Provention Bio, Inc.

Protocol PRV-031-001 (PROTECT)
NCT03875729

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)

Statistical Analysis Plan

Version: 5.0

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADA	Anti-drug antibodies
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
BMI	body mass index
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
CI	confidence interval
CL	clearance
cm	centimeter(s)
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
COVID-19	Coronavirus Disease 2019
CRF	case report form(s)
CTCAE	Common Terminology Criteria for Adverse Events
CVB	coxsackie virus b
DBili	direct bilirubin
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DNA	deoxynucleic acid
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	DTSQ Change

Abbreviation / Acronym	Definition / Expansion
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment
eCRF	electronic case report form
EMA	European Medicines Agency
EOSV	End of Study Visit
Fc	fragment crystallizable region of an antibody/immunoglobulin molecule
FcR	receptor binding to the Fc component of antibody molecules
FDA	Food and Drug Administration
g	gram(s)
GAD	glutamic acid decarboxylase
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eyes, ear, nose, throat
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HFS	Hypoglycemia Fear Scale
HPF	high power field
HRQL	Health-Related Quality of Life
IA	islet antigen
ICA	islet cell cytoplasmic autoantibody
ICE	intercurrent event
ICH	International Council for Harmonisation
Ig	immunoglobulin
IGRA	interferon gamma release assay
IL	interleukin
INR	international normalized ratio
ITT	intent to treat
IU	international unit(s)
IV	intravenous
KD	kilodalton
kg	kilogram

Abbreviation / Acronym	Definition / Expansion
L	liter(s)
LDL	low density lipoprotein
LFT	liver function test
ln	natural log (log base e)
LS	least squares
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MI	multiple imputation
min	minute(s)
mL	microliter(s)
mmHg	millimeters of mercury
mmol	millimole(s)
MMRM	mixed-effects repeated measures
MMTT	mixed meal tolerance test
MNAR	missing not at random
mol	mole(s)
NA	not applicable
NAb	neutralizing antibody
NCI	National Cancer Institute
NK	natural killer
nmol	nanomole(s)
NONMEM	nonlinear mixed effects modeling
NSAID	nonsteroidal anti-inflammatory drug
PCI	Potentially Clinically Important
PCR	polymerase chain reaction
PDC	Perceived diabetes control
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
pmol	picomole(s)
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
RR	respiratory rate

Abbreviation / Acronym	Definition / Expansion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	standard deviation
sec	second(s)
SOC	System Organ Class
T1D	type 1 diabetes
TB	tuberculosis
TBili	total bilirubin
TBNK	T cell, B cell, NK cell
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TIR	time in (glycemic target) range
TS	Treatment satisfaction
µmol	micromole(s)
U	unit(s)
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell
ZnT8	zinc transporter 8

1 INTRODUCTION

Type 1 diabetes (T1D) is a T cell-mediated autoimmune disease that targets and destroys insulin secreting β cells, resulting in the body's inability to sense glucose levels and produce insulin. In the absence of therapy, this leads to uncontrolled blood glucose (BG) elevation (hyperglycemia) and its short and long-term sequelae including rapid wasting and inevitable, near-term death. 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). 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 provide critical data 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.

The planned analyses identified in this statistical analysis plan (SAP) may be included in the clinical study report (CSR), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed, if included, will be clearly identified as such in the final CSR.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 4.0 (US, Canada, Germany, December 10, 2020), Version 4.1 (Belgium, Czech Republic, Poland, December 10, 2020), Version 4.2b (France, March 31, 2021), and 4.3 (UK, April 08, 2021)
- Electronic Case Report Form (eCRF), September 01, 2022

This SAP is developed in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9: Statistical Principles for Clinical Trials.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

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 primary estimand for the PROTECT study is defined as:

A. Population

   The treatment effect is to be estimated for the population of children and adolescents (8–17 years old) with newly diagnosed Type 1 Diabetes (T1D; within 6 weeks of T1D diagnosis) as defined by the protocol inclusion/exclusion criteria.

B. Endpoint

The primary endpoint of this study is area under the time-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed meal tolerance test (MMTT) at Week 78. The AUC will be computed using the trapezoidal rule and standardized by the duration of the MMTT test, i.e., divide AUC by the last blood sample collection time (240 minutes or the last collection time for 4h MMTT).

C. Intercurrent Events (ICEs)

All types of ICEs, including use of medications disallowed according to the protocol, modified dosing schedule due to COVID-19, premature discontinuation of study treatment, and non-adherence to the planned treatment regimen, will be handled using the treatment policy strategy, i.e., the values for the endpoint will be used regardless of whether ICEs occur. Missing data resulting from ICEs or other reasons will be imputed according to the imputation methodology specified in the SAP. Sensitivity analyses will be conducted to evaluate the effect of ICEs.

D. Population-level summary to compare groups

The mean change from baseline to Week 78 in C-peptide ln(AUC+1) will be estimated for each treatment group, and the teplizumab group will be compared to the placebo group using the difference in group least squares means.

2.2 Secondary Objective(s)

The secondary objectives of this study are as follows:

- To evaluate participant improvements in efficacy 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.

2.3 Exploratory Objective(s)

The exploratory objectives of this study are as follows:

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter study. This study will enroll male and female participants 8 to 17 years of age with newly diagnosed 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 inclusion criteria and none of the exclusion criteria.

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) 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.

For each stratification stratum, the range for the randomization numbers is pre-defined and the IWRS system fills each block with randomized patients until the block size is met and then it goes to the next block. In addition, the randomization number is scrambled, meaning the randomization number patients receive from the list are random compared to the sequence they are assigned in. Each block contains active and placebo patients based on the allocation ratio and block size.

As a result of the COVID-19 pandemic, study enrollment and dosing were temporarily interrupted. Some participants scheduled for the second course of treatment at 6 months were unable to receive this course. It was anticipated that approximately 10% of the participants would be affected by this interruption. As a result, the protocol was amended to allow for a modified-dosing schedule (MDS) whereby the 2nd course of treatment is administered at 12 months (Week 52) for this subset of participants.

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) or at approximately 12 months (Week 52) if following the MDS. Each course of treatment will include daily infusions for 12 days. 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. The total study duration for each participant will be up to 84 weeks, which includes a screening period of up to 6 weeks, a treatment period of two 12-day treatment courses separated by 6 or 12 months, and a post-treatment observation period of approximately 52 or 26 weeks, respectively. The final visit will take place at Week 78.

In order to evaluate the effects of teplizumab on pharmacodynamic (PD) measures of CD3 receptor occupancy and modulation as well as T cell activation, a substudy will be conducted at 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 as well as T cell activation. PD samples will be drawn concurrently with the PK blood samples at pre-infusion on Day 1, Day 4, Day 9, and Day 12; at 45 ± 15 minutes post-infusion on Day 9; and on Day 28.

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. Operational and logistical details are provided in the PRV-031-001 DMC charter.

Assessments of safety, efficacy, PK, immunogenicity, and other key evaluations will be conducted throughout this clinical trial. Refer to Appendix 1 for the complete schedule of assessments and Appendix 8 for MDS due to COVID-19 pandemic.

3.2 Endpoints

Primary Efficacy Endpoint

The primary endpoint of this study is 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 AUC will be expressed as area per unit time. i.e., divide AUC by the last blood sample collection time (240 minutes for 4h MMTT and 120 minutes for 2h MMTT).

Secondary Efficacy 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.

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, any infection requiring IV antimicrobial treatment or hospitalization, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection, significant viremia (i.e., 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
- Incidence of Potentially Clinically Important Laboratory Tests with associated listing of all values of that variable by visit (e.g., ALT is > 3x ULN at one visit; all ALT values will be listed)
- Incidence of Abnormal Clinically Significant Vital Signs based upon Investigator opinion with associated listings of all values of that variable by visit (e.g., heart rate is elevated at one visit; all heart rate values will be listed)
- Incidence of participants with ALT and/or AST ≥ 3x ULN and Total Bilirubin > 2x ULN with ALP < 2x ULN at same visit (i.e., meets Hy's Law)
- Distribution of participants Peak ALT by ULN (<ULN, >1x ULN, >2x ULN, >3x ULN, >5x ULN, >10x ULN, >15x ULN and >20x ULN

PK/Immunogenicity Endpoints

- Teplizumab serum concentrations
- Incidence and titers of anti-drug antibodies (ADA) after treatment courses.

Exploratory endpoints

β-Cell Function

- 4h MMTT C-peptide AUC over time
- 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.

T1D-Focused

- Exogenous insulin use (in U/kg/day) over time
- HbA1c levels over time
- 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 (i.e., spot check, fingerstick) glucometer readings
- Evaluations of glycemic control based on BG values obtained from CGM readings:
  - TIR
  - Time in hyperglycemia and hypoglycemia ranges
  - Daily, daytime, and nighttime average BG levels and estimated HbA1c
  - Glycemic variability
- Clinically important hypoglycemic episodes from randomization by treatment course
- 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 diabetic ketoacidosis (DKA) requiring medical attention, defined as a hyperglycemic episode with serum or urine ketones elevated beyond 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 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

Composite

- Participants with both HbA1c in the American Diabetic Association target range (published at the time of the initiation of this study, i.e., <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/kg/day)
- 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.

Immunologic/Endocrinologic

- 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 (e.g., glucagon, incretins, adiponectin) and other factors (e.g., lipokines, cholesterol, triglycerides) associated with the course of T1D pathophysiology.

Molecular/Genetic

- 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.

3.2.1 Efficacy Variables

Efficacy will be assessed by evaluating C-peptide using MMTT results, hemoglobin A1c (HbA1c) levels, insulin use, hypoglycemia events, and BG readings using CGM.

3.2.2 Safety Variables

Safety will be assessed by evaluating incidence of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), infusion-related reactions, severe infections, clinical laboratory tests, vital signs, and physical examinations. Potentially Clinically Important (PCI) clinical laboratory tests, Abnormal Clinically Significant vital signs will also be used to assess adverse events.

3.3 Pharmacokinetics (PK) and Immunogenicity Variables

Teplizumab concentrations will be analyzed in blood samples collected at specified time points throughout the study. ADA will also be determined, including those that are neutralizing antibodies (NAbs).

4 STATISTICAL METHODS

4.1 Analysis Quality Assurance

Rho, Inc., a Contract Research Organization, will conduct the statistical analyses for this study. All tables, figures and data listings to be included in the CSR will be independently checked for consistency, integrity and in accordance with Rho's standard operating procedures.

4.2 General Presentation Considerations

All data will be summarized by treatment group, presented in the order: Teplizumab, Placebo. Results for the treatment groups combined (Total) may also be presented as appropriate.

Categorical data will be summarized in terms of frequency counts and percentages. Any planned collapsing of categories will be detailed in the data displays. Percentages will be rounded to one decimal place except for 100%, which will have no decimal places. Percentages will not be presented for zero counts. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise stated.

All statistical inferences will be based on 2-sided tests with an α-level of 0.05 unless otherwise specified. In general, p-values will be presented to three decimal places. A p-value greater than 0.999 will be presented as ">0.999"; similarly, a p-value less than 0.001 will be presented as "<0.001".

4.2.1 Baseline

Baseline is defined as the most recent value collected on Day 1 prior to the first dose of study drug. If an assessment is not performed on Day 1, then the most recent value collected prior to Day 1 will be considered Baseline.

4.2.2 Analysis Visit Windows

Study day is relative to date of the first dose of study drug. Day -1 is the day before the first dose, and Day 1 is date of the first dose.

For the efficacy analyses (C-peptide, HbA1c, daily insulin use, intermittent BG, quality of life questionnaires, and CGM) analysis windows will be applied to ensure all data will be accounted for in the analyses including data collected within the protocol defined visit windows and data collected outside the protocol defined visit windows (Table 1 through Table 4). In principle, the analysis windows will be assigned around the target visit day which is the protocol defined visit day. The range of each analysis window is determined based on the midpoint of the two adjacent target visits days.

To evaluate the impact of data collected outside the protocol-defined visit windows on the primary endpoint (C-peptide), additional analysis windowing strategies will be applied in the sensitivity analyses (Section 4.10.2.1).

No analysis windows will be applied to the safety assessments. The by-visit analyses and summaries (e.g., laboratory tests, vital signs, etc.) will be presented using nominal visit time points.

Table 1 Analysis Windows for C-peptide Data

Analysis Visit	Target day	Analysis Window
Baseline	Day 1	≤ Day 1
Week 26	Day 182	Days 2 – 273
Week 52	Day 364	Days 274 – 455
Week 78	Day 546	Days 456 – End of Study

Table 2 Analysis Windows for HbA1c Data

Analysis Visit	Target day	Analysis Window
Baseline	Day 1	≤ Day 1
Week 12	Day 84	Days 2 –133
Week 26	Day 182	Days 134 – 227
Week 39	Day 273	Days 228 – 324
Week 52	Day 364	Days 325 – 409
Week 65	Day 455	Days 410 – 500
Week 78	Day 546	Days 501 – End of Study

Table 3 Analysis Windows for Data Reported Via e-Diary (Daily Insulin Use, Intermittent BG, Quality of Life Questionnaires)

Analysis Visit	Target day	Analysis Window
Baseline	Day 1	≤ Day 1
Week 12	Day 84	Days 2 –133
Week 26	Day 182	Days 134 – 227
Week 39	Day 273	Days 228 – 324
Week 52	Day 364	Days 325 – 409
Week 65	Day 455	Days 410 – 500
Week 78	Day 546	Days 501 – End of Study

Table 4 Analysis Windows for CGM Data

Analysis Visit	Target day	Analysis Window
Week 2	Day 12	Days 1 – 48
Week 12	Day 84	Days 49 –139
Week 27	Day 193	Days 140 – 233
Week 26 (MDS)	Day 182	Days 140 – 233
Week 39	Day 273	Days 234 – 318
Week 52	Day 364	Days 319 – 409
Week 53 (MDS)	Day 375	Days 319 – 409
Week 65	Day 455	Days 410 – 500
Week 78	Day 546	Days 501- End of Study

MDS = Modified Dosing Schedule

4.2.3 Partial Dates

Missing assessment dates will remain missing and no imputation will be applied.

When comparing the AE onset date and study treatment start date for the determination of TEAE, if the AE onset date is incomplete, the partial dates should be used as much as possible for the comparison. If the partial onset date is insufficient to make the determination or AE onset date is completely missing, the AE will be considered TEAE.

Similarly, when comparing medication start/stop dates and study treatment start date for the determination of concomitant medications, if the medication start/stop dates are incomplete, the partial dates should be used as much as possible for the comparison. If the partial dates are insufficient to make the determination or the start/stop dates are completely missing, the medication will be considered as a concomitant medication.

