course of teplizumab, suggesting that the persistence of efficacy may translate to a prolonged delay of Stage 3 T1D in some patients. Although not powered to detect differences across subgroups, the findings from the TN-10 study support the beneficial effects of teplizumab across the entire Stage 2 population studied.

The benefits of the observed minimum 2-year delay in the median time to diagnosis of clinical Stage 3 T1D and potential prevention of the onset of T1D in at-risk patients are clinically meaningful. Based on self-reported treatment preferences, families with children at high risk of developing Stage 3 T1D indicated their willingness to accept side effects of a novel treatment for a delay of 2 years before becoming insulin dependent (DiSantostefano et al 2020). A delay of 2 or more years lessens the amount of time that young people will experience the clinical implications and complications of Stage 3 T1D during their teenage or young adult years – a time in life when glycemic control is particularly difficult, likely due to reduced compliance with the complex demands of insulin therapy (Dayan et al 2019; Miller et al 2015; Wood et al 2013). It is now well established that exposure to hyperglycemia is the dominant factor in the etiology of microvascular complications in T1D and that an agent that reduces the level of glycemia will have long-term clinical benefits (Palmer et al 2004). Finally, it has been reported that patients diagnosed with clinical T1D early in life experience greater loss of life expectancy (Rawshani et al 2018). Thus, a treatment that delays the onset of clinical T1D beyond the childhood years could have important long-term impact.

The efficacy data from the TN-10 study is supported by the preservation of beta cell function as demonstrated by the statistically significant results of meta-analyses of C-peptide levels Stage 3 patients. Lower mean insulin use over time from the individual studies further support the C-peptide findings. Together, these data provide evidence that teplizumab protects beta cells throughout the disease continuum.

Given the experience to date, the main risks with teplizumab are mechanism-based, predictable and transient, with no evidence of increased risk of infections or malignancies. While not included in the pooled safety data, 7-year follow-up of teplizumab-treated Stage 3 or newly diagnosed patients in the AbATE study showed no increased risk of infections and no malignancies were observed (Perdigoto et al 2019).

Given multiple confounding factors, it is not clear if there a causal relationship between teplizumab treatment and the observed higher incidence of DKA and major hypoglycemic events in the Stage 3 T1D population. It should be noted that blinded data (120-day safety update; median follow-up 208 days) from 161 patients in the ongoing Phase 3 PROTECT study in Stage 3 T1D has not shown any DKA or hypoglycemic clinical events (seizure, unconsciousness or coma). If approved, Provention Bio is committed to promoting education for patients, caregivers, and healthcare professionals on the need for ketone and blood glucose monitoring, dietary adherence, and adjustment of insulin dosing for those who progress to clinical Stage 3 disease. These events will continue to be monitored in a post-marketing registry or surveillance program to determine if a causal relationship exists.

As described in Section 7.11, teplizumab will be administered in outpatient settings staffed by healthcare providers who are experienced in the administration of such drugs and the treatment of potential effects that can be associated with them. Clinical symptoms and laboratory values should be monitored during infusions, and routine follow-up care should be provided as part of the standard of care for teplizumab.

The magnitude of the treatment effects and the manageable risks should be considered in a proper clinical context. T1D is associated with significant short-term and long-term morbidity and complications, leading to decreased survival, particularly in those who develop the disease at a younger age (Rawshani et al 2018). As there is currently no available therapy for prevention of progression to clinical Stage 3 T1D, the risk of this innovative therapy that is predictable and characterized by transient and manageable symptoms is outweighed by the benefit of a delay of progression to clinical T1D. For the first time, there is a disease-modifying therapy that has the potential to improve long-term outcomes of patients with this devastating, life-changing disease.

The positive benefit/risk profile is summarized in Table 33.

Table 33: Summary of Teplizumab Benefit/Risk

Dimension	Evidence	Conclusions
Formulation/regimen:	• A single 14-day treatment course	Patients only need to undergo 1 treatment course and do not need to add to the treatment burden of T1D.
Population studied:	• TN-10 included 76 patients ages 8.5–49.5 years with Stage 2 T1D	The population studied is consistent with expectations for the proposed population in the post-marketing setting.
Clinical efficacy:	Teplizumab was effective in delaying the onset of T1D in patients with Stage 2 T1D. • In TN-10, a single 14-day course of teplizumab delayed the onset of T1D by a median of 2 years compared to placebo. • All sensitivity analyses were also statistically significant and support the robustness of the primary efficacy analysis results. • Subgroup analyses showed that teplizumab was effective across the study population. • Teplizumab also significantly improved C-peptide AUC levels compared with placebo, which showed an overall decline. • Teplizumab was also effective in preserving beta cell function compared to placebo or standard of care and reducing exogenous insulin use over time across 5 supportive studies in patients with newly diagnosed T1D. • A meta-analysis showed a statistically significant preservation of C-peptide with teplizumab at both 1 year and 2 years of follow-up. • Mean insulin use was significantly lower in the teplizumab group compared with control in 3 studies.	The benefits of the observed minimum 2-year median delay in the onset of clinical T1D in at-risk patients are significant, and the preservation of endogenous insulin production may reduce the need for exogenous insulin. Delaying the onset of clinical T1D can have a meaningful impact on the emotional and physical development of young patients, reduce the burden on families and caregivers, and shorten the lifetime duration of T1D. Delayed clinical T1D onset may also lead to better adherence to insulin treatment and better glycemic control if patients are on average older when they are diagnosed. It has been reported that patients diagnosed with clinical T1D early in life experience greater loss of life expectancy (Dayan et al 2019). A treatment that delays the onset of clinical T1D beyond the childhood years would have an important long-term impact on patient survival.
Acceptable safety profile:	There is a large safety dataset of nearly 800 patients with Stage 2 and Stage 3 T1D exposed to teplizumab. • The most common AEs in the Pooled Safety Population were lymphopenia, leukopenia, neutropenia, blood bicarbonate decreased, and rash. • Most AEs were mild to moderate in severity.	Data from nearly 800 patients exposed to teplizumab, constituting an appropriate population exposure, indicate that most of the AEs related to teplizumab treatment are mechanism-based, predictable, transient, and manageable. Teplizumab will be administered in outpatient settings staffed by trained healthcare

