Provention Bio, Inc.

Clinical Protocol

A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed Type 1 Diabetes (T1D)

PROTECT: Provention Bio's T1D Trial Evaluating C-Peptide with Teplizumab

Protocol PRV-031-001; Phase 3
NCT03875729

Teplizumab, PRV-031

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SUMMARY OF CHANGES

Protocol version 3.0 to 4.0

Protocol PRV-031-001 version 3.0 (approved 12 May 2020) has been amended to version 4.0 (approved 07 December 2020). Substantive changes to the previous version of the protocol are listed in the table below along with rationales. In addition, minor corrections and administrative/editorial changes and clarifications have been made throughout the document. All changes are clearly identified in the track-changes version of the amendment.

Section	Rationale for change	Original Text	Revised Text
SoA	A PK sample is added on Day 9 of Treatment Course 1 to better characterize the pharmacokinetic profile of teplizumab. The blood draw volume is updated to account for this additional sample.		X^9 = On Day 9 of Treatment Course 1, an additional PK sample will be obtained within 45 ± 15 minutes after infusion is completed.
SoA, 9.1.1	The SARS-CoV-2 test is removed at screening, and the testing window is updated from 3 days to 5 working days before the first dose of study drug to allow more operational flexibility without compromising safety.	X^8 = The test may be performed within ~~3~~ days before the first dose of study drug is given in each treatment course if not feasible on the day of dosing.	X^8 = The test may be performed within 5 working days before the first dose of study drug is given in each treatment course if not feasible on the day of dosing.
4.2	Permitted vaccination time window for non-infectious vaccines is updated to within 2 weeks to take into account the time period it takes to build immunity after vaccination with non-live vaccines and through 6 weeks after each treatment course to take into account teplizumab's half-life and effects on the immune system.	• Non-infectious (eg, recombinant, inactivated or otherwise "non-live") vaccines: Within ~~8~~ weeks before ~~or~~ after each dosing course.	• Non-infectious (eg, recombinant, inactivated or otherwise "non-live") vaccines: Within 2 weeks before through 6 weeks after each dosing course.

Section	Rationale for change	Original Text	Revised Text
6.1	Requirement for PVC infusion bag is removed based on updated compatibility data that became available in October 2020.	~~Polyvinyl chloride (PVC) infusion bags and tubing and normal saline should be used for study agent preparation and administration (Section 14.4).~~	(None.)
6.3	Requirement for PVC infusion bag is removed based on updated compatibility data that became available in October 2020.	Study drug (teplizumab or placebo) will be prepared and supplied ~~by designated personnel or pharmacist equivalent in an infusion bag. Because the study drug solution contains no preservative and drug loss occurs over time, administration of study drug (teplizumab or placebo) should begin within 2 hours after preparation. Before administering study drug, the responsible individual at the site must check the infusion bag to verify that the information is correct.~~ Assure that the vascular access is patent (see Section 6.2). ~~Intravenous drug delivery devices, including IV bags and tubing, must be composed of PVC. If a syringe pump is used, it must be composed of polypropylene. Syringe pumps may be used for study drug administration but will not be provided by the Sponsor. The preparation of the infusion solution for a syringe pump is different than that~~	Study drug (teplizumab or placebo) will be prepared and supplied by designated personnel or pharmacist equivalent <u>according to the Pharmacy Manual.</u> Assure that the vascular access is patent (see Section 6.2). <u>Pharmacy Manual should be followed to ensure that the IV drug delivery devices used are made of materials compatible with the study drug.</u>

Section	Rationale for change	Original Text	Revised Text
		~~for an IV bag. Instructions will be provided in the Pharmacy Manual.~~	
8.5	The time window for vaccination is updated. The instruction for urgent vaccination is clarified for safety considerations.	• Non-infectious (eg, recombinant, inactivated, or otherwise "non-live") vaccines generally should not be given from ~~8~~ weeks before the initiation of study drug through ~~8~~ weeks after the end of each course of study drug administration. • In some situations, a vaccine ~~in violation of these guidelines~~ may be required (eg, ~~influenza or~~ rabies vaccine) to protect the safety of the participant. ~~Before such a vaccine is given, the participant's lymphocyte counts must be at least 30% of the lower limit of normal.~~	• Non-infectious (eg, recombinant, inactivated, or otherwise "non-live") vaccines generally should not be given from 2 weeks before the initiation of study drug through 6 weeks after the end of each course of study drug administration. • In some situations, a vaccine may be urgently required (eg, rabies or meningococcal vaccine) to protect the safety of the participant and may be given. Influenza non-live vaccine can be given on an emergency basis, but all efforts should be made to follow the general guidance above.
9.3.1	Details are removed to allow flexibility in study procedures.	Venous blood samples will be collected~~, and each serum sample will be divided into 3 aliquots (1 each for PK, antibody/NAb and a back up)~~.	
9.4.3, 11.9, Appendix 4	A pharmacodynamic (PD) substudy is added to evaluate the PD effects of teplizumab treatment at time points concurrent with PK sampling during and after Treatment Course 1. The substudy is to be conducted at all North American study sites.		In order to evaluate the pharmacodynamic (PD) effects of teplizumab, namely its CD3 receptor occupancy and modulation, a substudy will be conducted in all North American sites. See Appendix 4 for a description of the PD substudy.

Section	Rationale for change	Original Text	Revised Text
9.7.8, Appendix 4	The ECG substudy, added in version 3.0, is removed, as the FDA granted a waiver. The previous Appendix 4 is replaced by the description of a pharmacodynamic substudy (see above).	~~In order to fully evaluate the effects of teplizumab on electrocardiograms (ECGs), a substudy will be conducted at selected US sites involving approximately 45 participants. See Appendix 4 for a description of the ECG substudy.~~	
10.2.1	Treatment discontinuation criteria due to certain laboratory abnormalities are revised to allow patients with Gilbert's syndrome to continue study treatment.	If any of the following lab values is observed (normal range per local lab standard), the next study drug dose should be held until a repeat test is obtained and evaluated. If the out-of-range result is confirmed on two consecutive dosing days, ~~the participant should be discontinued from any further study drug treatment.~~	If any of the following lab values is observed (normal range per local lab standard), the next study drug dose should be held until a repeat test is obtained and evaluated. If the out-of-range result is confirmed on two consecutive dosing days, the Medical Monitor must be contacted before making a decision about further treatment.
10.2.3	Treatment-withholding criterion based on bilirubin levels is revised to allow patients with Gilbert's syndrome to continue study treatment. If Course 2 treatment is withheld for a participant at Week 26 due to laboratory abnormalities, it may be given at Week 52 to provide more flexibility. Pregnancy is removed from the list of criteria for consistency with Section 12.3.4.	• Total bilirubin >1.5X ULN ~~• Pregnancy in a female participant~~	However, these participants may receive Course 2 at Week 52, if all of these criteria are resolved. • Total bilirubin >1.5X ULN, except for subjects with Gilbert's syndrome with normal ALT and AST with approval of the Medical Monitor.
12.1.3	AESIs are revised to harmonize with other teplizumab studies and with criteria agreed upon with the FDA.	See Section 12.1.3	See Section 12.1.3

Section	Rationale for change	Original Text	Revised Text
	Events will be pooled into categories. Only events reaching certain severities will be included.		
12.1.4.1	Clarification.		Grade 1 hypoglycemia does not need to be reported as an AE.
14.4	Requirement for PVC infusion bag is removed based on updated compatibility data that became available in October 2020.	~~Every effort should be made to start the infusion immediately after preparation but within 2 hours after preparation.~~ ~~The compatibility of teplizumab with common IV drug delivery materials has been tested. It was found that diluted solutions of teplizumab are not compatible with IV bags made of polyolefin but were compatible with IV bags made of polyvinylchloride (PVC) and syringes made of polypropylene. Tests also were conducted with IV administration sets made of PVC, which were found to be acceptable. Therefore, drug delivery devices, including IV bags and tubing, must be composed of PVC~~	Teplizumab should be stored, prepared, and handled according to the Pharmacy Manual. The Pharmacy Manual should be followed to ensure that intravenous drug delivery devices used are made of compatible materials.
Appendix 1	Clarification of procedures.		Note: In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
Appendix 2	Clarification of procedures. Sampling procedure instructions are referred to the Laboratory Manual for consistency and accuracy.	• For the 2-hour MMTT: Continue with blood sample collection (~~2~~ mL ~~in purple top~~ (C-peptide and insulin) and glucometer (BG) evaluation) at: 15,	• For the 2-hour MMTT: Continue with blood sample collection (3 mL collection tube (C-peptide and insulin) and glucometer (BG) evaluation) at:

Section	Rationale for change	Original Text	Revised Text
		30, 60, 90, and 120 minutes for a TOTAL of 7 samples (including the -10 and 0 min samples). • For the 4-hour MMTT: Continue with blood sample collection (~~2~~ mL ~~in purple top~~ (C-peptide and insulin) and glucometer (BG) evaluation) at 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes for a TOTAL of 11 samples (including the -10 and 0 min samples). Sample processing procedures: ~~• At each time point, draw one 2 mL sample into the purple-top tube for C-peptide and insulin and check the blood glucose using a drop of blood using the site's glucometer.~~ ~~• After each sample is collected, the tube must be inverted gently 8 to 10 times and then placed in a bucket of crushed ice or in a refrigerator set at 4°C for 20 to 30 minutes.~~ ~~• Keep the sample chilled or in the refrigerator no longer than one hour prior to centrifugation. Spin the tubes in a tabletop centrifuge cooled to 4°C at 1000-1300 g (~ 3000 RPM) for 10 minutes. Then transfer the plasma into a new vial appropriately labeled with participant number and timepoint.~~ ~~• Freeze the plasma sample at -80°C and store at -80°C and ship on dry ice~~	15, 30, 60, 90, and 120 minutes for a TOTAL of 7 samples (including the -10 and 0 min samples). • For the 4-hour MMTT: Continue with blood sample collection (3 mL collection tube (C-peptide and insulin) and glucometer (BG) evaluation) at 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes for a TOTAL of 11 samples (including the -10 and 0 min samples). Sample processing procedures are provided in the Investigator Laboratory Manual.

Section	Rationale for change	Original Text	Revised Text
		~~to the laboratory facility conducting the assay.~~ ~~• Record the glucometer reading in source and/or on the CRF.~~	

Protocol version 2.0 to 3.0

Protocol PRV-031-001 version 2.0 (approved 02 September 2019) has been amended to version 3.0 (approved 12 May 2020). Substantive changes to the previous version of the protocol are listed in the table below along with rationales. In addition, minor editorial corrections and administrative changes and clarifications have been made throughout the document. All changes are clearly identified in the track-changes version of the amendment.

Section	Rationale for change	Original Text	Revised Text
Synopsis, 2.2	The interval between the two study treatment courses is deleted to include those participants who are unable to receive the second course of treatment as scheduled because of the COVID-19 pandemic restrictions.	• To determine whether two courses of teplizumab ~~administered 6 months apart~~ slow the loss of β cells and preserve β cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who have been diagnosed with T1D in the previous 6 weeks.	• To determine whether two courses of teplizumab slow the loss of β cells and preserve β cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who have been diagnosed with T1D in the previous 6 weeks.
Synopsis, 3.1.3	Text is added to describe the modified dosing schedule for participants who are unable to adhere to the original dosing schedule and will receive the second treatment course starting at the Week 52 visit instead of the Week 26 visit.		*Modified dosing schedule for participants affected by COVID-19 pandemic restrictions:* To address COVID-19-imposed force majeure, those participants who are unable to receive the second treatment course approximately 6 months after randomization (scheduled for the Day 182 [Week 26] visit) due to COVID 19-related restrictions will initiate the second course at the Day 364 (Week 52) visit instead, approximately 12 months after randomization. References throughout the protocol (version 3.0 onward) to Day 364 (or Week 52) as the start of the second

Section	Rationale for change	Original Text	Revised Text
			course of treatment is only applicable to this group of participants.
Synopsis, 11.9	To address the planned analysis of participants on the modified dosing schedule due to COVID-19 restrictions.		Additional safety and efficacy analyses will be performed on the subgroup of participants who receive the second treatment course starting at the Week 52 visit because of the COVID-19 pandemic restrictions.
Schedule of Events	New Schedule of Events tables are added for participants on the modified dosing schedule due to COVID-19 pandemic restrictions.		See protocol.
Schedule of Events, 9.1.1, 9.7.5.2, 10.2.1, 10.2.3	A SARS-CoV-2 PCR testing requirement is added to the screening visit and before each treatment course begins to ensure that participants do not have current infection.		X^8 = SARS-CoV-2 PCR local testing is required for all participants entering the study from protocol version 3.0 onward. The result must be reviewed by the Investigator and be negative before the study drug can be administered. The test may be performed within 3 days before the first dose of study drug is given in each treatment course, if not feasible on the day of dosing.
3.1.3	A new figure (Figure 2) is added to illustrate the modified dosing schedule for participants who are under the modified dosing schedule due to COVID-19. Text is added to explain the rationale for the modified dosing schedule.		*Rationale for Modified Dosing Schedule* As noted above, participants who are unable to receive the second course of study treatment as scheduled at Week 26 will receive the second treatment

Section	Rationale for change	Original Text	Revised Text
			course at the Week 52 visit, approximately 12 months after the first course. In a previous Phase 2, randomized, 2-arm open-label, multicenter study known as the AbATE study, a 12-month dosing interval for teplizumab was evaluated in 77 participants aged 8 to 30 years with recent-onset (<8 weeks) T1D. They were randomly assigned at a 2:1 ratio to receive teplizumab plus standard diabetes management versus standard diabetes management alone. Subjects in the teplizumab group received a 14-day course of teplizumab, which was repeated 12 months later. A course comprised daily doses of 51 µg/m^2, 103 µg/m^2, 207 µg/m^2, 413 µg/m^2 during the first 4 days, respectively, and 10 subsequent daily doses of 826 µg/m^2. The primary efficacy endpoint of the AbATE study was the change from baseline in mean C-peptide area under the curve (AUC) in the 4h MMTT at Month 24.

Section	Rationale for change	Original Text	Revised Text
			After accounting for baseline difference, comparisons of the mean change from baseline in C-peptide AUC in the 4h MMTT at Month 24 showed statistically significant difference in favor of teplizumab. The teplizumab group had a mean decline in C-peptide secretion of -0.28 (95% CI: -0.36, -0.20) nmol/L, which was smaller than that of the control group (-0.46 [95% CI: -0.57, -0.35] nmol/L) (p=0.002). The most common AEs were rash, transient upper respiratory infections, headaches, and nausea. Study drug-related AEs were transient and resolved. The results from the AbATE study indicate that increasing the interval between the 2 treatment courses from 6 months to 12 months does not increase the safety risk, while still confer potential effects of teplizumab, in participants who are unable to adhere to the planned treatment schedule.
3.1.4, 6, 9, 9.7.3, 10.2.3	Text is added to address the modified dosing schedule.		For participants under the modified dosing schedule, the treatment courses are separated by an interval of approximately 12 months, and the post-treatment observation period is

Section	Rationale for change	Original Text	Revised Text
			approximately 26 weeks. The final visit will also take place at Week 78.
4.2	SARS-CoV-2 infection is added to the exclusion criterion regarding acute infections.		5. Participant has an active infection (including a positive SARS-CoV-2 test) and/or fever ≥38.5°C (101.3°F) within the 48 hours prior to randomization, is prone to infections, or has chronic, recurrent or opportunistic infectious disease, including but not limited to renal, respiratory or skin infections, *Pneumocystis carinii*, aspergillosis, latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis.
9.1.2	Corrections.	**• Study Visit Week 26: 4h MMTT and Treatment Course 2** *The visit window for these study visits are ±~~3~~ days from the target visit day.* On the days indicated in the Schedule of Events, ~~two~~ blood ~~draws~~ will be obtained for teplizumab serum levels. ~~One~~ within 30 minutes before study agent infusion ~~and the other within 30 minutes following study agent infusion and flush~~. In addition to time of study agent and flush start and stop, ~~and~~ the time of ~~these~~ blood draws ~~are~~ to be documented in the CRF.	**• Study Visit Week 26: 4h MMTT and Treatment Course 2** *The visit window for these study visits are ±7 days from the target visit day.* On the days indicated in the Schedule of Events, a blood sample will be obtained for teplizumab serum levels within 30 minutes before study agent infusion. In addition to time of study agent and flush start and stop, the time of the blood draw is to be documented in the CRF. **• Study Visits Week 30, 34, 39*, 52 and 65***

Section	Rationale for change	Original Text	Revised Text
		• Study Visits Week 30, 34, 39*, 52 and 65* The visit window for these study visits are ± 4 days from the target visit day.	The visit window for Weeks 30, 34, 39, and 52 study visits is ± 4 days from the target visit day. The visit window for Week 65 visit is ±7 days.
9.2.5.1, 9.7.6	To add flexibility to study participants and acknowledge the variance in glucometers and ancillary consumables supply in various study locations and health care systems.	At screening, participants will be offered a study-supplied glucometer and glucometer strips, but participants are permitted to use their own glucometers if they choose~~, in which case glucose monitoring strips will not be supplied~~	At screening, participants will be offered a study-supplied glucometer and glucometer strips, but participants are permitted to use their own glucometers if they choose.
9.7.3	Text is added to provide a guidance on the management of cytokine release syndrome.		See protocol text.
9.7.6	Clarification of procedures.	Participants/caregivers will collect data related to insulin use, hypoglycemic events, intermittent (eg, spot-check or fingerstick) glucose measurements, AEs and internal medical and social history to be reviewed at clinical trial visits. The data will be collected in the eDiary ~~during the screening visit~~. The participant will record all short-, intermediate- and long-acting insulin administered as intermittent injections or use with an "insulin pump" during the 7 days before randomization, and Week 12, 26, 39, 52, 65 and 78.	Participants/caregivers will collect data related to insulin use, hypoglycemic events, intermittent (eg, spot-check or fingerstick) glucose measurements, AEs and internal medical and social history to be reviewed at clinical trial visits. The data will be collected in the eDiary. The participant will record all short-, intermediate- and long-acting insulin administered as intermittent injections or use with an "insulin pump" in the eDiary during the 7 days before randomization, and Week 12, 26, 39, 52, 65 and 78.

Section	Rationale for change	Original Text	Revised Text
9.7.8, 11.8 Appendix 4	An electrocardiogram (ECG) substudy in approximately 45 participants at selected US sites is added to evaluate ECG data at time points when teplizumab serum concentrations reach peak levels.		In order to fully evaluate the effects of teplizumab on electrocardiograms (ECGs), a substudy will be conducted at selected US sites involving approximately 45 participants. See Appendix 4 for a description of the ECG substudy.
11.2	An analysis subset is added for participants under the modified dosing schedule due to COVID-19.		*Modified-Dosing Subset* Data from participants who receive the second course of treatment at Week 52 (instead of Week 26) due to COVID-19 pandemic restrictions will be included in the ITT population and Safety population. Additional subgroup analyses for these participants will also be performed.
11.4	A section is added to describe the planned steps of handling missing data in the statistical analyses.		**11.4. Handling of Missing Data** The amount, pattern (arbitrary or monotone in nature), and reasons for missing data (such as administrative, adverse event, lack of efficacy) will be described. Multiple imputation (MI) with pattern-mixture model under the missing not at random (MNAR) assumption will be used to impute the missing values for the primary endpoint as well as the secondary

Section	Rationale for change	Original Text	Revised Text
			endpoints of exogenous insulin use, HbA1c levels, and TIR. This method will be carried out using the standard three-step procedure: Step 1. Generation of imputed datasets: The MI procedure of the SAS system will be used to generate m sets of data where missing data from participants who drop out before the end of the study are imputed based on participants who similarly discontinued study drug in the same treatment group but have measurements taken at scheduled visits. The selection of m depends on the required computing time, but a reasonable range is 20 to 100 sets. Linear regression will be employed to model the missing values and will include treatment (teplizumab or placebo), age, and peak C-peptide at baseline as covariates. Step 2. Model-based analysis using each imputed dataset: Each of the m imputed data sets is analyzed using the same method as the corresponding endpoint analysis. Step 3. Pooling the results from each model-based analysis: The results from the analysis of each imputed dataset will be combined by the MIANALYZE procedure of the SAS system.

Section	Rationale for change	Original Text	Revised Text
12.1.4.1	Clarification.		Although all hypoglycemic events, including CTCAE Grade 1 events (BG <70 mg/dL or 3.9 mmol/L), should be recorded in the hypoglycemia eDiary, Grade 1 hypoglycemic events may not need to be reported as AEs, at the investigator's discretion.
12.3.4	Clarification.	For participants who withdraw from all study visits, the study staff will make every effort to obtain any pregnancy information through ~~one year after the last dose of study drug~~.	For participants who withdraw from all study visits, the study staff will make every effort to obtain any pregnancy information through the end of the study (Week 78 visit).
Appendix 1	Clarification.		Note: In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
Appendix 3	A table is added to display the blood draw volumes in the modified dosing schedule.		See protocol text.

SYNOPSIS

A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed Type 1 Diabetes (T1D)

Teplizumab (also known as PRV-031, hOKT3γ1 [Ala-Ala], and MGA031) is a humanized 150-kilodalton monoclonal antibody (mAb) that binds to the CD3-ε epitope of the T cell receptor. Teplizumab was developed when preclinical studies demonstrated that targeting T cells (the cells that are instrumental in initiating and coordinating the autoimmune process responsible for type 1 diabetes [T1D] mellitus) via this mechanism altered diabetes immunopathogenesis and prevented and reversed disease in relevant animal models. A number of clinical studies have demonstrated the ability of teplizumab to slow or even halt the destruction of the insulin-secreting β cells in populations of individuals with newly diagnosed T1D. The goal of this study is to evaluate teplizumab in patients who may be most responsive to it as suggested in previous studies, namely children and adolescents very recently diagnosed with T1D. Teplizumab holds the promise to be the first disease modifying therapy available to improve both the medical management and overall outlook in those who suffer the most devastating short- and long-term consequences of this disease.

HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Hypothesis

The hypothesis of this study is that teplizumab is safe, well-tolerated, and effective in slowing the loss of β cells and maintaining a clinically relevant level of β cell function in children and adolescents newly diagnosed with T1D while improving key aspects of T1D clinical management over an 18-month period.

Objectives

The primary objective is:

- To determine whether two courses of teplizumab slow the loss of β cells and preserve β cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who have been diagnosed with T1D in the previous 6 weeks.

The secondary objectives are:

- To evaluate participant improvements in key clinical parameters of diabetes management, including insulin use, glycemic control (including hemoglobin A1c [HbA1c] and time in glycemic target range [TIR]), and clinically important hypoglycemic episodes
- To determine the safety and tolerability of two courses of teplizumab, administered intravenously (IV)
- To evaluate the pharmacokinetics (PK) and immunogenicity of two courses of IV teplizumab

The exploratory objectives are:

- To assess β cell function and T1D-focused clinical parameters
- To evaluate immunologic, endocrinologic, molecular, and genetic markers

Endpoints

1. The primary endpoint is:

- The area under the time-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function, at Week 78.

2. The secondary endpoints are as follows:

A. Key Clinical Endpoints:

- Exogenous insulin use: defined as a daily average in units per kilogram per day (U/kg/day), at Week 78
- HbA1c levels: expressed in % and mmol/mol, at Week 78
- TIR: expressed as a daily average of the percentage of time in a 24-hour day a participant's blood glucose (BG) is >70 but ≤180 mg/dL (>3.9 to ≤10.0 mmol/L), assessed using continuous glucose monitoring (CGM), at Week 78
- Clinically important hypoglycemic episodes: defined as the total number of episodes of a BG reading of <54 mg/dL (3.0 mmol/L) and/or episodes of severe cognitive impairment requiring external assistance for recovery, from randomization through Week 78

B. Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
- Incidence of treatment-emergent infections of special interest, including but not limited to tuberculosis, an infection requiring IV antimicrobial treatment or hospitalization, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection, or significant viremia (ie, DNA-based polymerase chain reaction viral load >10,000 copies per mL or 10^6 cells), and herpes zoster
- Incidence and severity of immediate or delayed study drug infusion-related reactions, such as hypersensitivity reactions, pain requiring interruption or discontinuation of infusions, cytokine release syndrome, and serum sickness

C. PK and Immunogenicity Endpoints:

- Teplizumab serum concentrations
- Incidence and titers of anti-teplizumab antibodies after treatment courses

3. The exploratory endpoints are as follows:

A. Assessments of β cell function and health throughout the study:

- 4h MMTT C-peptide AUC
- Participants with the recognized clinically significant stimulated peak C-peptide of ≥0.2 pmol/mL during 4h and 2-hour (2h) MMTTs
- Proinsulin-to-C-peptide ratios, a measure of β cell endoplasmic reticulum stress and dysfunction

B. T1D-focused Clinical Endpoints during the study unless otherwise noted:

- Exogenous insulin use (in U/kg/day)
- HbA1c levels

- Participants with poor glycemic control, defined as HbA1c of ≥9%
- The number of participants who do not require exogenous insulin because they are able to achieve local, regional, or national age-based glycemic management goals for HbA1c and/or routine blood glucose levels
- Evaluations of glycemic control based on BG values obtained from intermittent (ie, spot-check, fingerstick) glucometer readings
- Evaluations of glycemic control based on BG values obtained from CGM readings, including but not limited to TIR; time in hyperglycemia and hypoglycemia ranges; daily, daytime, and nighttime average BG levels and estimated HbA1c; and glycemic variability
- Clinically important hypoglycemic episodes from randomization through Week 39 and from Week 39 through Week 78
- Incidence of "typical" hypoglycemia, defined as BG levels ≥54 mg/dL (3.0 mmol/L) but <70mg/dL (3.9 mmol/L) and/or non-severe clinical episodes
- Incidence of diabetic ketoacidosis (DKA) requiring medical attention, defined as a hyperglycemic episode with serum or urine ketones elevated beyond upper limit of normal (ULN) along with serum bicarbonate <15 mmol/L or blood pH <7.3, or both, and resulting in outpatient, emergency room visit or hospitalization
- Patient-reported outcomes measured by instruments, such as Quality of Life Inventory™ (PedsQL) Diabetes Module, the Hypoglycemia Fear Scale (HFS), and the Diabetes Treatment Satisfaction Questionnaire (DTSQ)
- Impact on family life, measured by the parent-reported PedsQL Family Impact questionnaire

C. Composite Clinical Endpoints:

- Participants with both HbA1c in the American Diabetic Association (ADA) target range (ie, <7.5%) and exogenous insulin dose in specific ranges (<0.25, 0.25 to <0.50, 0.50 to <0.75, 0.75 to <1.0, 1.0 to <1.25, and ≥1.25 U/k/d)
- Participants with both HbA1c of <6.5% and <7.0% and exogenous insulin dose of <0.5 U/kg/day or 0.25 U/kg/day

D. Immunologic and Endocrinologic Endpoints during the study:

- Phenotypic and functional characterizations of white blood cell (WBC) populations, including T cells, B cells, and natural killer (NK) cells
- Serum proinflammatory and regulatory cytokine profiles and other immune mediators
- Number, type, and titer of T1D autoantibodies
- Antibody subclass levels
- Evidence of recent infection with coxsackie virus B (CVB)
- Levels of circulating hormones (eg, glucagon, incretins, adiponectin) and other factors (eg, lipokines, cholesterol, triglycerides) associated with the course of T1D pathophysiology

E. Molecular and Genetic Endpoints during the study:

- Circulating methylated- and unmethylated-insulin DNA levels as assessments of β cell stress and damage
- Gene expression and transcriptome analyses

- Association of human leukocyte antigen (HLA) type with clinical, metabolic and immune assessments

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter study. Approximately 300 participants will be enrolled and randomly assigned at a ratio of 2:1 to either the teplizumab group (N=200) or the placebo group (N=100).

To minimize bias in treatment assignment, potential confounders, and enhance the validity of statistical analysis, participants will be randomized at a 2:1 ratio using randomly permuted blocks and stratification based on the following criteria:

- Peak C-peptide level at screening: within the range of 0.2 (inclusion criterion) to 0.7 pmol/mL (inclusive) versus >0.7 pmol/mL
- Age at randomization: within the range of 8 to 12 years (inclusive) versus >12 to 17 years

Teplizumab or matching placebo will be administered via IV infusion in two courses, with the first course starting on Day 1 (Week 1) and the second course approximately 6 months later at Day 182 (Week 26). Each course of treatment will include daily infusions for 12 days.

Modified dosing schedule for participants affected by COVID-19 pandemic restrictions:

To address COVID-19-imposed force majeure, those participants who are unable to receive the second treatment course approximately 6 months after randomization (scheduled for the Day 182 [Week 26] visit) due to COVID-19-related restrictions will initiate the second course at the Day 364 (Week 52) visit instead, approximately 12 months after randomization.

References throughout the protocol (version 3.0 onward) to Day 364 (or Week 52) as the start of the second course of treatment is only applicable to this group of participants.

The total study duration for each participant will be up to 84 weeks. This includes a screening period of up to 6 weeks and a post-randomization period of 78 weeks. The treatment period includes two 12-day treatment courses separated by 6 or 12 months and a post-treatment observation period of approximately 52 or 26 weeks, respectively.

An external, independent Data Monitoring Committee (DMC) will be commissioned for this study to provide oversight on safety and efficacy data and the conduct of the study. The DMC will make recommendations regarding the continuation, termination, or modification of the study.

STUDY POPULATION

This study will enroll male and female participants 8 to 17 years of age with new-onset T1D who are able to be randomized and initiate study treatment within 6 weeks of their diagnosis. To be eligible for randomization, participants must be positive for at least one T1D-associated autoantibody and have a peak stimulated C-peptide of ≥0.2 pmol/mL at screening. They must also meet all of the specific inclusion criteria and none of the exclusion criteria.

DOSAGE AND ADMINISTRATION

On the day of randomization (Day 1), each participant will receive the first dose of the study drug in the first 12-day treatment course, as shown in the table below. On approximately Day 182 or Day 364, each participant will receive the first dose of the second 12-day course. The study drugs (teplizumab or placebo) will be administered via IV infusion at the study site or other qualified facility by study-approved personnel. The doses of study drug will be calculated based on the participant's body surface area (BSA) measured on the first day of each treatment course. No dose adjustment is permitted.