4.3 Determination of Sample Size

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 the primary endpoint C-peptide AUC is skewed to the 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 (Table 5). Consequently, approximately 300 participants are planned for enrollment, assuming 2-sided α=0.05, 90% power, 2:1 randomization, and a 10% dropout rate.

Table 5 C-peptide AUC (nmol/L) Related Parameters Used in Sample Size Calculation

	Placebo		Teplizumab	Group level standard deviation (SD)
	Estimated mean across studies	Mean value used in sample size calculation	Mean value used in sample size calculation	
Mean [ln(AUC+1)]	0.22–0.32	0.25	0.33	0.18–0.22 (used 0.19 in the calculation)
Exp (mean [ln(AUC+1)])-1	0.25–0.38	0.28	0.392	

Justification for Choosing an Effect Size of 40% between Teplizumab and Placebo

Extensive data from natural history studies and those which have assessed "intensive" vs "conventional" glycemic control indicate that an increase of 50% in peak C-peptide is associated with statistically significantly lower risk of severe hypoglycemia (by ~8%), lower HbA1c (by ~0.07%), lower insulin use (by ~0.03 units/kg/day) and a reduction in longer term microvascular complications (i.e., lower risk of sustained retinopathy by 25%) (Lachin 2014). Data collected from the Protégé study, a Phase 3 trial evaluating efficacy and safety of teplizumab that was completed in 2011, showed that a 40% difference in C-peptide AUC corresponds to an approximately 58% difference in peak C-peptide (as detailed below). Hence, we believe a 40% increase in C-peptide AUC will translate to meaningful clinical benefits.

From the Protégé study, baseline C-peptide data collected in participants 8-17 years with baseline peak C-peptide levels >0.2 pmol/mL were examined. The relationship between ln(AUC+1) and peak C-peptide levels was established via a linear regression model:

$$\text{Peak C-peptide} = \mu + \beta * \ln(\text{AUC}+1)$$

A strong relationship was observed between peak C-peptide and ln(AUC+1). The estimated μ was -0.366 and the estimated β was 2.69, where R^2=0.87 and R (correlation coefficient) =0.93.

The observed mean C-peptide ln(AUC+1) for placebo participants in the Protégé study at 18 months was 0.31 pmol/mL, which corresponds to the actual mean C-peptide AUC (geometric

mean) of 0.36 pmol/mL. A 40% increase in mean C-peptide AUC for teplizumab participants is 0.50 pmol/mL, which corresponds to the mean ln(AUC+1) of 0.41 pmol/mL (Table 6).

Table 6 Anticipated C-peptide AUC at 18 months in Study PRV-031-001

	Placebo		Teplizumab
Mean ln(AUC+1)	0.31 pmol/mL		0.41 pmol/mL
	↓		↑
Mean AUC	0.36 pmol/mL	**40% difference →**	0.50 pmol/mL

Based on the fitted linear regression model, the mean ln(AUC+1) value of 0.31 pmol/mL for the placebo participants at 18 months predicts a mean peak C-peptide level of 0.47 pmol/mL. For the teplizumab participants, the mean ln(AUC+1) value of 0.41 pmol/mL at 18 months predicts a mean peak C-peptide level of 0.74 pmol/mL. Therefore, one can conclude that the 40% difference in mean C-peptide AUC (i.e., (0.50-0.36)/0.36) can be translated to a 58% difference in mean peak C-peptide (i.e., (0.74-0.47)/0.47) (Table 7).

Table 7 Anticipated C-peptide AUC and peak C-peptide at 18 months in Study PRV 031-001

	Placebo	Teplizumab	Difference
Mean ln(AUC+1)	0.31 pmol/mL	0.41 pmol/mL	
Mean AUC	0.36 pmol/mL	0.50 pmol/mL	40%
Mean peak C-peptide	0.47 pmol/mL	0.74 pmol/mL	58%

4.4 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated CFR Part 11 compliant environment.

4.5 Analysis Sets

The following analysis sets will be defined for this study:

Intent-to-Treat (ITT) Population: All randomized participants.

Per-Protocol (PP) Population: All randomized participants except those who have met the protocol deviation criteria that are considered likely to affect the evaluation of the efficacy endpoints. These criteria include, but are not limited to, the following:

- Selected eligibility criteria not met
- Received incorrect treatment
- Took prohibited medications during the study as defined in the protocol
- Treatment compliance <80% in treatment course 1 or treatment course 2

The participants excluded from the PP population will be identified and documented prior to the database lock and treatment unblinding. The analysis of the primary and secondary efficacy endpoints will be performed in the PP population, as appropriate.

Safety Population: All randomized study participants receiving any exposure to study drug.

PK Population: All participants in the safety population who have provided at least one evaluable PK sample.

Immunogenicity Population: All participants in the safety population who have provided at least one evaluable ADA sample.

The disposition, demography, baseline characteristics, treatment compliance, and efficacy summaries and analyses will be based on the ITT population. For this population, participants will be analyzed in the treatment group they are randomized to.

The treatment exposure and safety summaries and analyses will be based on the Safety population. For this population, participants will be analyzed in the treatment group they actually received. If the treatment received is different than the treatment assigned (i.e., study drug dispensing error) for a portion of the 12-day treatment course (e.g., one or two doses out of 12 doses), the participant will be classified to the treatment under which the majority of the doses were administered.

4.6 Study Participants

4.6.1 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to end of study participation.

Participant disposition by treatment group and overall will be tabulated for participants randomized, participants receiving any study drug, participants receiving full doses in treatment course 1, treatment course 2, and 2 courses combined, participants who received the second course of therapy at Week 26 vs Week 52, participants who discontinued from study drug, primary reason for discontinuing study drug, participants who discontinued from study drug but remained in the study until study completion, participants who discontinued from study drug and also discontinued from the study, participants completed or discontinued from study, and primary reason for discontinuing study.

The number and percentage of participants in each population will be presented by treatment group. The summary of participants who are excluded from the PP population and reasons for exclusions will be tabulated. A data listing of participants who are excluded from the PP population will also be provided.

Enrollment by country/site and the number of participants randomized to each stratum will also be summarized.

In addition, screening information will be summarized, including number of participants screened, participants with screening failure, and reasons for screening failure. Information on screening failure will also be provided in a data listing.

By-participant listings of enrollment details, randomization details, and withdrawal details (including primary reason for discontinuation from study drug and days on drug prior to discontinuation) for all randomized participants will also be provided.

4.6.2 Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the clinical study team and assessed as "major" or "minor."

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the participant's right, safety, well-being, and/or the validity of the data for analysis. Minor deviations include all deviations from the protocol excluding those considered as major.

A summary of participants with major protocol deviations including type of deviation will be provided. A by-participant listing of major protocol deviations will also be provided.

In addition, COVID-19 related protocol deviations will be tabulated by major vs minor. Under each category (major or minor), the specific type of COVID-19 related protocol deviations will also be summarized.

4.7 Demographic and Other Baseline Characteristics

The following demographics and baseline characteristics will be summarized for participants in the ITT population by treatment group and overall:

- Age at randomization (in years, as a continuous variable)
- Age group at randomization (8-11 years, 12-17 years)
- Sex (Male, Female)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)
- Height at baseline (in centimeters)
- Weight at baseline (in kilograms)
- Body Mass Index (BMI in kg/m^2)
- Time from T1D diagnosis to randomization (in weeks)
- Peak C-peptide group recorded in IRT (from 2h MMTT, 0.2-0.7 pmol/mL vs >0.7 pmol/mL)
- Mean C-peptide AUC at baseline (in pmol/mL)
- Insulin use at baseline (in U/kg/day)
- HbA1c level at baseline (in %)

The following disease characteristics of participants in the ITT population will be tabulated by treatment group and overall:

- History of DKA (yes)
- Type of T1D-related autoantibody (GAD 65, IA-2, ZnT8, ICA, insulin)
- Number of positive T1D autoantibodies (1, 2, 3, 4, 5)
- HLA genotyping at baseline (DR3 and DR4)

By-participant listings of demographic data and baseline characteristics and disease characteristics will also be provided.

Medical history that is coded with the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 26.0, March 2023) will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall, and will be listed in a data listing as well.

4.8 Concomitant Medication

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as prior or concomitant medications. Medications starting after completion of or withdrawal from study will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as prior medications. If a medication starts after the first dose of study drug or starts before the date of first dose of study drug and continues during the study, the medication will be classified as a concomitant medication.

If medications start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug for the classification of prior or concomitant medications. If the dates cannot be compared due to the missing dates, the medications will be considered concomitant medications.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD), version March 2023and will be summarized by ATC level 4 and preferred name. Participants with more than one medication in a given ATC level and preferred name will be counted only once in that category.

4.9 Treatment Compliance

Records of study drug administration will be used to assess compliance. Treatment compliance within a course will be calculated as [total amount of study drug administered (μg) / total amount of study drug prescribed (μg)] x 100 during the dosing period. The amount prescribed for each day within a treatment course is: 106 μg/m^2 for Day 1, 425 μg/m^2 for Day 2, and 850 μg/m^2 for Day 3-12. The total amount prescribed for the treatment course is the sum of each day's amount prescribed within that course. The amount of study drug administered on each day will be determined using the question 'Was the full dose administered?' on the CRF. If the answer is 'yes', then the amount administered for that day will equal the amount prescribed for that day. If the answer is "no", the amount of drug infused (in mL) entered on the CRF will be used to derive the actual dose administered to the participant. The derivation of the actual dose administered per dosing day is as follows:

- Full volume of study drug to be infused (mL) = 25 + (prescribed dose / 100)
- Actual volume infused (mL) = volume recorded on the CRF
- Actual dose administered (μg) = prescribed dose x (actual volume infused / full volume to be infused)
- Prescribed dose (μg):
    - 106 x BSA for Day 1
    - 425 x BSA for Day 2
    - 850 x BSA for Days 3-12
- BSA = SQRT (Height (cm) x Weight (kg) / 3600)

The detailed information on the conversion between volume (mL) and dose (μg) of study drug can be found in the study pharmacy manual.

The derivation of treatment compliance during each dosing course is as follows:

- Compliance (%) = sum of actual dose administered during the dosing course (μg) / sum of prescribed dose for the dosing course (μg) x 100

Treatment compliance as a continuous variable will be summarized for Course 1, Course 2, and total by treatment group. In addition, treatment compliance will be tabulated in the categories of <80%, 80 to <100%, and 100%. A data listing of treatment compliance will also be provided.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

Unless otherwise specified, all statistical tests will be carried out at a 2-sided nominal significance level of 0.05 and all confidence intervals (CIs) at a 2-sided level of 95%. The overall Type I error rate is controlled at 0.05 (2-sided) for the testing of the primary and secondary efficacy hypotheses.

Statistical Hypotheses for Trial Objectives

This study is designed to test for superiority. The null hypotheses for the primary and secondary efficacy endpoints will be that there is no difference between teplizumab and placebo in the efficacy measurements. The alternative hypotheses will be that there is a treatment difference between teplizumab and placebo. The hypothesis for each endpoint will be tested separately.

4.10.1.1 Multi-center Studies

All the statistical analyses will use data pooled from all study centers. Enrollment by country and by site will be summarized. In addition, subgroup analysis by region (North America and Europe) will be conducted for the primary efficacy endpoint to assess any potential treatment difference by region.

4.10.1.2 Adjustments for Covariates

In principle, the efficacy analyses will be adjusted for the randomization stratification factors, i.e., age group at randomization (8-12 vs >12-17 years) and screening peak C-peptide category (0.2-0.7 pmol/mL vs >0.7 pmol/mL). For the analysis on the primary efficacy endpoint, the baseline C-peptide AUC will be adjusted as a covariate in the model. In this case, the screening peak C-peptide will not be included in the model due to the collinearity between the baseline C-peptide AUC and screening peak C-peptide.

4.10.1.3 Handling of Dropouts or Missing Data

For the analyses of primary efficacy endpoint, missing data will be imputed using Multiple imputation (MI). The amount and patterns of missing data, and reasons for missing data will be summarized by treatment group. The change from baseline in C-peptide ln(AUC+1) over time will be plotted by treatment group and by visit completed. The imputation will be performed depending on the Week 78 data missing patterns, regardless of the reasons for dropouts:

- **Pattern 1**: Subjects discontinued study treatment early, discontinued study early, and did not have Week 78 data → imputation will be done using data from retrieved dropouts (i.e., patients who discontinued treatment before Week 78 but still had an efficacy measurement at Week 78)

- **Pattern 2**: Subjects discontinued study treatment early, completed study, and did not have Week 78 data → imputation will be done using data from retrieved dropouts (i.e., patients who discontinued treatment before Week 78 but still had an efficacy measurement at Week 78)

- **Pattern 3**: Subjects completed study treatment, discontinued study early, and did not have Week 78 data → imputation will be done using data from treatment completers

- **Pattern 4**: Subjects completed study treatment, completed study, and did not have Week 78 data → imputation will be done using data from treatment completers

This MI will be carried out following 3 steps:

Step 1. Generation of imputed datasets

The PROC MI procedure of the SAS system will be used to generate 100 sets of data. Linear regression model that includes treatment, age at randomization, gender, C-peptide ln(AUC+1) at previous time points, and baseline C-peptide ln(AUC+1) as covariates will be employed to generate each imputed dataset.

Step 2. Model-based analysis using each imputed dataset

Each of the 100 imputed datasets will be analyzed using the statistical model specified in Section 4.10.2.

Step 3. Pooling the results from each model-based analysis

The results from the analysis of each imputed dataset will be combined using Rubin's rule (Rubin 1987) by implementing the PROC MIANALYZE procedure of the SAS system.

Similar MI procedures will be applied to the analyses of the secondary efficacy endpoints of exogenous insulin use, HbA1c levels, and TIR.

4.10.1.4 Multiple Comparisons/Multiplicity

If the primary endpoint is found to be statistically significant at the 5% level ($p < 0.05$), then multiplicity among the efficacy secondary endpoints will be addressed using the Hochberg procedure (Hochberg 1988).

In general, Hochberg procedure is conducted as the following steps:

1. Suppose we have $H_1, \ldots, H_m$ null hypotheses tested and $P_1, \ldots, P_m$ their corresponding p-values. P-values are ordered in increasing order and denote them by $P_{(1)}, \ldots, P_{(m)}$.

2. For a given significance level α, find the largest k such that $P_{(k)} \leq \alpha/(m+1-k)$.

3. Reject the null hypothesis for all $H_{(i)}$ for i=1, …, k.

4.10.1.5 Interim Analyses

There is no formal interim analysis planned for this study.

