CLINICAL STUDY PROTOCOL

A Prospective Randomized Placebo-Controlled Double Blind Clinical Trial to Evaluate the Safety and Efficacy of CLBS03 (Autologous *Ex Vivo* Expanded Polyclonal [redacted] Regulatory T-cells [Tregs]) in Adolescents with Recent Onset Type 1 Diabetes Mellitus (T1DM)

The Sanford Project T-Rex Study

Protocol Number: CLBS03-P01

Version: 7.0

Original Protocol Date: 27-Oct-2014

Revision Date: 17-Jan-2017

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Sponsored by Caladrius Biosciences, Inc.

PROTOCOL APPROVAL FORM

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CLBS03-P01

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APPROVAL SIGNATURES:

[redacted]

SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the independent review boards. For information on the definition and assessment of adverse events (AEs), refer to Section 11.

ALL SAEs ARE TO BE REPORTED TO THE SPONSOR WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT.

PERSONNEL AND FACILITIES

Sponsor Caladrius Biosciences, Inc. 106 Allen Road, 4th Floor Basking Ridge, NJ 07920 Main: (908) 842-0100 [redacted] **Medical Monitor** [redacted]	**Contact for Reporting Serious Adverse Events** [redacted]
Study Manager (Primary Study Contact) [redacted]	**Back up Study Contact** [redacted]

Note: Changes to Personnel and Facilities do not constitute an amendment and will be updated as needed.

1. STUDY SYNOPSIS

Title	A Prospective Randomized Placebo-Controlled Double Blind Clinical Trial to Evaluate the Safety and Efficacy of CLBS03 (Autologous *Ex Vivo* Expanded Polyclonal [redacted] Regulatory T-cells [Tregs]) in Adolescents with Recent Onset Type 1 Diabetes Mellitus
Short Title	Exploratory Study of CLBS03 in Adolescents with Recent Onset T1DM
Investigational Product (IP)	CLBS03
Name(s) of Active Ingredient(s)	Autologous *Ex Vivo* Expanded Polyclonal [redacted] Regulatory T-cells
Control Type	Placebo (infusion solution only)
Clinical Phase	2
Sponsor	Caladrius Biosciences, Inc.
Treatment Description	Subjects will receive either a single infusion of CLBS03 [redacted] body weight [BW]) or placebo.
Study Purpose	The purpose of this study is to assess the safety and efficacy of CLBS03 in adolescents aged 8 to less than 18 years old with recent onset T1DM.
Primary Objective	The primary objective of this exploratory study is to assess the safety and potential efficacy of CLBS03 (either of the two doses [redacted] BW) to modify the T1DM disease course, including preservation of β-cell function and improvements in measures of disease severity, as compared with placebo, in adolescents with recent onset T1DM.
Secondary Objective	To assess the efficacy of CLBS03, including additional measures of T1DM severity, and to evaluate the effect of CLBS03 on the pathologic autoimmune response underlying T1DM and on the general immune responsiveness through 104 weeks.
Primary Efficacy Endpoint	The 4-hour Mixed Meal Tolerance Test (MMTT)-stimulated insulin connecting peptide (C-peptide) area under the curve mean (AUC mean) at 26 and 52 weeks.
Secondary Efficacy Endpoints	The 2-hour MMTT-stimulated C-peptide AUC mean at 13, 26, 52, 78, and 104 weeks and the 4-hour MMTT-stimulated C-peptide AUC mean at 104 weeks. Additional metabolic evaluations will include a comparison between the study treatment groups in: • Daily dose of insulin use (DDI) as measured by U/kg BW at weeks 4, 13, 26, 39, 52, 78 and 104. • Severe hypoglycemia, defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions, occurring from the time of treatment through weeks 13, 26, 52, 78 and 104. • HbA1c levels measured at 13, 26, 39, 52, 78, and 104 weeks.