Treatment name	**Teplizumab**	**Placebo**
Description	Sterile solution for injection	Sterile solution for injection
Doses in each course	Day 1: 106 μg/m^2 Day 2: 425 μg/m^2 Days 3-12: 850 μg/m^2 Total per course: 9.0 mg/m^2	Matching volumes to active drug
Frequency	Two courses starting at Week 1 and Week 26 or Week 52	Two courses starting at Week 1 and Week 26 or Week 52
Delivery method	IV infusion	IV infusion

KEY EVALUATIONS

- MMTT: In order to quantitate endogenous β cell function, participants will undergo standardized provocative metabolic testing for C-peptide (a 1:1 by-product of insulin production). Participants will consume a fixed amount of a beverage with known amounts of carbohydrates, fats, and protein. Following consumption, BG, insulin, and C-peptide levels will be measured over time. A 2h MMTT will be conducted at screening, and 4h MMTTs will be conducted at randomization and Weeks 26, 52, and 78 for key endpoint assessments.
- HbA1c: This is the percent of red blood cells (measured as hemoglobin) that has become non-enzymatic glycated proportional to blood glucose levels. This indicates, on average, approximately a 3-month average of blood glucose values. It is a key clinical target in the management of T1D. In this study, it will be determined by a central laboratory.
- Insulin use: As an average over 7 days of data collected before each specified visit to quantify exogenously injected insulin.
- Hypoglycemia: Clinically important and potentially life-threating hypoglycemia is the result of insulin therapy and more likely to occur in patients who are attempting to achieve glycemic control goals. This study will ask participants to record information regarding BG levels of <70mg/dL (3.9 mmol/L) and/or events that are consistent with hypoglycemia. A particular focus will be on clinically significant hypoglycemic events that are defined as a reliable glucose reading of <54 mg/dL (3.0 mmol/L) and/or severe cognitive impairment and/or physical status requiring external assistance for recovery.
- Glucose Monitoring: Intermittent glucose monitoring (eg, spot-check or fingerstick) performed by participants or caregivers multiple times a day as a necessary part of glycemic management to gauge insulin dosing and assist in diet and activity. All participants are to bring in their glucometers at all visits for review. In addition to data regarding glycemic control, at specified times during the study, participants will report their daily before-meal and before-bedtime BG readings and have glucose levels assessed for 2-week intervals using CGM.
- Quality of Life Questionnaires: Surveys will be used to assess the general health and wellbeing of participants and the effects of teplizumab, such as the PedsQL Diabetes Module, HFS, DTSQ, and parent-reported PedsQL Family Impact Module.

PHARMACOKINETIC and IMMUNOGENICITY EVALUATIONS

Teplizumab concentrations will be analyzed in blood samples collected at specified time points throughout the study.

Anti-teplizumab antibodies will be determined, including those that are neutralizing antibodies (NAbs).

SAFETY EVALUATIONS

- Adverse events, serious adverse events, and adverse events of special interest. The relatedness and severity will be evaluated by the investigator. Severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
- Infusion-related reactions
- Severe infections
- Clinical laboratory tests
- Vital signs and physical examination

STATISTICAL METHODS

General Considerations

All statistical inferences will be based on 2-sided tests with an α-level of 0.05. All data will be summarized by study drug group. Categorical variables will be summarized by number and percent of individuals falling within each category. Continuous variables will be summarized by mean, median, standard deviation, minimum and maximum. Unless otherwise noted, baseline values will be defined as the most recent value collected prior to the first dose of study drug.

For efficacy endpoints, the analysis population will be all randomized participants who receive any amount of study drug, referred to as the intent-to-treat (ITT) population. For this population, participants will be analyzed in the treatment group corresponding to the treatment to which they are randomized, regardless of what treatment they actually receive.

For the safety endpoints, the analysis population will consist of all randomized study participants receiving at least one dose of study drug, referred to as the safety population. For this population, participants will be analyzed in the treatment group corresponding to the treatment they actually received, regardless of the treatment to which they were randomized.

For PK and immunogenicity, the analysis population will be all participants in the safety population who have provided at least one evaluable sample.

Sample Size Determination

The study sample size is calculated based on the desired clinically relevant effects and the results from placebo-treated participants in previous teplizumab studies. Since C-peptide AUC is skewed right, the data will be transformed using ln(AUC+1) for analysis. C-peptide data at 18 months from prior studies in children and adolescents who entered the studies with a stimulated C-peptide AUC of >0.2 pmol/mL are limited. Estimates range from approximately 0.22 nmol/L to 0.32 nmol/L with a standard deviation between 0.18 and 0.22. Using an estimate of 0.25 nmol/L, the transformation to geometric mean in the placebo

group is exp(0.25)-1) = 0.28. This study is designed to show a difference of at least a 40% in C-peptide response between teplizumab and placebo. In geometric means this translates to a value of (1.4*0.28) = 0.392. Consequently, approximately 300 participants are planned for enrollment, assuming 2-sided α=0.05, 90% power, 2:1 randomization, and a 10% dropout rate.

Efficacy Analyses

The primary endpoint is the difference between treatment groups in C-peptide ln(AUC+1) at Week 78 using the ITT population. C-peptide will be measured in a 4h MMTT. Analysis of covariance (ANCOVA) will be used to assess the treatment difference in C-peptide at Week 78. Missing data from patients who drop out before the end of the study will be imputed based on those patients who similarly discontinue treatment in the same treatment arm but have measurement taken at scheduled visits. The model will include treatment (teplizumab or placebo), age, and peak C-peptide at baseline as covariates.

Sensitivity analysis will be performed using a tipping point approach. The same imputation and model will be used as in the primary analysis, but a tipping point that changes the C-peptide conclusion at 18 months will be sought. Repeated measures analysis may also be used to assess sensitivity.

The secondary clinical endpoints will be assessed using the Hochberg step-up method for addressing multiplicity if primary endpoint reaches $p < 0.05$.

Like the primary endpoint, ANCOVA will be used to assess treatment differences in insulin use, HbA1c, and the percentage of time participants' BG levels are within the target range of >70 to ≤180 mg/dL (>3.9 to ≤10.0 mmol/L) at Week 78.

Average total exogenous insulin use (in U/kg/day) will be self-recorded in an eDiary for 7 days prior to study visits and at randomization. Data from at least 5 of these 7 days will be used for analysis. The model will include age, baseline insulin use, peak C-peptide at baseline and treatment group as covariates.

The model used to assess HbA1c will include age, baseline HbA1c, treatment group, and baseline peak C-peptide as covariates.

Time in range for blood glucose will be defined as the average percentage of time in range for 10 to 14 days post each study visit. The model will include baseline time in range, treatment group, age and baseline peak C-peptide.

The rate (number of events/exposure time) of clinically important hypoglycemic episodes at Week 78 will be compared between groups. Data will be collected from intermittent glucose monitoring, continuous glucose monitors, participant eDiary and CRFs. A clinically important episode is defined as a reliable BG value of <54 mg/dL (3.0 mmol/L) and/or a hypoglycemia event requiring external assistance, (such as seizure, syncope, severe confusion with or without a confirmatory low BG reading). The event rate of clinically important hypoglycemic episodes per study participant will be assessed using a negative binomial model to allow for the potential for overdispersion in case episodes for hypoglycemia within participant groups are correlated. The model to assess clinically significant hypoglycemia will include age, treatment group, and baseline peak C-peptide as covariates.

Other Analyses

Other analyses, including those for safety, PK, and immunogenicity, and exploratory endpoints will be conducted using established and accepted statistical approaches.

Additional safety and efficacy analyses will be performed on the subgroup of participants who receive the second treatment course starting at the Week 52 visit because of the COVID-19 pandemic restrictions.

Study Oversight

The Sponsor recognizes that the study population, specifically children 8-17 years old recently diagnosed with T1D, is a vulnerable population at very high risk for disease- and therapy-related short- and long-term morbidity and mortality. There is no disease modifying therapy for T1D and the only therapeutic class of treatments approved for T1D was discovered almost a century ago. Therefore, the Sponsor has incorporated rigorous criteria and processes directed towards the best interest for the safety of study participants. This study will be regularly monitored, and data will be reviewed by the DMC, which will ensure the safe and appropriate conduct of this study and make decisions on the continuation, interruption, or termination of the study.

SCHEDULE OF EVENTS: SCREENING TO WEEK 20

Event	Pre-Screen[1]	Screen	Study Drug Treatment - Course 1												Post Course 1 Evaluations			
Week (Screening through Week 20)	(-6) - (-4)	(-5) - 0	1							2					4	8	12	20
Day (Screening through Day 140)	(-42) - (-28)	(-35) - 0	1	2	3	4	5	6	7	8	9	10	11	12	28	56	84	140
Visit Window (± days from target)	*N/A*	*N/A*	*N/A*							*N/A*					*± 4*	*± 4*	*± 4*	*± 4*
Informed Consent/Assent	(X[1])	X																
Inclusion/Exclusion Criteria/Review		X	X															X
Medical history/interval review		X	X												X	X	X	X
Tuberculosis exposure review		X	X												X	X	X	X
Height (cm) & Weight (kg)		X	X															
Vital Signs (P, BP, RR)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (C=Complete; P=Partial)		X[C]	X[P]						X[P]					X[P]	X[P]	X[P]	X[P]	X[P]
Previous/Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin Use Review (7 days)			X														X	
Fingerstick Glucometer Distribution (optional)		(X)																
Fingerstick Glucometer Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Continuous Glucometer Application														X[2]			X[2]	
Hypoglycemia Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires			X														X	
Randomization (w/ stratification)			X															
Study Drug Dose Calculation			X															
Premedication (NSAID[a], antihistamine); (X) = optional			X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)				
Study Drug Infusion			X[D1]	X[D2]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]				
CBC w/ Differential		X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X
Chemistry Panel and LFTs		X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X
Coagulation Panel		X																
Lipid Panel		X																
HbA1c		X	X														X	
Serum β-HCG (females only)		X																
IGRA (Blood TB test)		X																
HBV, HCV, HIV serology		X																
EBV, CMV, VZV serology		X																
EBV and CMV Viral PCR		X													X		X	X
SARS-CoV-2 PCR			X[8]															
HLA-typing			X															
TBNK/Quantitative Lymphocyte Panel			X											X	X		X	

Event	Pre-Screen[1]	Screen	Study Drug Treatment - Course 1												Post Course 1 Evaluations			
Week (Screening through Week 20)	(-6) - (-4)	(-5) - 0	1							2					4	8	12	20
Day (Screening through Day 140)	(-42) - (-28)	(-35) - 0	1	2	3	4	5	6	7	8	9	10	11	12	28	56	84	140
Visit Window (± days from target)	*N/A*	*N/A*	*N/A*							*N/A*					*± 4*	*± 4*	*± 4*	*± 4*
Quantitative Immunoglobulin Panel		X															X	
Urine β-HCG (females only)			X[5]												X[5]	X[5]	X[5]	X[5]
Urinalysis		X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X		X
Urine ketones[b]																		
2h MMTT		X																
4h MMTT			X															
T1D Autoantibodies (X 5)	X[1]	X															X	
Serum Teplizumab Levels			X[3]			X[3]					X[3,9]			X[3]	X			
Serum Anti-teplizumab Antibody			X											X	X	X		
Sample for PBMCs (exploratory)			X											X	X		X	
Sample for Serum (exploratory)			X											X	X		X	
Sample for Molecular Analysis (exploratory)			X											X	X		X	

SCHEDULE OF EVENTS: WEEK 26 TO WEEK 78

Detail	Study Drug Treatment - Course 2												Post Course 2 Evaluations						ET
Week (Week 26 – 78)	26							27					30	34	39	52	65	78/ EOSV	
Day (182 – 546)	182	183	184	185	186	187	188	189	190	191	192	193	210	238	273	364[a]	455	546	
Visit Window (± days from target)	± 7	*N/A*											± 4	± 4	± 4	± 4	± 7	± 7	*N/A*
Inclusion/Exclusion Criteria/Review	X																		
Medical History/interval review	X													X	X	X	X	X	X
Vital Signs (P, BP, RR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (cm) and Weight (kg)	X														X	X	X	X	X
Physical Exam (C=Complete; P=Partial)	X[P]						X[P]					X[P]	X[P]	X[P]	X[P]	X[P]	X[P]	X[C]	X[C]
Previous/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis (TB) exposure review	X												X	X	X	X	X	X	X
Insulin Use Review (7 days)	X														X	X	X	X	X
Fingerstick Glucometer Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Continuous Glucometer Application												X[2]			X[2]	X[2]	X[2]	X[2]	
Hypoglycemia Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires	X														X	X	X	X	X
Study Drug Dose Calculation	X																		
Premedication (NSAID[a], antihistamine); (X) = optional	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)							
Study Drug Infusion	X[D1]	X[D2]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]							
CBC with Differential	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X	X	X	X
Chemistry Panel and LFTs	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X	X	X	X
Lipid Panel	X															X		X	X
HbA1c	X														X	X	X	X	X
EBV, CMV, VZV serology																X		X	X
EBV and CMV Viral PCR													X		X	X		X	X
SARS-CoV-2 PCR	X[8]																		
TBNK/Quantitative Lymphocyte Panel	X											X	X		X	X		X	X
Quantitative Immunoglobulin Panel	X														X	X		X	X
Urine β-HCG (females only)	X[5]												X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Urinalysis	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X			X	X
Urine ketones[b]																			
4h MMTT	X															X		X	X
T1D Autoantibodies (X 5)	X															X		X	X

Detail	Study Drug Treatment - Course 2												Post Course 2 Evaluations						ET
Week (Week 26 – 78)	26							27					30	34	39	52	65	78/ EOSV	
Day (182 – 546)	182	183	184	185	186	187	188	189	190	191	192	193	210	238	273	364[a]	455	546	
Visit Window (± days from target)	± 7	*N/A*											*± 4*	*± 4*	*± 4*	*± 4*	*± 7*	*± 7*	*N/A*
Serum Teplizumab Levels	X[3]			X[3]					X[3]			X[3]	X						X[4]
Serum Anti-teplizumab Antibody	X					X						X	X	X	X	X	X	X	X
Sample for PBMCs (exploratory)	X											X	X		X	X	X	X	X
Sample for Serum (exploratory)	X											X	X		X	X	X	X	X
Sample for Molecular/genetic Analysis (exploratory)	X											X	X		X	X	X	X	X

MODIFIED DOSING SCHEDULE (DUE TO COVID-19) OF EVENTS: SCREENING TO WEEK 26

Event	Pre-Screen[1]	Screen	Study Drug Treatment - Course 1												Post Course 1 Evaluations				
Week (Screening through Week 26)	(-6) - (-4)	(-5) – 0	1							2					4	8	12	20	26
Day (Screening through Day 182)	(-42) - (-28)	(-35) - 0	1	2	3	4	5	6	7	8	9	10	11	12	28	56	84	140	182
Visit Window (± days from target)	*N/A*	*N/A*	*N/A*							*N/A*					*± 4*	*± 4*	*± 4*	*± 4*	*+28*
Informed Consent/Assent	(X^1)	X																	
Inclusion/Exclusion Criteria/Review		X	X															X	
Medical history/interval review		X	X												X	X	X	X	X
Tuberculosis exposure review		X	X												X	X	X	X	X
Height (cm) & Weight (kg)		X	X																X
Vital Signs (P, BP, RR)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (C=Complete; P=Partial)		X^C	X^P						X^P					X^P	X^P	X^P	X^P	X^P	X^P
Previous/Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin Use Review (7 days)			X														X		X
Fingerstick Glucometer Distribution (optional)		(X)																	
Fingerstick Glucometer Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Continuous Glucometer Application														X^2			X^2		X^2
Hypoglycemia Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires			X														X		X
Randomization (w/ stratification)			X																
Study Drug Dose Calculation			X																
Premedication (NSAID[a], antihistamine); (X) = Optional			X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)					
Study Drug Infusion			X^{D1}	X^{D2}	X^{D3}	X^{D3}	X^{D3}	X^{D3}	X^{D3}	X^{D3}	X^{D3}	X^{D3}	X^{D3}	X^{D3}					
CBC w/ Differential		X	X^L	X^L		X^L		X^L			X^L			X	X	X	X	X	
Chemistry Panel and LFTs		X	X^L	X^L		X^L		X^L			X^L			X	X	X	X	X	
Coagulation Panel		X																	
Lipid Panel		X																	
HbA1c		X	X														X		X
Serum β-HCG (females only)		X																	
IGRA (Blood TB test)		X																	
HBV, HCV, HIV serology		X																	
EBV, CMV, VZV serology		X																	
EBV and CMV Viral PCR		X													X		X	X	
SARS-CoV-2 PCR			X^g																

Event	Pre-Screen[1]	Screen	Study Drug Treatment - Course 1												Post Course 1 Evaluations				
Week (Screening through Week 26)	(-6) - (-4)	(-5) – 0	1							2					4	8	12	20	26
Day (Screening through Day 182)	(-42) - (-28)	(-35) - 0	1	2	3	4	5	6	7	8	9	10	11	12	28	56	84	140	182
Visit Window (± days from target)	*N/A*	*N/A*	*N/A*							*N/A*					*± 4*	*± 4*	*± 4*	*± 4*	*+28*
HLA-typing			X																
TBNK/Quantitative Lymphocyte Panel			X											X	X		X		X
Quantitative Immunoglobulin Panel		X															X		X
Urine β-HCG (females only)			X[5]												X[5]	X[5]	X[5]	X[5]	X[5]
Urinalysis		X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X		X	X
Urine ketones[b]																			
2h MMTT		X																	
4h MMTT			X																X
T1D Autoantibodies (X 5)	X[1]	X															X		
Serum Teplizumab Levels			X[3]			X[3]					X[3,9]			X[3]	X				X[3]
Serum Anti-teplizumab Antibody			X											X	X	X			X
Sample for PBMCs (exploratory)			X											X	X		X		X
Sample for Serum (exploratory)			X											X	X		X		X
Sample for Molecular Analysis (exploratory)			X											X	X		X		X

MODIFIED DOSING SCHEDULE (DUE TO COVID-19) OF EVENTS: WEEK 34 TO WEEK 78

Event	Post Course 1 Evaluations		Study Drug Treatment - Course 2												Post Course 2 Evaluations				ET
Week (Week 34 – 78)	34	39	52							53					56	60	65	78/ EOSV	
Day (238 – 546)	238	273	364	365	366	367	368	369	370	371	372	373	374	375	392	420	455	546	
Visit Window (± days from target)	*± 4*	*+ 28*	*± 7*						*N/A*						*± 4*	*± 4*	*± 7*	*± 7*	*N/A*
Inclusion/Exclusion Criteria/Review			X														X	X	X
Medical History/interval review	X	X	X														X	X	X
Vital Signs (P, BP, RR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (cm) and Weight (kg)		X	X														X	X	X
Physical Exam (C=Complete; P=Partial)			X[P]						X[P]					X[P]	X[P]	X[P]	X[P]	X[C]	X[C]
Previous/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis (TB) exposure review	X	X	X												X	X	X	X	X
Insulin Use Review (7 days)		X	X														X	X	X
Fingerstick Glucometer Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Continuous Glucometer Application		X[2]												X[2]			X[2]	X[2]	
Hypoglycemia Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires		X	X														X	X	X
Study Drug Dose Calculation			X																
Premedication (NSAID[a], antihistamine); (X) = optional			X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)					
Study Drug Infusion			X[D1]	X[D2]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]	X[D3]					
CBC with Differential	X	X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X	X
Chemistry Panel and LFTs	X	X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X	X
Lipid Panel			X															X	X
HbA1c		X	X														X	X	X
EBV, CMV, VZV serology[7]																		X	X
EBV and CMV Viral PCR		X[7]													X			X	X
SARS-CoV-2 PCR			X[8]																
TBNK/Quantitative Lymphocyte Panel		X	X											X	X	X		X	X
Quantitative Immunoglobulin Panel		X	X															X	X
Urine β-HCG (females only)	X[5]	X[5]	X[5]												X[5]	X[5]	X[5]	X[5]	X[5]
Urinalysis	X	X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X		X	X
Urine ketones[b]																			
4h MMTT			X															X	X
T1D Autoantibodies (X 5)			X															X	X
Serum Teplizumab Levels			X[3]			X[3]					X[3]			X[3]	X				X[4]
Serum Anti-teplizumab Antibody		X	X					X						X	X	X	X	X	X

Event	Post Course 1 Evaluations		Study Drug Treatment - Course 2												Post Course 2 Evaluations				ET
Week (Week 34 – 78)	34	39	52							53					56	60	65	78/ EOSV	
Day (238 – 546)	238	273	364	365	366	367	368	369	370	371	372	373	374	375	392	420	455	546	
Visit Window (± days from target)	*± 4*	*+ 28*	*± 7*						*N/A*						*± 4*	*± 4*	*± 7*	*± 7*	*N/A*
Sample for PBMCs (exploratory)		X	X											X	X	X	X	X	X
Sample for Serum (exploratory)		X	X											X	X	X	X	X	X
Sample for Molecular/Genetic Analysis (exploratory)		X	X											X	X	X	X	X	X

X^1 = Optional T1D autoantibody prescreening with specific informed consent. The result can be used in the place of the screening T1D autoantibody test.
X^2 = CGM device will be applied on the participants and will stay on for the following approximately 2 weeks at all these visits except Week 78. For Week 78 data, study personnel will call the participants or caregivers and remind each participant to apply the CGM sensor from Week 76 to Week 78.
X^3 = Teplizumab levels for pharmacokinetic analyses are to be obtained within 30 minutes before study drug infusion (where applicable).
X^4 = Draw teplizumab level only if the ET Visit is between Day 1 and Day 28 or between Day 182 and Day 210 (between Day 364 and Day 392 for participants on the Modified Dosing schedule).
X^5 = In addition to the urine β-HCG test, a serum β-HCG test may be performed at the Investigator's discretion.
X^6 = If the PBMC sample collection is scheduled on a day when overnight shipping is not available, the sampling should take place on the closest day prior to the scheduled day when shipping is available.
X^7 = EBV, CMV, and VZV serology as well as EBV and CMV PCR tests can be performed anytime between Week 39 and Week 52 visits before the start of treatment Course 2, if an infection is suspected.
X^8 = SARS-CoV-2 PCR local testing is required for all participants entering the study from protocol version 3.0 onward. The result must be reviewed by the Investigator and be negative before the study drug can be administered. The test may be performed within 5 working days before the first dose of study drug is given in each treatment course if not feasible on the day of dosing.
X^9 = On Day 9 of Treatment Course 1, an additional PK sample will be obtained within 45 ± 15 minutes after infusion is completed.
X^C = Complete physical exam
X^P = Partial physical exam
X^{D1}, X^{D2}, X^{D3} = Study drug infusion dose 1, dose 2, dose 3; X^{D1} = 106 μg/m^2, X^{D2} = 425 μg/m^2, X^{D3} = 850 μg/m^2
X^L = Performed by local laboratories. Local laboratory results must be reviewed prior to the start of study drug infusion.

[a] Acetaminophen should be given if NSAID is contraindicated.
[b] In participants who have discontinued insulin therapy, urine ketones should be checked once daily.

Laboratory test panels:
Complete blood count (CBC) with differential = White blood cell count (WBC), hemoglobin, hematocrit, and platelet count. percent and absolute count of neutrophils, lymphocytes, monocytes, eosinophils and basophils
Chemistry Panel = Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, albumin, total protein
Liver function tests (LFTs) = alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBili), direct bilirubin (DBili)
Coagulation Panel = partial thromboplastin time (PTT), prothrombin time (PT), and international normalized ratio (INR)
Lipid Panel = Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides
TBNK/quantitative lymphocyte panel = Percent and absolute counts of T cells, B cells, and Natural Killer (NK) cells

Questionnaires:
Quality of Life Questionnaires: See Section 9.6.
Tuberculosis (TB) exposure review: See Section 9.7.4.

Abbreviations for Schedule of Events:
AA = autoantibody
β-HCG = beta-human chorionic gonadotropin
BP = blood pressure

CBC = complete blood count
CGM = continuous glucose monitoring
cm = centimeters
CMV = cytomegalovirus
EBV = Epstein-Barr virus
EOSV = End of Study Visit
ET = Early Termination Visit
HbA1c = hemoglobin A1c
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus
HLA = human leukocyte antigen
IGRA = interferon-gamma Release Assays
kg = kilograms
LFT = liver function test
MMTT = mixed meal tolerance test
NSAID = nonsteroidal anti-inflammatory drug
P = pulse
PBMC = peripheral blood mononuclear cells
PCR = polymerase chain reaction
RR = respiratory rate
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
TB = tuberculosis
TBNK = T cell, B cell, NK cell (panel)
VZV = varicella zoster virus

ABBREVIATIONS

ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
β-hCG	beta-human chorionic gonadotropin
BG	blood glucose
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
°C	Celsius
CBC	complete blood count
CD	cluster of differentiation
CGM	continuous glucose monitoring
CL	clearance
C_{max}	maximum concentration
CMV	cytomegalovirus
COVID-19	Coronavirus Disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CTCAE	Common Terminology Criteria for Adverse Events
CVB	coxsackie virus b
DBili	direct bilirubin
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DNA	deoxynucleic acid
DPP-IV	dipeptidyl peptidase-4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EASD	European Association for the Study of Diabetes
EBV	Epstein-Barr virus
eCRF	electronic case report form
eDC	electronic data capture
EMA	European Medicines Agency
ET	early termination
°F	Fahrenheit
Fc	fragment crystallizable region of an antibody/immunoglobulin molecule
FcR	receptor binding to the Fc component of antibody molecules
FDA	Food and Drug Administration
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen

HR	heart rate
HFS	Hypoglycemia Fear Scale
IA	islet antigen
IB	Investigator Brochure
ICA	islet cell cytoplasmic autoantibody
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon gamma release assay
IHSG	International Hypoglycaemia Study Group
IL	interleukin
IM	intramuscular
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IRE	immediately reportable event
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KD	kilodalton
LDL	low density lipoprotein
LFT	liver function test
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MMTT	mixed meal tolerance test
MNAR	missing not at random
Nab	neutralizing antibody
NCI	National Cancer Institute
NK	natural killer
NONMEM	nonlinear mixed effects modeling
NSAID	nonsteroidal anti-inflammatory drug
PCR	polymerase chain reaction
PedsQL	Pediatric Quality of Life Inventory
PICC	peripherally inserted central catheter
PID	patient/participant identification number
PK	pharmacokinetic(s)
PMN	polymorphonuclear leukocyte
PQC	product quality complaint
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation

SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes
T1D AA	type 1 diabetes-associated autoantibody
TB	tuberculosis
TBili	total bilirubin
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TIR	time in (glycemic target) range
Treg	T regulatory cell
U	unit
ULN	upper limit of normal range
VZV	varicella zoster virus
WBC	white blood cell
ZnT8	zinc transporter 8

1. INTRODUCTION

Teplizumab (also known as PRV-031, hOKT3γ1 [Ala-Ala], and MGA031) is a humanized 150-kilodalton (KD) monoclonal antibody (mAb) that binds to the CD3-ε epitope of the T cell receptor (TCR). Teplizumab was developed after preclinical studies demonstrated that targeting T cells (the cells that are instrumental in initiating and coordinating the autoimmune process responsible for type 1 diabetes [T1D] mellitus) via this mechanism altered diabetes immunopathogenesis and prevented and reversed disease in relevant animal models. A number of clinical studies have demonstrated the ability of teplizumab to slow or even halt the destruction of the insulin-secreting β cells in populations of individuals with newly diagnosed T1D. The goal of this study is to evaluate teplizumab in patients who may be most responsive to it as suggested in previous studies, namely children and adolescents very recently diagnosed with T1D. Teplizumab holds the promise to be the first disease modifying therapy available to improve both the medical management and overall outlook in those who suffer the most devastating short- and long-term consequences of this disease.

For the most comprehensive nonclinical and clinical information regarding teplizumab, refer to the latest version of the Investigator Brochure (IB).

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

T1D is a T cell-mediated autoimmune disease that targets and destroys the insulin secreting β cells located in the islets of Langerhans in the pancreas (Ziegler 2010, Atkinson 2014). The loss of these cells results in the body's inability to sense glucose levels and produce insulin. In the absence of therapy, this leads to severe, unsustainable metabolic dysregulation, namely uncontrolled blood glucose elevation (hyperglycemia) and its short and long-term sequelae including rapid wasting and inevitable, near-term death.

T1D is an immediate and lifelong, life-threatening disorder afflicting millions of people worldwide. It most often presents in children and adolescents and is one of the three most prevalent severe chronic diseases of childhood, along with asthma and cancer. The annual incidence is highest in children and young adults with ~20 to 25 cases/100,000/year in those younger than 20 years old in North America and many Westernized countries and is over 40-60 cases/100,000/year in some areas in Northern Europe and Sardinia (Atkinson 2014, Bluestone 2010, Streisand 2014, Karvonen 2000). Due to its short- and long-term complications, T1D is both a daily and life-long burden for individuals and their families and also has significant socio-economic and societal-medical ramifications, which are intensifying as the worldwide incidence of T1D increases up to 5% annually (Karvonen 2000).

Exogenous insulin is needed immediately for those diagnosed with T1D and is required for their lifetime. Prior to the discovery of insulin almost 100 years ago, T1D was a disease that was uniformly fatal, often within weeks to months. Significant advancements have been made in the types and delivery of insulin and glucose monitoring – but none are able to replicate the body's

inherent ability to maintain metabolic control. Glycemic management is a daily challenge and individuals must constantly balance current blood glucose readings, caloric intake and composition, type and amount of injected insulin, injection site locations, time of the day, health status and activity level to determine even a single dosing of insulin per day. Although needed for survival for those with T1D, exogenous insulin has significant side effects and dosing errors can result in hypoglycemia, seizures and death. Iatrogenic hypoglycemia is thought to contribute to the "Dead in Bed" syndrome, which is a sudden unexplained death while sleeping in those with T1D (Secrest 2011). The medical community realizes the significant risks of insulin administration. In hospitals and healthcare facilities insulin is considered one of the top 5 "High Alert Medications" as it is a drug with a heightened risk of causing significant patient harm (Joint Commission 1999). There are likely few, if any, other medical conditions for which individuals self-administer a potentially lethal therapy drug multiple times a day that they store in their homes.

Even in the present day, with the availability of insulin and glucose monitoring and advanced understanding of T1D, failure of regular dosing can result in the prototypic T1D-associated conditions like hyperglycemia, dehydration, and diabetic ketoacidosis (DKA), which can result in cerebral edema and death. With even the most stringent control targeting current glycemic goals, those with T1D are at risk for longer-term complications including severe renal, cardiac, neurologic and micro- and macro-vascular disease (Atkinson 2014, Bluestone et al 2010, Steffes 2003). These translate into blindness, myocardial infarctions, strokes/cerebral vascular accident, extremity amputation, erosive non-healing foot ulcers, chronic local and systemic infections, and renal failure requiring dialysis or transplantation. Those who develop T1D early in life are at increased risk for significant neurocognitive disorders including behavioral issues, lower intellectual performance and motor dysfunction, and associated structural changes in the brain (Lin 2015).

The signs and symptoms of T1D, and thus the clinical diagnosis, occur when there is a significant reduction in β cell function (Matveyenko 2008, Campbell-Thompson 2016). The loss of function appears to be due to a combination of the immune destruction of β cells and β cell dysfunction based on heightened metabolic stress and a direct effect of the local proinflammatory immunologic milieu (Akirav 2008, Greenbaum 2012, Keenen 2010, Matveyenko 2008). However, recent studies suggest that nearly 40% of normal β cell numbers may be present at T1D diagnosis, albeit many or most appear temporarily dysfunctional due to metabolic and inflammatory stress, and glucotoxicity (Akirav 2008, Matveyenko 2008). Many individuals, especially children, who are diagnosed with T1D experience a "Honeymoon" period within the first year of diagnosis when there is a substantial reduction in exogenous insulin needs (and in some cases, insulin independence) but inevitably full replacement doses of exogenous insulin are needed (Abdul-Rasoul 2006, Mortensen 2009). This period is thought to be a critical time when the remaining β cells regain function. This phenomenon supports the premise that if these functional, and seemingly non-functional remaining β cells, can be spared from autoimmune destruction, substantial clinical benefit could be achieved.