	• SAEs occurred more frequently in the teplizumab group, and events that were associated with underlying T1D were most commonly reported. • AEs leading to withdrawal of study treatment occurred more frequently in the teplizumab group, and more than half were due to laboratory abnormalities that met protocol-defined discontinuation criteria. • Across studies, 3 patients died in the teplizumab group. None of the events occurred during the dosing period, and all were assessed as not related to treatment by the investigator. • Patients who develop clinical T1D may encounter potential risks of DKA or hypoglycemic events, which will be managed by education and counseling for appropriate signs and symptoms.	providers who are experienced in the administration of such drugs and the treatment of potential effects that can be associated with them. Patients should be monitored throughout their infusions and routine follow-up care should be provided to assess for adverse reactions and laboratory changes as part of the standard of care for teplizumab. To further augment patient education, Provention Bio plans to provide a medication guide to be distributed to all patients to inform them of the risks of receiving teplizumab.
Potential risk for infection and CRS:	• The overall incidence of infections was comparable between teplizumab and control groups. • CRS occurred more frequently in the teplizumab group. The majority of events were mild to moderate in severity and resolved within 2–3 days despite continued dosing.	While it is important to monitor for infection-related complications with immunomodulators, teplizumab was not associated with increased risk of serious infection. Events of CRS were manageable and resolved once T cells became quiescent.

Abbreviations: AEs=adverse events, AUC=area under the concentration-time curve, CRS=cytokine release syndrome, DKA=diabetes ketoacidosis, SAEs=serious adverse events, T1D=type 1 diabetes

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10 APPENDICES

10.1 Inclusion and Exclusion Criteria

For inclusion into the study, patients were required to fulfill all of the following criteria:

1. Patient was a patient in the TN-01 and thus a relative of a proband with T1D. (Note: A proband is an individual who was diagnosed with diabetes before the age of 40 years and started on insulin therapy within 1 year of diagnosis, or, if a patient with proband was considered to have T1D by their physician who did not meet this definition, the TrialNet Eligibility Committee for the TN-01 must have approved enrollment in TN-01.)
2. Between the ages of 1 and 45 years at the time of enrollment in TN-01 and ≥8 years at the time of randomization in this study.
3. Patient (or parent or legal guardian if the patient is a minor) was willing to provide Informed Consent.
4. Individuals <18 years of age at time of randomization must have had a TrialNet-conducted OGTT demonstrating abnormal glucose tolerance within 7 weeks (52 days) of the baseline visit (Visit 0). Abnormal glucose tolerance was defined as:
5. Fasting plasma glucose ≥110 mg/dL and <126 mg/dL, or
6. 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or
7. 30, 60, or 90-minute value on OGTT ≥200 mg/dL
8. Note: In this study, fasting glucose levels of 110–125 mg/dL qualified patients as having abnormal glucose tolerance, as it reflects the criteria used for entry into the DPT-1 study (National Diabetes Data Group 1979), which was used for the calculation of diabetes risk.
9. Individuals ≥18 years of age at the time of randomization had undergone 2 consecutive TrialNet-conducted OGTTs demonstrating abnormal glucose tolerance, the most recent of which had been within 7 weeks (52 days) of the baseline visit (Visit 0).
10. The patient had to be positive for 2 or more diabetes-related autoantibodies on 2 occasions. The second occasion had been within the 6 months prior to study drug administration but did not have to involve the same 2 autoantibodies as those found on the first occasion. The autoantibodies to be confirmed were anti-GAD65, anti-ICA512, mIAA, ZnT8 antibody, and/or ICA.
11. Patient weighed at least 26 kg at randomization.

12. If the patient was female with reproductive potential, she had to have a negative pregnancy test on Day 0 and be willing to avoid pregnancy for at least 1 year from randomization.
13. If patient was male, he had to be willing to avoid pregnancy in any partners for at least 1 year from randomization.
14. Patient was willing and medically acceptable to postpone live vaccine immunizations for 1 year after treatment.
15. Patient was willing to forego other forms of experimental treatment during the study.