	• Fasting blood glucose levels at weeks 13, 26, 52, 78 and 104 (based on MMTT). • [redacted]
Safety Endpoints	Adverse events, including SAEs and events of special interest (see Section 11), will be assessed in all treatment arms through week 104. [redacted]
Study Design	This will be a double-blinded, multi-center exploratory trial assessing two doses of CLBS03 [redacted] versus placebo. The study will include adolescent subjects aged 8 to less than 18 years old (pretreatment visit) with recent onset T1DM. [redacted] Approximately 111 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio (placebo, [redacted]
Sample Size	Approximately 111 subjects
Study Duration	All randomized subjects will be followed in the study for approximately 2 years after treatment.
Inclusion Criteria	1. Male and female subjects between the ages of 8 to less than 18 at the time of screening. 2. Diagnosis of T1DM within 100 days of IP administration (treatment visit) according to the American Diabetes Association (ADA) criteria (see Appendix 17.1). [redacted]

	[redacted] 4. Peak MMTT-stimulated C-peptide level >0.2 pmol/mL (at the screening visit). 5. Weight of ≥30 kg at the time of screening. 6. Body mass index (BMI) z-score less than 2.25 at the time of screening (see Appendix 17.3). 7. For females of childbearing potential, a negative urine pregnancy test is required at Screening and prior to the blood draw for Treg collection at Visit 2. A negative urine pregnancy test is also required prior to infusion of the treatment at Visit 3. 8. Females of child bearing potential (i.e., females who have reached puberty or have had their first menstrual bleeding) must: a) be surgically sterile, or b) be willing to practice an acceptable method of birth control for the duration of their participation in the study. Acceptable methods of birth control are: oral contraceptive tablets, hormonal implant device, hormonal patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, or abstinence. 9. Males must agree to use a reliable and acceptable method of contraception for the duration of their participation in the study. Acceptable methods of contraception are: condom with spermicide, or abstinence. [redacted] 11. Subject signing the study informed consent form (ICF). As the subject will be a minor at the time of consent, the subject must sign an assent form with the parent or legally authorized representative signing the ICF. 12. Able to comply with and undergo procedures as required for the study.
Exclusion Criteria*	1. Hemoglobin less than 12 g/dL at the time of screening. 2. Leukocytes <3,000/µL; neutrophils <1,500/µL; lymphocytes <800/µL; platelets <100,000/µL at the time of screening. [redacted] 6. Serious (requiring hospitalization or an antibiotics course of duration greater than 10 days) bacterial, viral, or fungal infections or clinically significant opportunistic infections within 90 days prior to Visit 3. 7. History of malignancy or serious uncontrolled (in the judgement of the investigator) cardiovascular, nervous system, pulmonary, renal, or gastrointestinal disease.

* Subjects with exclusionary test results can have the tests repeated for confirmation with approval from the sponsor, or if the clinical picture changes. If the new test results meet study criteria the subject can be enrolled or continue to be enrolled.

	8. Have serologic evidence of current or past viral infection: human immunodeficiency virus 1/2 (HIV), hepatitis B, hepatitis C, and human T-lymphotropic virus (HTLV) 1/2. [redacted] 12. Diagnosis of liver disease as defined by alanine aminotransferase (ALT) > 3x the upper limit of age-determined normal (ULN) or total bilirubin > 1.5 x ULN. 13. Pregnant or breast-feeding females. [redacted] 16. Subjects who have participated in an investigational drug study within 90 days prior to the screening visit. [redacted] 19. Any other condition which, in the opinion of the investigator, may preclude the subject from safe participation in the study or compromise data integrity.
Statistical Analyses	[redacted]

	[redacted]
Sample Size Estimation	The goal of this study, assuming that safety is acceptable, is to determine if there is sufficient evidence of clinically meaningful bioactivity to proceed with further development. Since there are no prior data in the current study population, sample size estimation was based on projected differences in the decreases in the 4-hour AUC mean MMTT-stimulated C-peptide in the control and active treatment groups at the Week 52 visit. [redacted]

2. LIST OF ABBREVIATIONS

^{2}H	Deuterium
ACLS	Advanced Cardiac and Life Support
ADA	American Diabetes Association
AE	Adverse event
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC mean	From the mixed meal tolerance test, the time-weighted average concentration of C-peptide; the C-peptide AUC divided by the duration of the mixed meal test.
β-cells	Pancreatic beta cells
BMI	Body mass index
BUN	Blood urea nitrogen
BW	Body weight
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CFSE	Carboxyfluorescein succinimidyl ester
CGM	Continuous glucose monitoring
CK	Creatine kinase
CMV	Cytomegalovirus
C-peptide	Insulin connecting peptide
CPDA	Citrate-phosphate-dextrose-adenine
CRF	Case report form
CRP	C-reactive protein