4.10.1.6 Examination of Subgroups

The treatment effects for the primary efficacy endpoint will be examined for the following subgroups:

- Age category (8-11 years, 12-17 years)
- Sex (Male, Female)
- Race (White, non-White)
- Region (North America, Europe)
- Baseline peak C-peptide category (0.2-0.7 pmol/mL, >0.7 pmol/mL)
- Baseline insulin use (<0.5 U/kg/day, ≥0.5 U/kg/day)
- Baseline HbA1c category (<7.5%, ≥7.5%)
- Number of positive T1D autoantibodies (1-2 vs ≥3)
- Participants who were on modified dosing schedules (MDS, yes vs no)
- Participants who were treated with Eli Lilly product vs AGC product (Lilly vs AGC)
- HLA type (DR3 positive vs negative, DR4 positive vs negative)
- BMI z-score (by quartile)

The least squares mean for each treatment group and the difference between teplizumab and placebo, the associated 95% confidence interval (CI), and p-values will be tabulated and displayed graphically using a forest plot.

To evaluate the effect of each subgroup described above on the treatment effects, the applicable statistical model for the analyses of the primary efficacy endpoint will be performed where an additional covariate of the subgroup will be included.

4.10.2 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the AUC of C-peptide after a 4h MMTT at Week 78. A 4h MMTT will be performed at randomization (Week 1) and at Weeks 26, 52, and 78 to obtain C-peptide AUCs. C-peptide AUC will be computed using the trapezoidal rule. To adjust the potential different durations of MMTT test performed on the participants, C-peptide AUC will first be standardized by the duration of the MMTT test for the analysis. Historical data have shown that C-peptide AUC data do not follow normal distributions and is skewed to the right; therefore, the standardized C-peptide AUC will be normalized by the log transformation using ln(AUC+1) when fitting the statistical models that are based on the normality assumptions (e.g., analysis of covariance [ANCOVA], mixed model for repeated measures [MMRM]).

The primary estimator for the primary estimand will account for the subjects who had missing data due to ICEs. After multiple imputation has been performed on the missing data of C-peptide ln(AUC+1) based on the approach described in Section 4.10.1.3, the change from baseline in C-peptide ln(AUC+1) at Week 78 (i.e., baseline-corrected C-peptide ln(AUC+1) at Week 78) will be

analyzed and the treatment difference will be tested using an ANCOVA model with treatment, age group at randomization (a randomization stratification factor), and baseline C-peptide ln(AUC+1) as covariates. The estimated mean change from baseline in ln(AUC+1) (i.e., the primary estimate) and the associated 95% CI for each treatment group, as well as the estimated mean difference in ln(AUC+1) between the treatment groups and the associated 95% CI, will be presented. The p-value from the statistical testing of treatment difference between teplizumab and placebo will be reported. The primary analysis will be performed on the ITT population and repeated on the PP population as a supportive analysis.

Descriptive statistics of the observed and change from baseline C-peptide ln(AUC+1) will be summarized by visit and treatment group for the ITT population. Graphic presentation of the change from baseline in C-peptide ln(AUC+1) over time within each treatment group will also be provided.

4.10.2.1 Sensitivity Analysis

The sensitivity estimators for the primary estimand will be used to evaluate the robustness of the primary estimate. The sensitivity estimators will include:

- Control-based imputation
- Tipping point analysis
- MMRM

In addition, the primary analysis described above will be repeated using alternative analysis windowing strategies as sensitivity analyses.

Control-Based Imputation

Control-based imputation assumes that participants in the active treatment group who dropped out the study early behave like those in the control group following their last observed time point (Carpenter 2013). The same MI procedure will be followed as described in Section 4.10.1.3, except that the missing data of C-peptide ln(AUC+1) in the teplizumab group will be imputed based on the available data from the placebo group, regardless of the missing patterns defined in Section 4.10.1.3.

Tipping Point Analysis

To evaluate the robustness of the statistically significant treatment effect (i.e., p-value < 0.05) from the primary analysis, a tipping point analysis will be conducted. The tipping point approach serves as a stress test to assess how much the estimated treatment effect can be diminished before overturning the conclusion from the primary analysis. The implementation of the tipping point analysis will follow the steps below:

1. Follow the MI Step 1 described in Section 4.10.1.3 to fill the missing data at each visit.

2. For each imputed dataset, the change from baseline ln(AUC+1) derived from the imputed values at Week 78 in the teplizumab and placebo groups will be adjusted by a pair of shift parameters, (Δ_t, Δ_p), respectively.

3. Follow MI Step 2 described in Section 4.10.1.3 to analyze each imputed dataset separately.

4. Follow MI Step 3 described in Section 4.10.1.3 to combine all the imputed datasets for inference.

5. Repeat Steps 2–4 for a range of (Δ_t, Δ_p) to fine-tune the tipping point until the p-value ≥ 0.05 (i.e., treatment effect loses statistical significance)

The range of the shift parameters will be determined such that the scenarios of departure from the treatment effects estimated from the primary analysis are clinically plausible. The increment of the shift parameters for each run will be empirically determined when searching for the tipping point that overturns the statistical significance of the treatment effect. The tipping point analysis results derived from adjusting the range and increments of the shift parameters will be presented in a summary table or a graphical display.

MMRM Analysis

MMRM analysis using observed data will be carried out as a sensitivity analysis on the change from baseline C-peptide ln(AUC+1) at Week 78. The model will include treatment, visit, age group, baseline C-peptide as fixed effects, and a treatment by visit interaction term. The unstructured covariance structure will be chosen for the MMRM model because it requires minimal assumptions. In the event that the model doesn't converge, first-order autoregressive will be chosen for the covariance structure. Estimates of treatment effect and the associated 95% confidence interval and p-values will be presented for Week 78.

Alternative Analysis Windowing

As part of the sensitivity analyses, alternative analysis windowing strategies will be applied to the analysis of the change from baseline C-peptide ln(AUC+1) at Week 78:

- For each analysis visit, data collected within 7 days of the protocol-defined target visit (i.e., target day ±7 days) will be included in the analysis.

- For each analysis visit, data collected within 30 days of the protocol-defined target visit (i.e., target day ±30 days) will be included in the analysis.

- For each analysis visit, data collected within 60 days of the protocol-defined target visit (i.e., target day ±60 days) will be included in the analysis.

After applying the analysis windows, the primary analysis of change from baseline C-peptide ln(AUC+1) at Week 78 will be repeated for each analysis windowing strategy.

4.10.3 Analyses of Secondary Efficacy Endpoints

To control the family-wise Type 1 error at the 0.05 level, the inference on the secondary efficacy endpoints will be drawn only if the hypothesis testing on the primary efficacy endpoint reaches statistical significance (i.e., p-value < 0.05). In that case, the Hochberg procedure (Hochberg 1988) for the multiplicity adjustment will be used when testing the secondary efficacy endpoints. Using this procedure, the nominal p-values associated with testing the 4 secondary efficacy endpoints will be ordered from smallest to largest.

- If the largest p-value is <0.050, then all 4 endpoints will be considered to reach statistical significance.

- Otherwise, if the largest p-value is ≥0.050 and the second largest p-value is <0.025, then the endpoints with the 3 smallest nominal p-values will be considered statistically significant.

- Otherwise, if the largest p-value is ≥0.050, second largest p-value is ≥0.025, and the third largest p-value is <0.0167, then the endpoints with the 2 smallest nominal p-values will be considered statistically significant.

- Otherwise, if the largest p-value is ≥0.050, second largest p-value is ≥0.025, third largest p-value is ≥0.0167, and the smallest p-value is <0.0125, then the endpoint with the smallest nominal p-value will be considered statistically significant.

4.10.3.1 Exogenous insulin uses at Week 78

Participants' daily insulin use will be self-reported in an eDiary for 7 days prior to randomization and at about Weeks 12, 26, 39, 52, 65 and 78. Two eDiary forms will be used: Insulin Injection form and Yesterday's Insulin Use Review form. The prescribed insulin will also be recorded in the medication CRFs (insulin name, dose, unit, frequency, route, etc.). The average daily use of insulin (unit/kg/day) at each time point will be derived from the eDiary data and body weight measured at each time point. If body weight is not measured for a given time point (e.g., Week 12), the average body weight measured at the closest prior and post time points will be used for the calculation of daily insulin use (e.g., average body weight at randomization and Week 26). Participants need to have insulin data for at least 3 days at each time point in order to calculate the average daily use. For participants who have more than 7 days of insulin use data for a given visit (after applying the analysis windows), the insulin data from the 7 days that are closest to the target day will be used in the calculation of the average daily insulin use.

After the missing data are imputed using the method discussed in Section 4.10.1.3, the average daily insulin use at Week 78 will be analyzed using an ANCOVA model that will include treatment group and randomization stratification factors (age group and screening peak C-peptide category). The estimated mean average daily use of insulin and the associated 95% CI for each treatment group, as well as the estimated mean difference in average daily use of insulin between the treatment groups and the associated 95% CI, will be presented. P-value from the statistical testing of treatment difference between teplizumab and placebo will be reported. The analysis will be performed on ITT population.

Descriptive statistics of average daily use of insulin will be summarized by visit and treatment group for the ITT population. Graphic presentation of average daily insulin use over time within each treatment group will also be provided.

4.10.3.2 HbA1c levels (%) at Week 78

HbA1c (%) will be collected at Screening, Day 1, Weeks 12, 26, 39, 52, 65, and 78. For the analysis and summaries of HbA1c, data collected from the central laboratory will be used.

After the missing data are imputed using the method discussed in Section 4.10.1.3, the change from baseline in average HbA1c (%) at Week 78 will be analyzed using an ANCOVA model that will include treatment group, randomization stratification factors (age group and screening peak C-peptide category), and baseline HbA1c (%) as covariates. The estimated mean change from baseline in average HbA1c (%) and the associated 95% CI for each treatment group, as well as the estimated mean difference in change from baseline in average HbA1c (%) between the treatment groups and the associated 95% CI, will be presented. P-value from the statistical testing of treatment difference between teplizumab and placebo will be reported. The analysis will be performed on ITT population. In addition, the mean HbA1c and the 95% CI at Week78 for each treatment group and the mean difference and 95% CI between the treatment groups at Week 78 will be estimated from the similar ANCOVA model described above.

Descriptive statistics of observed and change from baseline in average HbA1c (%) will be summarized by visit and treatment group for the ITT population. Graphic presentation of HbA1c (%) over time within each treatment group will also be provided.

4.10.3.3 TIR assessed using CGM at Week 78

CGM will be used to assess glycemic control approximately 7 times throughout the study: after Course 1 treatment (Week 2), after the completion of Course 2 treatment (Week 27 for non-MDS participants and Week 53 for MDS participants), after visits at Weeks 12, 26 (participants on MDS), 39, 52 (participants on regular dosing schedule), 65, and before the visit at Week 78. Time in range for blood glucose will be defined as the daily average percentage of time a participant's BG is ≥70 mg/dL and ≤180 mg/dL (≥3.9 mmol/L to ≤10.0 mmol/L). The derivation of TIR is as follows:

Step 1: For each participant, compute the daily TIR as number of CGM entries in range divided by the total number of CGM entries for a given day. For participants who have less than 8 hours CGM entries for a given day, the daily TIR for that day will be considered missing in the TIR analysis.

Step 2: For each participant, take the average of daily TIR across the total number of available days. For participants who have less than 3 days of daily TIR data for a given visit, the average TIR for that visit will be considered missing in the TIR analysis. For participant who have more than 14 days of daily TIR data for a given visit (after applying the analysis windows), the daily TIR data from the 14 days that are closest to the target day will be used in the calculation of the average TIR.

According to the CGM Data Transfer Specifications, CGM values ≤ 13 mg/dL will be excluded from the calculation of TIR as these extremely low CGM values were generated in the CGM device during the initial set up or in any scenarios where the CGM device is not able to generate valid CGM output.

After the missing data are imputed using the method discussed in Section 4.10.1.3, TIR at Week 78 will be analyzed using an ANCOVA model that will include treatment group and randomization stratification factors (age group and screening peak C-peptide category) as covariates. The estimated mean TIR and the associated 95% CI for each treatment group, as well as the estimated mean difference in TIR between the treatment groups and the associated 95% CI, will be presented.

P-value from the statistical testing of treatment difference between teplizumab and placebo will be reported. The analysis will be performed on ITT population.

Descriptive statistics of TIR will be summarized by visit and treatment group for the ITT population. Graphic presentation of TIR over time within each treatment group will also be provided.

4.10.3.4 Clinically important hypoglycemic episodes through Week 78

Clinically important and potentially life-threating hypoglycemia is the result of insulin therapy and more likely to occur in participants who are attempting to achieve glycemic control goals. A particular focus of this study will be on clinically important hypoglycemic events that are defined as a BG value of <54 mg/dL (3.0 mmol/L) (i.e., Level 2 Hypoglycemia, International Hypoglycemia Study Group, 2017) or a hypoglycemia event of severe cognitive impairment requiring external assistance (such as seizure, syncope, severe confusion with or without a confirmatory low BG reading) (i.e., Level 3 Hypoglycemia, International Hypoglycemia Study Group 2017).

Clinically important hypoglycemic events will be identified based on the data recorded in the Hypoglycemic Events eDiary. The Hypoglycemic Events eDiary is to be completed by the participants or caregivers that 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.

Clinically important hypoglycemic events are comprised of Level 2 or Level 3 events according to the following criteria (Study Protocol Section 12.1.4.1):

- Level 2 events: the lowest BG value of <54 mg/dL (3.0 mmol/L) recorded on the Hypoglycemic Events eDiary at the time of the reported event
- Level 3 events: hypoglycemia (with or without a blood glucose reading) recorded in the Hypoglycemic Events eDiary which resulted in
    - Severe clinical symptoms (passing out/fainting, seizure, coma) requiring either
        - non-medical intervention from another person (glucagon injection) OR
        - medical care (calling an ambulance, going to the emergency room, or hospital admission)

The rate (number of events/study follow-up time) of clinically important hypoglycemic episodes through Week 78 will be compared between groups. The event rate of clinically important hypoglycemic episodes will be analyzed and tested between treatment groups using a negative binomial model to allow for potential overdispersion of the count data. The negative binomial model will include treatment group and randomization stratification factors (age group and screening peak C-peptide category) as covariates. The estimated rate ratio (comparing teplizumab to placebo) and its 95% CI and the p-value will be provided.

The event rate will additionally be summarized by type (Level 2 vs Level 3) and treatment group. Level 3 events will also be summarized by clinical symptoms experienced as well as categories of support received. These further summaries by type or symptoms/support are considered exploratory (i.e., no formal testing will be done to compare groups). Detailed data on the clinically important hypoglycemic events, including Hypoglycemic Events eDiary data, will also be provided in data listings.

4.10.4 Analyses of Exploratory Efficacy Endpoints

4.10.4.1 Assessments of β cell function and health throughout the study

- 4h MMTT C-peptide AUC

Descriptive statistics summarizing 4h MMTT C-peptide AUC at each protocol-defined time point will be provided by treatment group. Graphic presentation of the mean change from baseline in C-peptide AUC over time within each treatment group will also be provided.