Any of the following was regarded as a criterion for exclusion from the study:

1. If a patient was ≥18 years old, he or she had a diagnosis of diabetes or had a screening OGTT in which:
2. Fasting plasma glucose was ≥126 mg/dL, or
3. 2-hour plasma glucose was ≥200 mg/dL.
4. If a patient was <18 years old, he or she had a diagnosis of diabetes or had a screening random glucose ≥200 mg/dL.
5. Lymphopenia (<1,000 lymphocytes/µL).
6. Neutropenia (<1,500 PMN [polymorphonuclear neutrophils]/µL).
7. Thrombocytopenia (<150,000 platelets/µL).
8. Anemia (hemoglobin <10 grams/deciliter [g/dL]).
9. AST or ALT >1.5 × ULN.
10. Total bilirubin >1.5 × ULN with the exception of patients with the diagnosis of Gilbert's syndrome who might be eligible if they had no other causes leading to hyperbilirubinemia.
11. International normalization ratio >0.1 above ULN at the study center's laboratory.
12. Chronic active infection other than localized skin infections.
13. A positive tuberculin PPD test.
14. Vaccination with a live virus within 8 weeks of randomization.
15. Vaccination with a killed virus within 4 weeks of randomization.
16. A history of infectious mononucleosis within the 3 months prior to enrollment.
17. Laboratory or clinical evidence of acute infection with EBV or CMV.
18. Serological evidence of current or past HIV, Hepatitis B or Hepatitis C infection.
19. Patient was currently pregnant or lactating or anticipated getting pregnant.
20. Chronic use of steroids or other immunosuppressive agents.
21. A history of asthma or atopic disease requiring chronic treatment.

22. Untreated hypothyroidism or active Graves' disease at randomization.
23. Current use of non-insulin pharmaceuticals that affect glycemic control.
24. Prior OKT3 or other anti-CD3 treatment.
25. Administration of an mAb within the year before randomization.
26. Participation in any type of therapeutic drug or vaccine clinical study within the 12 weeks before randomization.
27. Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the patient.

10.2 Patient Randomization by Study Site in TN-10

Table 34: Patient Randomization by Study Site in TN-10

Site Number	Age Group	Treatment	n	Site Number	Age Group	Treatment	n
1	<18	Placebo	3	**11**	<18	Placebo	1
1	<18	Teplizumab	4	**11**	≥18	Teplizumab	1
1	≥18	Placebo	1	**12**	<18	Teplizumab	1
1	≥18	Teplizumab	2	**13**	<18	Placebo	1
2	<18	Placebo	4	**13**	<18	Teplizumab	1
2	<18	Teplizumab	5	**13**	≥18	Teplizumab	2
2	≥18	Teplizumab	1	**14**	<18	Placebo	1
5	≥18	Teplizumab	1	**14**	<18	Teplizumab	1
6	≥18	Teplizumab	1	**15**	<18	Placebo	1
7	<18	Placebo	3	**15**	≥18	Teplizumab	1
7	<18	Teplizumab	3	**16**	<18	Teplizumab	1
7	≥18	Placebo	2	**225**	<18	Placebo	1
7	≥18	Teplizumab	3	**225**	<18	Teplizumab	1
9	<18	Placebo	1	**3,017**	<18	Placebo	1
9	<18	Teplizumab	2	**3,017**	<18	Teplizumab	2
9	≥18	Placebo	1	**3,126**	<18	Placebo	4
9	≥18	Teplizumab	2	**3,126**	<18	Teplizumab	3
10	<18	Placebo	5	**3,126**	≥18	Placebo	2
10	<18	Teplizumab	5	**3,126**	≥18	Teplizumab	1

10.3 Narratives

Protégé Death Narratives

1. A 20-year-old White woman who was randomized to the full 14-day teplizumab regimen in the Protégé study experienced fatal SAEs of DKA and intercapillary glomerulosclerosis. She received all 14 doses of study drug in Course 1 and 12 of 14 doses in Course 2. Approximately 9 months after receiving the last dose of study drug, the patient was hospitalized with a diagnosis of DKA and intercapillary glomerulosclerosis, which were fatal.

In addition to T1D, the patient's medical history included occupational exposure to air contaminants and a hazardous material (linoleum), diabetic angiopathy of the retina, neurocirculatory dystonia, diabetic angiopathy, and unstable chronic pancreatitis in remission stage. Medications included Actrapid, insulin detemir, and insulin aspart for a total insulin dose of 0.43 units/kg/day on Day 448. The patient experienced 4 prior SAEs of DKA within the previous 7 months (Study Days 272 to 285, 328 to 348, 423 to 426, 446 to 449). The investigator attributed these prior DKA SAEs to the patient's insulin dose insufficiency in relation to quantity of food/carbohydrate-rich meals (supported by HbA1c values of approximately 15%). After Study Day 350, the following nonserious AEs were reported, which had not resolved as of the time of the patient's death (with Study Day of onset): hemoglobin decreased (361), white blood cell count decreased (361), diabetic neuropathy (393), diabetic vascular disorder (393), diabetic encephalopathy (393), and left ventricular hypertrophy (423). On Day 492, the patient was admitted to the hospital complaining of weakness, 2 episodes of vomiting, and epigastric pain. She was diagnosed with DKA and intercapillary glomerulosclerosis. The patient died on Study Day 496.