T1D is known to be the result of a multifaceted autoimmune attack on β cells. T1D appears to develop in genetically predisposed individuals who encounter an environmental stimulus that breaks immune tolerance in β cell-specific self-reactive T cells (Ziegler 2010, Atkinson 2014).

Putative triggers have included specific foods and infections, with mounting data supporting that coxsackie virus B (CVB) infection can precipitate T1D autoimmunity in some individuals (Ziegler 2010, Laitinen 2014). A cascade of cellular and humoral immune mediators is activated over time (which may be many years) which destroys β cells until a critical mass is lost and an individual becomes symptomatic from hyperglycemia. Due to the autoimmune etiology of T1D, an immunomodulatory-based therapy is considered *the* most promising approach to preserve β cells and endogenous insulin production, which could translate into β cell retention of at least partial endogenous glycemic control – which recent studies indicate can be critical in improving many short- and long-term outcomes of T1D. $CD4^+$ and $CD8^+$ T cells are instrumental in the initiation of the T1D autoimmune process, direct killing of β cells and orchestrating the other immune processes involved with β cell destruction. Data from animal studies and several clinical trials support specifically that therapies targeting T cells, including abatacept (CTLA4Ig), alefacept (LFA3Ig) and antibodies targeting the CD3 complex, have the most potential, and have proven to be the most promising, to significantly slow or abrogate the ongoing immune destruction of β cells in humans with T1D (Rigby 2013, Rigby 2016, Herold 2002, Herold 2005, Herold 2013 (Abate), Hagopian 2013, Masharani 2010, Orban 2011).

Preventing, halting or even significant slowing of β cell destruction using a disease-modifying therapy, instead of just managing symptoms of hyperglycemia, is seen as the way to lessen the daily burden on those with T1D, and their families, and reduce the significant disease and therapies-associated morbidity and mortality (Mittermayer 2017). A clear example of this benefit was shown in the Diabetes Control and Complications Study (Diabetes Control and Complications Trial Research Group 1997) in which the rates of significant hypoglycemia were less in patients with residual β cell function, measured by the levels of stimulated C-peptide. Moreover, the risk of microvascular complications such as retinopathy and others were significantly reduced in those who maintained a C-peptide level of at least 0.2 pmol/mL (Lachin 2014, Palmer 2004, Palmer 2009). In recent years, potential therapies to modify the course of the disease by targeting key components of the immune response have been identified and have started to be evaluated in clinical trials. Although to date there are no approved products to modify the course of T1D, teplizumab has substantial clinical data supporting further study and development to become the first disease-modifying therapy for T1D.

1.2. Teplizumab Overview

Teplizumab was originally developed in the late 1980s, primarily as an investigational therapy for T1D following a number of preclinical studies showing efficacy in animal models of T1D. Teplizumab is a humanized monoclonal antibody (mAb) variation of OKT3 (Muromonab-CD3) that binds to the CD3ε epitope of the T cell receptor (TCR) (Masharani 2010, Herold 2002). It has a modified Fc portion aimed at disrupting Fc receptor and complement component C1q binding to minimize the cytokine-mediated toxicity of the parent mAb. The molecular weight of teplizumab is approximately 150 KD.

Teplizumab has been evaluated in a number of clinical trials in new onset T1D, and in renal and islet allo-transplantation, and psoriatic arthritis. There are ongoing studies evaluating teplizumab in children and adults at high risk of developing T1D and a combination therapy of teplizumab

with a genetically modified strain of *Lactobacillus* designed to secrete human pro-insulin and human interleukin-10.

By far the most extensive clinical trial experience is in children and adults with newly diagnosed T1D, where over 1000 individuals were enrolled in 7 clinical studies, of whom 829 have been treated with teplizumab. Results from these studies suggest that it is one of the most promising candidates for disease modification of T1D. In pilot and proof-of-concept clinical studies conducted in young children, adolescents, and adults, short courses (approximately 2 weeks) of teplizumab treatment have been shown to be safe and well tolerated, resulting in relative sparing of β cell function in those who were recently diagnosed with T1D (Herold 2002, Herold 2005, Herold 2013a, Herold 2013b).

As part of many of these clinical trials, there has been extensive mechanistic evaluation of teplizumab. These evaluations have shown a number of effects on specific subpopulations of T cells that are integral for the initiation and propagation of the β cell destructive autoimmune process. Circulating T cells (and other lymphocytes) are transiently reduced following teplizumab treatment, in a process that may include margination and depletion (Long 2017, Sherry 2011). In addition to reduced effector function of T cells, teplizumab appears to both increase the number and function of regulatory T cells (Tregs) (Ablamunits 2010, Bisikirska 2005, Long 2017, Waldron-Lynch 2012). More recent studies indicate that teplizumab induces immunologic "exhaustion" in a subset of effector $CD8^+$ T cells, perhaps making them more susceptible to regulation or deletion (Long 2016, Long 2017). Taken together, these mechanistic data suggest that teplizumab not only exerts a "suppressive" effect on β cell immune destructive processes but rather is an immune "modulator" favoring a rebalancing of effector and regulatory arms involved with T1D autoimmunity and supporting the notion that teplizumab may have the ability to contribute to the re-introduction of β cell self-tolerance (Lebastchi 2013).

A multi-arm, multinational Phase 2/3 study of teplizumab (known as the "Protégé" study) was previously conducted by MacroGenics and Eli Lilly and Company. Over 500 children and adults 8 to 35 years old with T1D were enrolled within 12 weeks of diagnosis and evaluated in 3 different teplizumab dosing regimens or placebo (Sherry 2011, Hagopian 2013). The study used a novel and untested composite primary endpoint integrating glycemic control, measured by hemoglobin A1c (HbA1c) level, and insulin use; specifically, participants were considered to meet the primary endpoint if they had HbA1c <6.5% and insulin use <0.5 units/kg/day at 1 year post randomization. Although the study did not meet this primary endpoint, the study results in the randomized treatment group (14-day regimen, 9 mg/m^2 dose per course) showed a statistically significant benefit in slowing the decline in C-peptide at 18 and 24 months, which supported the findings of previous studies that teplizumab does have the ability to preserve β cell function in those newly diagnosed with T1D (Hagopian 2013). Furthermore, the effect of teplizumab treatment was even more notable in participants with the following characteristics at the time of study entry: enrolled in sites in the United States, 8 to 17 years of age, higher baseline C peptide levels, and randomized within 6 weeks of TID diagnosis (Hagopian 2013).

In the Protégé and other clinical studies, teplizumab is generally very well tolerated. In general, there are no major differences in overall adverse events (AEs) of clinical concern and serious

adverse events (SAEs) between teplizumab and placebo groups. The most common AEs associated with teplizumab are a decrease in white blood cell counts, nausea and/or vomiting, upper respiratory infections or nasopharyngitis and elevations in AST or ALT and anemia, all usually mild or moderate. The most frequent observation is a decrease in white blood cell count (WBC), including, in order, transient lymphopenia, leukopenia, and neutropenia. Transient lymphopenia has occurred in ~2/3 of teplizumab recipients and is usually mild or moderate, which is consistent with teplizumab's mechanism of action (Sherry 2011, Hagopian 2013). These events are usually self-limited and occur with teplizumab dosing and spontaneously reconstitute. For example, lymphocytes return to 80% of baseline levels within approximately 14 days of dosing. Approximately half of those who receive teplizumab develop a mild rash, sometimes pruritic, during dosing cycles, which spontaneously resolves within 7-14 days. Due to its mechanism of action, cytokine release syndrome is a potential concern with teplizumab dosing but occurs in <10% of teplizumab-treated individuals (for example ~6% in the Protégé study) and is usually mild-to-moderate and well tolerated. Prophylactic administration of non-steroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen) and antihistamines (eg, diphenhydramine) appear to reduce the occurrence and the severity of its signs and symptoms significantly.

In the Protégé study, severe AEs were noted in approximately 63% and 30% of teplizumab and placebo participants, respectively (Sherry 2011, Hagopian 2013). The most common (though occurring in less than 10% of teplizumab treated participants) was decreased white blood cell counts. Three deaths occurred and were categorized by the principal investigator (in accordance with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines) and included in the IB. The specific causes of deaths and relationship with teplizumab are listed as: (1) "unknown" for which the relationship was listed as "none"; (2) "anterior myocardial infarction with ventricular tachycardia and cardio-respiratory arrest" for which the relationship was listed as "not related"; and (3) "diabetic ketoacidosis" for which the relationship was listed as "unlikely".

Despite the decrease in WBC, overall infections were not increased following teplizumab treatment. However, in the Protégé study there were 10 cases of herpes zoster (the result of reactivation of varicella zoster virus [VZV], the causative agent of chicken pox and shingles) in teplizumab-treated patients; all cases resolved without consequence. In the study, other herpes virus infections (eg, cytomegalovirus and Epstein-Barr virus) were not increased with teplizumab treatment (Sherry 2011, Hagopian 2013).

A significant body of data exists indicating that in the appropriate individuals, teplizumab can have a significant beneficial effect in maintaining β cell function and is well tolerated without side-effects that would limit its consideration as a viable disease modifying therapy for children and adolescents newly diagnosed with T1D.

In 2018, Provention Bio, Inc. acquired teplizumab (renamed as PRV-031) with a goal to further develop teplizumab as a first-in-class approved disease modifying therapy for T1D.

1.3. T1D and Teplizumab Experience in Children and Adults

Type 1 diabetes usually develops in childhood and adolescence; however, it can also present in adulthood as late as the 5th and 6th decades of life, although much less frequently (Atkinson 2014, Bluestone 2010, Streisand 2014). In addition to being more prone to some short- and long-term complications, there are differences in the clinical course and response to immune therapies between children/young adults and older adults. In the days or weeks before initial diagnosis, children and adolescents often suffer from severe diabetes symptoms, including polydipsia, polyuria, and weight loss, which could result in a clinical presentation of DKA and shock which requires hospitalization (Atkinson 2014, Bluestone 2010, Streisand 2014, Mittermayer 2017). Children and young adults with new-onset T1D usually have an immediate need for exogenous insulin.

This sharply contrasts with the experience of adults who develop T1D who often have months or years of non-specific symptoms or present asymptomatically from routine glycemic screening. These individuals can often be managed for prolonged periods of time (months or years) with diet or oral hypoglycemic agents before a demonstrable insulin need. More definitive studies have shown a different rate of decline of β cells according to age (Greenbaum 2012; Ludvigsson 2013). Following decades of study, the Diabetes TrialNet network has concluded that "age is the most important factor impacting the rate of decline of C-peptide post diagnosis" in that a significantly more rapid rate of decline occurs in children and adolescents compared to younger and older adults with new-onset disease. This more rapid decline appears to be due to a much more virulent and aggressive autoimmune process in children compared to adults, ostensibly supporting that there are important differences in T1D immuno-pathoetiology in younger versus older individuals (Greenbaum 2012, Campbell-Thompson 2016). Due to these fundamental differences, it is reasonable to expect that adults and children may respond differently to an immune-based disease modifying therapy. In other words, one treatment may be very effective in children but not effective at all in adults and vice versa (Rigby 2014).

These differences in disease pathophysiology between younger and older individuals with T1D are supported by the data from a number of recent new-onset T1D studies that have demonstrated differences in how younger and older individuals respond to immune interventions. Studies of abatacept, rituximab, alefacept, and teplizumab all appear to have a preferential effect on children and young adults; whereas thymoglobulin at doses at 6.5 mg/kg over four days appeared to preferentially spare β cells in adults, but not children (Rigby 2014, Rigby 2015, Orban 2011, Hagopian 2013, Gitelman 2013).

In the case of teplizumab, both children (as young as age 7 years) and adults (up to age 35 years) have been studied concurrently in all previous clinical trials. In studies demonstrating metabolic and clinical benefit, the average age of participants was ~12-13 years old (Herold 2002, Herold 2013b). Interestingly, although the Phase 3 study of teplizumab (the Protégé study) also enrolled children and adults (age 8 to 35 years old) the mean age was significantly higher than previous positive studies, at ~18 years old. Although the primary endpoint in Protégé was not met in the overall study population, post-hoc analysis showed that children and adolescents 8-17 years old

did have a statistically significant retention of C-peptide at key time points, including 12, 18, and 24 months post randomization (Hagopian 2013).

Children and adolescents are those at highest risk of developing disease and suffer most substantially from short- and long-term morbidity and mortality, and thus this group has the most to benefit from a disease modifying therapy (Wherrett 2015). This has recently been reinforced by a large study showing that those diagnosed with T1D in childhood and adolescence have a 4-6-fold increase in lifetime mortality risk, including seven times the risk of mortality from cardiovascular disease, compared to counterparts without T1D. This mortality risk is in sharp contrast to individuals diagnosed with T1D in adulthood, who have a ~3-fold higher risk from all-cause and cardiovascular disease-related mortality compared to their otherwise healthy peers (Rawshani 2017, Rawshani 2018). Recent reports indicate that those with T1D have a life expectancy ~11-13 years less than otherwise healthy-age matched individuals (Lind 2014, Huo 2016). While it is a goal in T1D research to reduce the morbidity and mortality for all with T1D, it is apparent that the most urgent need is for those who develop T1D in childhood and adolescence.

Because children and adolescents are those who appear to be most responsive to teplizumab and have the most to benefit from a disease modifying therapy, this study will enroll individuals who are 8-17 years old. Although adults (ie, those 18 years or older) with T1D may benefit with teplizumab, their response appears to be more variable than pediatric counterparts; therefore, inclusion of adults into this study may diminish, or even preclude, the ability to identify a positive effect of teplizumab in children and adolescents and hamper the development of an important therapy for these individuals. While not currently approved for use in children or adults, teplizumab has been studied for almost 20 years in over 1000 individuals ~8-35 years old, including over 450 who have been less than 18 years old. Thus far, in doses and regimens similar to one that will be used in this study, teplizumab has been well tolerated in all age ranges with no apparent differences in side effect profiles or safety signals in younger versus older individuals. Most importantly, as the urgent goal is to develop a therapy for those who will most likely benefit from it, this study will primarily focus on children and adolescents.

1.4. Overall Rationale for the Study

The clinical trial detailed herein, the PROTECT study, builds on the evidence from a number of previous clinical trials of teplizumab and focuses on patients who are likely to be the most responsive to this therapy. This study will enroll children and adolescents 8 to 17 years old who have been recently diagnosed with T1D (within the previous 6 weeks) and demonstrate a critical level of residual, and recoverable, β cell function. This population and approach to intervention can be considered a realistic paradigm to intervene in a disease with a significant unmet need in the population with this disease who have most to benefit from a disease modifying therapy.

The study will assess whether teplizumab can significantly and durably preserve β cell function and improve clinical management of T1D compared with the natural course of disease and current standard of care including exogenous insulin therapy. The preservation of β cell function is anticipated to translate to clinical and/or metabolic benefits consistent with improved ability to maintain glycemic control and short- and/or long-term outcomes. This study will be conducted in

North America and Europe in children and adolescents with recently diagnosed T1D who have a clinically relevant level of β cell function at study entry. Participants will be treated with two full courses of teplizumab. The study will assess the internationally accepted primary endpoint, the area under the time-concentration curve (AUC) of C-peptide following a mixed meal tolerance test (MMTT), at 78 weeks (18 months or 1.5 years), while also evaluating additional clinical endpoints (eg, insulin use, HbA1c, and clinically important hypoglycemic episodes), safety, and exploratory assessments over the course of the study.

The goal of this study is to provide critical data, in accordance with the current guidelines by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), to support the registration of teplizumab as a disease-modifying therapy for children and adolescents with T1D, those who have the most to benefit in both the short- and long-term from improved retention of β cell function following the diagnosis of T1D.

1.5. Risk and Benefit Assessment

Type 1 diabetes (T1D) is an autoimmune disease that results in a severe metabolic disease of glucose dysregulation. T1D is associated with significant short- and long-term complications and early death. Even with the best metabolic control using the most current insulins and glycemic monitoring devices, these risks are not eliminated. There is an urgent need to develop a disease modifying therapy for T1D.

Clinical studies with teplizumab in T1D have shown that it is effective in preserving beta cell function (as measured by C-peptide) and hence endogenous insulin production (Herold 2019). In the previous Protégé Study, teplizumab resulted in a statistically significant preservation of C-peptide, compared to placebo, at 2 years. As described in natural history studies, preservation of residual beta cell function (as measured by C-peptide levels) is protective against short- (hypoglycemic episodes) and long-term complications of T1D, including retinopathy, nephropathy and other cardiovascular events (Steffes 2003, Sorensen 2013, Lachin 2014, Kuhtreuber 2015).

Furthermore, the benefit of teplizumab in the preservation of beta cell function was more pronounced in younger participants (age 8-17 years), those who were treated early in the course of T1D (within 6 weeks of diagnosis), and those with higher baseline C-peptide levels. These latter characteristics were applied to the eligibility criteria in this study. In addition, a reduction in insulin use while maintaining glycemic control (as measured by HbA1c) was observed in participants who received teplizumab. In addition, consistent with teplizumab's potential for beta cell preservation, individuals with pre-symptomatic T1D (defined as the presence of at least two T1D-associated autoantibodies and dysglycemia), teplizumab was shown to delay the onset of clinical diabetes by at least 2 years (Herold 2019).

The main risks of teplizumab consist of transient lymphopenia and transient self-limited (mild to moderate) rash. Cytokine release syndrome is infrequent (~6%) and there is no overall increased risk of clinical infection or cancers.

Given the potential for important benefit in short- and long-term T1D outcomes compared to the transient, mild to moderate risks of teplizumab, the current study is investigating the previously

tested, two-course short-term dosing of teplizumab in younger patients who have the most to benefit from a disease-modifying therapy, specifically, children and adolescents with newly diagnosed T1D (within 6 weeks of diagnosis) and those with a critical threshold of endogenous production. Thus, the prospect of benefit outweighs the risk of participating in this study.

2. HYPOTHESIS, OBJECTIVES, ENDPOINTS

2.1. Study Hypothesis

The hypothesis of this study is that teplizumab is safe, well-tolerated, and effective in slowing the loss of β cells and maintaining a clinically relevant level of β cell function in children and adolescents newly diagnosed with T1D while improving key aspects of T1D clinical management over an 18-month period.

2.2. Study Objectives

The Primary Objective of this study is:

- To determine whether two courses of teplizumab slow the loss of β cells and preserve β cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who have been diagnosed with T1D in the previous 6 weeks.

The Secondary Objectives of this study are:

- To evaluate participant improvements in key clinical parameters of diabetes management, including insulin use, glycemic control (as measured by HbA1c and time in glycemic target range [TIR]), and clinically important hypoglycemic episodes
- To determine the safety and tolerability of two courses of teplizumab, administered intravenously (IV)
- To evaluate the pharmacokinetics (PK) and immunogenicity of two courses of IV teplizumab

The Exploratory Objectives of this study are:

- To assess β cell function and T1D-focused clinical parameters
- To evaluate immunologic, endocrinologic, molecular, and genetic markers

2.3. Study Endpoints

The Primary Endpoint of this study is:

- The area under the time-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function, at Week 78.

The Secondary Endpoints of this study are as follows:

A. Key Clinical Endpoints:

- Exogenous insulin use: defined as a daily average in units per kilogram per day (U/kg/day), at Week 78
- HbA1c levels: expressed in % and mmol/mol, at Week 78
- TIR: expressed as a daily average of the percentage of time in a 24 hour-day a participant's BG is >70 but ≤180 mg/dL (>3.9 to ≤10.0 mmol/L) assessed using continuous glucose monitoring (CGM), at Week 78
- Clinically important hypoglycemic episodes: defined as the total number of episodes of a BG reading of <54 mg/dL (3.0 mmol/L) and/or episodes of severe cognitive impairment requiring external assistance for recovery, from randomization through Week 78

B. Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
- Incidence of treatment-emergent infections of special interest, including but not limited to tuberculosis, an infection requiring IV antimicrobial treatment or hospitalization, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection, or significant viremia (ie, DNA-based polymerase chain reaction viral load >10,000 copies per mL or 10^6 cells), and herpes zoster
- Incidence and severity of immediate or delayed study drug infusion-related reactions, such as hypersensitivity reactions, pain requiring interruption or discontinuation of infusions, cytokine release syndrome, and serum sickness

C. Pharmacokinetic and Immunogenicity Endpoints:

- Teplizumab serum concentrations
- Incidence and titers of anti-teplizumab antibodies after treatment courses

The Exploratory Endpoints of this study are as follows:

A. Assessments of β cell function and health throughout the study:

- 4h MMTT C-peptide AUC
- Participants with the recognized clinically significant stimulated peak C-peptide of ≥0.2 pmol/mL during 4h and 2-hour (2h) MMTTs
- Proinsulin-to-C-peptide ratios, a measure of β cell endoplasmic reticulum stress and dysfunction

B. T1D-focused Clinical Endpoints during the study unless otherwise noted:

- Exogenous insulin use (in U/kg/day)
- HbA1c levels
- Participants with poor glycemic control, defined as HbA1c of ≥9%

- The number of participants who do not require exogenous insulin because they are able to achieve local, regional, or national age-based glycemic management goals for HbA1c and/or routine blood glucose levels
- Evaluations of glycemic control based on BG values obtained from intermittent (ie, spot-check, fingerstick) glucometer readings
- Evaluations of glycemic control based on BG values obtained from CGM readings, including but not limited to TIR; time in hyperglycemia and hypoglycemic ranges; daily, daytime, and nighttime average BG levels and estimated HbA1c; glycemic variability
- Clinically important hypoglycemic episodes from randomization through Week 39 and from Week 39 through Week 78.
- Incidence of "typical" hypoglycemia, defined as BG levels ≥54 mg/dL (3.0 mmol/L) but <70 mg/dL (3.9 mmol/L) and/or non-severe clinical episodes
- Incidence of DKA requiring medical attention, defined as a hyperglycemic episode with serum or urine ketones elevated beyond upper limit of normal (ULN) along with serum bicarbonate <15 mmol/L or blood pH <7.3, or both, and resulting in outpatient, emergency room visit or hospitalization
- Patient-reported outcomes measured by instruments, such as Quality of Life Inventory™ (PedsQL) Diabetes Module, the Hypoglycemia Fear Scale (HFS), and the Diabetes Treatment Satisfaction Questionnaire (DTSQ)
- Impact on family life, measured by the parent-reported PedsQL Family Impact questionnaire

C. Composite Clinical Endpoints:

- Participants with both HbA1c in the American Diabetic Association (ADA) target range (ie, <7.5%) and exogenous insulin dose in specific ranges (<0.25, 0.25 to <0.50, 0.50 to <0.75, 0.75 to <1.0, 1.0 to <1.25, and ≥1.25 U/k/d)
- Participants with both HbA1c of <6.5% and <7.0% and exogenous insulin dose of <0.5 U/kg/day or 0.25 U/kg/day

D. Immunologic and Endocrinologic Endpoints during the study:

- Phenotypic and functional characterizations of WBC populations, including T cells, B cells, and natural killer (NK) cells
- Serum proinflammatory and regulatory cytokine profiles and other immune mediators
- Number, type, and titer of T1D autoantibodies
- Antibody subclass levels
- Evidence of recent infection with CVB
- Levels of circulating hormones (eg, glucagon, incretins, adiponectin) and other factors (eg, lipokines, cholesterol, triglycerides) associated with the course of T1D pathophysiology

E. Molecular and Genetic Endpoints during the study:

- Circulating methylated- and unmethylated-insulin DNA levels as assessments of β cell stress and damage
- Gene expression and transcriptome analyses
- Association of human leukocyte antigen (HLA) type with clinical, metabolic and immune assessments

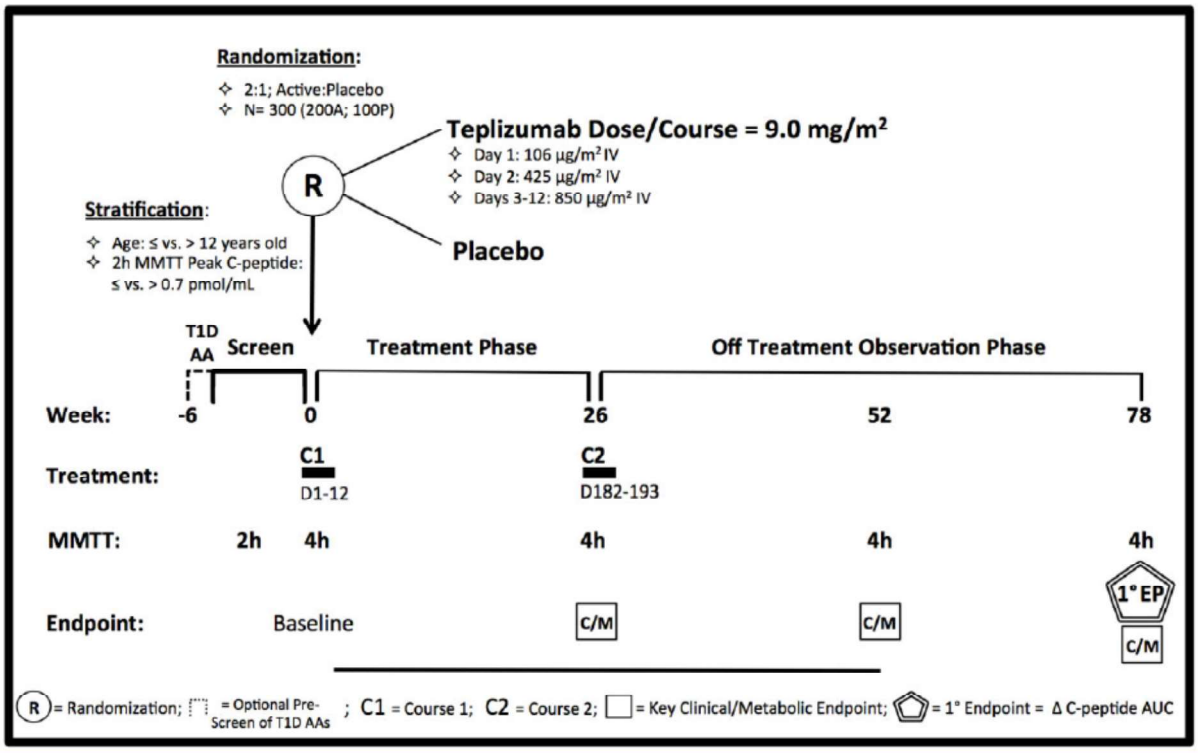
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter study. Approximately 300 participants will be enrolled and randomly assigned at a ratio of 2:1 to either the teplizumab group (N=200) or the placebo group (N=100).

A diagram of the study design is provided in Figure 1.

Figure 1. Schematic Overview of the Study



This study will enroll participants 8 through 17 years old who have been recently diagnosed with T1D. As described above (in Section 1.3) recent data indicate that the T1D immunopathogenesis, disease progression and even response to immune therapies varies based on age. Data from a number of previous studies of teplizumab support that the pediatric population (ie, those 8-17 years old) with T1D have a greater response to teplizumab than adults. There is recent recognition from diabetes experts and health authorities that it is reasonable, if not necessary, to conduct studies of interventional strategies for T1D in the appropriate age strata to determine efficacy in specific

populations, as long as there is a known and acceptable safety profile (Wherrett 2015, Greenbaum 2012, Rigby 2014). There are no exclusions based on gender, sex, ethnicity or race.

In addition, the study will focus on individuals who have a significant amount of β cell functional capacity. It is recognized that β cells continue to be lost following T1D diagnosis. To maximize the effect of β cell preservation in patients with a recoverable level endogenous insulin production, this study will recruit participants within 6 weeks from T1D diagnosis and a peak C-peptide level of ≥0.2 pmol/mL during a mixed meal tolerance test (MMTT). The value of 0.2 pmol/mL was chosen as it is a key and accepted threshold of C-peptide correlated with clinically important lower rates of T1D-associated short- and long-term complications (Lachin 2014, Palmer 2001, Palmer 2009). Analysis of previous clinical trials supports that individuals receiving teplizumab closer to the time of T1D diagnosis and those who have a higher, demonstrable levels of C-peptide have a more favorable response to teplizumab, in terms of maintenance of endogenous insulin production and clinically relevant benefits.

3.1.1. Screening and Participant Enrollment

The enrollment goal of this study is approximately 300 participants. Based on previous studies of teplizumab, the screen-failure rate is estimated to be ~33%, and it is anticipated that up to ~450 individuals may need to be screened for full enrollment.

3.1.2. Randomization and Stratification

Previous interventional studies in new-onset T1D (including earlier teplizumab clinical trials) suggest clinical and metabolic response may be influenced, at least in part, by age and β cell function near the time of diagnosis. The peak C-peptide stratification level was chosen based on data showing that 0.7 pmol/mL is a threshold indicating differential responsiveness to teplizumab (Hagopian 2013). The age stratification of 12 years was chosen as this is the mid-point of the age range of 8-17 years and an accepted threshold separating childhood from adolescence. Twelve years old has been used as a cut-off in T1D natural history studies and in the post hoc analyses of the Protégé study (Hagopian 2013, Greenbaum 2012).

Therefore, to minimize bias in treatment assignment, potential confounders, and enhance the validity of statistical analysis, participants will be randomized at a 2:1 ratio using randomly permuted blocks and stratification based on the following criteria:

- Peak C-peptide level at screening: within the range of 0.2 (inclusion criterion) to 0.7 pmol/mL (inclusive) versus >0.7 pmol/mL
- Age at randomization: within the range of 8 to 12 years (inclusive) versus >12 to 17 years

3.1.3. Study Treatment

Teplizumab or matching placebo will be administered via IV infusion in two courses, with the first course starting on Day 1 (Week 1) and the second course on approximately Day 182 (Week 26). Each course of treatment will include daily infusions for 12 days. See Section 6 for details.