- Participants with the recognized clinically significant stimulated peak C-peptide of ≥0.2 pmol/mL during 4h and 2h MMTTs

A summary of the number and percentage of participants with peak C-peptide ≥0.2 pmol/mL at each protocol-defined time point will be provided by treatment group. A generalized linear model for repeated measures using logit link function will be carried out on the proportion of participants with peak C-peptide ≥0.2 pmol/mL at each post-baseline visit. The model will include treatment, visit, age group, baseline peak C-peptide as fixed effects, and a treatment by visit interaction term. Estimates of treatment effect and the associated 95% confidence interval and p-values will be presented for each study visit.

- Proinsulin-to-C-peptide ratios, a measure of β cell endoplasmic reticulum stress and dysfunction

Proinsulin lab tests may be performed for future exploratory analysis.

4.10.4.2 T1D-focused Clinical Endpoints during the study

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

Descriptive statistics summarizing exogenous insulin use at each protocol-defined time point will be provided by treatment group. An MMRM analysis will be carried out on the insulin use at each visit. The model will include treatment, visit, randomization stratification factors (age group and screening peak C-peptide category) as fixed effects, and a treatment by visit interaction term. The unstructured covariance structure will be chosen for the MMRM model because it requires minimal assumptions. In the event that the model doesn't converge, first-order autoregressive will be chosen for the covariance structure. Estimates of treatment effect and the associated 95% confidence interval and p-values will be presented for each study visit.

- HbA1c levels (in %)

Descriptive statistics summarizing HbA1c level at each protocol-defined time point will be provided by treatment group. An MMRM analysis will be carried out on change from baseline HbA1c level at each visit. The model will include treatment, visit, randomization stratification factors (age group and screening peak C-peptide category), baseline HbA1c as fixed effects, and a treatment by visit interaction term. The unstructured covariance structure will be chosen for the MMRM model because it requires minimal assumptions. In the event that the model doesn't converge, first-order autoregressive will be chosen for the covariance structure. Estimates of treatment effect and the associated 95% confidence interval and p-values will be presented for each study visit.

- Participants with poor glycemic control, defined as HbA1c of ≥9%

A summary of the number and percentage of participants with HbA1c of ≥9% at each protocol-defined time point will be provided by treatment group. A generalized linear model for repeated measures using logit link function will be carried out on the proportion of participants with HbA1c of ≥9% at each visit. The model will include treatment, visit, randomization stratification factors (age group and screening peak C-peptide category), baseline HbA1c as fixed effects, and a treatment by visit interaction term. Estimates of treatment effect and the associated 95% confidence interval and p-values will be presented for each study visit.

- 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

Data on insulin use around the clinical visits are captured in the insulin use eDiaries and insulin dose prescribed for the participants by the investigator throughout the study are reported on the concomitant medication CRF page. These data will be used to determine if the participants discontinued insulin at Week 78. The number and percentage of participants who do not use exogenous insulin at Week 78 will be summarized by treatment group. A Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratification factors (age group and screening peak C-peptide category) will be used to test the treatment difference between the teplizumab and the placebo group.

- Evaluations of glycemic control based on BG values obtained from intermittent (i.e., spot check, fingerstick) glucometer readings

Intermittent glucose monitoring via a fingerstick glucometer will be used to measure BG levels for at least 4 times a day, including before each meal and at bedtime. Approximately 7 times throughout the study, participants will record their BG levels before breakfast, lunch, dinner, and at bedtime for 7 consecutive days in the glucose diary prior to the randomization visit and the visits at Weeks 12, 26, 39, 52, 65, and 78.

For each study visit, descriptive statistics of the average glucose level before breakfast, lunch, dinner, and at bedtime will be summarized by treatment group. Graphic presentation of glucose level before breakfast, lunch, dinner, and at bedtime overtime by study visit will be provided.

- 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

Similar analyses on the TIR described in Section 4.10.3.3 will be carried out for time in hyperglycemia range (BG >180 mg/dL), time in hypoglycemia range (BG <70 mg/dL), and time in severe hypoglycemia range (BG <54 mg/dL).

Daily, daytime, and nighttime average BG levels from CGM will be summarized descriptively and presented graphically for each study visit. Daytime will be defined as CGM data recorded during 8:00 am – 8:00 pm. Nighttime will be defined as CGM data recorded during 8:01 pm – 7:59 am.

- Clinically important hypoglycemic events from randomization by treatment course

Similar summaries as described in Section 4.10.3.4 will be provided for the clinically important hypoglycemic episodes reported from randomization and up to the start of treatment course 2, and from start of treatment course 2 and up to Week 78 separately.

- 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

Hypoglycemia events reported in the participant's hypoglycemia event diary will be used as the source data for identifying typical hypoglycemia events. The events will be identified as following:

- Hypoglycemic events reported in the eDiary accompanied with a BG reading ≥54 mg/dL but <70 mg/dL, or
- Hypoglycemic events reported in the eDiary accompanied with non-severe clinical symptoms (e.g., shakiness, dizziness) that do not require glucagon injection or medical care (calling an ambulance, going to the emergency room, or hospital admission)

Incidence of typical hypoglycemia defined above will be summarized by treatment group. A CMH test stratified by randomization stratification factors (age group and screening peak C-peptide category) will be used to test the treatment difference between the teplizumab and the placebo group.

- 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

Summary of incidence of DKA is described in Section 4.11.3.2.

- 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)

Analyses of Quality of Life questionnaires are described in Section 4.12.2.

- Impact on family life, measured by the parent-reported PedsQL Family Impact questionnaire

Analyses of Quality of Life questionnaires are described in Section 4.12.2.

4.10.4.3 Composite Efficacy Endpoints

• Participants with both HbA1c in the American Diabetic Association target range (published at the time of the initiation of this study, i.e., <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/day)

The numbers and percentages of participants in the following categories will be summarized by treatment group at each scheduled time point:

- HbA1c <7.5% and exogenous insulin dose <0.25 U/kg/day
- HbA1c <7.5% and exogenous insulin dose ≥0.25 and <0.50 U/kg/day
- HbA1c <7.5% and exogenous insulin dose ≥0.50 and <0.75 U/kg/day
- HbA1c <7.5% and exogenous insulin dose ≥0.75 and <1.0 U/kg/day
- HbA1c <7.5% and exogenous insulin dose ≥1.0 and <1.25 U/kg/day
- HbA1c <7.5% and exogenous insulin dose ≥1.25 U/kg/day

• 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

The numbers and percentages of participants in the following categories will be summarized by treatment group at each scheduled time point:

- HbA1c <6.5% and exogenous insulin dose <0.25 U/kg/day
- HbA1c <6.5% and exogenous insulin dose <0.50 U/kg/day
- HbA1c <7.0% and exogenous insulin dose <0.25 U/kg/day
- HbA1c <7.0% and exogenous insulin dose <0.50 U/kg/day

4.10.4.4 Immunologic and Endocrinologic Endpoints

- Phenotypic and functional characterizations of white blood cell (WBC) populations, including T cells, B cells, and natural killer (NK) cells

Descriptive statistics on T cells, B cells, and NK cells will be summarized by treatment group and study visit. Detailed descriptions of the summaries are provided in Section 4.11.4.

- Serum proinflammatory and regulatory cytokine profiles and other immune mediators

These measurements will be assessed in the future exploratory analysis.

- Number, type, and titer of T1D autoantibodies

Number and type of T1D autoantibody will be summarized descriptively. The titer of T1D autoantibody of each type will be summarized descriptively by treatment group and study visit using the original scale and the log scale.

- Antibody subclass levels

IgA, IgG, and IgM status (positive vs negative) will be summarized by treatment group and study visit. Detailed descriptions of the summaries are provided in Section 4.11.4.

- Evidence of recent infection with coxsackie virus B (CVB)

These measurements will be assessed in the future exploratory analysis.

- Levels of circulating hormones (e.g., glucagon, incretins, adiponectin) and other factors (e.g., lipokines, cholesterol, triglycerides) associated with the course of T1D pathophysiology

These measurements will be assessed in the future exploratory analysis.

4.10.4.5 Molecular and Genetic Endpoints

- Circulating methylated- and unmethylated-insulin DNA levels as assessments of β cell stress and damage

These measurements will be assessed in the future exploratory analysis.

- Gene expression and transcriptome analyses

These measurements will be assessed in the future exploratory analysis.

- Association of HLA type with clinical, metabolic and immune assessments

HLA typing results will be summarized by treatment group. To assess the effect of HLA on the efficacy endpoints, a subgroup analysis of the primary efficacy endpoint will be conducted for the main categories of HLA type (e.g., HLA-DR3, HLA-DR4).

A by-participant listing of HLA typing results along with glucagon, incretins, lipokines, adiponectin, and cholesterol values at each protocol-defined time point will also be provided.

4.11 Safety Evaluation

4.11.1 Extent of Exposure

Duration of study follow-up will be calculated as the date of the study completion or discontinuation – the start date of study treatment +1. Descriptive statistics of the duration of study follow-up will be summarized by treatment group for the Safety population.

Treatment exposure will be characterized by the number of doses of study drug that participants received and will be summarized descriptively (as a continuous variable as well as a categorical variable) by treatment group overall and by treatment course. Similarly, the descriptive statistics of actual total dose ($\mu g/m^2$) that participants received will be summarized by treatment group overall and by treatment course.

Number and percentage of participants who had infusion interruption during study drug administration in each treatment course and the reason of interruption will be summarized by treatment group. In addition, the number and percentage of participants who had study drug withheld (i.e., missed doses) in each treatment course and the reason of drug withheld will be summarized by treatment group. The detailed information of study drug administration will be presented in an individual data listing.

4.11.2 Adverse Events

Adverse events will be coded using the MedDRA version 26.0, March 2023. Relationship to study drug 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. Relationship to the study drug will be assessed and reported on the CRF by the investigators as unrelated, unlikely, possible, probable, and definite.

TEAEs are defined as those adverse events that either start or worsen in severity on or after the date/time of first dose of study treatment. Where dates are missing or are partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment.

Adverse Events of Special Interest (AESI)

The following events are AESI defined in the protocol (Table 8):

- All ≥Grade 3 infections (includes all opportunistic infections): viral, fungal, bacterial
- Acute mononucleosis-like illness (e.g., 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), i.e., an AST or ALT value >5.0x ULN or a bilirubin value >3.0x 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

Table 8 The Search Criteria for AESI

AESI	Search Criteria
≥Grade 3 infections (will include all opportunistic infections)	SOC – 'Infections and infestations'; ≥Grade 3
Acute mononucleosis-like illness (e.g., fever, pharyngitis, lymphadenopathy)	PT – 'Mononucleosis syndrome', 'Epstein-Barr virus antibody positive', 'Epstein-Barr virus test positive', 'Epstein-Barr viremia', 'Cytomegalovirus antibody positive', 'Cytomegalovirus test positive', 'Infectious mononucleosis', 'Lymphadenopathy', EBV IgM antibody positive, EBV Infection and CMV infection
Lymphomas or other malignancies	SOC – 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' and HLT – includes 'malignant' or 'lymphomas' or 'benign'
Severe Hypoglycemia	PT – 'Hypoglycemia', 'Hypoglycemic seizure', 'Hypoglycemic coma'; 'Hypoglycemic unconsciousness'; ≥Grade 3
≥Grade 3 liver function abnormalities (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin), i.e., an AST or ALT value >5.0 x upper limit of normal (ULN) or a bilirubin value >3.0 x ULN.	PT – "Alanine aminotransferase increased", "Aspartate aminotransferase increased", "Blood bilirubin increased", "Liver function tests increased", "Hypertransaminasemia", "Transaminase elevation", "Hyperbilirubinemia"; ≥Grade 3
≥Grade 3 thrombocytopenia (platelet counts less than 50,000/μL)	PT – 'Thrombocytopenia'; ≥Grade 3
≥Grade 3 neutropenia (<1000 polymorphonuclear leukocytes [PMN]/μL) on 2 consecutive evaluations performed on different days	PT – 'Neutropenia'; ≥Grade 3
≥Grade 4 allergic/hypersensitivity reaction, i.e., anaphylaxis	PT – 'Dermatitis allergic', 'Drug hypersensitivity', 'Anaphylactic reaction', 'Immune reaction', 'Anaphylaxis', 'Hypersensitivity', 'Infusion related reaction', 'Serum sickness'; ≥Grade 4
≥Grade 3 rash	SOC – 'Skin and subcutaneous tissue disorders'; ≥Grade 3
≥Grade 4 cytokine-release syndrome, i.e., life-threatening; pressor or ventilatory support indicated	PT – 'Cytokine release syndrome'; ≥Grade 4
Lymphocyte count <500 mm^3 for 7 days or longer	PT – 'Lymphopenia'; ≥Grade 3; at least 7 days

SOC = system organ class; PT = preferred term; HLT = high level term
Note: Nasopharyngitis, Pharyngitis, pharyngitis streptococcal should not be included to search criteria.

Study Drug Infusion-Related Reactions

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.

Search PTs for infusion related reactions that are reported during the treatment courses 1 and 2:

- "HYPERSENSITIVITY AND ALLERGIC REACTIONS"
- "ANAPHYLAXIS"
- "HYPERSENSITIVITY REACTIONS"
- "CYTOKINE RELEASE SYNDROME"
- "SERUM SICKNESS"
- "INFUSION RELATED REACTION"
- "CYTOKINE RELEASE SYNDROME (CRS)"

An overall summary of TEAEs will be provided for the number and percentage of participants in the following TEAE categories:

- Any TEAEs
- Any TEAEs by severity (Grades 1, 2, 3, 4, and 5)
- Any related TEAEs
- Any TEAEs leading to study drug withdrawal
- Any TEAEs leading to study discontinuation
- Any serious TEAEs
- Any serious related TEAEs
- Any treatment-emergent AESI
- Any treatment-emergent related AESI
- Deaths

Incidence of TEAEs will be summarized by system organ class (SOC) and preferred term (PT), by severity (CTCAE Grades 1, 2, 3, 4, and 5), and by relationship to the study drug (related vs not related). Related TEAEs are defined as TEAEs that are reported as possible, probable, and definite related by the investigators. Incidence of TEAEs will also be summarized by PT in the descending order of frequency in teplizumab group. A data listing of all AEs will also be provided.

Incidence of serious TEAEs, treatment-emergent AESI, infusion-related TEAEs and TEAEs leading to study discontinuation will be tabulated by treatment group. Listings of these AEs will also be provided.

Participants with multiple events will be counted only once for each SOC and PT category. Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the teplizumab group, and then similarly by decreasing frequency in the placebo group, and then alphabetically for SOC, and PT within SOC.

Summary of TEAEs and serious TEAEs that started during the treatment course and through 28 days after the last dose will be provided for each treatment course.