The investigator assessed the fatal events of DKA and intercapillary glomerulosclerosis as unlikely to be related to the study drug. The investigator considered the DKA to be related to the patient's noncompliance with diabetic diet and insulin dose. The investigator considered the intercapillary glomerulosclerosis to be possibly related to occupational exposure to hazardous substance. The death certificate listed the cause of death as insulin-dependent diabetes mellitus with kidney alteration. The autopsy report listed the direct cause of death as uremia, secondary to diabetic glomerulosclerosis, and underlying disease of insulin-dependent diabetes mellitus with kidney alteration.

2. A 27-year-old Asian male who was randomized to the one-third 14-day teplizumab regimen in the Protégé study experienced fatal SAEs of extensive anterior wall myocardial infarction with ventricular tachycardia resulting in sudden cardio-respiratory arrest. He received all 14 doses of study drug in Course 1 and Course 2. Approximately 14 months after the last dose of study drug the patient experienced 3 SAEs of acute myocardial infarction, cardio-respiratory arrest, and ventricular tachycardia, which were fatal.

In addition to T1D, the patient's medical history included occasional smoking and alcohol consumption. Medications included Lupisulin N (intermediate-acting insulin) and Lupisulin R (short-acting insulin) for a total insulin dose of 0.78 units/kg/day on Day 616. During the study he experienced Grade 1 hyponatremia 1 day after the completion of the first teplizumab treatment course, which lasted for 2 weeks. During the second treatment course, he experienced Grade 1 anemia, which resolved in 17 days, and 1 episode of hyperbilirubinemia, which resolved within 5 days. On Study Day 649, the patient reportedly felt uneasy with chest pain and vomiting for 6 hours, went to the hospital, and was admitted to the intensive coronary care unit. His general condition was poor; an electrocardiogram revealed ST elevation. He was given ramipril, lisinopril, nitroglycerine

drip, clopidogrel, isosorbide dinitrate, pentazocine, low molecular weight heparin, diazepam, metoprolol, and atorvastatin calcium. He experienced cardiopulmonary arrest with unsuccessful resuscitation attempt.

The investigator assessed the SAEs of acute myocardial infarction, cardio-respiratory arrest, and ventricular tachycardia as not related to study drug. Per the death certificate, the cause of death was extensive anterior wall myocardial infarction with ventricular tachycardia resulting in sudden cardio-respiratory arrest.

Protégé Extension Death Narrative

3. A 24-year-old Asian female who was randomized to receive the full 14-day teplizumab regimen in the Protégé study and participated in the Protégé Extension study experienced a fatal SAE (unknown cause). The patient received all 14 doses of study drug in Course 1 and Course 2, completed the Protégé study at Day 728, and enrolled in the Protégé Extension study.

Medical history included T1D; no other medical history was reported. Medication included Lupisilin for a total insulin dose of 0.941 units/kg/day on Day 728. On Study Day 980, 2 years and 2 months after receiving the last dose of study drug in Protégé, she experienced abdominal pain, vomiting and loose bowel movements for which she received unknown treatment for 5 days. She was not hospitalized but was reportedly taking insulin regularly. On Study Day 984, she experienced increased vomiting. On Study Day 996, the clinical site was informed that patient had died at home on Study Day 985. The patient was reported as experiencing an SAE of death (verbatim term: unknown cause of death).

The investigator assessed this SAE as unrelated to study drug. An autopsy was not performed. No further information was able to be recorded from the patient's provider or family.

Protégé Metastatic Melanoma Narrative

A 21-year-old White male was enrolled into the double-blind segment and randomly assigned to the one-third 14-day regimen of the Protégé study and began study drug on Study Day 0. On Study Day 3, he was reported to have a drug-related nonserious AE of hyperbilirubinemia that led to discontinuation of study treatment. On Study Day 189, he was reported to have a nonrelated serious AE of metastatic malignant melanoma.

Medical history included depression, dysplastic naevus syndrome and hemoglobin decreased. Infusion prophylaxis medications included diphenhydramine, ibuprofen, and IV diphenhydramine. Concomitant medications before the AE included fluoxetine. The patient's insulin dosing during the study included insulin glargine and insulin aspart injection.

He received 4 of the 14 study drug infusions of the first treatment course. On Study Day 3, he was reported to have a Grade 2 AE of hyperbilirubinaemia. Study drug infusions were

stopped. On Study Day 5, 2 days after the last dose of study drug, the AE of hyperbilirubinaemia was considered resolved.

The patient did not receive Course 2 treatment.