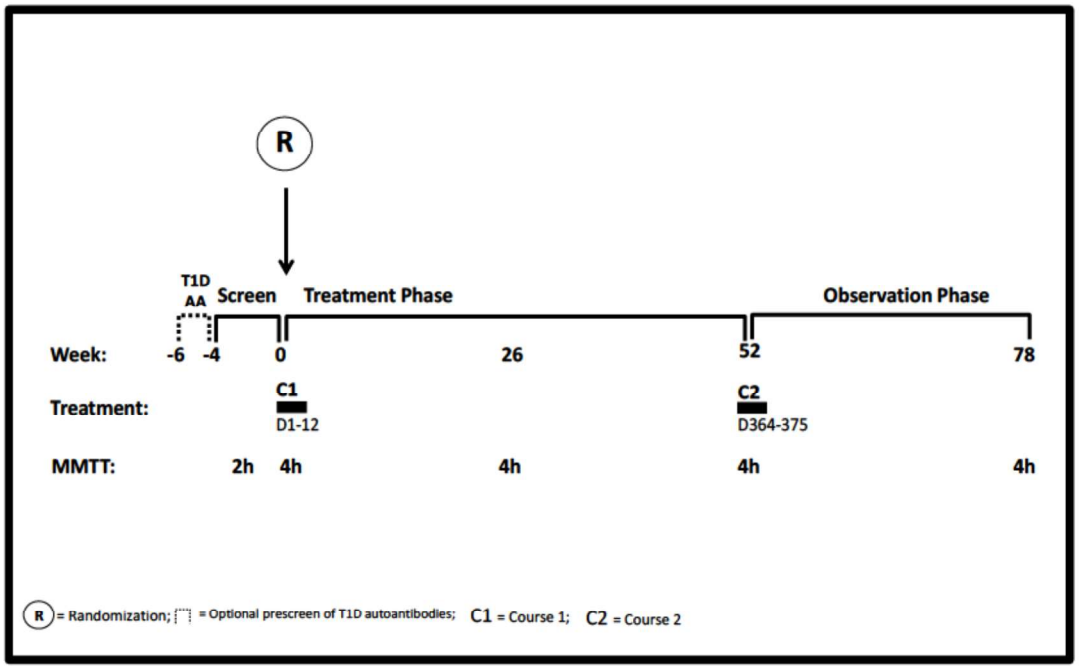
Modified dosing schedule for participants affected by COVID-19 pandemic restrictions:

To address COVID-19-imposed force majeure, those participants who are unable to receive the second treatment course approximately 6 months after randomization (scheduled for the Day 182 [Week 26] visit) due to COVID 19-related restrictions will initiate the second course at the Day 364 (Week 52) visit instead, approximately 12 months after randomization.

The modified dosing schedule is illustrated in Figure 2. These participants will undergo study procedures and assessments according to the Modified-Dosing Schedule of Events.

References throughout the protocol (version 3.0 onward) to Day 364 (or Week 52) as the start of the second course of treatment is only applicable to this group of participants.

Figure 2. Modified Dosing Schedule for Participants Affected by COVID-19 Pandemic Restrictions



Dose Justification

In previous clinical studies of teplizumab in T1D, a number of dosing regimens have been evaluated that have included children and/or adults. These studies have evaluated single multi-day courses of teplizumab and two multi-day courses either 6 or 12 months apart. Although the goals, stages of T1D, and entry criteria differed among these studies, all have shown that teplizumab was well tolerated with an acceptable safety profile and an ability to preserve β cell function and improve clinical outcomes in study populations or specific sub-populations. It is these effects that support further evaluation and clinical development of teplizumab as a first-in-class therapy for children and adolescents newly diagnosed with T1D (Herold 2002, Sherry 2011, Hagopian 2013, Herold 2005, Herold 2013).

The most extensive and detailed evaluation of teplizumab in T1D is from the Phase 2/3 "Protégé" study, in which two multi-day courses of teplizumab were given 6 months apart to children and adults 8 to 35 years old who were diagnosed with T1D within 12 weeks of T1D diagnosis. In that study, three dosing regimens of teplizumab were evaluated: (1) a 14-day course with a cumulative dose of 9.0 mg/m^2; (2) a 14-day course with a cumulative dose of 3.0 mg/m^2; and (3) a 6-day course with a cumulative dose of 2.4 mg/m^2. In the open-label Phase 2 segment of Protégé, participants received the 14-day regimen of 9.0 mg/m^2/course at enrollment and 26 weeks later to assess safety and tolerability before the double-blind study was started. The Phase 3 segment studied the three teplizumab dosing regimens in comparison to placebo. The open label Phase 2 segment of Protégé enrolled 38 participants, and the randomized, double-blind Phase 3 segment enrolled 207, 102, and 106 teplizumab-treated participants, respectively, and the placebo arm 98 participants (Sherry 2011, Hagopian 2013).

In addition to assessments of safety and efficacy, the Protégé study conducted extensive PK and immunogenicity evaluations. From this data, a detailed population PK model has been developed using a two-compartment (peripheral and central) model with saturable binding kinetics incorporating body surface area (BSA), proportional dosing, and teplizumab AUC, C_{min}, and C_{max}. These findings showed that PK was independent of age, gender, race, region, disease state or onset, although it was influenced by antidrug-antibody response.

As described earlier, although the previously untested and unevaluated composite primary endpoint was not met in the entire study population of Protégé, a positive effect of teplizumab in T1D was confirmed in Protégé subpopulations, supporting findings from a number of previous clinical studies. Specifically, participants from certain regions (eg, the United States) who were 8-17 years old, who had teplizumab initiated within 6 weeks of T1D diagnosis and with higher C-peptide levels at study entry showed significant retention of endogenous insulin production through 2 years compared to placebo treated participants.

Of note, the 14-day regimen evaluated in Protégé (and other previous studies) delivered 9.0 mg/m^2/course of teplizumab and was dosed in the following manner: Day 1: 51 µg/m^2, Day 2: 103 µg/m^2, Day 3: 207 µg/m^2, Day 4: 414 µg/m^2, and Days 5-14: 826 µg/m^2/day. In this regimen's 4-day ramp-up, approximately 8.6% of the total dose was given, with ~1.7% of the total dose in the first 2 days. In the last 10 days ~91% of the total dose was delivered in equally divided doses.

A 14-day course of treatment necessitates participants and their parents or guardians (required by pediatric participants) to be available every day for 2 entire consecutive weeks. This requirement is seen to be particularly challenging to children and adolescents and their families due to work and school obligations and therefore may have a negative influence on recruitment and retention as well as a significant bias in a pivotal study.

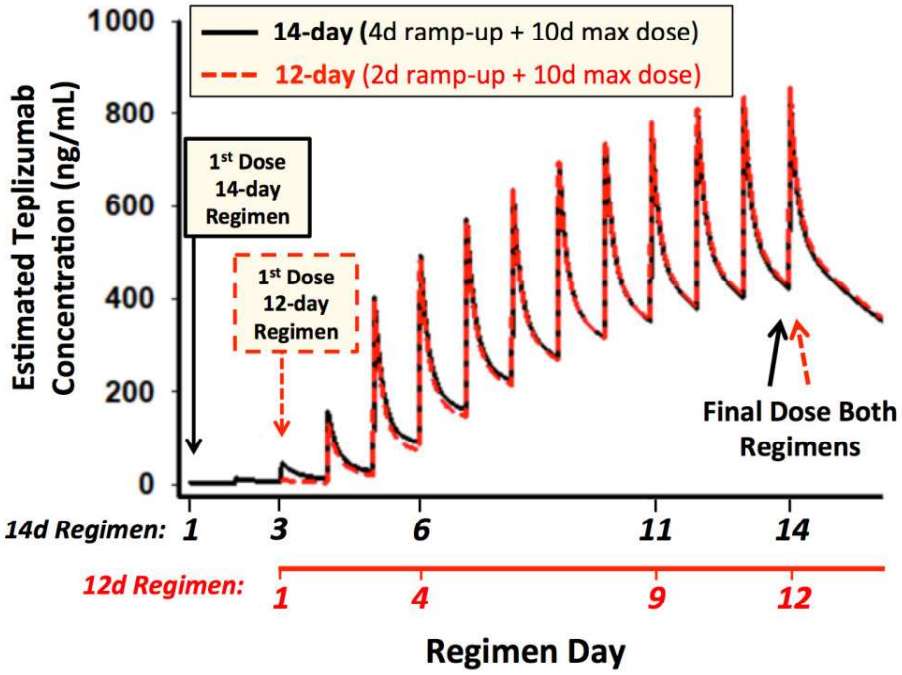
With the realization of the potential negative impact on many aspects of the clinical trial of a 14-day treatment course combined with the significant experience with teplizumab, this study sought to develop a more participant and family-friendly treatment regimen that delivered clinically overlapping exposures that could support approval for teplizumab.

In this study, participants will be randomized to placebo or teplizumab (9.0 mg/m^2/course) for two courses. Each course will be administered in a more convenient manner over 12 days: Day 1: 106 µg/m^2, Day 2: 425 µg/m^2, and Days 3-12: 850 µg/m^2/day. During the first 2 days of ramp-up, approximately 5.9% of the total dose is given. In the last 10 days, ~94% of the total dose is delivered in equally divided doses.

Compared to a 14-day dosing regimen, this study's 12-day teplizumab course has a modified 2-day ramp-up phase but also has a 10-day fixed-, maximal dosing period like the 14-day course. Based on calculations, the amount of teplizumab given in the 12- and 14-day approach only differs by 0.005 mg/m^2. But due to practical aspects of rounding and calculating the BSA and a given dose, these courses are considered clinically equivalent.

As shown in the PK simulations in Figure 3, the first 2 doses in the 14-day regimen are calculated to have very low, almost negligible, serum concentrations with serum concentrations of the last 11 doses of both regimens that are superimposable. In both instances, >90% of the total dose per course is given in the final 10 days in similar equally divided doses (0.850 mg/m^2 in the 12-day course versus 0.826 mg/m^2 in the 14-day course). The first 2 days of the 14-day course delivers a nominal amount (ie, <2.0%) of the course's total dose. The final trough concentrations (426±220 ng/mL [14-day regimen] and 435±225 ng/mL [12-day regimen]), as well as the elimination times are overlapping in both regimens.

Figure 3. PK Simulation of 12-Day and 14-Day Dosing Regimens



Taken together, this study will evaluate a more participant and family-friendly approach to deliver the same dose of 9.0 mg/m^2 of teplizumab given 6 months apart, which has been shown to be well tolerated, safe and effective in preserving β cell function. Because of the similarities and overlap

of the regimens and exposures, data from this study can be combined with data from other studies to support the application and approval for teplizumab as a disease modifying therapy for the study population in those recently diagnosed with T1D.

Rationale for Modified Dosing Schedule

As noted above, participants who are unable to receive the second course of study treatment as scheduled at Week 26 will receive the second treatment course at the Week 52 visit, approximately 12 months after the first course.

In a previous Phase 2, randomized, 2-arm open-label, multicenter study known as the AbATE study, a 12-month dosing interval for teplizumab was evaluated in 77 participants aged 8 to 30 years with recent-onset (<8 weeks) T1D. They were randomly assigned at a 2:1 ratio to receive teplizumab plus standard diabetes management versus standard diabetes management alone. Subjects in the teplizumab group received a 14-day course of teplizumab, which was repeated 12 months later. A course comprised daily doses of 51 $\mu g/m^2$, 103 $\mu g/m^2$, 207 $\mu g/m^2$, 413 $\mu g/m^2$ during the first 4 days, respectively, and 10 subsequent daily doses of 826 $\mu g/m^2$. The primary efficacy endpoint of the AbATE study was the change from baseline in mean C-peptide area under the curve (AUC) in the 4h MMTT at Month 24.

After accounting for baseline difference, comparisons of the mean change from baseline in C-peptide AUC in the 4h MMTT at Month 24 showed statistically significant difference in favor of teplizumab. The teplizumab group had a mean decline in C-peptide secretion of -0.28 (95% CI: -0.36, -0.20) nmol/L, which was smaller than that of the control group (-0.46 [95% CI: -0.57, -0.35] nmol/L) (p=0.002). The most common AEs were rash, transient upper respiratory infections, headaches, and nausea. Study drug-related AEs were transient and resolved.

The results from the AbATE study indicate that increasing the interval between the 2 treatment courses from 6 months to 12 months does not increase the safety risk, while still conferring potential effects of teplizumab, in participants who are unable to adhere to the planned treatment schedule.

3.1.4. Study Duration

The total study duration for each participant will be up to 84 weeks. This includes a screening period of up to 6 weeks and a post-randomization period of 78 weeks. The post-randomization period includes two 12-day treatment courses separated by 6 months and a post-treatment observation period of approximately 52 weeks. The final visit will take place at Week 78.

For participants under the modified dosing schedule, the treatment courses are separated by an interval of approximately 12 months, and the post-treatment observation period is approximately 26 weeks. The final visit will also take place at Week 78.

The overall study length and timepoints for key assessments were chosen due to the natural course of remaining β cell loss following the diagnosis of T1D and study goals to demonstrate durability of effect and to confirm post-treatment safety profiles of teplizumab. At the time of diagnosis

there can be substantial β cell reserves, often estimated at 10-20% but in some cases over 40% of normal β cell mass (Matveyenko 2008, Campbell-Thompson 2016). At T1D diagnosis, the majority of this reserve appears to be functionally impaired due to metabolic or immunologic (ie, cytokine induced) stress. With exogenous insulin treatment and correction of pH, electrolyte and fluid disturbances (ie, DKA) that are often present at diagnosis, some β cell function may return for days, weeks or many months. This observation is often referred to as the "Honeymoon period" where insulin requirements can be substantially reduced and at times independence from exogenous insulin can be achieved. These effects are transient and over time, usually within a year from diagnosis, inevitably full insulin replacement is required due to autoimmune elimination of these remaining β cells. Due to the known individual variability in the natural history of β cell loss, the effect of disease modifying therapies intended to preserve β cell function is difficult to distinguish from the Honeymoon period effects during the first 12 months of T1D diagnosis.

The 18-month time point for the primary and key secondary clinical endpoints will provide key data needed for the acceptance of teplizumab as a T1D disease modifying therapy into regular medical practice and is consistent with existing guidelines for endpoints recommended by the EMA and FDA. Data from T1D natural history studies and interventional trials show that β cell loss in those with T1D can be quite variable, especially within the weeks to months following diagnosis. As this study is enrolling participants in close proximity to T1D diagnosis (ie within 6 weeks) who are younger, there may be the added complexity of the consideration of the Honeymoon phenomenon (or spontaneous, transient partial remission) - that may last up to ~1 year in the study population (Abdul-Rasoul 2006). The 18-month timing of the primary and key secondary clinical endpoints allows for a substantial amount of the inherent, natural metabolic variability due to different trajectories of β cell loss and/or transiently enhanced β cell function due to the Honeymoon phenomenon to be minimized - so that the true effect on teplizumab on β cell function and clinical parameters can be differentiated from chance.

Other key assessments will be done at randomization, Week 26 (6 months) and Week 52 (12 months) to better understand the natural history of β cell decline and the effect of teplizumab in this specific study population.

In addition, the primary and key clinical endpoints will be assessed approximately 1 year after the last dose of study drug administration (except participants who receive the modified dosing schedule). The length of effect is recognized as an important property of an intermittent disease modifying therapy for T1D. A 12-month off-therapy period whilst maintaining positive metabolic and clinical effects can, at this time, be considered a reasonable time frame to substantiate an assertion of a metabolically and clinically relevant durable benefit.

Lastly, combined with the substantial body of data from previous clinical trials of teplizumab for T1D over the past 15-20 years, an 18-month trial provides additional critical data for and verification of the tolerability and safety of teplizumab. Throughout this study, participants will be assessed regularly via in-person and remote interviews, physical exams, self-reports, and laboratory examinations. Assessments occur daily during the two 12-day treatment courses and regularly between the courses and the post-treatment follow-up period. The on- and off-therapy observation times in this study are well within, if not significantly beyond, the periods traditionally

used to assess for safety and side effects for immune therapies approved for other autoimmune conditions, including those for pediatric indications. In doses and regimens similar to that being used in this study, teplizumab has overall been well tolerated with minimal side effects and no signals of significant short- or long-term adverse effects. It is anticipated that with additional, confirmatory data from this study, the side-effect profile of teplizumab will continue to be considered acceptable for its integration into care plans for children and adolescents newly diagnosed with T1D.

3.1.5. Data Monitoring Committee and Data Reviews

An external, independent Data Monitoring Committee (DMC) consisting of individuals with medical, scientific and biostatistical expertise will be commissioned for this study to provide oversight on safety and efficacy data and the conduct of the study. The DMC will make recommendations regarding the continuation, termination, or modification of the study. Refer to Section 11.11 for details.

The DMC will monitor the progress of the study throughout its execution at scheduled intervals or as requested. The DMC will review safety and efficacy data as well as study conduct, and make recommendations regarding continuation, termination, or modification of the study. The DMC will review tabulated safety summaries and efficacy data (ie, C-peptide, glycemic control and insulin use) in an unblinded fashion and may request additional blinded or unblinded data to assure safe and proper conduct of the study.

The DMC will be notified ad hoc of specific events, such as significant or unexpected events related to participant safety, when a study agent discontinuation criterion is met, unblinding has occurred, or any issue considered significant during a regular data review by the study's Medical Monitor or designee. A formal review can be prompted by these notifications if deemed warranted by the DMC.

An organizational DMC meeting will take place prior to the start of study site initiation and scheduled data review meetings will occur approximately every 4 months following randomization of the first participant through the second course of teplizumab of the final study participant. At that point scheduled DMC meetings will take place approximately every 6 months until the last randomized participant completes their final study visit. Meeting schedules may be modified by the DMC as requested. Other intermittent scheduled meetings may take place at the request of the DMC, the Sponsor, and/or health authorities.

The specific DMC responsibilities, authorities, and procedures will be documented in its charter.

3.1.6. Study Oversight

One major objective of this study is to assess the safety and tolerability of teplizumab in children and adolescents with recent-onset T1D. The Sponsor recognizes that the study population, specifically children 8-17 years old recently diagnosed with T1D, is a vulnerable population at very high risk for disease- and therapy-related short- and long-term morbidity and mortality. There is no disease modifying therapy for T1D and the only therapeutic class of therapies approved for T1D was discovered almost a century ago. Therefore, the Sponsor has incorporated rigorous

criteria and processes directed towards the best interest for the safety of study participants. This study will be regularly monitored, and data will be reviewed by the DMC, which will ensure the safe and appropriate conduct of this study and make decisions on the continuation, interruption, or termination of the study.

This study has detailed criteria for interruption and/or discontinuation of study treatment and participant withdrawal, which will automatically trigger cessation of study drug dosing and in-depth investigation in individual participants and the study in general (Section 10.2).

3.2. Discussion of Study Design

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical, safety, metabolic and exploratory endpoints that may occur in the absence of active treatment. Randomization with stratification will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of all study endpoints.

4. STUDY POPULATION

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the Investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Participant is male or female.

2. Participant is 8 to 17 years of age, inclusive, at the time of randomization/initiation of study drug administration.

3. Participant has received a diagnosis of T1D according to ADA criteria (Appendix 1)

4. Participant is able to be randomized and initiate study drug within 6 weeks (42 days) of the formal T1D diagnosis according to the ADA criteria.

5. Participant has a peak stimulated C-peptide of ≥0.2 pmol/mL from a 2-hour mixed meal tolerance test (2h MMTT) at screening. (Note: This screening 2h MMTT must occur only after 6 days following diagnosis to allow for reduction of metabolic instability.)

6. Participant has a positive result on testing for at least one of the following T1D-related autoantibodies before randomization:

    - Glutamic acid decarboxylase 65 (GAD65) autoantibodies
    - Islet antigen 2 (IA-2) autoantibodies
    - Zinc transporter 8 (ZnT8) autoantibodies
    - Islet cell cytoplasmic autoantibodies (ICA) or
    - Insulin autoantibodies (if testing obtained within the first 14 days of insulin treatment)

7. Female participants of childbearing potential must have a negative result on highly sensitive serum (β human chorionic gonadotropin [β-HCG]) at screening.

8. Participants who have reached puberty must agree to adhere to the following contraceptive requirements. (Note: In countries with legislation for the age of sexual activity, the participant must comply with the local age limit regarding the use of contraception.)

    - Females with childbearing potential (defined as premenopausal females who are capable of becoming pregnant, ie, having reached menarche or having reached Tanner stage 3 breast development even without menarche) or who gain childbearing potential during the study must practice abstinence or use 2 forms of contraception (including oral, transdermal, injectable, or implanted contraceptives, intrauterine device, female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner, or a sterile sexual partner) continuously from 30 days before the first dose of study drug through the end of the study.

    - Males who have reached puberty (ie, spermatogenesis) with partners of childbearing potential must use barrier contraception in addition to having their partners use another method of contraception from 1 week before each study agent dose through 120 days (a complete spermatogenesis cycle) after receiving the last dose in each treatment course.

9. Prior to receiving study drug, participant must be up to date with and/or agree to receive routine age-appropriate immunizations and comply with the guidelines for immunosuppressed individuals and those with chronic disease (diabetes mellitus) according to current local, regional and/or country-specific guidelines.

10. Participant agrees not to receive other forms of experimental treatment during the study, particularly agents that may be immune modulatory in nature and/or stimulate pancreatic β cell regeneration or insulin secretion

11. Participant and/or appropriate legal guardian must sign an informed consent form (ICF) and/or assent according to local, regional and/or country-specific guidance for study participation.

4.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Participant has known allergies, severe reaction, intolerance, hypersensitivity, or anaphylaxis to human, humanized, or murine monoclonal antibodies, teplizumab or any of its components or its excipients.

2. Participant has been an active participant in a therapeutic drug, invasive medical device, or vaccine clinical trial within 12 weeks before the first dose of study drug or has received an investigational treatment with the potential for T1D disease modification.

3. Participant has significant renal, cardiac, vascular, pulmonary, gastrointestinal, neurologic, hematologic, rheumatologic, oncologic, psychiatric disease, or immune deficiency.

4. Participant has any autoimmune disease other than T1D (eg, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis, systemic lupus erythematous), with the exception of clinically stable thyroid or celiac disease.

5. Participant has an active infection (including a positive SARS-CoV-2 test) and/or fever ≥38.5°C (101.3°F) within the 48 hours prior to randomization, is prone to infections, or has chronic, recurrent or opportunistic infectious disease, including but not limited to renal, respiratory or skin infections, *Pneumocystis carinii*, aspergillosis, latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis.

6. Participant has a history of or serologic evidence at screening of current or past infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).

7. Participant has any of the following in regards to tuberculosis (TB):

    - A history of latent or active TB

    - Signs and/or symptoms of TB

    - Recent close contact with a person with known or suspected active TB, unless appropriate isoniazid prophylaxis for tuberculosis was given

    - A history of a chest X-ray consistent with active TB or old, inactive TB,

- A history of a positive purified protein derivative skin test result (>10 mm induration); or

- At screening is positive or repeatedly indeterminate with an approved interferon-gamma release assay (IGRA; eg, QuantiFERON-TB test)

- If required by local, regional or national regulations, a recent (within 3 months) chest X-ray or one conducted at screening read by a qualified radiologist consistent with current, active TB or old, inactive TB

8. At screening, participant has a clinically active infection with EBV, including but not limited to infectious mononucleosis, or an EBV viral load ≥10,000 copies per mL or per 10^6 lymphocytes obtained at study screening (Rosenzweig 2010).

9. At screening, participant has a clinically active infection with CMV or a CMV viral load 10,000 copies per mL or per 10^6 lymphocytes (Verkryse 2006).

10. Participant has a diagnosis of significant liver disease or at screening alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2X or total bilirubin (TBili) of >1.5X of the age- and sex-specific upper limit of normal (ULN) according to the central laboratory. (Note: Participants with Gilbert's syndrome may be allowed to enroll upon approval by the Medical Monitor.)

11. An individual has any of the following hematologic parameters, confirmed by repeat tests, within 10 days before randomization/first dose of study drug:

    - Lymphocyte count: <1000/µL

    - Neutrophil count: <1000/µL

    - Platelet count: <100,000 platelets/µL

    - Hemoglobin: <10 g/dL

    Note: specific hematologic, oncologic or other systemic conditions that might otherwise result in exclusion and/or is heretofore unrecognized should be considered in individuals who have one or more blood cell counts below or above the normal ranges

12. Current or prior (within 30 days before screening) treatment that is known to cause a significant, ongoing change in the course of T1D or immunologic status, including high-dose inhaled, extensive topical, or systemic glucocorticoids. (Note: Short courses, ie, approximately 2 weeks or less, of corticosteroids for transient conditions are allowed.)

13. Current or prior (within 30 days before screening) use of drugs other than insulin to treat hyperglycemia (eg, metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, dipeptidyl peptidase-4 [DPP-IV] inhibitors, or amylin).

14. Current or prior (within 30 days before screening) use of any medication known to significantly influence glucose tolerance (eg, atypical antipsychotics, diphenylhydantoin, niacin).

15. Current or planned highly restrictive dietary regimen(s) intended for T1D management, such as very-low or ultra-low carbohydrate diets.

16. Recent or planned vaccinations as follows:

    - Live vaccines (eg, varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, and smallpox): Within the 8 weeks before randomization and initiation of study drug or planned/required administration through Week 52 or Week 78 (if Modified-Dosing Schedule is followed) of the study.

    - Non-infectious (eg, recombinant, inactivated or otherwise "non-live") vaccines: Within 2 weeks before through 6 weeks after each dosing course.

17. A female who is pregnant, has a positive β-HCG blood test at screening or a positive urine β-HCG test prior to initiation of study drug, wishes to become pregnant, is planning on donating eggs (ova, oocytes), and/or is lactating with the intent to provide her own breast milk to a baby during the entire study.

18. A male who is planning to father a child or donate sperm from 1 week before each study agent dose through 120 days (a complete spermatogenesis cycle) after receiving the last dose in each treatment course.

19. An individual who has a history of alcohol, drug, or chemical abuse within 12 months prior to study screening.

20. An individual who has a medical, psychological or social condition that, in the opinion of the Principal Investigator, would interfere with safe and proper completion of the trial.

21. An individual who is an employee of the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, as well as family members of the employees or the Investigator.

Although there is **not** a specific exclusion based on weight, due to country, regional and/or local difference in blood draw limits for participants in a research study there may be weight-based criteria for participation depending on the location of the participant. Investigators are to confirm that potential participants meet any specific weight-based criteria due to any of these location-specific blood volume limitations.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Treatment Allocation

Procedures for Randomization and Stratification

Participants will be randomly assigned to 1 of 2 treatment groups in a 2:1 ratio for participants in the teplizumab group and the placebo group, respectively. The randomization will be balanced by using randomly permuted blocks and will be stratified by peak C-peptide level at screening (0.2 to 0.7 pmol/mL inclusive, versus >0.7 pmol/mL) and age at randomization (8 to 12 years inclusive, versus >12 to 17 years). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant details to uniquely identify the participant.

5.2. Blinding

This is a double-blind study. Blinding will be maintained for all study participants throughout the study. In addition, all personnel at the sites, the Contract Research Organization, third-party laboratory vendors, and the Sponsor (Provention Bio, Inc.) will be blinded to the treatment assignment through the completion of the study. The Sponsor's Quality Assurance, Regulatory Affairs, Product Safety, Clinical Supplies, and Clinical Laboratory representatives or designee are excepted.

Teplizumab and placebo will be supplied to the sites in vials and kits that appear identical. Each kit will have a unique number printed on all labels, including the outer carton label and the label of each vial inside the kit. Detailed instructions for handling the blinded study drug kits will be provided in the Pharmacy Manual.

Teplizumab may cause transient reductions in WBC (including lymphocytes and neutrophils). Central laboratory results for WBC total and differential counts and platelet counts, as well as TBNK panel, will be reported to study sites in a blinded fashion (Section 10.2). If, at any time, the Investigator has any concern about the health or safety of a participant and request the participant's current or previous WBC or platelet count from the central laboratory, they will be provided with the unblinded laboratory results.

During the study treatment courses (except the last day of dosing), WBC and differential and platelet counts are measured by local laboratories at the study site and reviewed by the Investigator

prior to dosing; these results are not blinded. If a result meets a stopping rule, the Investigator should contact the Medical Monitor and conduct appropriate clinical and laboratory follow-up.

The treatment designation codes will be available to members of the DMC, the supporting independent statistician, the vendor for study product labeling, packaging and distribution, the Interactive Web Response System (IWRS) vendor, select individuals at Provention Bio, Inc. and other study associated personnel as indicated above.

5.3. Emergency Unblinding

Emergency unblinding is rarely required for medical reasons. If the Investigator believes that unblinding is necessary for a participant's safety, the Investigator may access the study assignment for the participant. Two methods are available for emergency unblinding. The Investigator may unblind via IWRS independently. If the Investigator is unable to access the IWRS for any reason to perform the unblinding, an emergency unblinding telephone number is also available.

6. DOSAGE AND ADMINISTRATION

On the day of randomization (Day 1), each participant will receive the first dose of the study drug in the first 12-day treatment course, as shown in the table below. On approximately Day 182, each participant will receive the first dose of the second 12-day course. The study drugs (teplizumab or placebo) will be administered via IV infusion at the study site or other qualified facility by study-approved personnel. The doses of study drug will be calculated based on the participant's BSA measured on the first day of each treatment course. No dose adjustment is permitted.

Modified Dosing Schedule

Participants who are unable to receive the second 12-day course due to COVID-19 pandemic restrictions will be given the second course on approximately Day 364 (Week 52 visit). See Section 3.1.3.

The study drug infusion on each treatment day should be administered within 20 to 28 hours after the previous dose. For example, if the dose on Day 1 is given at noon, the dose on Day 2 should be given within the interval of 8 am and 4 pm.

Description of Interventions

Treatment name	**Teplizumab**	**Placebo**
Description	Sterile solution for injection	Sterile solution for injection
Doses in each course	Day 1: 106 µg/m^2 Day 2: 425 µg/m^2 Days 3-12: 850 µg/m^2 Total per course: 9.0 mg/m^2	Matching volumes to active drug
Frequency	Two courses at Week 1 and Week 26 or Week 52	Two courses at Week 1 and Week 26 or Week 52
Delivery method	IV infusion	IV infusion

6.1. Study Drug Preparation

At the beginning of each 12-day course of study drug administration, the participant's current BSA will be calculated using the Mosteller formula, BSA=square root [height (cm) x weight (kg) / 3600], using the height and weight obtained on that day.

Teplizumab and placebo will be prepared according to the Pharmacy Manual provided to the site. The study drug will be prepared by qualified site personnel and administered by qualified site staff to the participant.

Two (2) mL of study drug should be drawn from the study drug vial and slowly diluted in 18 mL of 0.9% sodium chloride solution for injection by gentle mixing. The resulting 20 mL of 1:10 dilution will be used as the initial study drug solution, which contains either placebo or teplizumab at a concentration of 100 µg/mL. This initial drug solution should then be added to 25 mL 0.9% sodium chloride solution. Finally, this resulting preparation should be gently mixed before administration to the participant.

6.2. Vascular Access and Intermediate-Use Intravenous Catheters

This study requires two courses of intravenous infusions and blood draws over 12 days. It is recognized that intravenous access (for infusions and blood draws for laboratory sampling) in the pediatric population that is the focus of this study may pose a challenge. Children have smaller veins than adults, veins that may be more challenging to insert catheters and they may have a significant resistance to catheter placement and/or phlebotomy.