The following summaries of TEAEs will also be provided by teplizumab product (Lilly vs AGC):

- TEAEs by SOC and PT
- TEAEs by SOC and PT during the treatment course and through 28 days after the last dose for each treatment course
- TEAEs by PT in the descending order of frequency
- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC and PT during the treatment course and through 28 days after the last dose for each treatment course
- TEAEs leading to study drug withdrawal by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- Treatment-emergent AESI
- Cytokine Release Syndrome that are reported during the dosing period and 28 days after the completion of dosing for each treatment course
- Hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm.

4.11.3 Anticipated Adverse Events

An anticipated adverse 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 this study hypoglycemia and DKA will be considered as anticipated adverse events.

4.11.3.1 Hypoglycemia

One of the secondary efficacy endpoints of this study is the clinically important hypoglycemia, 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. The summaries and analysis of this endpoint are described in Section 4.10.3.4.

For the summary of the anticipated events of hypoglycemia, events reported in AE CRF will be used as the source data. The hypoglycemia will be identified based on the question asked in AE CRF, “Was the AE a hypoglycemic Event?”. If the answer is “Yes” then the event is flagged as hypoglycemia. The incidence of hypoglycemia will be summarized by SOC and PT, by severity, and by the classification (clinically important, non-severe symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, pseudo-hypoglycemia). A data listing of the anticipated hypoglycemic events will also be provided.

4.11.3.2 Hyperglycemia and Diabetic Ketoacidosis (DKA)

Hyperglycemia events are the 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
- Requiring medical attention such as unplanned outpatient care, emergency room care, or hospitalization

Incidence of hyperglycemia and DKA reported in AE CRF during the study will be summarized by treatment groups. A by-participant listing of all anticipated AEs will be provided.

4.11.4 Clinical Laboratory Evaluation

All lab values will be reported and summarized using standard international (SI) units with the exception that HbA1c will be reported in %. A list of the SI units to the laboratory parameter is provided in Appendix 2. Lab data collected from the central lab will be used for summarizing lab tests that include observed and change from baseline values by visit, and potentially clinically important (PCI) lab values. PCI lab values are defined in Appendix 3. Shift from baseline to the worst CTCAE grade post-baseline may be presented for the lab tests, if deemed necessary.

- For liver function tests, a summary of participants with post-baseline abnormal test results based on the central and local lab data will be provided overall and by study visit in the following categories: >1x ULN, >2x ULN, >3x ULN, >5x ULN, and >10x ULN. Summaries on the potential Hy's law (ALT/AST > 3x ULN and Total bilirubin > 2x ULN with ALP < 2x ULN) and eDISH plot may be provided as appropriate.

Lymphocyte count data collected from local labs during each treatment course on dosing days 1, 2, 4, 6, and 9 will be used in a graphic presentation of lymphocyte count change from baseline over time by treatment group. All laboratory data collected from the central and local labs will be provided in the laboratory data listings.

The following clinical safety laboratory tests will be tabulated and/or listed:

- Hematology Panel: WBC with differential, Hemoglobin, Hematocrit, Platelet count.
- Serum Chemistry Panel with Liver Function Tests: Sodium, Potassium, Chloride, Bicarbonate, Blood urea nitrogen (BUN), Creatinine, Glucose, Calcium, Phosphate, Albumin, Total protein, 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).
- Urinalysis: pH, Specific gravity, Protein, Glucose, Ketones, Bilirubin, Nitrites, Leukocyte esterase, Blood cells/hemoglobin.
- Diabetes-Related: Type 1 diabetes autoantibodies (anti-insulin, anti-GAD-65, ICA, anti-ZnT8, anti-IA2)
- Other Tests only at screening (Listing only): Serum pregnancy testing (females of childbearing potential), HIV antibody serology, HBV antibody serology /antigen panel, HCV antibody serology, Interferon-gamma Release Assay (IGRA) Tuberculosis testing.
- MHC haplotype at baseline (Listing only)
- CMV serology, EBV serology, CMV DNA PCR, EBV DNA PCR and VZV antibody serology

The continuous test results for each test parameter and changes from baseline will be summarized at each visit by treatment group using descriptive statistics. The categorical test results for each test parameter will be summarized using frequencies and percentages at each visit by treatment group.

Laboratory values will be listed by participant and study time point including changes from baseline (where available). All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values (high vs low) along with the clinically significant flag will be presented in the listings. Laboratory values of PCI will also be listed in a by-participant data listing.

4.11.5 Vital Signs and Physical Examinations

4.11.5.1 Vital Signs Assessments

The following vital signs will be measured at screening, on each day of the two treatment courses, at Weeks 4, 8, 12, 20, 30, 34, 39, 52, 65, and 78:

- Temperature (°C)
- Pulse/heart rate (beats/min)
- Respiratory rate (breaths/min)
- Blood pressure (mmHg).

All vital signs (absolute values and change from baseline) will be summarized at each visit by treatment group. In addition, the number and percent of participants with vital signs judged to be clinically significant as per CRF will be summarized by treatment group. Clinically significant values will be listed by treatment group.

A by-participant listing of vital signs data will be provided, with clinically significant values flagged.

4.11.5.2 Physical Examination Assessments

A complete physical exam will be conducted at screening and Week 78 that includes: evaluation of general appearance; head, eyes, ears, nose, and throat (HEENT); respiratory system; cardiovascular system; gastrointestinal system; musculoskeletal system, skin, genitourinary system, neurological system; and Tanner staging.

A partial physical examination will be conducted at Days 1, 7, 12, 28, 56, 84, 140, 182, 188, 193, Weeks 30, 34, 39, 52, and 65 that includes: general appearance, HEENT, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system, and skin.

Height (cm) and weight (kg) will be measured at screening, Day 1, Weeks 26, 39, 52, 65, and 78.

Clinically significant abnormal findings of physical examinations will be summarized by study visit and by treatment group using frequencies and percentages. Tanner staging will be summarized by study visit and by treatment group. Descriptive statistics on height, weight, and BMI will be summarized by study visit and by treatment group and presented graphically.

Analysis on height-for-age, weight-for-age, and BMI-for-age will be conducted to evaluate growth of the study population in teplizumab and placebo groups. Z-scores will be derived using the growth chart from the general population (e.g., CDC Growth Charts, https://www.cdc.gov/growthcharts/clinical_charts.htm). ANCOVA model will be used to analyze change from baseline to the end of study in Z-scores by pubertal status classified by baseline Tanner Stage < 3 vs ≥ 3 that includes treatment and baseline Z-score as covariates.

By-participant listings of physical examination data will also be provided.

4.11.6 Data Monitoring Committee (DMC)

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.

The DMC will 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. 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.

Details of the composition, roles, and responsibilities of members and DMC procedures will be described in a separate DMC charter.

4.12 Other Analyses

4.12.1.1 Pharmacokinetics (PK), Pharmacodynamic (PD), and Immunogenicity

4.12.1.2 Pharmacokinetics

Observed teplizumab serum concentration

The observed serum concentration of teplizumab at each collection time point will be summarized descriptively for the teplizumab group overall and by teplizumab product (Lilly vs AGC) and listed in the individual data listing.

Predicted PK parameters

A separate data analysis plan on developing population PK model for the estimation of PK parameters will be provided by a PK vendor who will perform the analysis on the predicted PK parameters. The brief description of the planned analysis for PK is provided below.

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 (e.g., 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 (for AUC, C_{max} and their derived parameters), median, range, standard deviation, and coefficient of variation.

4.12.1.3 Pharmacodynamic

PD measures of CD3 receptor occupancy and modulation and T cell activation will be collected in a substudy that is conducted at North American sites. PD samples will be drawn concurrently with the PK blood samples at pre-infusion on Day 1, Day 4, Day 9, and Day 12; at 45 ± 15 minutes post-infusion on Day 9; and on Day 28.
Observed and change from baseline in CD3 receptor occupancy and modulation and T cell activation parameters will be summarized with descriptive statistics at each visit by treatment group. MMRM will be used to analyze each PD parameter. The MMRM model will include treatment, visit, treatment-by-visit interaction term, and baseline value of the PD parameter as a covariate. Least square means for each treatment group and the differences between treatment groups in least square means along with the 95% CIs and p-values will be presented for each visit.

Boxplots of each PD parameter by treatment group will be used to graphically present the distribution of the observed values.

4.12.1.4 Immunogenicity

The incidence of positive ADA and ADA titers will be summarized for all participants who receive at least 1 dose of teplizumab and have appropriate samples for antibody detection (i.e., participants with at least 1 sample obtained after their first dose of teplizumab) for teplizumab group overall and by teplizumab product (Lilly vs AGC).

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.

4.12.2 Patient Reported Outcome (PRO) Measures

The patient reported outcome (PROs) measures that will be used to assess the general health and well-being of participants are the Pediatric Quality of Life Inventory™ (PedsQL) Diabetes and Family Impact Modules, the Hypoglycemia Fear Scale (HFS), and the Diabetes Treatment Satisfaction Questionnaire (DTSQ). The participants will complete these questionnaires on Day 1, Weeks 12, 26, 39, 52, 65, and 78.

4.12.2.1 Pediatric Quality of Life Inventory™ (PedsQL) Diabetes Module

The PedsQL™ 3.2 Diabetes Module is composed of 33 items comprising 5 dimensions for ages 8-45 years (Appendix 4). For ages 2-7 years, the PedsQL™ 3.2 Diabetes Module is composed of 32 items comprising 5 dimensions (one less item for the Worry Scale).

DESCRIPTION OF THE DIABETES MODULE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Diabetes Symptoms	15	1-15	1-15	Higher scores indicate better outcomes.
Treatment Barriers	5	1-5	1 - 5	
Treatment Adherence	6	1-6	1 - 6	
Worry	3 (2 for ages 2-7 years)	1-3 (1-2 for ages 2-7 years)	1-3 (1-2 for ages 2-7 years)	
Communication	4	1-4	1 - 4	

SCORING DIMENTIONS:

Item Scaling	5-point scale from 0 (Never) to 4 (Almost always) 3-point scale: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Child Report for Young Children (ages 5-7)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate scores by Dimension** • If more than 50% of the items in the dimension are missing, the dimension score should not be computed,

	• Mean score = Sum of the items over the number of items answered. **Total Score:** Sum of all the items over the number of items answered on all the dimensions.
Missing Data	Missing data will remain missing and no imputation will be conducted for this analysis.

The PedsQL™ 3.2 Diabetes Module total score (observed and change from baseline scores) at each visit will be summarized by treatment group. The change from baseline of Diabetes Module total and each dimension score at Week 78 will be analyzed separately using MMRM models that include treatment group, randomization stratification factors, visit, the corresponding baseline score, and treatment by visit interaction term as fixed effects.

4.12.2.2 Pediatric Quality of Life Inventory™ (PedsQL) Family Module

The parent report of the PedsQL™ 2.0 Family Impact Module is composed of 36 items comprising 8 dimensions (Appendix 5).

DESCRIPTION OF THE FAMILY IMPACT MODULE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	6	1-6	1-6	Higher scores indicate better outcomes.
Emotional Functioning	5	1-5	1-5	
Social Functioning	4	1-4	1-4	
Cognitive Functioning	5	1-5	1-5	
Communication	3	1-3	1-3	
Worry	5	1-5	1-5	
Daily Activities	3	1-3	1-3	
Family Relationships	5	1-5	1-5	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed to a 0 to 100 scale.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0 **Step 2: Calculate Scores by Dimensions**

	• If more than 50% of the items in the dimension are missing, the dimension score should not be computed, • Mean score = Sum of the items over the number of items answered. **Step 3: Total Scores** • The Total Score is the sum of all 36 items divided by the number of items answered • The Parent HRQL Summary Score (20 items) is computed as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning dimensions. • The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered in the Daily Activities and family Relationships dimensions.
Missing Data	Missing data will remain missing and no imputation will be conducted for this analysis.

at each visit will be summarized by treatment group. The change from baseline of Family Impact Module total and each dimension score at Week 78 will be analyzed separately using MMRM models that include treatment group, randomization stratification factors, visit, the corresponding baseline score, and treatment by visit interaction term as fixed effects.

4.12.2.3 Hypoglycemia Fear Scale (HFS)

The HFS comprises two subscales: the behavior subscale and worry subscale (Appendix 6). The Child and the parent give responses for both items of the subscales. The items are rated on a five-point Likert scale, 0 (never) to 4 (always).

The first 10 (11 in parent questionnaire) items assess behaviors individuals/parents may engage in as a result of fear of hypoglycemia and next 15 items assess worry concerning episodes of hypoglycemia and its consequences.

The mean subscale scores will be compared between treatment groups over the time. A higher score on the behavior subscale reflects a greater tendency to avoid hypoglycemia and/or its negative consequences. A higher score on the worry subscale indicates more worry concerning episodes of hypoglycemia and its consequences.

If more than 75% of the items have responses the subscale scores (i.e., 8 items if scoring in the behavior scale and 12 items if scoring the worry scale) will be calculated as the item score sum dividing by the number of questions answered. If less than 75% of the data is available, the score for that subscale should be counted as missing as it may not be a true reflection of participants' behaviors and/or worries.

The HFS Worry and Behavior subscales for individual and parent assessments (observed and change from baseline scores) at each visit will be summarized by treatment group. The change from baseline of HFS Worry and Behavior subscales for individual and parent assessments at Week 78 will be analyzed separately using MMRM models that include treatment group, randomization stratification factors, visit, the corresponding baseline score, and treatment by visit interaction term as fixed effects.

The episodes of Hypoglycemia (severe, moderate, and mild) and how upsetting was your worst episode will be summarized descriptively for both assessments of individuals and parents.

4.12.2.4 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The DTSQ will be used to assess patients' and teens' satisfaction with their diabetes treatment for over the past 2 weeks. The measures under consideration here are the 12-item Diabetes treatment satisfaction questionnaires for teens (DTSQ-Teen) and 14-item measure for parents (DTSQ-Parent). Each question is rated in 7-point Likert scale (0 to 6) where high scores indicate better outcomes (except for questions 3 and 4). The measures are based on the widely used eight-item DTSQ for adults (Bradley 1990, Bradley 1994), developed and expanded using extended interview work with parents and teenagers, to improve relevance, accessibility and intelligibility for teenagers (Woodcock 2007). These measures enable self-report by teenagers with diabetes, and comparison with their parents' reports. These questionnaires are provided in Appendix 7. For this exploratory analysis the following subscales treatment satisfaction (TS-Parent and TS-Teen), diabetes control, and perceived hypoglycemia will be analyzed:

- The TS-Parent, total score computed as sum of 8 items, 1, 5-8, 11, 13-14
- The TS-Teen, total score computed as sum of 8 items: 1, 5-9, 11-12
- Perceived diabetes control (PDC)-Parent and PDC-Teen, total score computed as sum of items 2 and 3 (after reversing the scoring of the latter)
- Perceived hypoglycemia, score computed from item 4.