On Study Day 189, he was reported to have a Grade 3 SAE of metastatic malignant melanoma (verbatim term: pigmented epithelioid melanocytoma with lymph node metastases). The patient underwent a partial excision of a persistent pigmented scalp lesion of several years duration on Study Day 189. The excised lesion was 2.1 mm deep with a positive deep margin, and the pathology report revealed a low-grade melanoma.

On Study Day 262, he was evaluated by an oncologist. Computerized tomography scan of the chest (with contrast) indicated a solitary aortopulmonary window lymph node which was mildly enlarged, and the region of the thymus appeared somewhat bi-lobed, which together raised the question of metastasis.

On Study Day 311, lymphoscintigraphy identified sentinel nodes in the left supraclavicular and left suprascapular regions. The patient underwent a wide excision of melanocytoma and biopsy of the left neck sentinel lymph node and several lymph nodes. The pathology showed multiple deposits of metastatic pigmented epithelioid melanocytoma. He underwent a left posterior neck regional lymph node (21) dissection on Study Day 386. The immunohistochemical studies carried out on multiple lymph node blocks showed no evidence of metastatic melanocytic population.

On Study Day 386, 383 days after his last dose of study drug, the SAE of metastatic malignant melanoma was considered resolved. He continued in the study until the last scheduled study visit on Study Day 721. Follow-up information confirmed that, as of last contact with the patient at 1 year after the last study visit, there had been no recurrence of the metastatic malignant melanoma.

Liver Function Test Narratives

1. The patient was a 17-year-old White male with T1D and was the first patient in Cohort 2 of Study ITN017AI. Because stopping criteria were not met in Cohort 1 (cumulative dose ~9.9 mg/m^2), he received 25% higher dose (cumulative dose ~12.3 mg/m^2). He presented with symptoms consistent with CRS on Day 1, including headache, fever up to 101.2^{o}F within 6 hours of the infusion, along with nausea, and vomiting on Day 2. He was also noted to have severe hyperbilirubinemia due to disseminated intravascular coagulopathy and hemolysis (Hb drop 16.1 g/dL to 13.3 g/dL). Study drug was discontinued after Day 2. An ultrasound revealed unexplained splenomegaly on Day 3. He was discharged on Day 4 complaining only of upset stomach. Transaminases increased on Day 7 as the bilirubin was coming down and then decreased subsequently. The patient was felt to be clinically stable on Day 7 and resolved by Day 26. Additional laboratory tests beyond Day 7 are not available in the Council for International Organizations of Medical Sciences report.

Concomitant medications included multivitamin, diphenhydramine, ibuprofen, acetaminophen, hydroxyzine, prochlorperazine.

Study Day	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	GGT (U/L)	LDH (U/L)	Comments
ULN	1.3	0.38	41	38		221	
Screening	0.7	0.1	11	15	-		Hb 16.1 g/dL
1	-	-	-	-			
2	3.3 (2.5 × ULN)	1.3	56	66 (1.7 × ULN)			Last Dose Day 2 Received 2 doses
3	11.3 (8.7 × ULN)	6.6	52	61 (1.6 × ULN)	121	268	Ultrasound - splenomegaly
3	9.0 (6.9 × ULN)	5.8	52	61 (1.6 × ULN)		PT 22.8 (12.8–14.7)	INR 1.91 aPTT 39.8 (25.1–38.7)
4	6.5 (5.0 × ULN)	4.2	46	35\		PT 16.4	INR 1.25 aPTT 27.4 D-Dimer 3.31 (0.22–0.62) Fibrinogen normal
5							Hb 13.3 Low platelets
7	2.8 (2.2 × ULN)	1.3	167 (4.1 × ULN)	235 (6.2 × ULN)			

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, aPTT= activated partial thromboplastin time, Hb=hemoglobin, INR= international normalized ratio, GGT=gamma-glutamyl transferase, LDH=lactic acid dehydrogenase, PT=prothrombin time, ULN=upper limit of normal

The serum level of study drug was 509 ng/mL one hour after dosing, where 3 other patients had undetectable levels and 1 patient had a serum level of 31 ng/mL. The residual volume of drug was tested and found to be as expected. The 25% higher dose was also re-calculated and found to be as expected. Therefore, a dosing error was ruled out. The potency was also checked and found to be the same as other vials in the manufacturing lot. The only explanation is decreased clearance of the drug. This and the unusually high levels of bilirubin in the face of hemolysis suggests possibly unrecognized UGT1A1 polymorphism or Gilbert's syndrome as noted with tocilizumab (Lee et al 2011).

2. The patient was a 42-year-old White male enrolled in the ITN011AI study and received hOKT3yl 1 mg per protocol. Approximately one hour after the start of the first infusion he developed shaking and chills without fever. He complained of general myalgias, arthralgias, and moderate headache and rash. The chills resolved promptly after treatment with IV diphenhydramine 50 mg. However, the fatigue, myalgias, and moderate headache persisted. Over the course of the day, the patient developed hypotension, blood pressure approximately 90/60 mm Hg, and mild occasional dizziness with

ambulation. He was treated with IV diphenhydramine, IV fluids and Tylenol #3 for headache.