In recognition of the above, in addition to the use of "traditional" intravenous peripheral catheters, this study will permit the use of temporary, intermediate term approaches for vascular access. Specifically, "midlines" or peripherally inserted central catheter (PICC) lines may be used for study drug infusions and blood draws (if appropriate according to the properties of the access line and local, regional or national guidance).

A midline is longer than a regular IV and usually put into a vein in the arm but can be inserted into a leg or other vein. Midlines can be used for vascular access for up to approximately one month. A PICC line is most often inserted into a larger vein in the upper extremity (but can be inserted into other areas) and most typically end in a larger vein – often in or near the heart. A PICC line can often be used for vascular access for more than a month.

Mid- or PICC-lines will require specific informed consent, which would document risks, benefits and language according to local, regional or national practice. Risks of these catheters often include pain or irritation, bleeding, and/or a specific risk of infection. These and other risks must be weighed against the potential need for multiple traditional IV catheter insertions and/or need for regular intermittent phlebotomy.

Both types of vascular access require specific approaches for insertion (ie, sterile conditions) care and maintenance that may include, but not be limited to, specific approaches to regular cleaning,

dressing and flushing. As with most intravenous catheters (both peripheral and central) these catheters may experience access disruptions (eg, infusion administration and/or blood drawing) due to presumptive blood "clot". Often there are approved approaches to "clear the line" and regain functionality.

Not all sites are anticipated to have the ability to offer all approaches to vascular access. If a participant has a choice of vascular access and is a good candidate, all options should be presented by the Investigator. A site-specific informed consent will be completed as needed per local, regional or national requirements for the participant's choice of catheter. Any AEs related to any IV catheter (whether traditional IV, midline or PICC line) need to be appropriately identified, documented and reported by the study site Investigator.

6.3. Premedication and Study Drug Infusion

Study participants will receive oral premedication consisting of an NSAID drug (tablet or liquid) and a locally approved antihistamine (tablet or liquid), according to local availability and practice standard, for at least the first 5 days of each study drug course and can receive one or both of these for the rest of the study drug doses if the Investigator judges it to be appropriate for the tolerability of infusions. The premedication should be given at least 30 minutes prior to initiation of the study drug infusion. If an NSAID is contraindicated, oral acetaminophen (tablet or liquid) may be given.

Study drug (teplizumab or placebo) will be prepared and supplied by designated personnel or pharmacist equivalent according to the Pharmacy Manual.

Assure that the vascular access is patent (see Section 6.2). The Pharmacy Manual should be followed to ensure that the IV drug delivery devices used are made of materials compatible with the study drug.

Teplizumab for intravenous administration may only be prepared with 0.9% sodium chloride. No solutions other than 0.9% sodium chloride may be running through the same intravenous line when teplizumab is being administered. If the same intravenous line must be used for infusion of other drugs or solutions, the line should be flushed with 0.9% sodium chloride solution before and after infusion of teplizumab.

Study drug will be administered IV over a minimum of 30 minutes according to standard practices.

When the infusion solution has been completely administered, infuse an additional volume of saline equal to the volume contained in the infusion tubing at the same constant rate to ensure that all study drug has been cleared from the infusion tubing. The starting and ending times for the infusion must be recorded.

During the infusions and for an additional 60 minutes following the infusions, participants are to have vital signs (ie, BP, RR, and HR) assessed every 15 min and be monitored for signs or symptoms of infusion reactions. These include but are not limited to fever, chills, headache, nausea, vomiting, infusion-site pain, anaphylaxis, wheezing, dyspnea, urticaria, and hypotension. If there are signs or symptoms of infusion reaction in a participant during the 60-minute post-

infusion observation period, the participant should be observed for an additional 60 minutes or until the reaction resolves, whichever is longer.

6.4. Location of Infusion

Infusions will be administered at a location consistent with adequate safety oversight and monitoring, to be determined by each site Investigator in accordance with any applicable local, regional, or country-specific regulations. The location could be in a hospital, ambulatory clinic, infusion center, or other similar facility.

In addition to those facilities, if considered appropriate and consistent with local, regional and/or national regulations, study drug administration for the 5th through the 11th dose in each treatment course may occur at a site more convenient for the study participant. This shall only occur if (a) the site Investigator has documented that the dosing and procedures conducted on the first 4 infusions in a course have been well tolerated and without consequence; (b) approved by the site Investigator and the participant and/or their parent/guardian and (c) that there is a documented level of monitoring, oversight and access to emergency precautions as there would be at the site. In the event where it is opted to conduct such study visits out of the research clinic, the participant can, at any time, return to the study clinic for upcoming visits. The visit for the final (12th) infusion in each treatment course must take place at the study site.

6.5. Emergency Precautions

Before every infusion of study drug, appropriate emergency equipment and trained personnel should be present. At a minimum, the following will be available:

- Epinephrine for IM or IV injection
- Dexamethasone (or equivalent glucocorticoid) for IV injection
- Antihistamine for oral administration or IV injection
- Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction
- Resuscitation doses of all drugs according to local, regional, or national recommendations

If AEs develop during infusion, the infusion may be slowed or interrupted, as determined by the Investigator. If interrupted, the infusion may be restarted, preferably at a slower rate, if deemed reasonable by the Investigator. Any changes in the infusion rate must be recorded with the reason for the change. In any cases of AEs determined or suspected to be related to the infusion of the study drug, the participant should be treated using appropriate medical practices and procedures.

During or after the infusion of study drug, if a participant experiences any of the following signs, the participant will be observed, and the severity of the reaction will be evaluated:

- Fever of >38.5°C (101.3°F)
- Rigors or myalgias
- Pain, swelling, or edema near the infusion site

- Local or systemic rash
- Mucosal congestion or edema
- Significant (eg, 30%) drop in systolic or diastolic blood pressure or increase in resting heart rate
- Hyperventilation, wheezing or difficulty breathing
- Change in mental status

Acetaminophen (or similar drug) and/or additional NSAID may be given if needed, and considerations made for glucocorticoid therapy. The participant should be treated using appropriate medical practices and procedures. The participant will be continuously monitored until their clinical status returns to baseline or is significantly improved.

If an infusion is discontinued, an estimate on the amount of the infusion given and a quantitative assessment of the remaining volume should be documented.

The Medical Monitor should be notified of all cases of actual or suspected infusion reactions and AEs thought to be related to the study drug infusion.

If cytokine release syndrome is suspected, see Section 9.7.3 for guidance.

6.6. Deviations from Study Drug Administration Schedule

The Medical Monitor must be notified immediately if any study drug infusion is delayed beyond the permitted interval or is missed for any reason. Administration of study drug should be permanently discontinued for a participant if any of the criteria in Section 10.2 are met. If more than 2 consecutive doses are missed, the Medical Monitor must be consulted if the remaining doses of study drug administration should be administered (Section 10.2).

Study drug administration for a participant may also be discontinued or interrupted for mild or moderate acute illness or an abnormal laboratory result that, in the opinion of the participant and/or guardian or Investigator, raises safety concerns. If the illness does not resolve, the Medical Monitor must be notified. Study drug administration may be restarted as detailed in Section 10.2.

7. TREATMENT COMPLIANCE

The study drug (teplizumab or placebo) will be administered as IV infusions by qualified study-site personnel. The details of each administration will be recorded in the CRF (including date, start and stop times of the IV infusion, and whether full dose is administered).

8. CONCOMITANT THERAPY

8.1. Documentation of Concomitant Therapy

Concomitant therapies must be recorded throughout the study, beginning at screening through Week 78.

Concomitant therapies should also be recorded beyond Week 78 only in conjunction with ongoing SAEs.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Recorded information will include a description of the name and type of the drug, the time of use, the amount of drug used, the route of administration, and the indication.

8.2. Diabetes Management and Insulin Use

All enrolled participants, with assistance of their health-care providers, should receive intensive diabetes management of their T1D using approved therapies according to the recommendations of American Diabetes Association (ADA) or local, regional, or national recommendations to achieve glucose levels that appear to decrease some of the short-term and long-term sequelae of T1D. Currently the glycemic targets by the ADA are focused at management strategies to achieve a HbA1c level of <7.5% (58 mmol/mol) for individuals 17 years old and younger, and <7.0% (53 mmol/mol) 18 years and older while minimizing severe or frequent hypoglycemic events. If there are local, regional, or national recommendations to be followed that supersede ADA recommendations, these glycemic control targets (ie, HbA1cs or glucose levels) should not be more liberal (ie, higher) than the ADA recommendations. The Investigator will document in the CRF the glycemic goals.

The glycemic goal should be attempted through proper glycemic monitoring, administration of exogenous insulin, and monitoring of activity level and diet. Exogenous insulin may include rapid, intermediate, and/or long-acting insulins, administered intermittently or via the use of a personal insulin pump. Blood glucose levels should be measured at least 4 times a day, including before meals and before bedtime. Approaches to achieve these HbA1c goals will be the responsibility of the participant, their caregivers, and their healthcare providers.

Insulin use, including the type of products, dosages, and dosing schedules, is expected to change during the course of the study. As part of routine T1D clinical care, if the caring physician judges it to be clinically appropriate, a participant's insulin dose may be increased, reduced, or even discontinued.

If participants are not meeting the glycemic goals, the study team should contact the participant's primary clinical care team about possible adjustments in the insulin regimen, referral to a registered dietitian, or other approaches that may improve the glucose control.

<u>Insulin Discontinuation</u>

If a participant has achieved a HbA1c level of ≤6.5% with insulin use of ≤0.25 U/kg/day, insulin therapy can be discontinued. The participant's blood glucose and HbA1c levels should continue to be monitored per protocol, and urine ketones should be monitored once a day. During routine blood glucose monitoring, if the participant's blood glucose level exceeds 200 mg/dL (11.1 mmol/L) and/or urine ketone is moderate or greater, the participant should consult with their primary physician and/or the clinical site staff for further evaluation. If the fasting blood glucose exceeds 126 mg/dL (7 mmol/L) or HbA1c exceeds 6.5%, as documented by repeat testing, the resumption of insulin therapy should be considered.

8.3. Permitted Medications

There are no medications specifically contraindicated for use with teplizumab, so participants may continue to receive medications as needed for existing medical conditions, taking into account the exclusion criteria (Section 4.2), prohibited medicines during the study (Section 8.4) and guidance for vaccine administration (Section 8.5). Specific permitted medications that participants may need during the study include but are not limited to:

- Low-dose estrogen oral contraception
- Acetaminophen or similar analgesics
- NSAIDs (eg, ibuprofen and naproxen) (acetaminophen if NSAID is contraindicated)
- Diphenhydramine or other antihistamines
- Antibiotics as prescribed by a healthcare provider for a specific condition

8.4. Prohibited Medications

The following drugs are not permitted concomitantly during the study from randomization through Week 78:

- Agents other than subcutaneously administered insulin that may influence insulin sensitivity or secretion, which include but are not limited to inhaled insulin, oral hypoglycemic drug (eg, sulfonylureas), metformin, diphenylhydantoin, thiazide or other potassium-depleting diuretics, systemic β-adrenergic blockers, or niacin
- Drugs other than insulin to treat hyperglycemia for example metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, dipeptidyl peptidase-4 (DPP-IV) inhibitors, or amylin
- Agents that may result in immunosuppression or immunomodulation. This includes the initiation of long-term or chronic use of high-dose inhaled corticosteroids, extensive use of topical corticosteroids, and systemic corticosteroids. This also includes biologic immune modulators. Note: A short course (ie, approximately 2 weeks or less) of systemic (including oral, inhaled or parenteral) corticosteroids may be used for treatment of a transient condition.
- Vaccines (see Section 8.5 below)

The Investigator may decide to administer a prohibited medication to a participant if necessary. The Investigator should subsequently discuss with the Medical Monitor whether the participant should remain in the study.

The Sponsor must be notified as soon as possible after any instances in which prohibited therapies are administered.

8.5. Vaccines

Because vaccines are an important component of current general medical care, and because teplizumab is considered an immunomodulatory therapy for those with chronic diseases like T1D, participants and Investigators are required to adhere by the following guidance for this study:

- Prior to receiving study drug, participants must be up to date with and agree to receive routine age-appropriate immunizations according to current local, regional and/or country-specific guidelines and to comply with relevant guidelines for immunosuppressed individuals and those with chronic disease (diabetes mellitus). Documentation of all vaccines given during screening and the treatment period in the study must be provided to the study site.
- Live vaccines (eg, varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, and smallpox) cannot be given from 8 weeks before the initiation of study drug through Week 52 or Week 78, if Modified-Dosing Schedule is followed.
- Non-infectious (eg, recombinant, inactivated, or otherwise “non-live”) vaccines generally should not be given from 2 weeks before the initiation of study drug through 6 weeks after the end of each course of study drug administration. If a vaccine is considered necessary within the time window, the Investigator should consult with the Medical Monitor as soon as possible.
- In some situations, a vaccine may be urgently required (eg, rabies or meningococcal vaccine) to protect the safety of the participant and may be given. Influenza non-live vaccine can be given on an emergency basis, but all efforts should be made to follow the general guidance above.

8.6. Contraception

Contraception (including abstinence) is required for all participants who have reached puberty (see Section 4).

Females with childbearing potential or who gain childbearing potential (having reached menarche or having reached Tanner stage 3 breast development without menarche) during the study must practice abstinence or use 2 forms of contraception (including oral, transdermal, injectable, or implanted contraceptives, intrauterine device, female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner, or a sterile sexual partner) continuously from 30 days before the first dose of study drug through the end of the study. Males who have reached puberty with partners of childbearing potential should use barrier contraception in addition to having their partners use another method of contraception from 1 week before the first dose of study drug through 120 days (a complete spermatogenesis cycle) after the last dose in each treatment course.

In countries with legislation for the age of sexual activity, the participant must comply with the local age limit regarding the use of contraception.

Participants should discuss all issues related to contraception methods with the study medical staff and personal healthcare providers.

9. STUDY EVALUATIONS

Participants who are not affected by the COVID-19 pandemic restrictions are required to undergo study procedures and assessments according to the Schedule of Events.

Those participants who are unable to receive the second course of treatment as scheduled because of COVID-19 pandemic restrictions will begin the second course of treatment at the Week 52 (Day 364) visit. These participants will undergo all study procedures and assessments according to the Modified-Dosing Schedule of Events.

9.1. Study Procedures

9.1.1. Screening Procedures

For the purpose of this study, the date of T1D diagnosis for any subject is defined as the date on which a formal diagnosis of T1D is made according to the ADA diagnostic criteria for T1D.

For participants randomized in this study, all screening procedures (with the possible exception of the T1D autoantibody assessments) are to take place at least 6 days after the T1D diagnosis. This interval allows for the reduction of metabolic instability that can be present at the time of T1D diagnosis and may interfere with the screening MMTT and other assessments. Screening may take place over 1 day. Prior to screening, the Investigator or designee will explain the study's rationale, procedures, and risks, and ask each potential participant/caregiver to consent/assent to participate. The start of the screening period of the study will be defined as the day written informed consent/assent is obtained. Participants will be assigned a unique participant number and evaluation for inclusion/exclusion criteria will be performed, which will include clinical and laboratory evaluations and the 2h MMTT (Appendix 2). A master log will be maintained by individual investigative sites of all screened participants, including the reason for screening failure.

The eDiary used to collect participant-reported data will be issued, and study-supplied glucometers and glucose monitoring strips will be provided to participants who request them. Training will be provided for use of these instruments to collect, for example, insulin use, blood glucose levels, hypoglycemic events (all), and AEs between study visits. Note: In situations where participants are not randomized in the study, they will be directed on how to return devices.

Laboratory and clinical assessments performed during the screening visit are identified in the Schedule of Events. Documentation of vaccines must be provided. In anticipation of successful screening and continued interest in the study, study personnel should schedule a date for

randomization, recognizing that randomization must occur within 6 weeks (42 days) of the diagnosis of T1D and that the treatment course will be daily infusions over approximately 2 weeks.

As part of the screening procedure, individuals must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known exposure to individuals with active or suspected TB, and clinical or radiographic evidence of TB, and past testing for TB, including responses to tuberculin skin or other TB testing. Screening includes a validated approved interferon-gamma release assay (IGRA; ie, QuantiFERON-TB test). Individuals with a positive IGRA must be excluded from the study and should be referred for additional assessment outside of the study. If an individual's first IGRA test result is indeterminate, they cannot be randomized, and the test should be repeated. In the event that the second IGRA test result is also indeterminate, the individual should be excluded from the study and should be referred for additional assessment by their primary healthcare provider.

Starting from protocol version 3.0 onward, participants will undergo local SARS-CoV-2 PCR testing before the first dose of each treatment course is given. The result must be negative before each treatment course can be initiated.

Type 1 Diabetes Autoantibody Pre-screening

Study sites will be given the option of evaluating individuals for the presence of T1D-associated autoantibodies (T1D AAs) prior to engaging in the bulk of the screening evaluations. It is anticipated that Investigators and/or their designee may have the ability to introduce the opportunity to participate in this clinical trial when an individual first presents to a healthcare facility which may include inpatient hospitalization for a number of days for medical stabilization, T1D education and initiating insulin therapy. One of the key study inclusion criteria is presence of at least 1 T1D AAs to confirm the diagnosis of T1D.

Although often assessed at diagnosis, there are different clinical practice patterns of assessing the (complete) panel of T1D autoantibodies used in this study and such assessments (if not conducted by a study-approved laboratory) would not be valid to meet entry criteria. At the time near diagnosis individuals and their families are likely to be busy learning how to manage their new condition. As such they may be hesitant to partake in the full screening procedure (which may take most of the day) which can only take place 6 days after diagnosis to allow for metabolic stabilization for the MMTT assessment.

To assist in determining if the individual would meet the basic T1D AA entry criterion for this study, Investigators will have the ability to send an individual's blood sample for study qualifying T1D AA analyses following completing the Informed Consent Form. If an individual participates in this "pre-screening" procedure and the T1D AA testing is positive, they do not have to repeat the T1D AA evaluations but must complete the rest of the screening procedures (eg, MMTT and other screening assessments) such that randomization and initiation of study drug administration will occur within 6 weeks (42 days) of T1D diagnosis.

Retesting

If an individual undergoes screening but does not meet all study participation criteria, they may be eligible for retesting that may lead to randomization. Retesting of laboratory tests will be allowed once and will take place during an unscheduled visit in order to be eligible for randomization within 6 weeks (42 days) of T1D diagnosis.

Rescreening

Participants may be rescreened and be randomized as long as inclusion and exclusion criteria are met, and the participant is able to be randomized within 6 weeks (42 days) of T1D diagnosis. If rescreening is a possibility, the site should consult the Sponsor. Rescreening is allowed only once. Individuals who are rescreened will receive a new participant number, repeat the informed consent process, and then restart a new screening phase.

9.1.2. Randomization, Treatments and Monitoring

- **Study Visit Week 1 (Day 1): Randomization, 4h MMTT, and Study Drug Initiation**

  Future target visit days are based on date of the first study day (Day 1)

For all participants randomized in this study, randomization must occur within 6 weeks (42 days) of the diagnosis of T1D.

On Study day 1, randomization, additional clinical and laboratory assessments and study drug dosing initiation will occur. This visit, as well as other visits where study drug is administered, is in a location consistent with adequate safety oversight and monitoring, to be determined by each Principal Investigator and any applicable local or country-specific regulations. The location may be a hospital, ambulatory clinic, infusion center, or a similar medical facility.

The Investigator or designee will confirm that the participant has signed the proper informed consent and/or assent forms. All assessments are to be conducted according to the Schedule of Events tables. For example, vital signs, weight and height determination, and a brief physical exam will be conducted. All inclusion and exclusion criteria, concomitant medications, interval medical history and laboratory evaluations should be reviewed documenting that the individual remains eligible for participation in the study. Documentation of vaccine records will be confirmed. All participant collected data (eg, insulin use, glucometer reading, hypoglycemic and AE records) will be collected and reviewed, noting that individuals are to have at least 5 days of daily insulin use recorded within the 7 days immediately preceding randomization. Individuals will be randomly assigned to receive teplizumab or placebo using central automated system as detailed in Section 5.1.

Additional laboratory (including but not limited to complete blood count [CBC], chemistries, HLA-typing, and blood samples for exploratory assessments) and quality of life questionnaires will be completed as applicable, and the 4h MMTT will be conducted (Appendix 2).

The participant will then be able to receive study drug (teplizumab or placebo) with dosing based on the BSA using the height and weight obtained at this visit and the Mosteller formula

(BSA=square root [height (cm) x weight (kg)/3600].) The site Investigator or designee should assure that all emergency precautions (Section 6.5) are in place before any study drug is administration is started.

Participants will receive premedication of an NSAID (eg, ibuprofen) (acetaminophen if NSAID is contraindicated) and an antihistamine (eg, diphenhydramine) for at least the first 5 days of the treatment course, unless contraindicated by drug allergy or sensitivity. They can receive one, the other or both for the additional study drug administrations if the Investigator judges it to be appropriate to improve the tolerability of infusions. After at least 30 minutes following the premedication administration, the infusion of study drug can begin. Administration of study drug should be performed according to the Pharmacy Manual. If there is a delay in administration of study drug such that it will not be administered on the day of preparation, the study monitor must be notified immediately. Study drug should be planned to be administered intravenously over 30 minutes according to standard practices, but it may be slowed if there are signs or symptoms of intolerance. When the infusion solution has been completely administered, an additional volume of saline equal to the volume contained in the infusion tubing, at the same constant rate is to be infused to ensure that all study drug has been cleared from the infusion tubing. The starting and ending times for the infusion are to be recorded.

On the days indicated in the Schedule of Events, blood samples will be drawn for trough teplizumab serum concentration within 30 minutes before the start of infusion, and the time of these blood draws are to be documented in the CRF.

During the infusions and for an additional 60 minutes following the end of infusions, participants are to be monitored for signs or symptoms of infusion reactions including but not limited to fever, chills, headache, nausea, vomiting, infusion-site pain, anaphylaxis, wheezing, dyspnea, urticaria, and hypotension. The participant is then able to leave the facility for return the following day for the next study drug infusion.

Day 2-12: Continued Treatment Course 1 Infusions

Participants will return to the clinical trial site and the Investigator or designee will review the status of the participant and complete assessments as indicated in the Schedule of Events tables. If there are no clinical or laboratory concerns, the participant can proceed with the next infusion as described above at least 30 minutes following administration of prophylactic NSAID (acetaminophen if NSAID is contraindicated) and antihistamine. Close monitoring is to occur during the infusions and for 60 minutes following the infusions for any signs or symptoms of intolerability or infusion reactions.

Day 2-11*

On Days 2-11, the participant is then able to leave the facility and return the following day for the next study drug infusion.

**Days 5-11*

Where approved by appropriate local, regional and/or national authorities and where there is appropriate medical care and services, some or all evaluations, laboratory testing and study agent administration to be conducted from Day 5 through 11 may be performed outside of the research clinic at a site more convenient for the study participant (see Section 6). The visit on Day 12 must take place at the study site.

Days 12

The Day 12 visit must take place at the study site and all of the assessments and procedures will take place according to the Schedule of Events tables. Following the completion of the final infusion for this course and at least a 30-minute observation a continuous Glucose Monitoring (CGM) sensor will be applied and the participant is to be given instructions on CGM monitoring care and use.

- **Study Visits Weeks 4, 8, 12*, and 20***

  The visit window for these study visits are ±4 days from the target visit day.

During these visits, participants will return to the site for their scheduled visit and have clinical and/or laboratory assessments conducted as indicated in the Schedule of Events tables. Of note at Week 12, a CGM sensor will be applied and the participant is to be given instructions on CGM monitoring care and use.

At the Week 20 visit, give participant instructions for Week 26 4h MMTT including overnight fast and pre-MMTT insulin dosing.

**Study Visit Weeks 12 and 20*

Where approved by appropriate local, regional and/or national authorities and where there is appropriate medical care and services, the evaluations and laboratory testing for Study Visits at Weeks 12 and 20 may be performed outside of the research clinic at a site more convenient for the study participant. This shall only occur if the site Investigator and participant and/or their parent/guardian approve. In the event where it is opted to conduct such study visits out of the research clinic, the participant can, at any time, return to the study clinic for upcoming visits.

- **Study Visit Week 26: 4h MMTT and Treatment Course 2 (or Week 52, if Modified-dosing schedule followed)**

The visit window for these study visits are ±7 days from the target visit day.

Days 182-193*

Participants are to return to the clinical trial site on Day 182 for the clinical and laboratory assessments (including a 4h MMTT) as detailed in the Schedule of Events tables and for initiation of the second course of study drug administration.

Of specific note, height and weight are to be obtained at this visit and used for the BSA based dosing calculation for course 2. Following the guidance as with study drug course 1, the site Investigator or designee should assure that all emergency precautions (Section 6.5) are in place, the participant is to be premedicated with an oral NSAID (acetaminophen if NSAID is contraindicated) and anti-histamine at least 30 minutes before the first 5 study drug infusions is started (and on an as needed basis with subsequent infusions), administration of study drug should be performed according to the Pharmacy Manual, and an additional volume of saline equal to the volume contained in the infusion tubing is to be infused. During the infusions and for an additional 60 minutes following the infusions participants are to be monitored for signs or symptoms of infusion reactions.

On the days indicated in the Schedule of Events, a blood sample will be obtained for teplizumab serum levels within 30 minutes before study agent infusion. In addition to time of study agent and flush start and stop, the time of the blood draw is to be documented in the CRF.

Days 183-192 (Day 2-11 of Course 2 dosing)

On Days 183-192, the participant may leave the facility and return the following day for the next study drug infusion.

**Days 186-192 (Day 5-11 of Course 2 dosing)*

Where approved by appropriate local, regional and/or national authorities and where there is appropriate medical care and services, some or all evaluations, laboratory testing and study agent administration to be conducted from Day 186 through 192 may be performed outside of the research clinic at a site more convenient for the study (see Section 6).

Day 193 (Day 12 of Course 2 dosing)

The Day 193 visit must take place at the study site and all of the assessments and procedures will take place according to the Schedule of Events. Following the completion of the final infusion for this course and at least a 30-minute observation, a CGM sensor will be applied and the participant is to be given instructions on CGM monitoring care and use.

- **Study Visits Week 30, 34, 39*, 52 and 65***

  The visit window for Weeks 30, 34, 39, and 52 study visits is ± 4 days from the target visit day. The visit window for Week 65 visit is ±7 days.

During these visits, participants will return to the site for their scheduled visit and have clinical and/or laboratory assessments conducted as indicated in the Schedule of Events tables.

Of specific note, at the Week 52 visit, a 4h MMTT will be conducted.

At the end of the Week 39, 52, and 65 visits, a CGM sensor is to be applied and additional training and instruction updates on CGM care and use will be given as needed.

Study Visits Week 39 and Week 65

Give participant instructions for Week 52 and Week 78, respectively, 4h MMTT including overnight fast and pre-MMTT insulin dosing. At the Week 65 visit, dispense to participant CGM equipment for home application to start around Week 76.

Study Visit Week 39 and 65

Where approved by appropriate local, regional and/or national authorities and where there is appropriate medical care and services, the evaluations and laboratory testing for Study Visit at Week 39 may be performed outside of the research clinic at a site more convenient for the study participant. This shall only occur if the site Investigator and participant and/or their parent/guardian approve. In the event where it is opted to conduct such study visits out of the research clinic, the participant can, at any time, return to the study clinic for upcoming visits.

- **Study Visit Week 78**

  The visit window for this study visit is ± 7 days from the target visit day.

During this visit participants will return to the site for their scheduled visit and have clinical and/or laboratory assessments conducted as indicated in the Schedule of Events table. The 4h MMTT will be conducted.

The study staff will call to remind the participant or caregiver to apply a CGM sensor 2 weeks before the Week 78 visit. The CGM sensor will be returned to the study site at the Week 78 visit.

9.1.3. Blood Draw Volume Required for Study Assessments

The volume of blood drawn required in this study is described in Appendix 3.

It is recognized that the amount of blood that may be drawn for research purposes in children and adults may not exceed certain limits, both at a single visit and over a set amount of time. In any participant whose clinical condition might be adversely affected by removal of the blood volumes stated, for example, a participant with significant anemia or compromised cardiac output, Investigators should consider further limiting the volume of blood withdrawn for research purposes. In instances of medical need, it is the responsibility of the Investigator and/or participant's healthcare providers to determine if blood draws in excess of the protocol-stated volumes should occur. Because blood sampling in excess of those mandated by the protocol may be taken in the course of providing care during this study, sites must ensure that all instances of blood collection in excess of permitted volumes are recorded and justified in the participant's record.

9.2. Efficacy Evaluations

9.2.1. Mixed Meal Tolerance Tests

The 2h and 4h MMTTs will be performed during this trial as indicated in the Schedule of Events. A 2h MMTT will be performed at screening to determine study eligibility (based on peak

C-peptide level). A 4h MMTTs will be performed at randomization and at Weeks 26, 52, and 78 to obtain 4h C-peptide AUCs and other data. A 4h MMTT is used at and post-randomization as it has been shown to be more precise and reliable in assessing the MMTT-induced C-peptide AUC than the 2h MMTT (Boyle 2015, Rigby 2013, Rigby 2016). Alternatively, the 2h-MMTT is used at screening as it is sufficient to capture the peak C-peptide level needed for study entry. Samples from these assessments will be assessed for C-peptide, serum glucose, and insulin. Samples will be stored for potential future evaluations including but not limited to proinsulin levels. The measurements of C-peptide and glucose in serum samples will be done in an approved laboratory. MMTTs are to take place in the morning between approximately 7:00 a.m. and 10:00 a.m. after an overnight fast with strict guidance on insulin use. The 2-hour MMTT takes approximately 130 minutes to perform, and the 4-hour MMTT takes approximately 250 minutes.

The MMTT procedures are explained in Appendix 2.

9.2.2. Hemoglobin A1c

HbA1c will be assessed as a blood test at select study visits as indicated in the Schedule of Events tables.

9.2.3. Insulin Use

Participants' daily insulin use will be documented by the participant in an eDiary at select times for 7 days prior to randomization and at about Weeks 12, 26, 39, 52, 65 and 78 visits. The participant will record all short-, intermediate- and long-acting insulin administered as intermittent injections or use with an "insulin pump" during this time. Insulin use data are not recorded on the day before or the day of the study visit. If a participant forgets to record insulin use on one or more days before a visit, they should continue to record insulin use for up to 72 hours post-dose to obtain up to 7 days of data. Every effort should be made to collect a total of 7 days of insulin use data for all the aforementioned visits except Week 78 (final visit), as participants will return the eDiary at the final visit.

The criteria for potential insulin discontinuation are outlined in Section 8.2.

9.2.4. Episodes of Hypoglycemia

Clinically important and other non-severe and non-serious hypoglycemic episodes are defined in Section 12.1.4. These episodes will be recorded throughout the study by participants and through evaluation of glucometer readings.