Scores for each subscale will be calculated if ≥75% of the questions for the subscale were answered. If less than 75% of the data is available, the score for that subscale will be counted as missing as it may not be a true reflection of participants' treatment satisfaction.

In addition to above subscales, the guideline is also recommended to use DTSQ (change abbreviated as DTSQc, Appendix 7) Parent/Teen questionnaires for the past 12 weeks since the study has series of follow-ups over longer period of time. The questions for DTSQc are administered at Week 12 and rated in 7-point Likert scale (-3 to 3) where positive numbers indicate improvement and negative numbers indicate worsening (except for questions 3 and 4).

For the assessments of TS-Parent, TS-Teen, Perceived hypoglycemia, PDC-Parent, and PDC-Teen, observed and change from baseline scores at each visit will be summarized by treatment group. The change from baseline score of each assessment at Week 78 will be analyzed separately using MMRM models that include treatment group, randomization stratification factors, visit, the corresponding baseline score, and treatment by visit interaction term as fixed effects. For DTSQc Parent and DTSQc Teen scores, the observed scores at Week 12 will be summarized by treatment

group and analyzed separately using ANCOVA models that include treatment group and randomization stratification factors as fixed effects.

4.13 Changes in the Planned Analysis

This section is to document any changes from the planned analyses described in the study protocol.

Item	Protocol Text	SAP Text	Justification
ITT population definition	Section 11.2: 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.	Section 4.5: Intent-to-Treat (ITT) Population: All randomized participants.	To follow the intent-to-treat principle and include all randomized participants in the primary efficacy analyses regardless of whether or not they received study drug.
Primary analysis model for C-peptide ln(AUC+1) at Week 78	Section 11.5.1: 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.	Section 4.10.2: After multiple imputation has been performed on the missing data of C-peptide ln(AUC+1) based on the approach described in Section 4.10.1.3, the change from baseline in C-peptide ln(AUC+1) at Week 78 (i.e., baseline-corrected C-peptide ln(AUC+1) at Week 78) will be analyzed and the treatment difference will be tested using an ANCOVA model with treatment, age group at randomization (a randomization stratification factor), and baseline C-peptide ln(AUC+1) as covariates.	Change from baseline value of C-peptide ln(AUC+1) is a better indicator of the treatment effect on the C-peptide measure, compared to the observed C-peptide ln(AUC+1) value. Regarding covariates adjusted in the ANCOVA model, baseline C-peptide ln(AUC+1) is considered having higher correlation with Week 78 C-peptide ln(AUC+1), compared to baseline peak C-peptide. Therefore, we decide to include baseline C-peptide ln(AUC+1) in the ANCOIVA model, as opposed to including baseline peak C-peptide.
Time in glycemic range (TIR)	Section 2.3: 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	Section 3.2: 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	"≥70 mg/dL" is consistent with the ADA guidelines for the glycemic control target range.

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6 APPENDICES

Appendix 1 Schedule of Assessments

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 154)	(-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
Insulin Use Review (7 days)			X														X	
Fingerstick Glucometer Distribution (optional)		(X)																
Fingerstick Glucometer Download/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, 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	X		X		X			X			X	X	X	X	X
Chemistry Panel and LFTs		X	X	X		X		X			X			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
HLA-typing			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 154)	(-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*
TBNK/Quantitative Lymphocyte Panel			X											X	X		X	
Quantitative Immunoglobulin Panel		X															X	
Urine β-HCG (females only)			X												X	X	X	X
Urinalysis		X	X	X		X		X			X			X	X	X		X
2h MMTT		X																
4h MMTT			X															
T1D Autoantibodies (X 5)	X[1]	X															X	
Serum Teplizumab Levels			X[3]			X[3]					X[3]			X[3]	X[4]			
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	

Detail	Study Agent Treatment - Course 2												Post Course 2 Evaluations						EOSV
Week (Week 26 – 78)	26							27					30	34	39	52	65	78	
Day (182 – 546)	182	183	184	185	186	187	188	189	190	191	192	193	210	238	273	364	455	546	
Visit Window (± days from target)	± 3												± 4	± 4	± 4	± 4	± 7	± 7	*N/A*
Informed Consent/Assent																			
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^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 Download/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	X
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
Randomization																			
Study Drug Dose Calculation	X																		
Premedication (NSAID, 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		X			X			X	X	X	X	X	X	X	X
Chemistry Panel and LFTs	X	X		X		X			X			X	X	X	X	X	X	X	X
Coagulation Panel																			
Lipid Panel	X															X		X	X
HbA1c	X														X	X	X	X	X
Serum β-HCG (females only)																			
IGRA (Blood TB test)																			
HBV, HCV, HIV serology																			
EBV, CMV, VZV serology																X		X	X
EBV and CMV Viral PCR													X		X	X		X	X
HLA-typing																			
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												X	X	X	X	X	X	X
Urinalysis	X	X		X		X			X			X	X	X	X			X	X

Detail	Study Agent Treatment - Course 2												Post Course 2 Evaluations						EOSV
Week (Week 26 – 78)	26							27					30	34	39	52	65	78	
Day (182 – 546)	182	183	184	185	186	187	188	189	190	191	192	193	210	238	273	364	455	546	
Visit Window (± days from target)	*± 3*												*± 4*	*± 4*	*± 4*	*± 4*	*± 7*	*± 7*	*N/A*
2h MMTT																			
4h MMTT	X															X		X	X
T1D Autoantibodies (X 5)	X															X		X	X
Serum Teplizumab Levels	X[3]			X[3]					X[3]			X[3]	X[3]						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

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 = Continuous glucose monitoring device will be provided to the participants at these visits and will stay on for the following 2 weeks.
X^3 = Teplizumab levels for pharmacokinetic analyses are to be obtained within 30 minutes before study drug infusion (where applicable). The time of blood draws and study drug flush start and completion (where applicable) are to be documented in the CRF.
X^4 = Draw teplizumab level if the End of Study Visit is between Day 1 and Day 28 or between Day 182 and 210.
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

Appendix 2 Clinical Laboratory Tests Standardized (SI) Units

Panel	Parameter	SI Unit
Hematology	White Blood Cell (WBC) Count	10^9/L
Hematology	White Blood Cell (WBC) Differential	%
Hematology	Hemoglobin	g/L
Hematology	Hematocrit	L/L
Hematology	Platelets Count	10^9/L
Chemistry	Sodium	mmol/L
Chemistry	Potassium	mmol/L
Chemistry	Chloride	mmol/L
Chemistry	Bicarbonate	mmol/L
Chemistry	Blood Urea Nitrogen (BUN)	mmol/L
Chemistry	Creatinine	µmol/L
Chemistry	Glucose	mmol/L
Chemistry	Calcium	mmol/L
Chemistry	Phosphate	mmol/L
Chemistry	Albumin	g/L
Chemistry	Total Protein	g/L
Chemistry (Liver Function)	Total Bilirubin	µmol/L
Chemistry (Liver Function)	Direct Bilirubin	µmol/L
Chemistry (Liver Function)	Aspartate Aminotransferase (AST)	U/L
Chemistry (Liver Function)	Alanine Aminotransferase (ALT)	U/L
Chemistry (Liver Function)	Alkaline Phosphatase (ALP)	U/L
Quantitative Lymphocyte TBNK	CD4+ T Cells	NA
Quantitative Lymphocyte TBNK	CD8+ T Cells	NA
Quantitative Lymphocyte TBNK	B Cells	NA
Quantitative Lymphocyte TBNK	NK Cells	NA
Quantitative Immunoglobulin	IgA	µmol/L
Quantitative Immunoglobulin	IgG	µmol/L
Quantitative Immunoglobulin	IgM	µmol/L
Lipid	Total Cholesterol	mmol/L
Lipid	HDL	mmol/L
Lipid	LDL (Assayed)	mmol/L
Lipid	Triglycerides	mmol/L
Coagulation	Prothrombin Time (PT)	sec
Coagulation	Partial Thromboplastin Time (PTT)	sec
Coagulation	International Normalized Ratio (INR)	NA
Urinalysis	pH	NA
Urinalysis	Specific Gravity	NA
Urinalysis	Total Protein	NA
Urinalysis	Glucose	NA
Urinalysis	Ketones	NA
Urinalysis	Bilirubin	NA
Urinalysis	Nitrites	NA
Urinalysis	Leukocyte Esterase	NA
Urinalysis	WBC	HPF
Urinalysis	RBC	HPF
Urinalysis	Hemoglobin	NA
Other	Pregnancy (Serum, Urine)	IU/L
Other	HIV Antibody Serology	NA
Other	HBV Antibody Serology	NA
Other	HCV Antibody Serology	NA
Other	VZV Antibody Serology	NA
Other	CMV Serology	NA

Panel	Parameter	SI Unit
Other	EBV Serology	NA
Other	CMV DNA PCR	NA
Other	EBV DNA PCR	NA
Other	MHC Haplotype	NA
Other	IGRA Tuberculosis Testing	NA
Other	HbA1c	mmol/mol
Diabetes-Related	T1D Antibodies	kU/L
Diabetes-Related	C-Peptide	nmol/L
Diabetes-Related	Insulin	pmol/L
Diabetes-Related	Proinsulin	pmol/L

Appendix 3 Potentially Clinically Significant (PCI) Criteria for Clinical Laboratory Tests

Test Name	Reference Range	Units	PCI Criteria
Hematology			
Hemoglobin Age 6 to < 12	11.5 - 13.5	g/dL	< 10 or > 16
Hemoglobin females 12-17	12.0 - 14.0	g/dL	< 10 or > 16
Hemoglobin males 12-17	13 - 14.5	g/dL	< 10 or > 16
WBC	4.5 - 13.5	$x10^3/\mu L$	<2 or >16
Eosinophils (absolute)	0.0 - 0.2	$x10^3/\mu L$	>=3
Neutrophils (absolute)	1.5 - 8.0	$x10^3/\mu L$	<1
Lymphocytes (absolute)	1.2 - 6.8	$x10^3/\mu L$	< 1 and >8
Platelets	150 - 350	$x10^3/\mu L$	<100 or >1000
Chemistry			
Protein (Total)	6.0 - 8.3	gm/dL	<4.0
Albumin	3.6 - 5.2	gm/dL	<2.0
ALT age < 12	10 - 35	U/L	>= 3X ULN
ALT age 12-17	10 - 45	U/L	>=3X ULN
AST Females	13 - 35	U/L	>=3X ULN
AST Males	15 - 40	U/L	>=3X ULN
ALP Females and age < 12	100 - 320	U/L	>=2X ULN
ALP Males age 12-17	100 - 390	U/L	>=2X ULN
Direct Bilirubin	< 0.2	mg/dL	>= 2X ULN
Bilirubin (total)	< 1.5	mg/dL	>=2X ULN
Bicarbonate	22 - 26	mmol/L	<18 or >30
BUN females	7 - 17	mg/dL	>34
BUN males	9 - 20	mg/dL	>40
Calcium	8.4 - 10.8	mg/dL	<7 or >11
Chloride	97 - 107	mmol/L	<90 or >120
Creatinine age < 12	0.3 - 0.7	mg/dL	>=1.2
Creatinine age 12- 17	0.5 - 1.0	mg/dL	>=1.7
Glucose	65 - 140	mg/dL	<70 or >180
HbA1c, this should be under Hematology	< 7.5%	%	>8.0%
Phosphate	3.3 - 5.4	mg/dL	<2.0 or > 6.0
Potassium	3.4 - 5.1	mmol/L	<3.0 or > 6.0
Sodium	135 - 145	mmol/L	<125 or >155
Total Cholesterol	120 - 170	mg/dL	>200
Triglycerides	24 - 145	mg/dL	>250
High Density Lipoprotein (HDL)	>35	mg/dL	< 25
Low Density Lipoprotein (LDL)	< 110	mg/dL	>130
Urinalysis			
Bacteria	Negative		Many
Bilirubin	Negative		3+ or +++
Crystals (any)	Negative		Numerous= MANY
Epithelial cells (any)	0 - 5	per HPF	Numerous = MANY
Glucose (urine)	Negative		3+, 4+, +++, ++++, 3+ or >=1000, >=1000
Granular casts	None	per LPF	>0
Hemoglobin (urine)	Negative		3+ 250 or highest category

Test Name	Reference Range	Units	PCI Criteria
Hyaline casts	0 - 1	per LPF	>1, 1-3, 1-5
Ketones	Negative		3+ or +++
Leucocyte esterase	Negative		3+
Nitrite	Negative		3+
Protein (total) (urine)	Negative		>=300, 3+, +++, 4+, ++++
RBC	0 - 2	per HPF	>=10
RBC casts	None	per LPF	>0, 0-1
Specific gravity	1.003 - 1.030		n/a
Urobilinogen	Negative		3+
Waxy casts	None	per LPF	>0
WBC	0 - 5	per HPF	>=10
WBC casts	None	per LPF	>0

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CPK=creatine phosphokinase, GGT=gamma-glutamyl transferase, HPF=high-power field, LPF=low-power field, PT=prothrombin time, RBC=red blood cell count, WBC=white blood cell count.