The next day, the laboratory tests revealed slightly elevated bilirubin, increased SGOT/AST and SGPT/ALT with prolonged prothrombin time and INR 1.5. Laboratory values 6 hours later but the bilirubin was more elevated. The patient remained hospitalized an additional night for observation. He remained stable except for a severe headache overnight, treated successfully with Tylenol #3. The patient reported having similar headaches approximately every 6 months. The patient's maximum temperature during the hospitalization was 100.5ºF. Treatment for the SAE included IV diphenhydramine, IV fluids, oral hydration and Tylenol #3 for headache.

Concomitant medications also included methotrexate 20 mg weekly for psoriatic arthritis and folic acid.

On Day 3, the laboratory tests revealed further increase in bilirubin 3.7 mg/dL, but improvement in the SGOT/AST 104 U/L and SGPT/ALT 207 U/L, and prothrombin time. Other abnormal laboratory tests included: decreased total protein and platelets, increased D-dimer, decreased Factor VII. The patient reported improvement with only residual fatigue, mild headache, and arthralgias. He was discharged to home.

On Day 4, the patient returned to the clinic as instructed and lab values showed a decreased haptoglobin 29 mg/dL (51–192), creatinine 1.0 mg/dL, albumin 3.9 g/dL, total protein 5.6 g/dL, platelets 91 $x10^3/mm^3$, D-dimer 2.25 μg/mL, and Factor VII 144%.

Cytokines measured before treatment were normal (IL-10 <1 pg/mL [60.2–240.1], IL-6 <2 pg/mL [129.5–572.5], TNF-α 16.7 pg/mL [133.9–376.1]); the repeat measurements after treatment revealed increases IL-10 50.5 pg/mL (60.2–240.1), IL-6 301.4 pg/mL (129.5–574), TNF-α 789.5 (133.9–376.1), and the final were IL-10 (not measured), IL-6 >2024 pg/mL, and TNF-α 407.3 pg/mL**.** These data confirm increases in TNF-α and IL-6 with the clinical findings of CRS.

Approximately 3 weeks later, a hepatic ultrasound revealed mild fatty liver. A liver biopsy was performed approximately due to consideration for continued methotrexate therapy. The liver biopsy revealed no inflammation or fibrosis, mild hepatocyte unrest and mild macro-vesicular steatosis.

The investigator reported the causal relationship of CRS with hyperbilirubinemia, DIC, and transaminitis to study medication as definitely related. The serious criterion was prolonged hospitalization. The patient has no history of liver disease, occasional alcohol consumption and psoriatic arthritis inadequately controlled with oral methotrexate 20 mg weekly.

Study Day	Total Bilirubin (mg/dL)	ALT/SGPT (U/L)	AST/SGOT (U/L)	PT/INR (seconds)	Comments
Normal range	(0.1–1.0)	(8–35)	8–37	12.0–14.3 0.87–1.13	
Screening	0.3	97	38		ALP 124 U/L
1	0.3	69	32		ALP 100 U/L
2	1.8 (1.8× ULN) (Direct bilirubin 1.6)	332 (9.5× ULN)	234 (6.3× ULN)	16.9/1.5	ALP 115 U/L Last Dose Day 1; received one dose
2 repeat	2.8 (2.8× ULN)	331 (9.5× ULN)	209 (5.6× ULN)	18/1.5	6 hours later
3	3.7 (3.7× ULN)	207 (5.9× ULN)	104 (2.8× ULN)	14.2	D-dimer 8.28 μg/mL (normal, <0.4) Low platelets 95 x10^3/mm^3 (normal, 150–400) Factor VII 51% (normal, 65–140%) Total Protein 4.3 g/dL (normal, 6.0–8.3)
Day 4	3.4 (3.4× ULN) (Direct bilirubin 2.6)				Haptoglobin 29 mg/dL (normal, 51–192) Total Protein 5.6 g/dL Albumin 3.9 g/dL Platelets 91 x10^3/mm^3 D-dimer 2.25 μg/mL Factor VII 144%
Week 6	0.6	33	22		ALP 97

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, INR=international normalized ratio, PT=prothrombin time, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, ULN=upper limit of normal

3. The patient was a 14-year-old White female with recent onset T1D, enrolled in the Protégé study, who was enrolled into the double-blind segment and randomly assigned to the teplizumab full 14-day regimen. She began receiving study drug on Study Day 0 (02 Jun 2009). On Study Day 2, the patient was reported to have a drug-related nonserious AE of gamma-glutamyltransferase increase that led to discontinuation of study treatment with the last infusion occurring on Study Day 1. The patient did not receive any Course 2 dosing. On Study Day 682 a nonrelated serious AE of diabetic ketoacidosis unrelated to study drug.

Other medical history included drug hypersensitivity, hypocalcemia, proteinuria, food allergy, hypothyroidism, anxiety, depression, obsessive-compulsive disorder, leukopenia, lymphopenia and neutropenia.

Concomitant Medications:

Infusion prophylaxis medications that the patient took included diphenhydramine and ibuprofen. The patient's insulin dosing during the study included Lantus and Novolog.