9.2.5. Glucose Monitoring

9.2.5.1. Intermittent Glucose Monitoring (Fingerstick)

Blood glucose levels outside of MMTT and CGM will be recorded and analyzed as an endpoint at various times. As part of routine care, BG levels are usually measured by a fingerstick glucometer at least 4 times a day, including before each meal and at bedtime. At screening, participants will be offered a study-supplied glucometer and glucometer strips, but participants are permitted to use their own glucometers if they choose. Each participant is instructed to bring their glucometer (or

glucometers if they use more than one, eg, at home and in school) to each visit for review. In addition, approximately 7 times throughout the study, participants will record their BG levels before breakfast, lunch, and dinner and at bedtime for 7 consecutive days in their study eDiary prior to the randomization visit and the Weeks 12, 26, 39, 52, 65, and 78 visits. Like the recording of the insulin use data (Section 9.2.3), BG data on the day before and the day of the study visit will not be recorded. If a participant forgets to record fingerstick glucose measurements before a visit, they should do so for 72 hours immediately after the visit. Every effort should be made to collect a total of 7 days of BG data for all the aforementioned visits except Week 78 (final visit), as participants will return the eDiary at the final visit.

If a participant is using an approved CGM device for regular, routine care in lieu of "fingerstick" BG monitoring (which could include the study supplied CGM), values from the CGM can be recorded instead of specific unplanned "fingerstick" values for these intermittent BG assessments. The device used to obtain the intermittent BG values will be documented.

9.2.5.2. Continuous Glucose Monitoring

"Continuous" glucose monitors record interstitial glucose levels (which closely approximate blood glucose values) at regular intervals, eg every 5-15 minutes depending on device. Increasingly clinical studies are supporting that such measurements and their assessments provides valuable and unique insights to glycemic control in diabetes. In this study, CGM assessments will be conducted to provide key secondary clinical and exploratory endpoint data to address if and how teplizumab affects glycemic control, such as glucose excursions, time in select glucose ranges, and average daily glucose values (Steck 2014, Helminen 2016, Danne 2017). A recent international consensus statement on CGM monitoring supported the use of percentages of time in ranges (target, hypoglycemia, and hyperglycemia) and measurement of glycemic variability as key diabetes control metrics in clinical trials (Danne 2017).

CGM will be used to assess glycemic control approximately 7 times throughout the study: after the completion of treatment courses at randomization and Week 26; after the visit at Weeks 12, 39, 52, and 65; and before the visit at Week 78. CGM sensors will be placed by qualified study staff, and education and training on CGM use and care will be given. Sensors will remain in place for up to 2 weeks. If during that 2-week period a sensor comes off, it can be replaced by the participant, a knowledgeable family member/guardian, or a qualified medical professional.

To reduce any confounding factors of glucose measurements during study drug infusions, CGM sensors will be placed on participants after the study drug administration has completed for Course 1 and Course 2 and other clinical and laboratory assessments have been made on the days specified in the Schedule of Events tables. At the Weeks 12, 39, 52, and 65 visits, the sensor will be placed on participants after all clinical and laboratory assessments and the MMTT have completed. In addition, for Week 78 CGM data, study personnel will call the participants or caregivers and remind each participant to apply the CGM sensor from Week 76 to Week 78.

Study CGM readings are not intended for medical management of participant's diabetes but can be under the supervision of a participant's health care team. Of note, routine use of the personal CGM under guidance of a participant's regular healthcare provider is permitted.

Spot-check and CGM blood glucose assessments are anticipated to include but are not be limited to mean BG, glycemic variability (BG standard deviation [SD]), maximum and minimum BG values over time and incidence and/or percent time with BG >70 but ≤180 mg/dL (>3.9 but ≤10.0 mmol/L, Level 1 (>180 but ≤250 mg/dL (>10 but ≤13.9 mmol/L)) and Level 2 HYPERglycemia (>250 mg/dL (>13.9 mmol/L)) and Level 1 (≤70 but ≥54 mg/dL (≤3.9 but ≥3.0 mmol/L)) and Level 2 (<54 mg/dL (<3.0 mmol/L)) HYPOglycemia (Seaquist 2013, International Hypoglycaemia Study Group [IHSG] 2017, Agiostratidou 2017).

9.2.6. Additional Metabolic, Clinical, Immunologic, and Molecular Evaluations

Additional evaluations will be performed to assist in the understanding of how teplizumab may affect other metabolic parameters, general and T1D-specific immune and metabolic responses, and quality of life. These studies may help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups in this study that respond preferentially to teplizumab and thus characteristics of those with T1D who might benefit the most from teplizumab therapy in the future.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Venous blood samples will be collected for measurement of serum concentrations of teplizumab, anti-teplizumab antibodies and neutralizing antibody (NAb) according to the Schedule of Events tables. Additionally, samples should also be collected at the Early Termination Visit for subjects who discontinue study treatment early and from subjects who experience an AE suspected to be related to immunogenicity (eg, infusion reactions, injection site reactions or hypersensitivity).

Venous blood samples will be collected. Samples collected for analyses of teplizumab serum concentration and antibody to teplizumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

The actual dates and times of blood sampling will be recorded in the CRF and/or laboratory requisition form. It is extremely important to accurately record the date and time of each serum sample collection as well as the start and stop time of each study drug infusion. Instructions for the collection, handling, and shipment of these samples are found in the Laboratory Manual.

9.3.2. Analytical Procedures

Serum samples will be analyzed using validated, specific, and sensitive immunoassay methods.

9.3.3. Pharmacokinetic Parameters

Nonlinear mixed effects modeling (with NONMEM software) will be used to analyze the serum concentration-time data of teplizumab to obtain the primary PK parameters, clearance (CL) and volume of distribution. The PK profiles will be used, along with other available data, to develop a population PK model while including the effect of major covariates (eg, sex, ethnicity, race, antibody) on CL and volume of distribution. The starting model will be a previously developed model for teplizumab. All PK parameters will be presented by listings and descriptive summary statistics including, arithmetic mean, geometric mean (AUC, C_{max} and their derived parameters), median, range, standard deviation and coefficient of variation. The data of this study may be pooled with data from other studies.

9.4. Exploratory and Other Assessments

9.4.1. Immune and Serologic Assessments

Immune assessments may include but are not limited to monitoring T cell profiles and B cell profiles by flow cytometry. In addition, serum levels of circulating pro- and anti-inflammatory cytokines and other soluble factors that can impact T1D progression may be assessed.

To investigate if and how teplizumab induces changes in lymphocyte subpopulations and expression of markers indicative of functional state (ie, activation and exhaustion), flow cytometry is anticipated to be performed as part of an exploratory endpoint. As indicated in the Schedule of Events, quantitative subpopulation analysis that includes assessment of CD4+ T cells, CD8+ T cells, B cells and NK cells (ie, Quantitative Lymphocyte Subset Panel or TBNK panel) will be conducted by a licensed central laboratory on fresh samples. In addition, samples for PBMC evaluation will be collected at the indicated timepoints, processed and stored for future “deep” phenotypic analysis, antigen-specific analyses (ie, tetramer) and also functional responses to antigen-specific and non-specific stimuli. Some of these analyses may take place by traditional flow cytometry, mass cytometry (CyTOF) or other technology.

To determine if and how teplizumab affects cytokine levels due to cytokine release or lymphocyte modulation, blood samples will be collected at select timepoints before and after study drug administration. Samples will be processed and stored. It is anticipated that analyses will be conducted only at select intervals that may include after a critical number of participants have completed the Week 52 visit or other key timepoints. Examples of cytokines that may be evaluated are interleukin (IL) 2 (IL-2), IL-4, IL-5, IL-6, IL-8, IL-10, interferon-gamma and tumor necrosis factor-alpha. In addition, other serum assessments, including those of hormones or other metabolically active substances (eg, glucagon, incretins, lipokines, adiponectin, or cholesterol) that may have an effect on metabolic control, may be performed. Approaches to evaluations may include antibody-based multiplex panels, modified-aptamer binding technology, or other platforms.

Key markers for the presence of the autoimmune processes directed against pancreatic islets include assessing the presence and titers of anti-GAD65, anti-insulin, anti-IA-2, anti-ZnT8, and anti-ICA autoantibodies. Detection of these autoantibody combinations has proven to be an

accurate predictor of T1D in several natural history studies. Therapies that impact the progression of T1D may change the presence or shift titers of autoantibodies. In addition, teplizumab may have an effect on antibody subclasses in general. As such, it will be important to evaluate effects of teplizumab on T1D autoantibodies presence and titer in the context of assessment of total antibody subclasses. Qualitative and quantitative assessments of antibody subclasses, eg, IgG, IgA, and IgM, may indicate a change in the type of T-helper cell responses to T1D-associated autoantigens.

Recent data suggest that infection with CVB may be a trigger that breaks self-tolerance in those predisposed to T1D and heralds destruction of β cells and eventually T1D. Improved understand regarding the relationship of CVB infection in those newly diagnosed with T1D may assist in developing novels therapies to treat and/or prevent T1D. Blood samples obtained for exploratory analysis can be used for serologic, molecular and other assessments of CVB infection.

To allow for exploratory assessment as described above, blood samples will be collected as indicated in the Schedule of Events and processed and analyzed or stored for future testing.

9.4.2. Assessment of β cell Stress

The disease progression has been proposed to be involved with alterations in "β cell stress," specifically due to attempts at enhanced endogenous insulin production in residual β cells that may overwhelm intracellular processes and direct or bystander injurious inflammatory meditators. It proposed that measurement of specific β cell products may be markers of this process and that β cell recovery due to immune interventions may result in a decrease of these markers. In this study, exploratory evaluation of two such markers, proinsulin-to-C-peptide ratios and serum levels of circulating methylated-insulin DNA, are to be evaluated. Samples that can be used for these analyses will be collected, processed and stored at times indicated in the Schedule of Events for future testing.

9.4.3. Pharmacodynamic Substudy

In order to evaluate the pharmacodynamic (PD) effects of teplizumab, namely its CD3 receptor occupancy and modulation, a substudy will be conducted in all North American sites. See Appendix 4 for a description of the PD substudy.

9.5. Pharmacogenomic (DNA) Evaluations

The HLA system is a grouping of genes that encode the major histocompatibility complex (MHC) proteins in humans. An individual's MHC haplotype gives insight to interactions of distinct types of lymphocytes that may cause T1D and may help to identify those who are at risk of developing T1D (Roark 2014). The MHC haplotype of participants will be determined. The results of genotype analyses can be used to correlate with disease progression, therapeutic responses and identify subgroups that respond preferentially to teplizumab.

Pharmacogenomic studies on DNA, RNA or other genetic matter may also provide insights into the mechanism of teplizumab's effect on T1D, the immune system or individuals who preferentially respond to teplizumab. One example is the methylated insulin-DNA assessment anticipated (see Section 9.4.2), but also may include studies on the transcript/transcriptome,

microarrays, or whole genome assessments. Samples that can be used for these analyses will be collected, processed and/or stored at times indicated in the Schedule of Events for future testing.

9.6. Quality of Life Assessment

Individuals with T1D may outwardly look healthy, but the management of their disease is a daily task for the rest of their life that requires multiple assessments and treatments per day along with close monitoring of diet, health status and exercise. As such there is a daily significant burden on those with T1D and their families (Monaghan 2015, Mittermayer 2017). In addition, those with even the most aggressively managed T1D are at risk for significant short and long-term morbidity and mortality. Therefore, it is realized that there are not just medical sequelae for those with T1D, but significant emotional, personal, familial and mental burdens as well (Monaghan 2015). Understanding if and how therapies may impact these other "quality of life" measures is an increasingly recognized aspect of beneficial effects of therapies that may alter the disease course in T1D. This study will have participants complete questionnaires such as the PedsQL Diabetes Module, HFS, DTSQ, and PedsQL Family Impact Module at time points indicated in the Schedule of Events tables (Driscoll 2016, Trancone 2016, Bradley 2009, Gonder-Frederick 2011, Varni 2018).

9.7. Safety Evaluations

There will be thorough monitoring and evaluation of participants by the Sponsor and Investigators and their respective teams in this study focusing on study drug and disease-related safety issues.

Regulatory requirements followed by this study include FDA regulations, ICH Guideline for Good Clinical Practice (E6, R1), applicable EU Clinical Trials Directive and any other local regulatory requirements for safety monitoring and reporting responsibilities of Sponsors and Investigators to ensure the safety and protection of human participants participating in clinical trials.

9.7.1. Responsibilities

The Sponsor (Provention Bio, Inc) is responsible for:

- Conducting ongoing safety evaluation of investigational products
- Notifying all Investigators and regulatory authorities of findings that could affect adversely the safety of participants or impact the conduct of the trial.
- Reporting to the applicable regulatory authorities and Investigators certain SAEs (as expedited safety reports) and other relevant new safety information (safety updates and periodic reports) as required by applicable regulatory requirements

Investigators participating in this clinical trial are responsible for:

- Protecting the safety and welfare of participants
- Evaluating participant safety including physician assessment of AEs for seriousness, severity and causality

- Notifying the Sponsor of SAEs and other immediately reportable events (IREs) (see Sections 12.3.2 and 12.3.3) within 24 hours, and providing necessary documentation requested by the Sponsor
- Informing the IRB/IEC of AEs as required by applicable regulatory requirements.

Details regarding the independent DMC are provided in Section 11.11 and the DMC Charter.

9.7.2. Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) starting after the informed consent form is signed and for the duration of the study. Adverse events will be followed by the Investigator as specified in Section 12, Adverse Event Reporting.

Specific Adverse Event Monitoring

Disease-related Hypoglycemia

As indicated elsewhere, participants, and when applicable their caregivers, must agree to follow the current recommendations of intensive glycemic control, for example blood glucose checks at least 4 times daily and insulin administration to achieve HbA1c of <7.5% (58 mmol/mol) if younger than 18 years old or <7.0% (53 mmol/L) if 18 years old or older (ADA 2018). If there are local, regional, or national recommendations to be followed that supersede ADA recommendations, these glycemic control targets (ie, HbA1cs or glucose levels) should not be more liberal (ie, higher) than the ADA recommendations. The Investigator will document in the CRF the glycemic goals.

In order to achieve glycemic goals, this may require enhanced blood glucose monitoring and greater amounts and frequency of insulin administration and may have the unintended side effects of hypoglycemia.

Hypoglycemia may have severe sequelae including loss of consciousness, coma or death. Participants and their caregivers must work with local Investigators and their primary health care providers to determine an approach that is best, and most safely, allows participants to target their specific HbA1c goal.

Study Drug-related, Laboratory-based Events

Safety evaluation will include regular monitoring of clinical laboratory tests, including blood cell counts and subsets, serum chemistry panels, and liver and renal function tests.

Infections of Special Interest and Malignancies

Teplizumab is a known immune modulator that suppresses certain aspects of the immune system. Some of the primary functions of the immune system are to fight viral, bacterial and fungal infections and also surveillance for and destruction of malignant cells. Although there are currently no data indicating an increased risk of significant infections or cancer, there is a potential that

teplizumab may increase the risk for these events. Using both laboratory-based and clinical assessments, participants will be closely monitored for any signs or symptoms suggestive of either. For example, there will be active laboratory monitoring of early detection of significant CMV and EBV viremia to detect primary infection or reactivation of these viruses in those who have been infected previously. In addition, questioning about TB risks, exposures and signs and symptoms will be conducted at each study visit. Physical examinations, systems reviews and laboratory assessments (CBCs, chemistries and urinalysis) will employed to assess for malignant or pre-malignant conditions.

9.7.3. Study Drug Infusion-Related Reactions

Infusion reactions which may include but are not limited to hypersensitivity and allergic reactions, anaphylaxis, and cytokine release syndrome have been observed with infusion of monoclonal antibodies targeting lymphocytes. Previous experience with teplizumab suggests that a small percentage (<10%) may experience such reactions, and they are usually characterized as mild to moderate. Mild to serious local and systemic reactions (including anaphylaxis) may occur at any time during the administration of study drug.

Study drug must not be administered to individuals with known or suspected intolerance or hypersensitivity to any biologic medication or known allergies or clinically significant reactions to human proteins, to monoclonal antibodies or antibody fragments, or to any components of teplizumab or its excipients.

Two courses of study drug infusion daily for 12 days will be administered starting at the Week 1 (randomization) visit and the Week 26 visit (except participants who require the modified dosing schedule). These infusions will be given in an appropriate medical setting (eg, clinic, hospital, or infusion center) that has appropriate staff and cardiovascular and respiratory supplies to care for an individual undergoing a severe infusion reaction and have a plan for post resuscitation care. A physician must be immediately available during all infusions of study drug. Prior to each administration of study drug appropriate emergency equipment and trained personnel should be present. At a minimum, the following will be available: epinephrine for IM or IV administration, dexamethasone for IV administration, diphenhydramine (or equivalent antihistamine) and appropriate cardiovascular and respiratory resuscitation equipment and other supplies for the emergency management for a serious infusion reaction.

As indicated in Section 6.3, participants in this study will receive oral premedication NSAID drug (eg, ibuprofen) (acetaminophen if NSAID is contraindicated) and an antihistamine (eg, diphenhydramine) for at least the first 5 days of the treatment course, unless contraindicated by drug allergy or sensitivity.

During the infusions and for an additional 60 minutes following the infusions, participants are to be monitored for signs or symptoms of infusion reactions. If there are signs or symptoms of infusion reaction in a participant during the 60-minute post-infusion observation period, the participant should be observed for an additional 60 minutes or until the reaction resolves, whichever is longer.

An infusion reaction may include but not be limited to any unfavorable or unintended sign or symptom that occurs at the time or in close temporal proximity to study drug administered intravenously. Signs and symptoms of an infusion reaction may include but not be limited to fever, chills, headache, change in mental status, nausea, vomiting, or pain, swelling, itching, induration, warmth, redness/erythema, local or systemic rash, bleeding, bruising at or distal to the infusion site, hypotension, tachycardia, hyperventilation, wheezing or other breathing difficulties.

Any signs or symptom consistent with an infusion reaction, allergy, anaphylaxis or cytokine release syndrome and the type of reaction should be recorded on the AE page of the CRF.

As noted in Section 9.1.2, where approved by appropriate local, regional and/or national authorities and where there is appropriate medical care and services, study agent administration to be conducted from Day 5 through 11 of each course of study drug may be performed outside of the research clinic at a site more convenient for the study participant. In these instances, qualified medical personnel must be available to evaluate and manage these events.

Management of Cytokine Release Syndrome

In previous Phase 3 studies of teplizumab, ~6% of participants with T1D experienced cytokine release syndrome after receiving teplizumab. Symptoms of cytokine release syndrome included but were not limited to rash, headache, nausea, vomiting, chills/rigor, and fever. Most of the symptoms occurred during the first few days of treatment and are mild or moderate in severity. Cytokine release syndrome was time-limited and appeared to dissipate regardless of whether teplizumab dosing was interrupted.

The possibility exists that participants in this study may experience cytokine release syndrome despite premedications and may require supplemental therapy and/or modification of study drug administration. Recommendations for the management of these symptoms are as follows.

Supplemental Therapy

Supplemental therapy is intended for symptom management. The same premedications can be used as follows:

- Locally approved NSAIDs should be given in compliance with appropriate age restrictions and practice standards, such as ibuprofen (tablet or liquid), diclofenac, naproxen, meloxicam, or tenoxicam

- Acetaminophen may be added or used instead of a NSAID if the latter cannot be used. Continuation of NSAID dosing should be considered if necessary.

- Antihistamines may be continued.

For more severe or prolonged symptoms, the following may be administered as consistent with local practice standard:

- Antihistamines, eg, IV diphenhydramine
- Acetaminophen can be combined with antihistamines and can be repeated every 4 to 6 hours; hydroxyzine can be used during the day to avoid sedation
- NSAIDs with higher potency, eg, ketorolac
- Acetaminophen with codeine or meperidine for myalgias, chills and rigors.
- Ondansetron for managing GI symptoms such as nausea and vomiting
- Saline boluses to help with hemodynamic support

Modification of Study Drug Administration

- If the cytokine release syndrome is associated with anaphylaxis or angioedema with or without requiring hemodynamic support (ie, epinephrine and/or blood pressure medications) or mechanical ventilation, study drug should be permanently discontinued (Section 10.2.1)
- Symptoms alone generally do not lead to study drug modification. However, if the cytokine release syndrome is associated with the following laboratory abnormalities, the drug should be withheld:
    - Study drug should be permanently discontinued: ALT and/or AST >5X ULN, Total Bilirubin >3X ULN. ALT and/or AST >3X ULN AND Total Bilirubin >2X ULN (Hy's Law criteria); platelet count <50,000/µL, neutrophil count <500 cells/µL, hemoglobin of <8.5 g/dL (laboratory test(s) should be confirmed on 2 consecutive dosing days (Section 10.2.1).
    - Study drug may be interrupted temporarily: ALT and/or AST >3X ULN but ≤5X ULN, Total Bilirubin >2X ULN but ≤3X ULN, platelet count >50,000 but ≤100,000, hemoglobin >8.5 g/dL but ≤10 g/dL (laboratory tests may be repeated on the same day). If the repeated test normalizes, that day's dose may be given. If the value is still in the above range or worsens, or if the test cannot be repeated on the same day, that day's dose should be withheld (Section 10.2.2).
        - If the above events resolve within 2 days, study drug dosing may be resumed according to the original schedule.
        - If the above events do not resolve after 2 consecutive days of interruption, the Medical Monitor must be consulted regarding continuation of study drug dosing.

Glucocorticoids (eg, prednisone 1-1.5 mg/kg/d given twice daily) should be reserved for intractable symptoms or Grade 3 or higher events that cannot be relieved with the above

medications. There is some evidence that glucocorticoids may interfere with the mechanism of action of teplizumab and therefore should be given for as short a duration as possible. If the investigator feels that glucocorticoids are necessary to resolve intractable signs or symptoms, they should follow applicable standard of care recommendations and treatment guidelines and inform the medical monitor without any delays. Blood glucose levels should be monitored carefully during glucocorticoid administration.

Delayed Drug Reactions

Reactions to intravenous administration of certain agents may occur up to approximately 21 days following infusion and presentation can be variable, and include, for example, myalgia, arthralgia, fever and/or rash. In some cases, these may be accompanied by other symptoms including pruritus, localized or systemic edema, dysphagia, urticaria, sore throat, and/or headache. Any such reactions and the type of reaction should be recorded on the AE page of the CRF.

9.7.4. Assessment of Infections

Any Infection

As teplizumab is an immune modulator capable of suppressing certain aspects of protective immunity, there is an increased potential risk of infections in recipients. In the Protégé study, 52% and 56.1% of teplizumab and placebo participants, respectively, were noted to have infections recorded as AEs. The most prevalent infections in all participants were upper respiratory tract infections, nasopharyngitis, pharyngitis, sinusitis, influenza, rhinitis, gastroenteritis, herpes zoster, viral upper respiratory tract infection. The percent of Protégé participants who had of AEs of infections that were grade 3 or higher on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) was 3.1% in recipients of any dosing regimen of teplizumab and 2.0% of the placebo participants and included viral gastroenteritis and herpes zoster (Sherry 2011, Hagopian 2013).

In the Protégé study, the incidence of Adverse Events of Special Interest (AESI) of infection was 49% in all teplizumab groups and was 58% in the placebo group. For ~95% of participants with AESIs of infection, the maximum severity of the infection was grade 1 or 2; 3% to 6% of participants had a serious infection across the treatment groups. The overall incidence of serious infections was 3.4% in participants receiving teplizumab and 3.1% in those receiving placebo. These included upper respiratory infection, influenza, sinusitis, and nasopharyngitis. Bacterial infections appeared lower in those that received teplizumab groups than in the placebo group, and there was no difference in the occurrence of fungal infection (Sherry 2011, Hagopian 2013).

Even though it is unclear to what extent teplizumab may increase the risk of infection, if at all, all participants will be closely monitored for any and all infections and classified and recorded.

Herpes Zoster

In the Protégé study, herpes zoster occurred in 10 of the 417 (2.4%) teplizumab-treatment participants and no participants in the placebo group. Herpes zoster (also referred to as shingles)

is a disease characterized by a localized, painful, blistering skin rash that is the result of reactivation of VZV, the causative agent for chicken pox. The age range was 12 to 34 years old. No cases were reported as SAEs, and 2 participants had grade 3 events (Sherry 2011, Hagopian 2013). Three participants had herpes zoster within 28 days of starting course 1 all of whom discontinued receipt of study drug. There was one grade 3, one grade 2, and one grade 1 event. Five events of herpes zoster occurred after 270 days. Although it is unclear how teplizumab impacts the occurrence of herpes zoster, all participants will be closely monitored for herpes zoster outbreaks. During screening all participants will undergo serologic evaluation (IgM and IgG) for VZV. Although study entry will not be based on these results, if there are participants who develop VZV-related infections or conditions, the serology data may assist in understanding risk. If it is believed that serologic status does influence VZV-related conditions (including herpes zoster) the study team in conjunction with the DMC will discuss modifying entry criteria.

EBV and CMV

Cytomegalovirus (CMV) is an infection that is usually acquired in childhood and is usually asymptomatic but may cause fever and fatigue and other more significant symptoms. Lifelong latent CMV infections persist and are usually of no consequence. However, individuals with impaired T-lymphocyte functions, recipients of solid organ or bone marrow transplants on significant immune suppression and individuals with cancer receiving chemo- or radiation-therapy are at risk for reactivation of CMV and sequela, some significant. Fever, malaise and fatigue can result. More severe effects include hematological abnormalities like leukopenia or thrombocytopenia, hepatitis/elevated LFTs, retinitis, and blindness, encephalitis, pneumonia, and gastrointestinal ulcers. In Protégé, CMV significant disease or reactivation did not appear higher in teplizumab-treated participants than in placebo-treated participants, although there were some participants with apparent transient re-activation.

Epstein Barr Virus (EBV) is also a viral infection that is usually first acquired in childhood and adolescence which can be asymptomatic or result in a syndrome know as infectious mononucleosis characterized by extreme fatigue, fever, sore throat, myalgias, swollen lymph nodes, liver and spleen. In situations of immune deficiency or immune suppression EBV can reactive and cause multisystem damage and an aggressive lymphoproliferative disorder and lymphoma. In Protégé, EBV reactivation was rare and acute mononucleosis syndrome was not increased.

To date, there has not been any association of teplizumab with significant AEs associated with CMV or EBV primary infection or reactivation. As this study will focus on younger individuals who may not been exposed to CMV or EBV previously, at screening participants will be serologically screened for previous exposure (ie, viral IgG positivity) and status documented. Recent studies in T1D and others suggest that quantitative polymerase chain reaction (PCR)-based assessment of viral DNA is a precise approach to document significant CMV and EBV infections and reactivations. Thus, this study will conduct CMV and EBV DNA viral load monitoring by quantitative PCR at screening and at other key times in the study and use the threshold of >10,000 copies per ml blood or 10^6 cells as a definition of a clinically significant infection or reactivation (Rosenzweig 2010, Verkruyse 2006). An EBV or CMV DNA viral load of >10,000 copies should trigger a confirmatory assessment and evaluation of the participant. If there is a confirmed viral

load of >10,000 copies and/or concerning signs or symptoms an immediate assessment should take place and if appropriate consultation with an infectious disease specialist.

Tuberculosis

Individuals who are receiving immunosuppressants may be at risk of acquiring a more severe course of primary infection with or reactivation of latent TB.

In the Protégé study, 2 participants were diagnosed with TB infections: one in India who received the low dose 14-day regimen of teplizumab; and one in Ukraine who received placebo who were evaluated and treated for SAEs of TB (Sherry 2011, Hagopian 2013).

In this study, potential participants will undergo serologic screening via an interferon gamma release assay (IGRA; ie, Quantiferon Gold) test. A positive or repeat indeterminate result is an exclusion for participation. Questions regarding exposure and/or history will be asked and also can result in exclusion from study participation. In addition, to assist in the early detection of TB during the study, participants are to be evaluated for signs and symptoms of active TB, including questions regarding the following signs:

- A new cough with a duration of more than 14 days
- Change in a chronic cough
- Persistent fever
- Unintentional weight loss
- Night sweats
- Close contact with an individual with active TB

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation will be undertaken, including consultation with a physician specializing in TB if necessary.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a chest radiograph, a repeat IGRA test, and referral to a physician specializing in TB if possible to determine the participant's risk of developing active TB and whether treatment for latent TB is warranted.

Study drug administration should be interrupted during a TB-related investigation. If the IGRA test result is indeterminate, the test should be repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol.

9.7.5. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The Investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

9.7.5.1. Central Laboratory Tests

The following tests will be performed by a standard central laboratory:

Hematology Panel (at specific visits per Schedule of Events)

- WBC with differential
- Hemoglobin
- Hematocrit
- Platelet count

Serum Chemistry Panel with Liver Function Tests (at specific visits per Schedule of Events)

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen (BUN)
- Creatinine
- Glucose
- Calcium
- Phosphate
- Albumin
- Total protein

Liver Function Tests

- Total bilirubin (TBili)
- Direct bilirubin (DBili)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)

Quantitative Lymphocyte Subset (TBNK) Panel

- $CD4^+$ T cells
- $CD8^+$ T cells

- B cells
- NK cells

Quantitative Immunoglobulin Panel

- IgA
- IgG
- IgM

Lipid Panel (only done at select fasting visits)

- Total cholesterol
- High density lipoprotein (HDL)
- Low density lipoprotein (LDL)
- Triglycerides

Coagulation Panel (only at screening)

- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- International normalized ratio (INR)

Urinalysis (at specific visits per Schedule of Events)

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Nitrites
- Leukocyte esterase
- Blood cells/hemoglobin

Other Tests

- Serum pregnancy testing (only at screening for females of childbearing potential)
- HIV antibody serology (only at screening)
- HBV antibody serology /antigen panel (only at screening)
- HCV antibody serology (only at screening)
- VZV antibody serology
- CMV serology

- EBV serology
- CMV DNA PCR
- EBV DNA PCR
- MHC haplotype (only at Week 1, ie, randomization)
- Interferon-gamma Release Assay (IGRA) Tuberculosis testing
- HbA1c

The following diabetes-related laboratory tests will be analyzed at an approved central laboratory:

- Type 1 diabetes antibodies (anti-insulin, anti-GAD-65, ICA, anti-ZnT8, anti-IA2)
- Connecting peptide (C-peptide)
- Insulin
- Proinsulin

9.7.5.2. Local Laboratory Tests

The following tests will be performed at the local study site or local laboratory:

- Urine pregnancy testing (for females of childbearing potential)
- Fingerstick BG levels as needed
- Hematology, chemistry, LFTs, and urinalysis from the first to the 11th day in each treatment course
- SARS-CoV-2 PCR test

During the study, all abnormal laboratory values will require further explanation from the Investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the Investigator.

9.7.6. Data Collected by Participants or Caregivers

Participants/caregivers will collect data related to insulin use, hypoglycemic events, intermittent (eg, spot-check or fingerstick) glucose measurements, AEs and internal medical and social history to be reviewed at clinical trial visits. The data will be collected in the eDiary. Training on data collection tools will be conducted by study-site staff at screening and at subsequent visits as needed. All data recorded by participants will be reviewed by study staff during study visits.