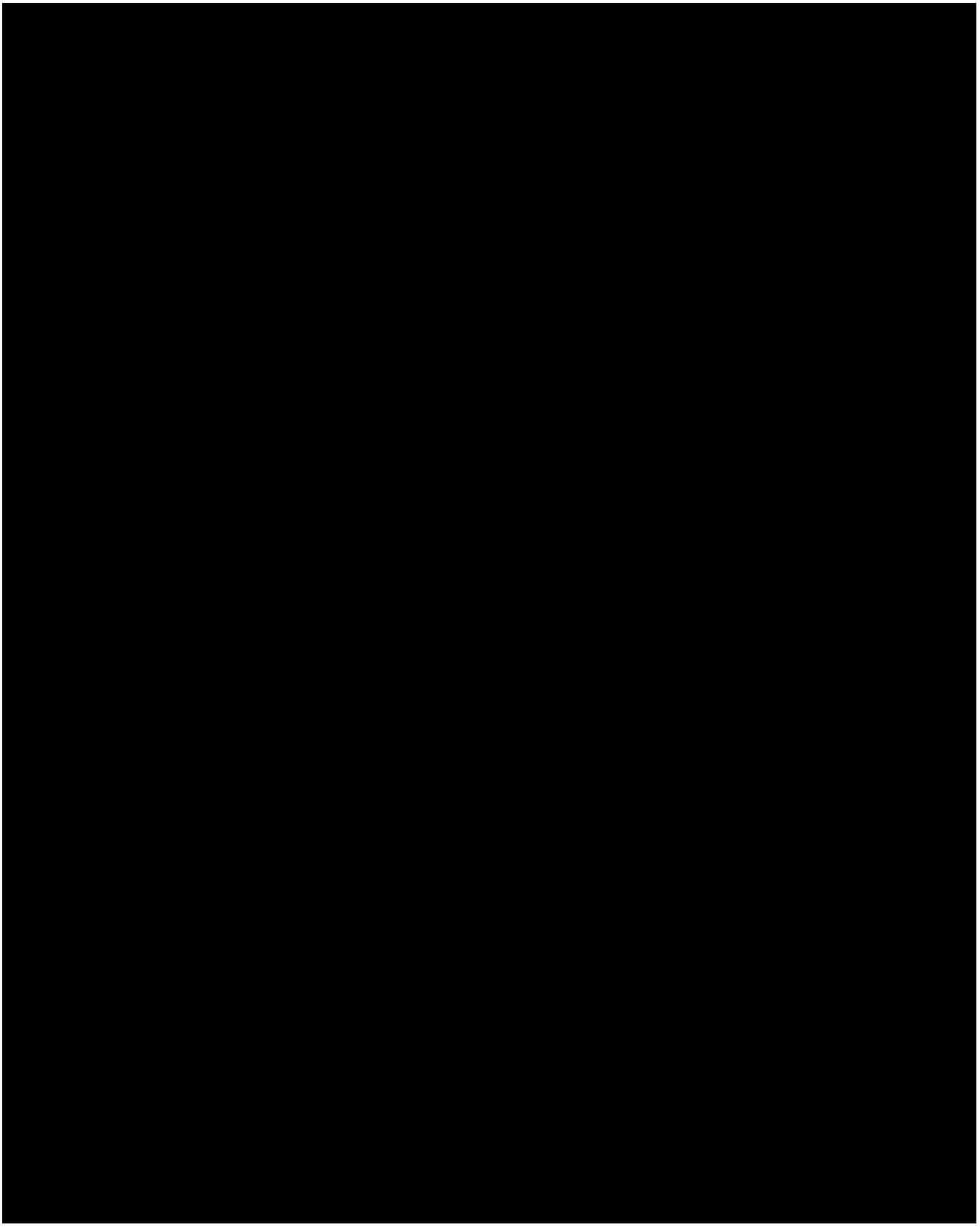
Appendix 4 PedsQL™ Diabetes Module for Patient Self-report

Scales	Items
Diabetes Symptoms	I feel hungry
	I feel thirsty
	I have to go to the bathroom too often
	I have stomachaches
	I have headaches
	I feel like I need to throw up
	I go “low”
	I go “high”
	I feel tired
	I get shaky
	I get sweaty
	I feel dizzy
	I feel weak
	I have trouble sleeping
	I get cranky or grumpy
Treatment Barriers	It hurts to get my finger pricked
	It hurts to get insulin shots
	I am embarrassed by my diabetes treatment
	My parents and I argue about my diabetes care
	It is hard for me to take blood glucose tests
Treatment Adherence	It is hard for me to take blood glucose tests
	It is hard for me to take insulin shots
	It is hard for me to exercise or do sports
	It is hard for me to keep track of carbohydrates
	It is hard for me to snack when I go “low”
Worry	I worry about going “low”
	I worry about going “high”
	I worry about long-term complications from diabetes
Communication	It is hard for me to tell the doctors and nurses how feel
	It is hard for me to ask the doctors and nurses questions
	It is hard for me to explain my illness to other people
	I am embarrassed about having diabetes

All responses are either in 5-point scale from 0 (Never) to 4 (Almost always) or 3-point scale: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Child Report for Young Children (ages 5-7)

Appendix 5 PedsQL™ Family Impact Module – General Comment of Scales

Appendix 6 The Hypoglycemic Fear Survey (HFS)



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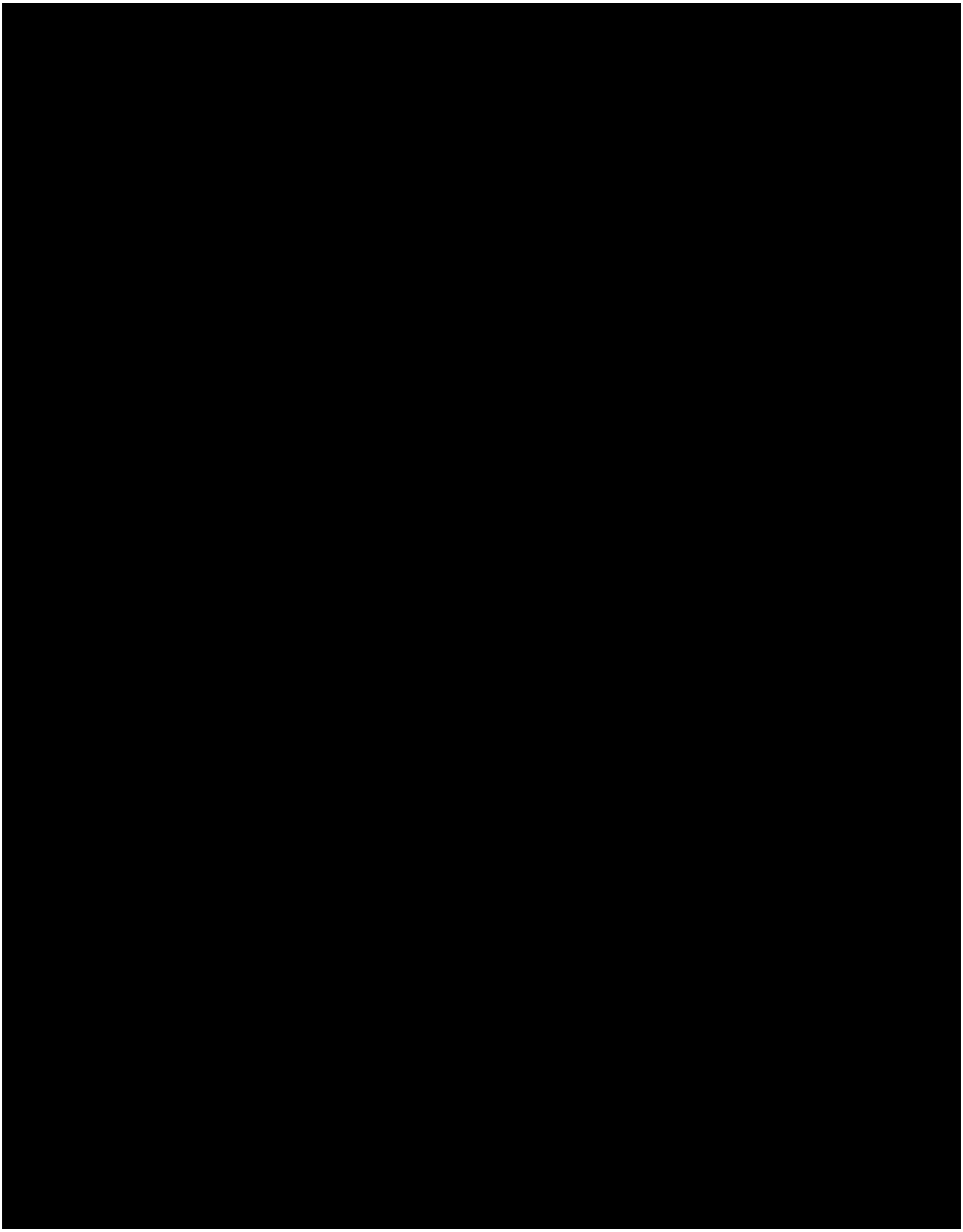
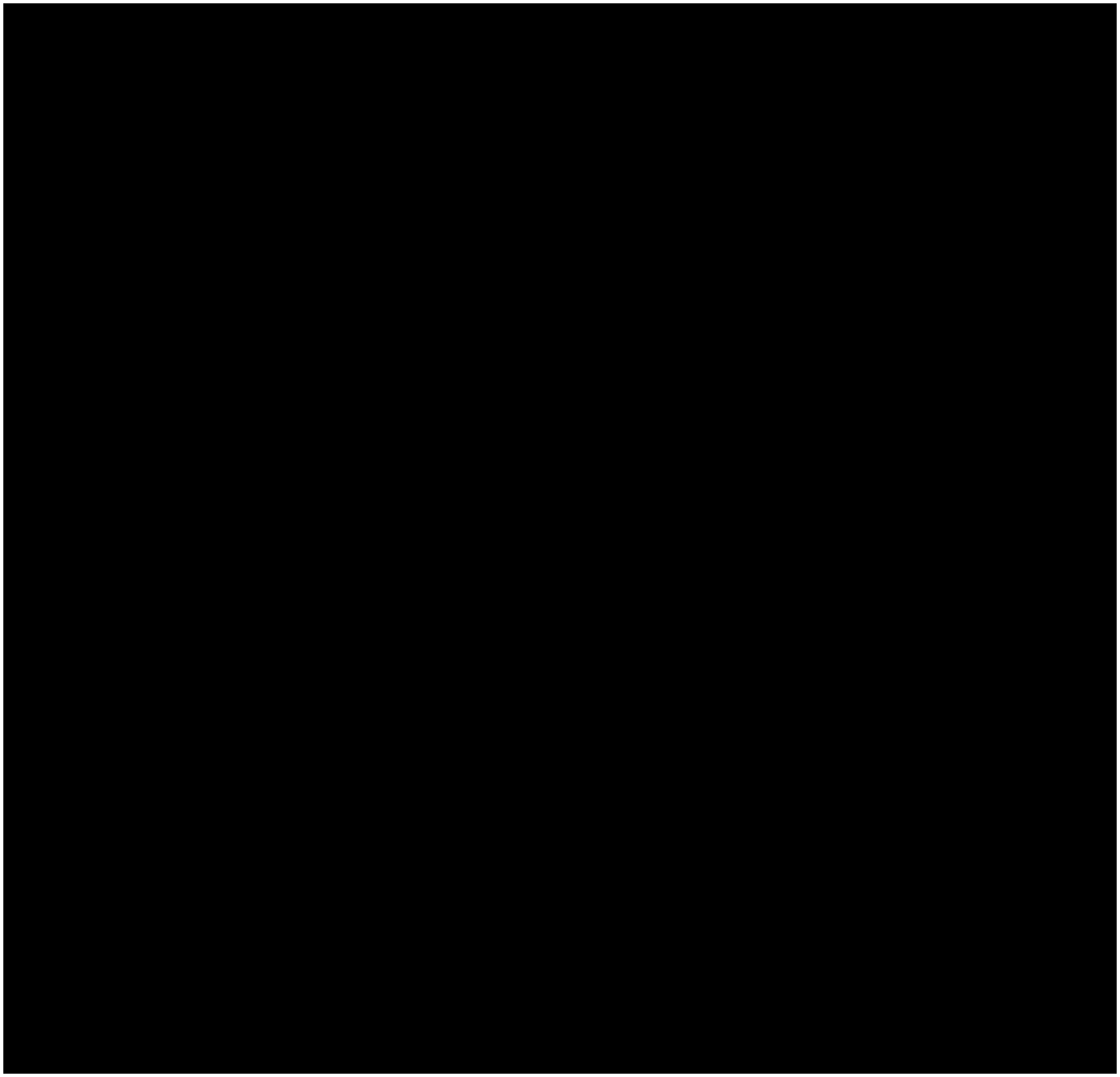
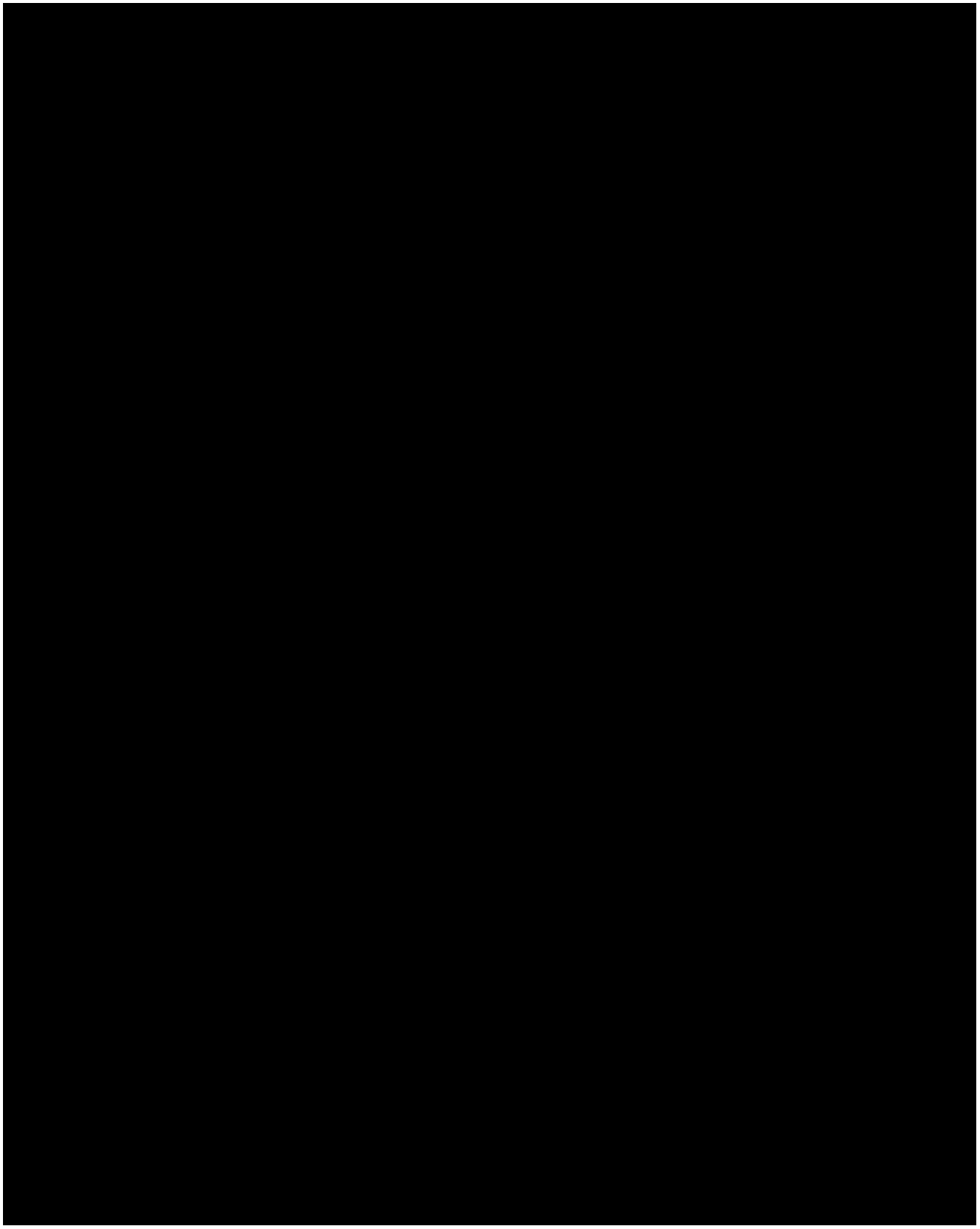