The patient received 2 of the 14-day treatment course. On Study Day 2, the patient was reported to have a Grade 3 AE of gamma-glutamyltransferase increased (elevated GGT). Within 24 hours of the AE of GGT increased, the patient had numerous other AEs (related and nonrelated) reported, including increase liver enzymes, bilirubin and ALP, and decreased albumin, hemoglobin, platelets, neutrophils, and lymphocytes. She also complained of oro-pharyngeal and pleuritic chest pain.

The bilirubin returned to normal by Day 3 and the AST by Day 4. On Day 14 the remaining liver enzymes of GGT and ALT returned to normal. Although not designated as CRS, the rapid onset of study drug (teplizumab) associated observations of cytopenias and pain associated with abnormal liver function tests make this likely, especially in light of the other cases reported with teplizumab (Shimabukuro-Vornhagen et al 2018).

Study Day	Total Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	GGT (U/L)	Comments
ULN	1.3	33	22	17	
Screening	0.3	12	17	11	
1	0.4	23	21	14	
2	0.6	22	29	14	
3	2.8 (2.2× ULN)	118 (3.6× ULN)	148 (6.7× ULN)	145 (8.5× ULN)	Last Dose Day 2; received 2 doses
4	0.5	85 (2.6× ULN)	56 (2.5× ULN)	130 (7.6× ULN)	
5	0.3	61 (1.8× ULN)	28 (1.3× ULN)	103 (6.0× ULN)	
8	0.4	88 (2.7× ULN)	65 (2.9× ULN)	91 (5.3× ULN)	
14	0.4	21	16	59 (3.4× ULN)	

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyl transferase, ULN=upper limit of normal

4. The patient was a 15-year-old female with recent onset T1D, enrolled in AG019-T1D-101 study, who developed an AE of myalgias on Day 1 of dosing with AG019 and teplizumab which was followed by AEs of fever and abdominal pain on Day 2. On Day 3 pre-dose, the liver enzymes and bilirubin were elevated therefore no further teplizumab infusions were given. AG019 was continued. On Day 4, decreased leukocytes and lymphocytes were noted with improvement in the bilirubin. By Day 7, while the leukocytes and lymphocytes remained low, the only liver enzyme still elevated was the ALT. LFTs steadily improved and returned completely to normal by Day 12. While this patient was not formally diagnosed with CRS, the symptoms are consistent with those outlined by Lee et al (Lee et al 2014).

Concomitant medications: Insulin 29 IU/day

Study Day	Total Bilirubin (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	LDH (U/L)	Comments
ULN	1.2	44	50	230	645	
Screening	0.6	13	33	107	523	
1	0.9	15	29	92	523	
2	0.8	13	21	-	356	Last dose Day 2, Received 2 doses
3	2.7 (2.3× ULN)	123 (2.8× ULN)	214 (4.3× ULN)	-	1109 (1.7× ULN)	
4	1.2	133 (3.0× ULN)	142 (2.8× ULN)	196	659	
7	0.7	64	40	117	493	
12	0.9	22	25	107	385	

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, LDH=lactic acid dehydrogenase, ULN=upper limit of normal

5. The patient was a 13-year-old female with new onset T1D enrolled in PRV-031-001 (PROTECT study [NCT03875729]) who developed decreased appetite in the evening of Day 1 and then nausea, vomiting and subjective fever at 2 AM. She was treated with Zofran and Tylenol at 2 AM, 6:30 AM and 10:30 AM. On Day 2 she was subjectively much better and tolerated the infusion well throughout the day. On Day 3, her temperature was 103ºF before the infusion and she developed fever, chills and nausea during the infusion. These were treated with fluids, Tylenol, Zofran and 2 mg dexamethasone IV. During the day, her temperature was 103.2. On Day 4 the patient felt well but safety labs showed increased transaminases, total and direct bilirubin and a normal ALP. The dose was held since labs met the hold criteria. An abdominal ultrasound showed splenomegaly and was otherwise normal. She received no study drug after Day 3.

Concomitant medications included insulin.

Study Day	Total Bilirubin	Direct Bilirubin	ALT (U/L)	AST (U/L)	ALP (U/L)	Comments
ULN	0.7	0.4	24	35	280	
Screening	0.7	-	24	35	-	
1	0.5	0.3	10	17	119	
2	1.0	0.4	36	52	119	
3	-	-	-	-		Last Dose Day 3, Received 3 doses
4	3.0 (4.3× ULN)	2.1	372 (15.5× ULN)	182 (5.2× ULN)	277	
4	2.6 (3.7× ULN)	-	364 (15.2× ULN)	163 (4.7× ULN)	296 (1.1× ULN)	
5	1.3 (1.9× ULN)	0.8	231 (9.6× ULN)	54	254	
6	1.1 (1.6× ULN)	0.7	276 (11.5× ULN)	175 (5.0× ULN)	265	
12	0.8	0.2	82	24	160	
28	0.7	0.2	15	16	142	

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal

Other laboratory abnormalities included: decreased leukocytes (screening: 4 x 10^9/L, Day 6: 3.3 x 10^9/L; decreased lymphocytes Day 2: 0.24 x 10^9/L; decreased neutrophils 1.07 x 10^9/L).