Exogenous insulin use: The participant will record all short-, intermediate- and long-acting insulin administered as intermittent injections or use with an “insulin pump” in the eDiary during the 7 days before randomization, and Week 12, 26, 39, 52, 65 and 78. These measurements will be used to calculate a mean daily insulin use per kg of body weight. Recording of insulin use data is not to be collected the day before or the day of the study visit due to preparation for MMTTs. If a participant forgets to record insulin use in the eDiary before a study visit, they may do so at the visit or for 72 continuous hours immediately after the visit. All effort should be made to collect a total of 7 days of data prior to Week 78 visit.

Hypoglycemia: Clinically important and non-serious and non-severe hypoglycemic episodes are defined in Section 12.1.4. All data regarding any BG reading of ≤70 (3.9 mmol/L) and/or symptoms consistent with hypoglycemia are to be collected throughout the 78-week duration of the study by study participants and through evaluation of glucometer readings. A specific focus should be made on recording data regarding BG levels of <54 mg/dL (3.0 mmol/L) or more severe events requiring assistance from another person. Data recorded in the eDiary should include information on specific blood glucose levels, clinical symptoms (including but not limited to change in mental status or loss of consciousness), length of the event, therapies used to treat the event, and if assistance or medical care (including clinic, emergency room or hospitalization) was required for the event (see Section 12.1 for AE definitions and reporting). In addition, data on glucose values meeting hypoglycemia criteria from both intermittent and continuous glucose monitors will be assessed.

Intermittent (fingerstick) blood glucose readings: As part of routine diabetes care, blood glucose levels should be checked at least 4 times a day including before each meal and at bedtime. At screening, participants will be offered a study supplied glucometer and glucometer strips, but participants are permitted to use their own glucometers if they choose. For the endpoint evaluations of finger-stick glucose values, participants are to bring their glucometer (or glucometers if they use more than one, such as at home and school) to each visit for data review and/or download.

In addition, 7 times throughout the study, participants will record pre-breakfast, lunch, dinner, and bedtime blood glucose levels for 7 days in the eDiary prior to the randomization and Weeks 12, 26, 39, 52, 65, and 78 visits. Like the collection of the insulin use data, recording BG data is not to be collected the day before or the day of the study visit due to preparation for MMTTs. If a participant forgets to record finger-stick glucose measurements before a visit, they may do so for 72 hours immediately after the visit.

9.7.7. Clinical Assessments

During screening and throughout the study a number of laboratory assessments will be obtained for safety assessment. These include, but are not limited to, CBC with differential account, chemistry panel, liver function tests, urinalysis, and CMV and EBV quantitative PCR analyses.

9.7.7.1. Vital Signs

The following vital signs will be measured at time points indicated in the Schedule of Events tables:

- Temperature (using an approved device, eg oral, tympanic, or forehead)
- Pulse/heart rate
- Respiratory rate
- Blood pressure

Blood pressure and pulse/heart rate measurements can be assessed with a completely automated device. Manual techniques will be used if an automated device is not available. Blood pressure

and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

9.7.7.2. Physical Examination

Physical examinations (complete or partial) sometimes including height and body weight will be conducted at times indicated in the Schedule of Events tables.

A complete physical exam includes: evaluation of general appearance, head, eyes, ears, nose, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, external evaluation of genitalia with Tanner Staging, evaluation of extremities and skin, and gross neurologic evaluation of strength, sensation and balance.

A partial physical examination includes: general appearance, head, eyes, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, evaluation of extremities and skin.

Any clinically relevant finding or change in physical exam occurring during the study must be recorded on the Adverse Event CRF.

Weight and height will be measured using calibrated scales. At each measurement, participants will be instructed to remove shoes and outdoor apparel and gear. Details on how to conduct these measurements will be provided to sites.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF and/or laboratory requisition form.

Refer to the Schedule of Events for the timing and frequency of all sample collections. For visits with study drug administration, all blood samples for assessing teplizumab concentration and antibodies must be collected according to the laboratory manual.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. PARTICIPANT COMPLETION, INTERRUPTION/DISCONTINUATION OF STUDY TREATMENT OR WITHDRAWAL FROM THE STUDY

10.1. Participant Completion

A participant will be considered to have completed the study if he or she has completed assessments at Week 78 of the study. It should be specified on the CRF whether or not the participant completed the study follow-up procedures through Study Day 546.

Participants who prematurely terminate study participation for any reason before completion of the study will not be considered to have completed the study and can initiate the prohibited medications and activities (Section 8.4).

Participants will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the participant's status at Study Day 546. Investigators must document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, follow- up should resume according to the protocol.

10.2. Interruption or Discontinuation of Study Treatment

A participant will not be automatically withdrawn from the study if they have to temporarily or permanently discontinue study drug before the end of the treatment regimen.

If a participant permanently discontinues study drug for any reason before the end of the treatment period (~Week 28, or ~Week 54 for the Modified Dosing Schedule), they should be encouraged to continue with all scheduled visits to and including the final study visit (Week 78) but without receiving study drug administration. If the participant is unwilling or unable to participate in all visits, they should be encouraged to participate in as many of the planned study visits as possible for continued assessment but without receiving study drug administration. If the participant is not able to attend the next 2 sequential study visits that include an MMTT, they should be encouraged to return for the Early Termination visit approximately 10 weeks after the last study drug administration, as applicable.

Similarly, if a participant withdraws following the treatment period (after ~Week 28), they should be encouraged to attend the Week 52 and Week 78 visits, as applicable. If a participant follows the Modified Dosing Schedule and is withdrawn after ~Week 54, the participant should be encouraged to attend Week 78 visit. If the participant is unwilling or unable to complete any of the remaining scheduled study visits, they should be encouraged to return for the Early Termination visit approximately 10 weeks after their last dose administration, as applicable.

In the period between Week 1 and Week 78, consecutive MMTTs should not be repeated if the time interval between them is less than 10 weeks. The MMTT can be repeated in less than 10 weeks only for repeat testing during the screening period or for rescreening.

SAEs must be reported for participants who withdraw early from the study for a year after their last study drug dose (Section 12.3.2).

Study drug may be temporarily or permanently discontinued due to events described below.

10.2.1. Events That Lead to Discontinuation of Study Treatment During Course 1 or Course 2

- The participant withdraws consent.
- The Investigator believes that for safety reasons or tolerability reasons it is in the best interest of the participant to discontinue study drug.
- A female participant becomes pregnant. Note: The "Pregnancy Report Form" should be submitted for all pregnancies that occur in a study participant. Pregnancy should be followed for outcome and any premature terminations reported. The health status of the mother and child including date of delivery and the child's sex and weight should be reported after delivery.
- A severe infection requiring inpatient hospitalization or repeated doses of parenteral antibiotics
- A severe hypersensitivity reaction, such as anaphylaxis or angioedema with or without requiring hemodynamic support (ie, epinephrine and/or blood pressure medications) or mechanical ventilation, to the study drug or an infusion reaction (including cytokine release syndrome) with signs or symptoms categorized as an SAE.
- The participant has a clinically significant cardiovascular event.
- The participant is diagnosed with a malignancy, lymphoma or a lymphoproliferative disorder.
- The participant is deemed ineligible for receipt of study drug according to the following TB criteria:
  - A diagnosis of active TB is made.
  - Symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination; or the participant has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
  - A chest radiograph with evidence of current active TB
  - A positive-IGRA test (ie, Quantiferon-TB test) result and/or an indeterminate IGRA test result on repeat testing (Section 9.7.4)
- Clinical suspicion of significant CMV or EBV disease (ie, infectious mononucleosis) or a CMV or EBV viral DNA PCR titer of >10,000 copies per ml serum or 10^6 cells
- If any of the following lab values is observed (normal range per local lab standard), the next study drug dose should be held until a repeat test is obtained and evaluated. If the out-of-range result is confirmed on two consecutive dosing days, the Medical Monitor must be contacted before making a decision about further treatment.
  - ALT and/or AST >5X ULN
  - Total Bilirubin >3X ULN
  - ALT and/or AST >3X ULN **AND** Total Bilirubin >2X ULN (Hy's Law criteria)
  - Platelet count <50,000/µL

  - Neutrophil count <500 cells/µL
  - Hemoglobin of <8.5 g/dL
- Any ≥Grade 3 AE during dosing other than:
  - Lymphopenia
  - Neutropenia
  - Low total WBC
  - Hypoglycemia or symptoms and signs of a hypoglycemic episode
  - Hyperglycemia or symptoms and signs related to hyperglycemia
  - Fatigue or malaise
  - Insomnia
  - Cheilitis
  - Dry skin
  - Nail changes
  - Hot flushes or flashes
  - Headache
  - Myalgia
  - Flu-like syndrome
- Any medically important event, such as a concurrent illness, complications, or abnormal laboratory result, that, in the opinion of the Investigator, contraindicates continued dosing of the participant
- Administration of prohibited medication or dose modification of concomitant medications that necessitate discontinuation of study drug administration
- A general lack of compliance with study visits and procedures per study team or missing 3 consecutive study drug administrations
- A positive SARS-CoV-2 PCR test (protocol version 3.0 onward)

The Study Medical Monitor must be notified within 24 hours of any participant who is permanently discontinued from study drug dosing. Participants who have study drug dosing permanently discontinued will be encouraged to receive follow-up care and evaluation as scheduled, unless consent for follow-up is withdrawn.

10.2.2. Events Resulting in Interruption of Study Treatment in Course 1 or Course 2

Study drug dosing may be interrupted temporarily, for an individual participant, if a medically important event occurs, such as concurrent illnesses, complications, or abnormal laboratory results:

- A significant infection, defined as:

  - Any severe infection meeting SAE criteria (Section 12.1.2), or
  - Any clinically significant infection not meeting SAE criteria but per Investigator's judgment might put the participant at risk, or

- An SAE, a study drug-related severe AE, or an AE that puts a participant at risk, defined as:
  - Any SAE (as defined in Section 12.1.2) or
  - Any severe AE that is considered related (possibly, probably, or very likely related) to study drug (as defined in Section 12.1.2), including but not limited to an infusion reaction categorized as a severe or SAE by the Investigator.
  - Any AE (including mild or moderate) of any relatedness to study drug that leads the Investigator to believe that further dosing of study drug during that course puts the participant at undue risk.
- If any of the following out-of-range lab results is observed (normal range per local lab reference ranges), the test may be repeated on the same day. If the repeated test result normalizes, that day's dose may be given. If the value is still in the indicated range or worsens, or if the test cannot be repeated on the same day, that day's dose should be withheld.
  - ALT and/or AST >3X ULN but ≤5X ULN
  - Total Bilirubin >2X ULN but ≤3X ULN
  - Platelet count >50,000 but ≤100,000
  - Hemoglobin >8.5 g/dL but ≤10 g/dL

Note: When clinical and laboratory abnormalities are considered related to T1D disease activity (ie, hypoglycemia and hyperglycemia) and study drug is not considered a contributing factor, administration may not need to be modified. The site Investigator should consult with the Medical Monitor and Sponsor if this is encountered.

If the above events resolve within 2 days, study drug dosing may be resumed according to the original schedule. The treatment course will not be extended beyond 12 days.

If the above events do not resolve after 2 consecutive days of interruption, the Medical Monitor must be consulted regarding continuation of study drug dosing.

10.2.3. Criteria to Withhold Initiation of Course 2

Participants will have a scheduled study visit at Week 20, approximately 4 weeks before the scheduled study drug infusion in Course 2. If any of the following criteria are met and not resolved by Week 26, Course 2 of the study drug shall not be administered. However, these participants may receive Course 2 at Week 52, if all of these criteria are resolved.

- ALT and/or AST >2X ULN
- Total bilirubin >1.5X ULN, except for subjects with Gilbert's syndrome with normal ALT and AST with approval of the Medical Monitor

- Hemoglobin <10 g/dL
- Lymphocyte count <1000 cells/μL
- Neutrophil count of <1000 cells/μL
- Platelet count <100,000 cells/μL
- Any condition consistent with a significant EBV or CMV infection or reactivation defined by clinical signs of infection; or if the EBV viral load is >10,000 copies per mL or 10^6 cells or the CMV viral load is >10,000 copies per mL or 10^6 cells
- A positive SARS-CoV-2 PCR test
- The development HIV, HBV of HCV infections. Noting that testing for these viruses is not required unless suspected by Investigator

In addition, if any of the following is present at the scheduled time of study drug administration, the second course of study drug will not be administered:

- Evidence of active infection, such as fever ≥38.5°C (101.3°F) common cold symptoms, sore throat, cough, vomiting or diarrhea
- Antibiotics or any other active treatment for an infection.

In addition, at the Week 26 visit prior to receipt of the second course of the study drug, the Investigator should review all inclusion and exclusion criteria to determine if there are any conditions that should disqualify the participant from further study drug administration.

Modified Dosing Schedule

Participants under the modified dosing schedule will be evaluated according to the same criteria at their Week 39 visit, before they begin the second course of treatment at the Week 52 visit.

Note: The above criteria are recommendations and can be overridden by Investigator's clinical judgment in consultation with the Medical Monitor.

Participants who have study drug dosing permanently discontinued for any reason will be encouraged to receive follow-up care and evaluation as scheduled, unless consent for follow-up is withdrawn.

10.3. Withdrawal from the Study

10.3.1. Participant Withdrawal

A participant will be withdrawn from the study treatment for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent/assent
- Death
- Study Investigator or Sponsor, for any reason, decides the participant should be withdrawn from the study.

- Pregnancy

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a participant withdraws before completing the study, the Sponsor and the DMC chair is to be notified and the reason for withdrawal is to be documented in the CRF and in the source document. The study drug assigned to the withdrawn participant may not be assigned to another participant.

Participants who withdraw will not be replaced. If a participant withdraws from the study before the end of study, all attempts should be made to obtain Early Termination visit assessments.

10.3.2. Withdrawal from the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

The collected samples will be retained and used in accordance with the participant's original separate informed consent/assent for optional research samples.

The participant may withdraw consent/assent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the Investigator must notify the Sponsor study-site contact of withdrawal of consent/assent for the optional research samples and to request sample destruction. The Sponsor study-site contact will, in turn, contact the facilities and representative storing the sample(s) to execute sample destruction. If requested, the Investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

The participant may withdraw consent/assent for use of samples for future research. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF/assent.

11. STATISTICAL METHODS

11.1. General Considerations

All statistical inferences will be based on 2-sided tests with an α-level of 0.05.

All data will be summarized by study drug group. Categorical variables will be summarized by number and percent of individuals falling within each category. Continuous variables will be summarized by mean, median, standard deviation, minimum and maximum.

Unless otherwise noted, baseline values will be defined as the most recent value collected prior to the first dose of study drug.

Data summaries and tabulations will be conducted using Statistical Analysis Software (SAS).

A detailed description of the statistical methods used in this protocol is in the Statistical Analysis Plan (SAP).

11.2. Analysis Data Sets

Intent-to-Treat (ITT) Population

For efficacy endpoints, the analysis population will be all randomized participants who receive any amount of study drug. This population will be referred to as the intent-to-treat population. For this population, participants will be analyzed in the treatment group corresponding to the treatment to which they are randomized, regardless of what treatment they actually receive.

Safety Population

For the safety endpoints, the analysis population will consist of all randomized study participants receiving any exposure to study drug. For this population, participants will be analyzed in the treatment group corresponding to the treatment they actually receive, regardless of the treatment to which they are randomized.

PK/Immunogenicity Population

For PK and immunogenicity, the analysis population will be all participants in the safety population who have provided at least one evaluable sample.

Modified-Dosing Subset

Data from participants who receive the second course of treatment at Week 52 (instead of Week 26) due to COVID-19 pandemic restrictions will be included in the ITT population and Safety population. Additional subgroup analyses for these participants will also be performed.

11.3. Sample Size Determination

The study sample size is calculated based on the desired clinically relevant effects and the results from placebo-treated participants in previous teplizumab studies. Since C-peptide AUC is skewed right, the data will be transformed using ln(AUC+1) for analysis and the assessment of sample size. Analyses at 18 months from prior studies in children and adolescents who entered the studies with a stimulated C-peptide AUC of >0.2 pmol/mL are limited. Estimates range from approximately 0.22 nmol/L to 0.32 nmol/L with a standard deviation between 0.18 and 0.22. Using an estimate of 0.25 nmol/L, the transformation to geometric mean in the placebo group is exp(0.25) -1 = 0.28. This study is designed to show a difference of at least a 40% in C-peptide response between teplizumab and placebo. In geometric means this translates to a value of (1.4*0.28) = 0.392. Consequently, approximately 300 participants are planned for enrollment, assuming 2-sided α=0.05, 90% power, 2:1 randomization, and a 10% dropout rate.

11.4. Handling of Missing Data

The amount, pattern (arbitrary or monotone in nature), and reasons for missing data (such as administrative, adverse event, lack of efficacy) will be described. Multiple imputation (MI) with pattern-mixture model under the missing not at random (MNAR) assumption will be used to impute the missing values for the primary endpoint as well as the secondary endpoints of exogenous insulin use, HbA1c levels, and TIR.

This method will be carried out using the standard three-step procedure:

Step 1. Generation of imputed datasets: The MI procedure of the SAS system will be used to generate *m* sets of data where missing data from participants who drop out before the end of the study are imputed based on participants who similarly discontinued study drug in the same treatment group but have measurements taken at scheduled visits. The selection of *m* depends on the required computing time, but a reasonable range is 20 to 100 sets. Linear regression will be employed to model the missing values and will include treatment (teplizumab or placebo), age, and peak C-peptide at baseline as covariates.

Step 2. Model-based analysis using each imputed dataset: Each of the *m* imputed data sets is analyzed using the same method as the corresponding endpoint analysis.

Step 3. Pooling the results from each model-based analysis: The results from the analysis of each imputed dataset will be combined by the MIANALYZE procedure of the SAS system.

11.5. Efficacy Analyses

11.5.1. Primary Endpoint Analysis

The primary endpoint is the difference between treatment groups in C-peptide ln(AUC+1) at Week 78 using the ITT population. C-peptide will be measured in a 4h MMTT. Analysis of covariance (ANCOVA) will be used to assess the treatment difference on C-peptide at Week 78. Missing data from patients who drop out before the end of the study will be imputed based on those patients who similarly discontinue treatment in the same treatment arm but have measurement taken at scheduled visits. The model will include treatment (teplizumab or placebo), age, and peak C-peptide at baseline as covariates.

Sensitivity analysis will be performed using a tipping point approach. The same imputation and model will be used as in the primary analysis, but a tipping point that changes the C-peptide conclusion at 18 months will be sought. Repeated measures analysis may also be used to assess sensitivity.

11.5.2. Secondary and Exploratory Clinical Endpoints

The secondary clinical endpoints will be assessed using the Hochberg step-up method for addressing multiplicity if primary endpoint reaches $p < 0.05$.

Like the primary endpoint, ANCOVA at 78 weeks will be used to assess treatment differences in insulin use, HbA1c, and percentage of time participants' BG levels are within the target range of >70 to ≤180 mg/dL (>3.9 to ≤10.0 mmol/L) at Week 78.

Average total exogenous insulin use (in U/kg/day) will be self-recorded in the eDiary for 7 days prior to study visits and at randomization. Participants need to record at least 5 of the 7 days in order for this data to be used in the analysis. The model will include age, baseline insulin use, peak C-peptide at baseline and treatment group as covariates.

The model used to assess HbA1c will include age, baseline HbA1c, treatment group, and baseline peak C-peptide as covariates.

Time in range for blood glucose will be defined as the average percentage of time in range for 10 to 14 days post each study visit. The model will include baseline time in range, treatment group, age and baseline peak C-peptide.

The rate (number of events/exposure time) of clinically important hypoglycemic episodes at Week 78 will be compared between groups. Data will be collected from intermittent glucose monitors, continuous glucose monitors, the eDiary, and CRFs. A clinically important episode is defined as a reliable BG value of <54 mg/dL (3.0 mmol/L) and/or a hypoglycemia event requiring assistance of another, such as seizure, syncope, severe confusion with or without a confirmatory low BG reading). The event rate of clinically important hypoglycemic episodes per study participant will be assessed using a negative binomial model to allow for the potential for overdispersion in case episodes for hypoglycemia within participant groups are correlated. The model to assess clinically significant hypoglycemia will include age, treatment group, baseline peak C-peptide as covariates.

11.6. Pharmacokinetic and Immunogenicity Analyses

PK analyses of teplizumab will be described in a separate PK analysis plan.

The incidence of positive anti-teplizumab antibodies will be summarized for all participants who receive at least 1 dose of teplizumab and have appropriate samples for antibody detection (ie, participants with at least 1 sample obtained after their first dose of teplizumab).

A listing of participants who are positive for antibodies to teplizumab will be provided. The maximum titers of antibodies to teplizumab will be summarized for participants who are positive for antibodies to teplizumab.

Other PK and immunogenicity analyses, including NAb, may be performed to further characterize the immune responses generated.

11.7. Concomitant Medications

Concomitant medications throughout the study will be collected and coded using the World Health Organization dictionary. The number and percent of study participants receiving each medication will be summarized.

11.8. Safety Analyses

Adverse Events

Safety and tolerability will be assessed primarily by summarizing AEs and SAEs including severe infection rates and drug infusion reactions through Week 78. AEs and SAEs will be summarized by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Events will be summarized by severity and relationship to study drug (assessed by Investigator). Participants will be counted only once for each preferred term, once for each system organ class and by the highest event severity, regardless of how many events a participant experienced.

These events will be recorded by the Investigators in the CRFs. Verbatim terms will be coded to the lower level terms in the MedDRA coding dictionary.

Only TEAEs will be summarized. An ongoing TEAE that increases in severity will be captured as a single event using the maximum severity experienced during the duration of the event.

Participants with AESIs (defined in Section 12.1.3) will be counted or listed.

Clinical Laboratory Tests

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by lab panel (e.g. hematology, blood chemistry, and urinalysis) and will be displayed by visit for each lab parameter.

Laboratory values will be classified based on CTCAE toxicity criteria (NCI 2018). Shift tables will be used to display the percent of study participants who have a shift in their lab values from normal at baseline to each post-baseline visit by CTCAE severity grade.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled timepoint. The percentage of participants with values beyond clinically important limits will be summarized and a corresponding listing will be provided.

Physical Examination

Proportion of participants with abnormal physical examination findings will be summarized at each scheduled timepoint. Participants with any post-treatment abnormalities will be listed.

11.9. Exploratory Endpoint Analysis

Clinical, metabolic, immunologic, molecular and genetic exploratory endpoints will be summarized by treatment group. No multiplicity adjustment will be used for these endpoints. Detailed descriptions of these summaries are included in the SAP.

Additional safety and efficacy analyses will be performed on the subgroup of participants who receive the second treatment course starting at the Week 52 visit because of the COVID-19 pandemic restrictions.

PD Substudy

Data from the CD3 receptor occupancy and modulation assays and respective changes from baseline (see Appendix 4) will be listed and summarized by treatment and sample collection time point. Mean (±SE) absolute values and changes from baseline will be plotted by treatment and time point. If notable trends over time in the teplizumab group are observed, further exploratory regression analyses on these repeated-measures data will be conducted to further elucidate any relationship. Additional exploratory analyses may be performed, and methods and results will be documented in the CSR or under separate cover.

11.10. Interim Analysis

No interim analysis is planned.

11.11. Data Monitoring Committee

An external, independent DMC consisting of at least 3 voting members who are medical and/or scientific field experts will be established to monitor data on an ongoing basis. The members are independent of the study with no scientific, financial, or other conflicts of interest related to the trial. A chairperson (voting member) will lead the committee and be its primary contact. An independent liaison statistician who is experienced in clinical trials conduct will be appointed as a nonvoting member. Details of the composition, roles, and responsibilities of members will be described in a separate DMC charter.

The DMC will periodically review safety data and the conduct of the study and make recommendations regarding study continuance, pausing, termination, or modification. The DMC will have access to unblinded data and review tabulated safety summaries (if appropriate) and any additional data deemed warranted during the conduct of the study.

An organizational DMC meeting will take place prior to the start of study site initiation and scheduled data review meetings will occur approximately every 4 months following randomization of the first participant through the completion of the second course of study drug administration by the final study participant. At that point, scheduled DMC meetings will take place every 6 months until the last randomized participant completes their final study visit.

The DMC will be notified ad hoc of specific events occur, including events indicating significant or unexpected safety concerns, when study stopping rules are met, when unblinding has occurred, or any other issue considered significant during a regular data review by the study's Medical Monitor or designee. A formal review can be prompted by these notifications if deemed warranted by the DMC.

As an outcome of each meeting, the DMC will make recommendations to continue, modify or terminate the clinical trial. If additional information (blinded or unblinded) is required for the DMC

to make its recommendation the DMC can defer its recommendation until that data is obtained and reviewed. If warranted, additional recommendations to the trial conduct can be made by the DMC.

Cumulative safety data will be reviewed by the Medical Monitor and/or DMC, as expeditiously as is reasonable, if any of the following occurs:

- Death of an enrolled participant
- Occurrence of a CTCAE v5.0 Grade 4 allergic/hypersensitivity reaction (anaphylaxis, manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation)
- Occurrence of a Grade 4 AE or SAE for:
  - Cytokine-release syndrome during dosing that is prolonged and not rapidly responsive to symptomatic medication and/or brief interruption of study drug administration AND is associated with other serious sequelae such as renal impairment or pulmonary infiltrates
  - EBV or CMV reactivation at any time during the study that results in serious, life-threatening disease manifestations such as splenic rupture or other serious sequelae such as hepatitis or liver function abnormalities or have viral PCR DNA titers of > 10,000 copies per mL serum or 10^6 cells
  - Any malignancy, lymphoma, or lymphoproliferative disorder appearing at any time during the study
  - Liver function abnormalities (TBili, AST or ALT) during dosing that do not return to ≤2x ULN for AST and ALT and ≤1.5x ULN for TBili within 72 hours of discontinuing study drug administration
  - Occurrence of 1 participant that meets Hy's Law of drug-induced liver injury, defined as: The occurrence of ALT or AST >3x ULN and bilirubin >2x ULN and the absence of a cause other than the study drug, eg, acute viral hepatitis, alcoholic and autoimmune hepatitis, biliary tract disorders, or cardiovascular causes, such as right heart failure, or concomitant medications.
  - An overall pattern of symptomatic clinical or laboratory events that the Medical Monitor or DMC considers possibly, probably, or definitely related to the study drug, which may appear minor individually but collectively may represent a serious potential concern for safety.

When events occur that appear to meet, in the opinion of the Medical Monitor or DMC, one or more of the criteria listed above, cumulative safety data will be reviewed as expeditiously as is reasonable for all participants. Upon completion of this review, the DMC will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

The DMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

The determination of seriousness, severity and causality must be made by the physician Investigator who is qualified to review adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment.

12.1. Definitions

12.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant from the time they formally agree to participate in the study (eg, by providing informed consent/assent) through their last study contact (eg, last visit or status update). An adverse event does not necessarily have a causal relationship with the study drug. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug (investigational or non-investigational product), whether or not related to that study drug (investigational or non-investigational product).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs after the first dose of study drug administration (Day 1) through the end of the study or early termination.

12.1.2. Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death: A death that occurs during the study or that comes to the attention of the principal Investigator during the protocol-defined follow-up period must be reported regardless of whether it is considered treatment related or not.
- Is life-threatening: The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is Medically Important: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Serious adverse event reports will be provided to the DMC members on an ongoing basis. The DMC will have access to unblinded data and review tabulated safety summaries (if appropriate) and any additional data that the DMC may request during the conduct of the study.

The Investigator must follow all SAEs (including serious AESIs) until resolution even if this extends beyond the study-reporting period. Resolution of a SAE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic. At any time after completion of the study, if an Investigator becomes aware of a serious adverse event that s/he suspects is related to study drug, the Investigator should report the event to the Pharmacovigilance contact.

12.1.3. Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs):

- ≥Grade 3 infections (includes all opportunistic infections): viral, fungal, bacterial
- Acute mononucleosis-like illness (eg, fever, pharyngitis, lymphadenopathy, clinical EBV and CMV infections and reactivations)
- Malignancies including lymphomas
- Severe hypoglycemic episodes that require assistance by another individual through the administration of oral or parenteral dextrose, glucagon or intervention
- ≥ Grade 3 liver function abnormalities (AST, ALT, bilirubin), ie, an AST or ALT value >5.0 x ULN or a bilirubin value >3.0 x ULN
- ≥ Grade 3 thrombocytopenia (platelet counts less than 50,000/µL)
- ≥ Grade 4 allergic/hypersensitivity reaction (anaphylaxis)
- ≥ Grade 3 Rash
- ≥ Grade 4 cytokine-release syndrome
- ≥ Grade 3 neutropenia (<1000 PMN/µL on 2 consecutive evaluations performed on different days)
- Lymphocyte count <500/mm^3 for 7 days or longer

Non-serious AESIs will be reported on the eCRF only.

For all other AEs, record all information in source documents and the corresponding eCRF. Additionally, any other event that the Investigator believes should be recorded is to be documented in the CRF.

12.1.4. Disease-Specific Adverse Events

12.1.4.1. Hypoglycemia

Participants in this study are to follow current guidance for glycemic control using intensive insulin therapy. Specifically, a goal HbA1c of <7.5% in those 17 years old or younger and <7.0% in those 18 years old and above (ADA 2018). If there are local, regional, or national recommendations to be followed that supersede ADA recommendations, these glycemic control targets (ie, HbA1cs or glucose levels) should not be more liberal (ie, higher) than the ADA recommendations. The Investigator will document in the CRF the glycemic goals.

Although glycemic control goals are suggested to reduce long-term complication of T1D, they have been shown to significantly increase the incidence of low blood glucose levels, vis-à-vis hypoglycemia. The ADA and EASD define hypoglycemia as a confirmed blood glucose reading of ≤70 mg/dL (3.9 mmol/L). In addition, there are other definitions of hypoglycemia based on "typical" symptoms without needing confirmatory BG reading. Minor symptoms of hypoglycemia and BG values of or slightly under 70 mg/dL (3.9 mmol/L) are not necessarily of clinical significance. Although all hypoglycemic events, including CTCAE Grade 1 events (BG <70 mg/dL or 3.9 mmol/L), should be recorded in the hypoglycemia eDiary, Grade 1 hypoglycemic events may not need to be reported as AEs, at the investigator's discretion.

Recently the International Hypoglycemia Study Group from the ADA and EASD published a position statement on hypoglycemia suggesting that clinical trials report as clinically important hypoglycemia BG values of <54 mg/dL (3.0 mmol/L), termed "Level 2 Hypoglycemia", and also significant impairment consistent with hypoglycemia requiring assistance often referred to as "severe" hypoglycemia, even in the absence of a BG reading, termed "Level 3 Hypoglycemia" (IHSG 2017). Level 3 events may include cognitive impartment, altered/loss of consciousness, confusion, seizure, syncope/fainting, or coma, and support may be general assistance, glucagon, or oral carbohydrate (ie, fruit juice or glucose tablets). These events may or may not require medical attention or hospitalization. A BG assessment demonstrating a low glucose level is not required to categorize severe hypoglycemia.