Appendix 7 Treatment Satisfaction Questionnaire (DTSQ)



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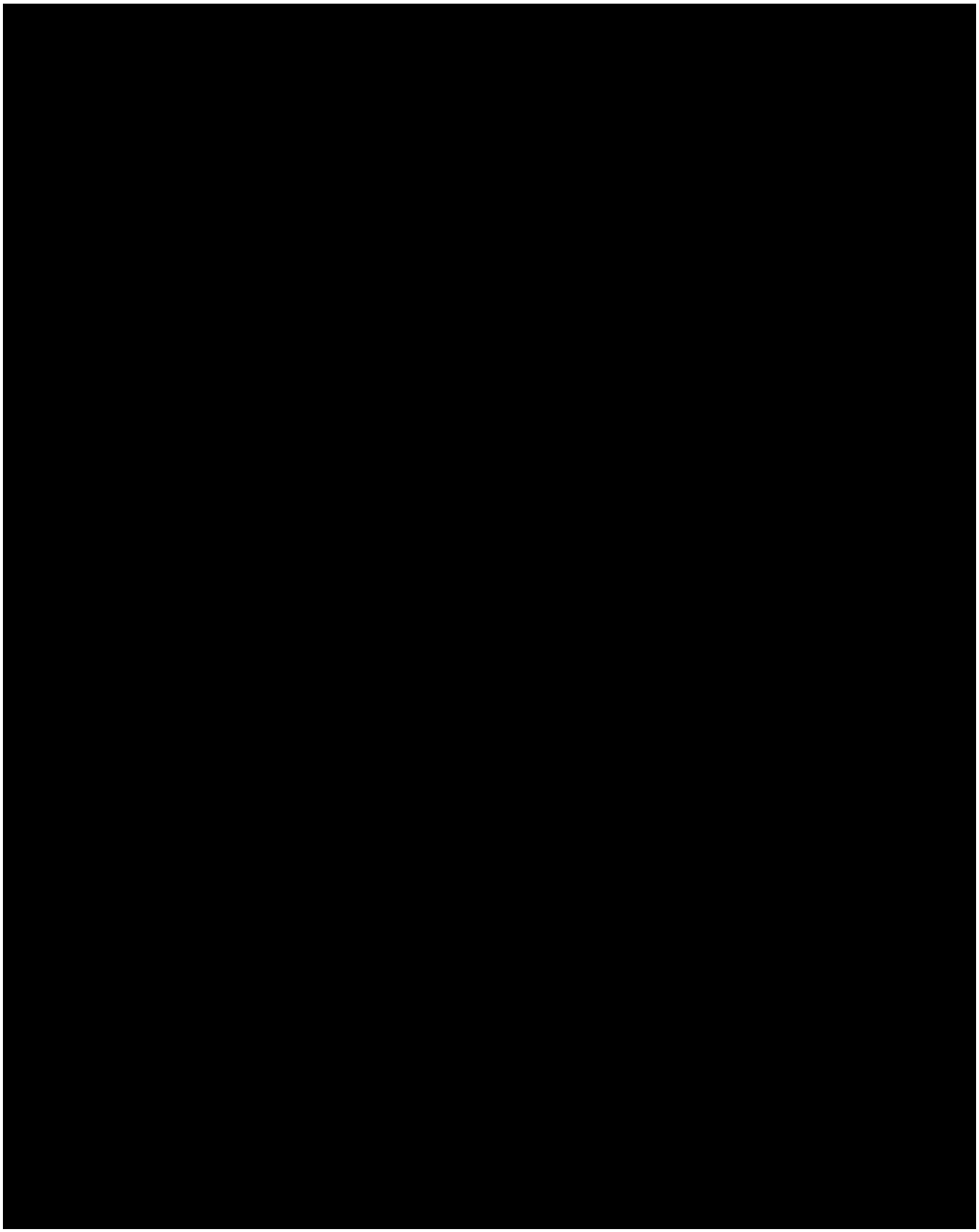

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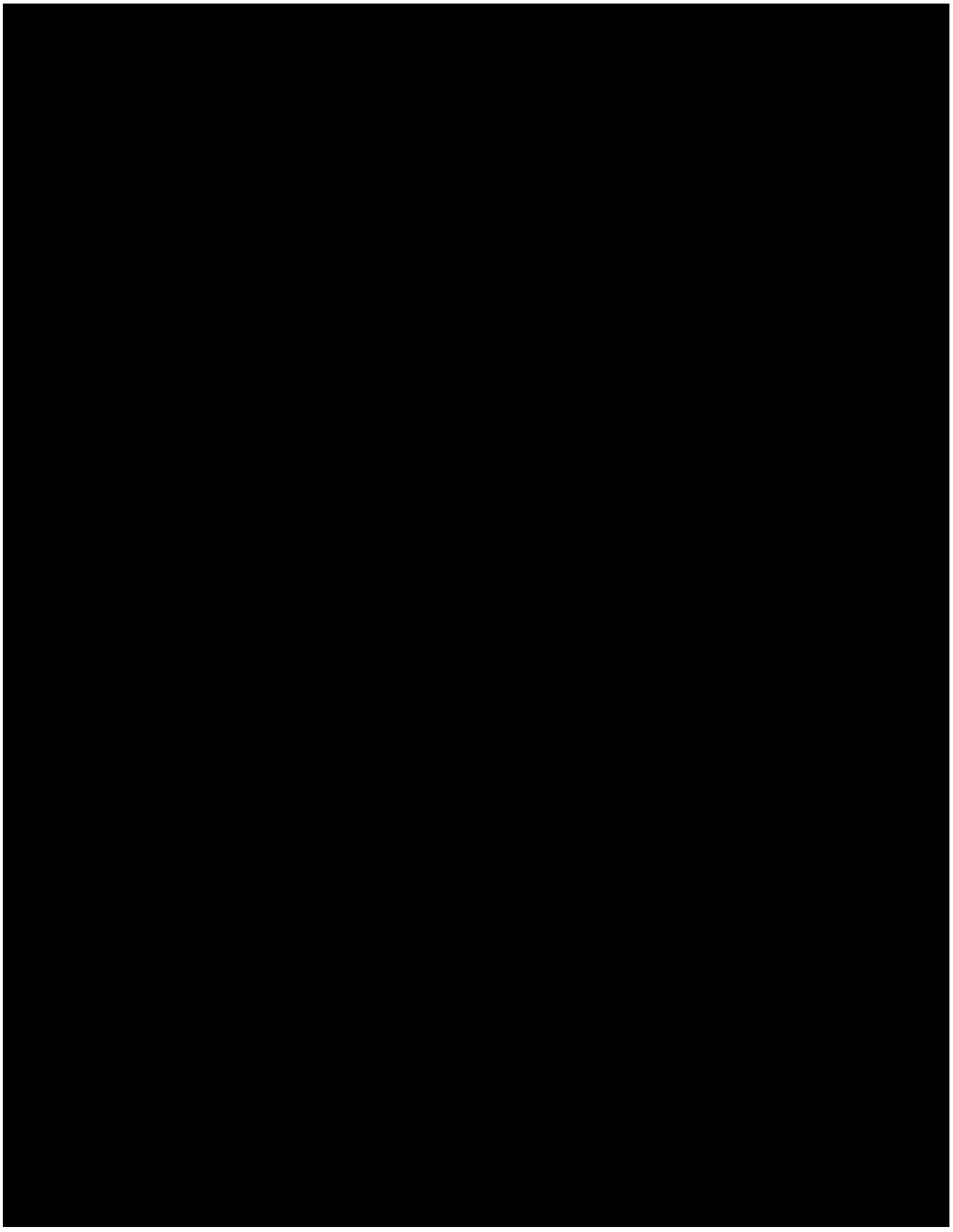

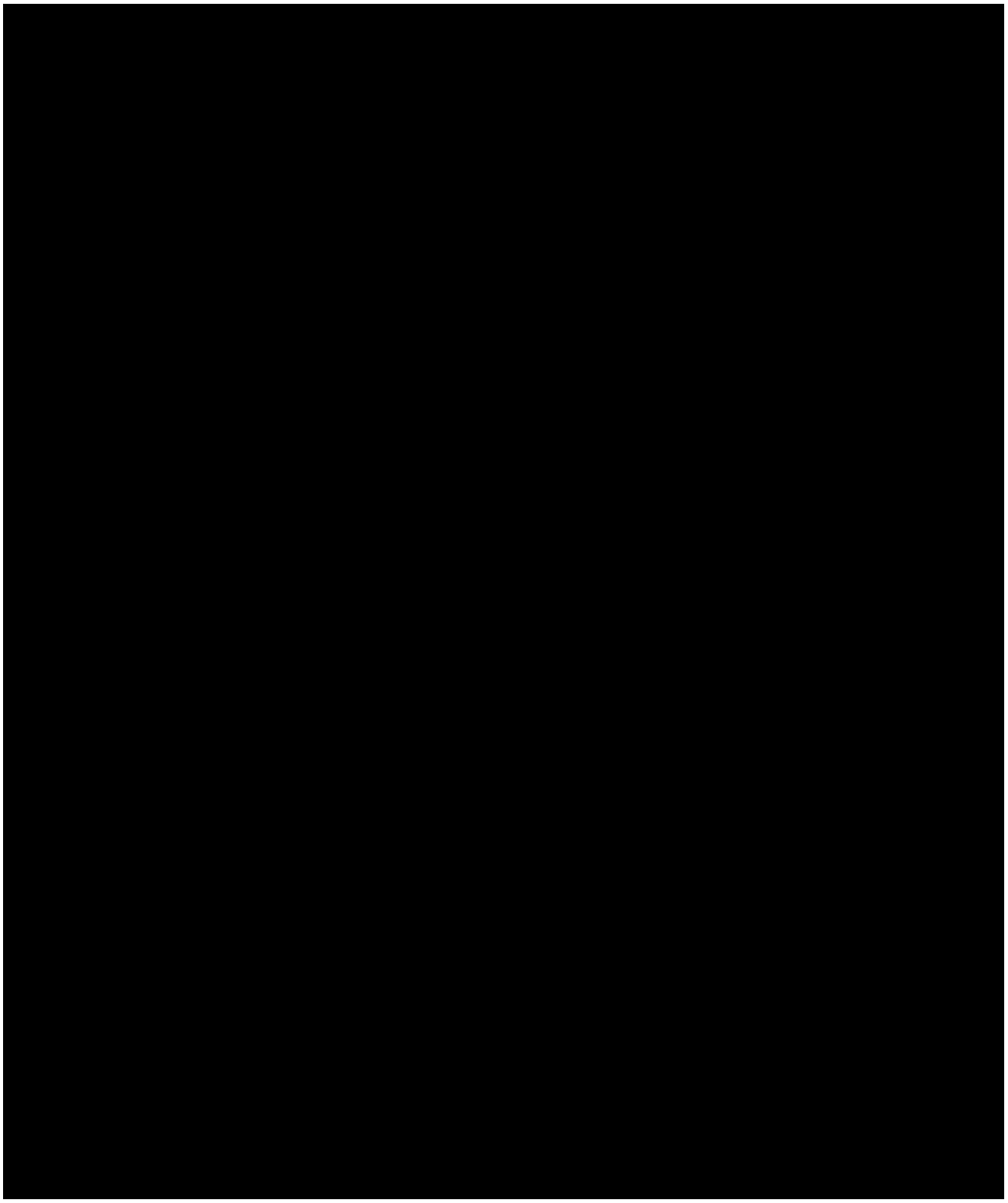

Appendix 8 Modified-Dosing Schedule of Events: Screening to Week 26

Event	Pre-Screen[1]	Screen[a]	Study Drug Treatment - Course 1												Post Course 1 Evaluations				
Week (Screening through Week 20)	(-6) - (-4)	(-5) - 0	1							2					4	8	12	20	26
Day (Screening through Day 154)	(-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	
Quality of Life Questionnaires			X														X		X
																			X
Randomization (w/ stratification)			X																
Study Drug Dose Calculation			X																
Premedication (NSAID[b], 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]					
ECG		X[(M)]												X[(M)]					
CBC w/ Differential		X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X	X[L]
Chemistry Panel and LFTs		X	X[L]	X[L]		X[L]		X[L]			X[L]			X	X	X	X	X	X[L]
Coagulation Panel		X																	
Lipid Panel		X																	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	
HLA-typing			X																
TBNK/Quantitative Lymphocyte Panel			X											X	X		X		X
Quantitative Immunoglobulin Panel		X															X		X

Event	Pre-Screen[1]	Screen[a]	Study Drug Treatment - Course 1												Post Course 1 Evaluations				
Week (Screening through Week 20)	(-6) - (-4)	(-5) - 0	1							2					4	8	12	20	26
Day (Screening through Day 154)	(-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*
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[c]																			
2h MMTT		X																	
4h MMTT			X																X
T1D Autoantibodies (X 5)	X[1]	X															X		X
Serum Teplizumab Levels			X[3]			X[3]					X[3]			X[3]	X[4]				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 of Events: Week 30 to Week 78

Detail	Post Course 1 Evaluations			Study Agent Treatment - Course 2												Post Course 2 Evaluations				ET
Week (Week 26 – 78)	34	39		52							53					56	60	65	78/ EOSV	
Day (182 – 546)	238	273		364	365	366	367	368	369	370	371	372	373	374	375	392	420	455	546[a]	
Visit Window (± days from target)	*± 4*	*+ 28*		*± 7*	*N/A*													*± 7*	*± 7*	*N/A*
Inclusion/Exclusion Criteria/Review				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^{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																			X	X
EBV and CMV Viral PCR		X														X	X		X	X
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	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

Detail	Post Course 1 Post Course 1 Evaluations			Study Agent Treatment - Course 2												Post Course 2 Evaluations				ET
Week (Week 26 – 78)	34	39		52							53					56	60	65	78/ EOSV	
Day (182 – 546)	238	273		364	365	366	367	368	369	370	371	372	373	374	375	392	420	455	546[a]	
Visit Window (± days from target)	*± 4*	*+28*		*± 7*	*N/A*											*± 4*	*± 4*	*± 7*	*± 7*	*N/A*
Serum Teplizumab Levels				X[3]			X[3]					X[3]			X[3]	X[3]				X[4]
Serum Anti-teplizumab Antibody		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

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 210.
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^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
X^M = Up to 45 subjects randomized in the US only. Three separate 12-lead electrocardiogram (ECG) tracings, 1 minute apart should be obtained. Pre-dose ECG measurement should be performed within 2 weeks of Day 1 of dosing; if patient is unable to accommodate additional visit for this procedure during Screening, pre-dose ECG can be performed on Day 1 of first course of treatment before the infusion; post-dose ECG measurement should be performed in approximately 1h after infusion on Day 12 of first course of treatment.

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