Concomitant medications included: Claritin as needed for seasonal allergies and acetaminophen and ibuprofen as needed for muscle aches.

CRS improved rapidly after study drug discontinuation and supportive care including a single dose of IV steroids and IV fluids. She improved clinically and was afebrile with no hypotension or hypoxia. Her hepatic enzymes and bilirubin improved rapidly, and all completely resolved by Day 28.

Hypoglycemic Seizure Narratives

1. This 14-year-old Asian male, enrolled in the Encore study, experienced an SAE of Hypoglycemic Seizure on Study Day 149. On Day 149, the patient awoke disoriented and experienced a tonic clonic seizure. Sugar was administered orally, and the patient was treated at an emergency department and hospitalized, where glucose values of 92–225 mg/dL were reported. Relevant medications included regular insulin and Neutral Protamine Hagedorn (NPH) insulin. HbA1c was 15.2 at baseline and 7.4 on Study Day 140. During the study, several low serum glucose values ranging from 43 to 65 mg/dL were recorded. No precipitating event was identified. The event resolved that day and was considered possibly related to study medication; the insulin dose was decreased. The patient completed the study.

2. This 19-year-old White female, enrolled in the Protégé study, experienced an SAE of Hypoglycemic Seizure on Study Day 369, 179 days after receiving the second teplizumab dose cycle. The patient was found by her roommate with convulsions after an evening meal. The patient was transported to an emergency department with a glucose of 25 mg/dL, which rose to the 60s with treatment. She had taken Novolog 1.5 hours prior to the meal. Relevant medications were Lantus (insulin glargine), Humalog (insulin lispro) and Novolog (insulin aspart). She was reported to be non-compliant with diet and glucose monitoring, and over-treatment with Novolog was suspected. A previous low serum glucose value of 54 mg/dL was reported during the study. HbA1c was 7.2 at baseline and 6.7 on Day 364. The event resolved the same day and was considered definitely not related to study medication. The patient completed the study.

3. This 13-year-old White male, enrolled in the Protégé study, experienced an SAE of Severe Hypoglycemic Seizure on Study Day 123. On Study Day 122, the patient exercised more than usual and experienced glucose values of 44 to 78 mg/dL, which he treated with food but did not change insulin doses. He ate less than usual at dinner and reported a glucose level of 90 mg/dL at bedtime. The next morning (Day 123), he was found unconscious by his mother with a glucose of 54 mg/dL. Intramuscular glucagon was administered with resolution of symptoms and glucose increase to 83 mg/dL. Relevant medications included Lantus (insulin glargine) and Novolog (insulin aspart). HbA1c at baseline was 8.7 and 6.4 on Day 91. The event resolved the same day and was considered possibly related to study medication. The patient completed the study.

4. This 13-year-old White male, enrolled in the Protégé study, experienced an SAE of Hypoglycemia with Unconsciousness/Hypoglycemia with Seizure on Study Day 20. The patient was unconscious for a few minutes and regained consciousness with oral glucose. No glucose value was measured. Relevant medications included NPH insulin, Insulatard (insulin isophane), Levemir (insulin detemir), Novorapid (Novolog, insulin aspart). HbA1c was 8.5 at baseline and 6.0 on Day 91. No precipitating event was identified, and the event was considered possibly related to study medication. The patient completed the study.

5. This 9-year-old White female, enrolled in the Encore study, experienced an SAE of Hypoglycemic Seizure on Study Day 521. On Day 521 the patient experienced a full-body convulsion of approximately 1 minute duration which caused her to fall and hit her face. At an emergency department, glucose was 81 mg/dL. During hospitalization, she was reported to be post-ictal for 3–5 days with headache, cough, weakness and epistaxis. A CT scan of the head was normal. Relevant medications were Lantus (insulin glargine) and Novolog (insulin aspart). HbA1c was 7 at baseline and 8.3 on Day 546. Multiple low serum glucose values ranging from 40 to 69 were recorded throughout the study but no precipitating cause was identified for the SAE. She was discharged the day after the event. The SAE was considered definitely not related to study medication. The patient completed the study.

6. This 10-year-old White male, enrolled in the Encore study, experienced 2 SAEs of Hypoglycemic Seizure on study days 222 (26 days after cycle 2) and 361 (165 days after cycle 2). On Day 222, the patient experienced a convulsion after waking but before breakfast, with glucose of 58 mg/dL after receiving oral carbohydrate. Paramedics stabilized the patient at home, and his insulin dose was decreased. On Day 361, the patient experienced a grand mal seizure while playing a video game. Glucose was 169 mg/dL after receiving intramuscular glucagon. Paramedics were called, and he was brought to the emergency room where he was evaluated and discharged. Relevant medications included Lantus (insulin glargine) and Humalog (insulin lispro), and glucagon. HbA1c was 5.9 at baseline, 5.9 on Day 183, 7.5 on Day 273, and 7.5 on Day 364. Multiple low serum glucose values ranging from 53 to 69 were reported throughout the study. No specific precipitating cause was identified for the events. The patient completed the study.