Taking together this guidance above, this study will consider clinically important hypoglycemia Level 2 and/or Level 3 Hypoglycemia using the definitions above. These events will constitute one of key secondary endpoints.

Recognizing that there may be episodes of hypoglycemia that might not meet these criteria, BG values of 54-70 mg/dL (3.0–3.9 mmol/L) and other milder symptoms should also be recorded and will be part of the exploratory analyses (Seaquist 2013, IHSG 2017). Participants are to collect and record such BG readings (if available), signs and symptoms, level of support, medical care and hospitalization (if needed), and other relevant information on health and wellbeing, recent insulin use, recent diet, exercise and concomitant medicines.

It is anticipated these non-Level 2 and 3 hypoglycemia events will be categorized as follows, using existing definitions from the ADA (Seaquist 2013, IHSG 2017):

- Documented non-severe symptomatic hypoglycemic: Non-severe hypoglycemia symptoms with a BG glucose reading of ≤70 mg/dL (3.9 mmol/L) but ≥ 55 mg/dL (3.0 mmol/L)
- Asymptomatic hypoglycemia: A BG reading ≤70 mg/dL (3.9 mmol/L) but ≥55 mg/dL (3.0 mmol/L) not accompanied by hypoglycemia symptoms
- Probable symptomatic hypoglycemia: Non-severe hypoglycemia symptoms not accompanied by a BG measurement
- Pseudo-hypoglycemia: Non-severe hypoglycemia symptoms but with a BG of >70 mg/dL (3.9 mmol/L)

In terms of adverse event reporting in this study, the severity of a hypoglycemia adverse event should be identified by the site Investigator and classified according to CTCAE v5.0 hypoglycemia as follows:

- Grade 1 hypoglycemia: A BG reading of 55-70 mg/dL (3.0–3.9 mmol/L). This is considered mild and either asymptomatic or with mild symptoms. It requires observation (clinical or diagnostic) only. Specific interventions are not indicated.
- Grade 2 hypoglycemia: A BG reading of 40–54 mg/dL (2.2–2.9 mmol/L). This is considered moderate with minimal, local or noninvasive intervention indicated. It limits age-appropriate activities
- Grade 3 hypoglycemia: A BG reading of 30–39 mg/dL (1.7–2.1 mmol/L). This is considered severe or medically significant but not immediately life-threatening. Hospitalization or prolongation of hospitalization is likely indicated. It is considered disabling and limits self-care.
- Grade 4 hypoglycemia: A BG reading of ≤29 mg/dL (1.6 mmol/L). This is considered life threatening (eg. seizures) with urgent intervention indicated.
- Grade 5 hypoglycemia: This is defined as hypoglycemia resulting in death.

AEs of hypoglycemia will be classified by the site Investigator as mild, moderate, or severe or an SAE along with relatedness to study drug as described in Sections 9.7.2 and 9.7.3.

Grade 1 hypoglycemia does not need to be reported as an AE.

12.1.4.2. Hyperglycemia and Diabetic Ketoacidosis

In this study hyperglycemia will be reported as a disease-specific AE if it meets Grade 4 severity and/or if associated with clinically significant DKA, defined as:

- Current (or very recent) hyperglycemia, for example, a BG level of >180 mg/dL (10 mmol/L)
- Acidemia, for example a venous or arterial bicarbonate level <15 mmol/L and/or blood pH <7.3,
- Ketonemia or ketonuria – for example serum or urine ketones elevated beyond the upper limit of the normal, **and**

- Requiring medical attention such as unplanned outpatient care, emergency room care, or hospitalization

12.1.4.3. Anticipated Adverse Events

An anticipated event is any adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

1. Hypoglycemia. This is a condition of low BG that can occur in individuals with T1D on insulin therapy. The definition is provided above in Section 12.1.4.1).

2. DKA. This is a condition of ketosis and metabolic acidosis that can occur in individuals with T1D. The definition is provided above in Section 12.1.4.2.

Both hypoglycemia and DKA may present along a spectrum of severity. The principal Investigator will be responsible for the AE classification according to Section 12.1.7.

Reporting of Anticipated Events

These events will be captured on the CRF and reported to the Sponsor as described in Section 12.2.2.1. Any event that meets serious adverse event criteria will be reported to the Sponsor within the appropriate timeline as described in Section 12.2.2. These anticipated events are exempt from expedited reporting as individual single cases to health authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the Sponsor will report these events in an expedited manner.

12.1.5. Unlisted or Unexpected Serious or Nonserious Adverse Events

An adverse event, the nature or severity of which is not consistent with the applicable product reference safety information (eg, IB for an unapproved investigational study drug product). For teplizumab, the expectedness of an adverse event will be determined by whether it is listed in the IB.

12.1.6. Attribution Definitions

The Investigator is required to provide an assessment of causality or relationship of adverse events to the study drug based on 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The causality assessment categories that will be used for this study are described below.

Causality assessments considered **not** related to study drug:

- Unrelated: The event is related to an etiology other than the study drug (the alternative etiology must be documented in the participant's medical record).

- Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.

Causality assessments considered **related** to study drug:

- Possible: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the participant's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out and/or the event re-appeared on re-exposure to the study drug.

12.1.7. Severity Criteria

An assessment of severity grade for each AE will be made by the site Investigator according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0. This document (referred to herein as the "CTCAE V5.0") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs. The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

Adverse events will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade 1 = Mild adverse event.
- Grade 2 = Moderate adverse event.
- Grade 3 = Severe adverse event.
- Grade 4 = Life-threatening or disabling adverse event.
- Grade 5 = Death

12.2. Special Reporting Situations

12.2.1. Safety Events of Interest

Safety events that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Accidental or occupational exposure to a Sponsor study drug

- Medication error involving a sponsor product (with or without participant exposure to the Sponsor study drug, eg, name confusion)
- Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

12.2.2. Expedited Safety Report

An expedited safety report is a written narrative report summarizing a serious adverse event that meets expedited safety reporting criteria (7- or 15-day report), which is documented using the appropriate form and format, and submitted within the required reporting timeframe of applicable regulatory authorities and/or IRBs/IECs of participating countries.

12.2.2.1. Anticipated Adverse Event

An anticipated event is any adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. These anticipated events (Section 12.1.4.3) are exempt from expedited reporting as individual single cases to health authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the Sponsor will report these events in an expedited manner.

12.2.3. Immediately Reportable Events

Immediately reportable events (IREs) include events other than SAEs that must be reported immediately within 24 hours of being identified. An IRE includes but is not limited to:

- AESIs of viral, fungal, or bacterial infection Grade 3 or higher
- Events leading to discontinuation of study drug in an individual participant
- Protocol deviations/violations due to emergency or accident
- Non-serious AEs including laboratory results identified during the DMC review to be reported immediately, eg, lymphocyte counts <500 cells/μL that persist for 1 week
- A participant missing a full dose on any dosing day

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious adverse events, including those spontaneously reported to the Investigator within 52 weeks after the last dose of study drug (which is the end of the study), must be reported using the Serious Adverse Event Form. In addition, SAEs will be requested to be submitted for participants who withdraw early from the study for a year after their last study drug dose. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Section 12.1.4.3.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug or device, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

Continuous glucose monitors are to be applied at specified Study Visits and worn for up to 2 weeks to record participant glucose levels at a high frequency. If there are any AEs associated with the CGMs (ie, device-related AEs) will be investigated and may include the return of the device to the Sponsor for inspection.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the Investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). Further, local regulation regarding reporting requirements for SUSARs will be applied. The Investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating Investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient period, the participant must be provided with a “wallet (study) card” and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a study drug should be reported as an SAE, Important Medical Event, and/or according to any other applicable seriousness criteria.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness, worsening of a preexisting condition, or an event considered possibly, probably, or definitely related to the study or study agent (Section 12.1.6). For example, a hospitalization for social reasons such as pending placement in long-term care facility
- Surgery or elective procedure not considered possibly, probably, or definitely related to the study or study agent (Section 12.1.6) or planned before entry into the study.

Disease progression should not be recorded as an adverse event or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Section 12.1.2).

12.3.3. Procedure for Serious Adverse Event Reporting

Within 24 hours of identifying an SAE (Section 12.1.2), regardless of the presumed relationship to the study drug, the Investigator must obtain an SAE report form, complete the form, and transmit it to the designated Pharmacovigilance contact.

Minimum information to be documented on the SAE report form:

- Protocol number; name and contact phone number of the Principal Investigator
- Participant number and year of birth
- Serious adverse event, date of event onset, date of last study drug administration, current status of participant, and Investigator causality assessment
- Concomitant Medication information
- Relevant laboratory/diagnostic test results and medical record progress notes

Pharmacovigilance contact information for SAE report will be provided to the study sites.

12.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be provided to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study drug administration.

Any pregnancy (in female participants or female partners of male participants) that occurs at any time during study participation should be reported. For participants who withdraw from all study visits, the study staff will make every effort to obtain any pregnancy information through the end of the study (Week 78 visit).

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.3 Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

The Sponsor will provide adequate supplies of the study drugs: teplizumab and placebo sterile solution for injection.

The formulation of teplizumab will consist of 10 mM sodium phosphate, 150 mM sodium chloride, and 0.05 mg/mL Tween 80 with pH 6.1. The final drug product will be provided at a concentration of 1 mg/mL for a total of 2 mg of recoverable drug product per vial.

The placebo formulation will consist of the same formulation buffer without teplizumab.

14.2. Packaging

Teplizumab and placebo will be supplied in 2 mL type 1 glass vials with rubber stoppers and flip-off seals.

14.3. Labeling

The study drugs (teplizumab and placebo) will be labeled with, at a minimum, the protocol number, vial number, kit number, pharmaceutical dosage form (including product name and quantity in kit), directions for use, storage conditions, expiry date (if applicable), batch number, the statements "For clinical trial use only," and/or "CAUTION: New Drug – Limited by Federal (United States) Law to Investigational Use," and the Sponsor's name and address. Any additional labeling requirements for participating countries will also be included on the label.

Please see the Pharmacy Manual for detailed information about the packaging of the study drug or placebo and additional labeling information.

14.4. Preparation, Handling, and Storage

Teplizumab should be stored, prepared, and handled according to the Pharmacy Manual. The Pharmacy Manual should be followed to ensure that intravenous drug delivery devices used are made of compatible materials.

Compatibility testing of teplizumab with solutions other than 0.9% sodium chloride has not been conducted. Teplizumab for IV administration may only be prepared with 0.9% sodium chloride. No solutions other than 0.9% sodium chloride may be running through the same IV line when

teplizumab is being administered. If the same intravenous line must be used for infusion of other drugs or solutions, the line should be flushed with 0.9% sodium chloride solution before and after infusion of teplizumab.

The vials should be stored at controlled temperatures from 2°C to 8°C (36°F to 46°F) and must *not* be frozen. To ensure compliance, temperature logs will be maintained. The refrigerator should have a digital min/max thermometer.

Refer to the Pharmacy Manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The Investigator or his designee is required to maintain accurate drug accountability records. A binder containing instructions and the required accountability documentation will be provided to the Investigator or his designee. When the study is completed, study drug accountability records must be sent to the Sponsor. The drug accountability records must be maintained with the rest of the documentation at the site in accordance with Section 17.7. All unused study drug must be returned to the Sponsor or disposed of upon authorization by the Sponsor or its designee. All records regarding the disposition of study drug must be available for inspection by the study monitors.

Study drug should be dispensed under the supervision of the Investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to participants participating in the study. The Investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15. STUDY-SPECIFIC MATERIALS

The Investigator will be provided with study-specific manuals and materials, including the following:

- Pharmacy manual
- Laboratory manual
- NCI CTCAE Version 5.0
- IWRS manual
- CRF Completion Guidelines
- Sample ICF
- eDiary

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected is noted in Section 9.1.3. The local, regional and national acceptable amount of blood to be collected over this time period from the population is detailed in Appendix 3.

16.1.1. Investigator Responsibilities

The Investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.1.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the Investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments

- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

16.1.3. Informed Consent and Assent Form

Each participant and a legally acceptable representative must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the study-site personnel must explain to potential participants and their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the Investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF/assent, the participant and legally acceptable representative are authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations.

The participant and legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, assent/consent should be appropriately recorded by means of the participant's and his or her legally acceptable representative's personally dated signature. After having obtained the assent/consent, a copy of the ICF must be given to the participant and his or her legally acceptable representative.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the assent/ICF after the oral consent of the participant or legally acceptable representative is obtained.

Children (minors) or participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. Written assent should be obtained from participants who are able to write. A separate assent form written in language the participant can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the participant, and to the participant's parent or if applicable legally acceptable representative.

16.1.4. Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. The objectives of the study and the nature and detail of the personal data to be recorded by the Sponsor as a consequence of study participation will be explained to each study participant (or their legally acceptable representative) in the ICF and during the consent process.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. In Europe the Study will be conducted in compliance with Regulation (EU) 2016/679 “General Data Protection Regulation”. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to participants’ personal data shall be approved by the local IEC/IRB and shall agree to keep the participants’ personal data confidential.

The informed assent/consent obtained from the participant and his or her legally acceptable representative shall include explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory authority inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request access to his or her personal data and the right to request rectification of any data that are not correct or complete. Details of which party to contact in respect

of such requests shall be included in the ICF and in the consent process. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In addition to these rights, a participant may restrict the processing of incorrect data, request a copy of the data or ask for them to be transferred to a third party (portability). A participant can also withdraw consent on the data, in which case no further information about the participant will be collected from that moment onward.

Any limitation placed upon the participant's right to erasure of their personal data from study records resulting from the need to conduct the study in compliance to locally applicable regulations and laws shall be explained in the ICF and in the consent process.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not necessarily be returned to participants or Investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.1.5. Long-Term Retention of Samples for Additional Future Research

Samples collected from randomized participants in this study may be stored for up to 15 years or more (or according to local regulations) for additional research. Samples can be used to understand the effects of teplizumab on Type 1 diabetes, differential drug responders, and to develop tests/assays related to teplizumab or other autoimmune conditions. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 10.3.1, Withdrawal From the Use of Samples in Future Research).

16.1.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor and signed and dated by the

Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the Investigator or other physician in attendance will contact the appropriate Sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. Protocol deviations will be documented.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the Sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the Principal Investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an Investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of Investigator (eg, Form FDA 1572), if applicable
- Documentation of Investigator qualifications (eg, curriculum vitae)

- Completed Investigator financial disclosure form from the Principal Investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first participant:

- Completed Investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Participant Identification, Enrollment, and Screening Logs

The Investigator agrees to complete a participant identification, screening, and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site

- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol.

17.5. Case Report Form Completion

Study-specific CRFs are prepared for each participant in electronic format.

Electronic Data Capture (EDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto electronic CRFs (eCRF) via the secure EDC system in accordance with the study calendar, and within the timeframe agreed upon between the Sponsor and the study site.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

When necessary, queries will be generated in the EDC system. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study personnel can make corrections in the EDC system at their own initiative or as a response to a query (from the EDC system).
- Sponsor or Sponsor delegate can generate a query for resolution by the Investigator and study-site personnel.

All CRF entries, corrections, and alterations must be made by the Investigator or authorized study-site personnel. The Investigator must verify that all data entries in the CRF are accurate and correct. Investigator will review, sign, and date completed CRFs at regular intervals as determined by the Sponsor.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the Investigator and study-site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

Clinical monitors will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/institution must permit access to such reports.

17.8. Monitoring

The Sponsor will use a combination of monitoring techniques (eg, central, remote, or on-site monitoring) to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will

be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the Sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study will be considered to have completed when the database is locked after the last participant's last visit.

The Investigator will notify the IRB/IEC when the study has been completed.

17.9.2. Study Termination

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The Investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding teplizumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the Investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the Sponsor's prior written consent.

The Investigator must agree to send to the Sponsor for review all manuscripts, abstracts and presentations using data from this study prior to their submission for publication. The Sponsor reserves the right to delete from such materials any part or parts deemed to be confidential or proprietary.

The Investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of teplizumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the Investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the Investigator. The Investigator has the right to publish study site-specific data after the primary data are published. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for

filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, Investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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APPENDICES

Appendix 1: American Diabetes Association T1D Diagnostic Criteria

As defined by the American Diabetes Association (ADA) for the diagnosis of diabetes, the individual must meet one of the following 4 criteria:

- A fasting plasma glucose (FPG) of ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
- A 2-hour plasma glucose (PG) of ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
- A hemoglobin A1C (HbA1c) of ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG of ≥200 mg/dL (11.1 mmol/L).

Note: In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

For the diagnosis of Type 1 diabetes (T1D), the ADA suggests that plasma blood glucose rather than HbA1C should be used to diagnose the acute onset of T1D in individuals with symptoms of hyperglycemia.

According to ADA, a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥200 mg/dL [11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some providers may also want to know the HbA1C to determine how long a patient has had hyperglycemia. In addition, T1D, previously called “insulin-dependent diabetes” or “juvenile-onset diabetes,” accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (GAD65), insulin, the tyrosine phosphatases IA-2 and IA-2β, and ZnT8. T1D is defined by the presence of one or more of these autoimmune markers.

Appendix 2: Mixed Meal Tolerance Test (MMTT) Procedures

The procedure below for the mixed-meal tolerance test (MMTT) is an overview of how participants and study personnel should prepare for and perform the test. Additional details will be provided in the Laboratory manual. Minor adjustments to this procedure may be made by the sponsor that will not necessitate a protocol amendment.

Overview

The preparation for both 2h and 4h MMTTs are the same; the difference primarily lies in the length of the assessment.

The MMTT is to be performed in the morning between approximately 7:00 a.m. and 10:00 a.m., meaning that the Boost High Protein Nutritional Energy Drink® (Mead-Johnson) is to be consumed within this time. It is recommended that the tests be scheduled early in the morning (7:00–7:30 am) because blood glucose is more likely to be within the target range. The 4h MMTT takes approximately 250 minutes to complete, and the 2-hour MMTT takes approximately 130 minutes.

There are several types of Boost nutritional drinks that contain different amounts of carbohydrates, fats and protein. This test should specifically use Boost High Protein Nutritional Energy Drink with the following content per bottle:

- Total volume of drink per bottle: 8 ounces (237 mL)
- Total calories: 240
- Total fat: 6 grams (saturated fat 1 gram and trans fat 0 grams)
- Total carbohydrates: 28 grams (Sugars 15 grams)
- Total protein: 20 grams

If a participant has a known food allergy to one or more components of Boost, an equivalent substitution may be used contingent upon agreement with the study team and consultation with the Medical Monitor.

Dietary Guidelines and Pretest Instructions

Carbohydrates should not be restricted from the diet before the test. A general guideline is that pre-adolescents should consume at least 25 kcal (6.25 g)/kg/day in carbohydrates and adolescents and adults should consume at least 15 kcal (3.75 g)/kg/day in carbohydrates for 3 days before the test. These are minimum amounts of carbohydrates; most diets will include more carbohydrates. There is no need to alter the participant's diet unless he or she has been on a carbohydrate-restricted diet.

Participant Preparation

Food and (non-insulin) medicines:

- Fast for at least 10 hours but not more than 16 hours before the test. Fasting should start the night before the test and continue up until the start of the test. Participants should not eat or drink anything except water. Coffee, tea, soda, cigarettes, alcohol, or chewing gum are prohibited.
- Refrain from vigorous exercise during the fasting period.
- Refrain from working during the fasting period.
- If medically feasible, medications should be held from the start of the fast to the study visit. If a medicine must be taken during the fast, the participant is to consult with the investigator.

Insulin before the test:

- At least routine monitoring of blood glucose should be conducted the evening and the night before and the morning of the test and be used to gauge insulin treatment.
- Short-acting insulin analogues may be administered up to 2 hours before the test (eg, lispro or l-aspart).
- Regular insulin may be administered up to 6 hours before the test.
- Intermediate-acting insulin may be administered on the evening before the MMTT, but NOT on the morning of the test. Participants managed with intermediate-acting insulin (NPH or Lente) should administer their usual dose on the evening before the MMTT but not on the morning of the test.
- Long-acting basal insulin or continuous subcutaneous insulin infusions may be administered before, during, and after the test as usual. Participants on glargine may take their usual injection at the appropriate time. those on continuous subcutaneous insulin infusion may continue with their usual basal settings.

Glucose management and target blood glucose at the start of test:

The target glucose level at the start of the test is between 70 and 200 mg/dL (3.9-11.1 mmol/L). The investigator and the study participant should discuss the individual situation for insulin administration to attain the goal of meter capillary glucose values within the range of 70-200 mg/dL (3.9-11.1 mmol/L) at the start of the test.

For example, participants may be instructed to check their blood glucose by glucometer at home 2 hours before the start of the test, so that marked hyperglycemia can be treated with a short-acting insulin analogue. Alternatively, participants who arrive at the research unit with elevated blood glucose can receive additional short-acting insulin analogues at the time of their arrival, if the test is started at least 2 hours after insulin administration and occurs before 10 a.m.

If a participant's blood glucose is below 70 mg/dL (3.9 mmol/L) prior to performing the MMTT, the participant should be treated according to local practice, and the MMTT should be rescheduled.

Study site preparation for the MMTT

Calculating the dose of BOOST:

- The participant's weight (in kg) should be obtained on the morning of the test.
- The dose of BOOST is 6 kcal/kg. BOOST has a caloric concentration of 1 kcal/kg.
- The maximal volume of BOOST a participant should consume is 360 mL.
- The study coordinator/investigator is to document the volume of BOOST to give the participant.
- BOOST may be consumed at room temperature, refrigerated, or chilled on ice but should not be mixed with any other substances. It can be consumed directly from a cup or via a straw.
- The participant is to be instructed that the BOOST is to be consumed in no more the 5 minutes.

Preparation for sample collection:

- As the MMTT may be fast paced and it is important to draw blood as close to the planned time points as possible; it is important to be prepared.
- Blood drawing supplies, including syringes, needles, and flush solutions are obtained.
- The sample collecting tubes are pre-labeled with times of the draw with spare tubes available.
- An ice bucket is available to temporarily store the samples.
- The centrifuge is readily assessable and cooled to 4°C.
- A fingerstick/spot check glucometer and strips should be available.

Participant preparation:

- The intravenous (IV) catheter should be in place and confirmed to be able to draw blood.
- There is no restriction on the size of the IV catheter to use, but smaller catheters (especially 24 gauge) can be prone to clotting and malfunction and are not recommended. If possible, a larger catheter (18 or 20 gauge) is preferred.
- If a participant receives the study drug infusion via a midline or PICC-line, blood can be drawn from those catheters for MMTT at visits when the study drug is administered.
- The catheter is to be flushed after each draw with saline or heparin solution according to local practice.
- The participant should remain sitting or resting in bed quietly throughout the test and until the test is completed. Quiet, nonstrenuous activities, such as reading, playing cards, or

watching TV are allowed. The participant may walk to the bathroom between blood draws if necessary.

Blood draw time points:

- The first blood sample should be taken at least 10 minutes after establishing the IV and when the participant is calm and relaxed as much as possible.
- Draw the "-10 min" blood sample for C-peptide and insulin and blood glucose (using the glucometer).
- After the "-10 min" blood sample, prepare the BOOST dose for consumption as described above.
- Draw the second, "0 min" blood sample and have the participant drink the BOOST right away (and consume in no more than 5 minutes) and process the sample.
- **For the 2-hour MMTT**: Continue with blood sample collection (3 mL collection tube (C-peptide and insulin) and glucometer (BG) evaluation) at: 15, 30, 60, 90, and 120 minutes for a TOTAL of 7 samples (including the -10 and 0 min samples).
- **For the 4-hour MMTT**: Continue with blood sample collection (3 mL collection tube (C-peptide and insulin) and glucometer (BG) evaluation) at 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes for a TOTAL of 11 samples (including the -10 and 0 min samples).
- A window of ±5 minutes is allowed for the sampling timepoints specified above.

Sample processing procedures are provided in the Investigator Laboratory Manual.

At the conclusion of the test, check participant's blood glucose by glucometer, advance diet, and resume insulin as per participant's standard plan.

The study team should confirm all data, including details of the BOOST (type and volume consumed), BG levels at presentation and during the test, timing of tests, confirmation of blood draws and sample processing, type and placement of IV catheter, and any problems or deviations during the test, including a clogged IV catheter or missed samples in source and/or on the CRF.

MMTT DATA SHEET EXAMPLE

Date: Day: _____ Month: _____ Year: _____	**Participant is here for a: (circle one)** 2-hour MMTT 4-hour MMTT
IV Catheter: Detail if needed: Gauge: _____ Anatomic site of catheter: _____	**Participant Weight:** Kg: _____

Time of Day (24:00)	**Study/Sample Time**	**BG value (circle mg/dL or mmol/L)**	**C-peptide sample collected/processed correctly**
_____:_____	At Presentation to Facility		N/A
_____:_____	-10 min		[ ] YES Detail if needed: [ ] NO
_____:_____	0 min		[ ] YES Detail if needed: [ ] NO
_____:_____	Consume BOOST	BOOST Type: _____ Volume to be consumed: _____ ml (= 6 mls x ___kg OR Max 360 ml) All BOOST consumed: [ ] YES; [ ] NO Consumed in 5 min or less: [ ] YES; [ ] NO	
_____:_____	15 min		[ ] YES Detail if needed: [ ] NO
_____:_____	30 min		[ ] YES Detail if needed: [ ] NO

(Continued)			
_____:_____	60 min		[ ] YES Detail if needed: [ ] NO
_____:_____	90 min		[ ] YES Detail if needed: [ ] NO
_____:_____	120 min		[ ] YES Detail if needed: [ ] NO
If a 2-hour MMTT is being performed, put a "X" in Time and BG column and Skip next section. Continue with additional assessments ONLY with the 4-hour MMTT			
_____:_____	150 min		[ ] YES Detail if needed: [ ] NO
_____:_____	180 min		[ ] YES Detail if needed: [ ] NO
_____:_____	210 min		[ ] YES Detail if needed: [ ] NO
_____:_____	240 min		[ ] YES Detail if needed: [ ] NO
Pre-discharge assessments _____:_____	Participant Discharge		Participant back to baseline T1D management: [ ] YES; [ ] NO CRF Complete: [ ] YES; [ ] NO

Appendix 3: Blood Draw Volumes

The estimated blood volumes drawn during the study, corresponding to the Schedule of Events, are shown in the table below.

Study participants are otherwise healthy, except for their recently diagnosed T1D, with no significant respiratory or cardiovascular disease. Participants will be monitored for clinical consequences of blood draws. Throughout the study, the Principal Investigator has the discretion to modify the blood draw schedule for safety considerations.

Appendix Table: Estimated blood draw volume at each study visit (without PD substudy)

Visit Period	Pre-Screen	Screen	Study Drug Treatment: Course 1						Post Course 1				Study Drug Treatment: Course 2						Post Course 2						ET	Total[b]
Week	(-6) – (-4)	(-5) - 0	1				2		4	8	12	20	26				27		30	34	39	52	65	78		
Day	(-42) – (-28)	(-35) – 0	1	2	4	6	9	12	28	56	84	140	182	183	185	187	190	193	210	238	273	364	455	546		
Blood volume per visit (mL)	7	76 - 79.5[a]	64.5	5.5	8.5	5.5	11.5	27.5	34	8.5	45	12	74.5	5.5	8.5	8.5	8.5	27.5	34	8.5	41	89.5	27.5	89.5	89.5	**721.5 - 725**

Modified Dosing Schedule: estimated blood draw volume at each visit (without PD substudy)

Visit Period	Pre-Screen	Screen	Study Drug Treatment: Course 1						Post Course 1							Study Drug Treatment: Course 2						Post Course 2				ET	Total[b]
Week	(-6) – (-4)	(-5) - 0	1				2		4	8	12	20	26	34	39	52				53		56	60	65	78		
Day	(-42) – (-28)	(-35) – 0	1	2	4	6	9	12	28	56	84	140	182	238	273	364	365	367	369	372	375	392	420	455	546		
Blood volume per visit (mL)	7	76 - 79.5[a]	64.5	5.5	8.5	5.5	11.5	27.5	34	8.5	45	12	62	5.5	41	74.5	5.5	8.5	8.5	8.5	27.5	34	27.5	27.5	89.5	89.5	**718.5 - 722**

ET=early termination visit

[a] The blood draw volume is 76 mL without the serum β-HCG test or 79.5 mL with the test.

[b] Total maximum volume does not include the pre-screen and ET visit.

Appendix 4. Pharmacodynamic Substudy at North American Sites

In order to evaluate the effects of teplizumab on pharmacodynamic (PD) measures of CD3 receptor occupancy and modulation, a substudy will be conducted at all North American sites.

In addition to all of the study procedures described in the protocol, participants in the PD substudy will provide additional blood samples for the assessment of CD3 receptor occupancy and modulation.

PD samples will be drawn concurrently with the PK blood samples at the following time points:

- During Treatment Course 1:
  - Pre-infusion: Day 1, Day 4, Day 9, Day 12
  - 45 ± 15 minutes after the end of infusion: Day 9
- Day 28

Estimated blood draw volume at each study visit (including PD substudy):

Visit Period	Pre-Screen	Screen	Study Drug Treatment: Course 1						Post Course 1				Study Drug Treatment: Course 2						Post Course 2						ET	Total [b]
Week	(-6) – (-4)	(-5) - 0	1				2		4	8	12	20	26				27		30	34	39	52	65	78		
Day	(-42) – (-28)	(-35) – 0	1	2	4	6	9	12	28	56	84	140	182	183	185	187	190	193	210	238	273	364	455	546		
Blood volume per visit (mL)	7	76 -79.5[a]	66.5	5.5	10.5	5.5	15.5	29.5	36	8.5	45	12	74.5	5.5	8.5	8.5	8.5	27.5	34	8.5	41	89.5	27.5	89.5	89.5	**733.5 - 737**

Modified Dosing Schedule: estimated blood draw volume at each visit (including PD substudy)

Visit Period	Pre-Screen	Screen	Study Drug Treatment: Course 1						Post Course 1							Study Drug Treatment: Course 2						Post Course 2				ET	Total[b]
Week	(-6) – (-4)	(-5) - 0	1				2		4	8	12	20	26	34	39	52				53		56	60	65	78		
Day	(-42) – (-28)	(-35) – 0	1	2	4	6	9	12	28	56	84	140	182	238	273	364	365	367	369	372	375	392	420	455	546		
Blood volume per visit (mL)	7	76 - 79.5[a]	66.5	5.5	10.5	5.5	15.5	29.5	36	8.5	45	12	62	5.5	41	74.5	5.5	8.5	8.5	8.5	27.5	34	27.5	27.5	89.5	89.5	**730.5 - 734**

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted]

Organization: Provention Bio, Inc

Signature: _____ [redacted]

Note: If the address or telephone number of the Investigator changes during the course of the study, written notification will be provided by the Investigator to the Sponsor, and a protocol amendment will not be required.