CRS	Cytokine release syndrome
DDI	Daily dose of insulin
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
eCRF	Electronic case report form
FDA	US Food and Drug Administration
FOXP3	Forkhead box P3
FPG	Fasting plasma glucose
GAD	Glutamate decarboxylase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMU	Gdańsk Medical University
GvHD	Graft-versus-host disease
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
hCG	Human chorionic gonadotrophin
HDL	High-density lipoprotein
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-lymphotropic virus
IA	Insulinoma antigen
IAA	Insulin autoantibody
IB	Investigator's brochure
ICA	Islet cytoplasmic antibodies
ICF	Informed consent form
ICH	International Council on Harmonisation
Ig	Immunoglobulin

IL-2	Interleukin-2
IL-10	Interleukin-10
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IU	International unit
IV	Intravenous
mAbs	Monoclonal antibodies
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMTT	Mixed meal tolerance test
NaCl	Sodium chloride
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGSP	National Glycohemoglobin Standardization Program
NIH	National Institutes of Health
NK cells	Natural killer cells
NOD	Non-obese diabetic
NPH	Neutral protamine Hagedorn
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PCT	PCT, a Caladrius Company
PDGF	Platelet derived growth factor
PG	Plasma glucose
PP	Per-protocol
PPD	Purified protein derivative

PT	Prothrombin time
PVC	Polyvinyl chloride
QA	Quality assurance
RMSE	Root mean square error
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SIC	Subject identification code
SMBG	Self-monitoring blood glucose
SNPs	Single nucleotide polymorphism
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
TB	Tuberculosis
T-bil	Total bilirubin
T-cho	Total cholesterol
Tdap	Tetanus, diphtheria and pertussis vaccination
TG	Triglyceride
TGF-β	Transforming growth factor-β
Th	T helper
TNFα	Tumor necrosis factor alpha
T-pro	Total protein
Tregs	Regulatory T-cell
TSDR	Treg specific demethylation region
UCSF	University of California, San Francisco
ULN	Upper limit of normal
WHO	World Health Organization
USP	United States Pharmacopoeia
Yale	Yale University
ZnT8	Zinc transporter 8

3. TABLE OF CONTENTS

4. SCHEDULE OF STUDY ASSESSMENTS

[redacted]

[redacted]

5. BACKGROUND AND SIGNIFICANCE

5.1 Summary

It is hypothesized that CLBS03 or autologous *ex vivo* expanded, polyclonal [redacted] regulatory T-cells (Tregs) administered to participants with recent onset Type 1 Diabetes Mellitus (T1DM) will be safe and effective in preserving β-cell function. This protocol describes an exploratory Phase 2 trial to assess this therapy.

[redacted]

5.2 Clinical and Scientific Rationale

5.2.1 Type 1 Diabetes Mellitus

T1DM is one of the most common and costly pediatric diseases.[2] It is estimated that up to 1 million Americans are living with T1DM[3] and more than 18,000 children are diagnosed with T1DM annually in the US. The incidence of T1DM has been increasing by approximately 3% annually in the US and abroad.[4] Currently, the number of youth (age <20 years) with T1DM is projected to increase by at least 23% by 2050.[5]

T1DM results from autoimmune destruction of pancreatic β-cells by islet-specific T-cells.[6-8] This destructive process takes place over a period of months, before and after the onset of clinical diabetes.[9] While interruption of this destructive process before disease onset can prevent clinical disease,[10] cessation of autoimmune cell destruction even after disease onset provides for the possibility of clinical benefit.[11]

The importance of maintaining glycemic control in T1DM is well established in epidemiologic observations and prospective studies. Results from these studies demonstrated that intensive treatment slowed the loss of β-cell function (as measured by C-peptide in subjects with residual β-cell function) and maintained substantially lower mean HbA1c for 5 to 6 years while lowering the risk for development of microvascular complications.[12] Treatments for T1DM specifically aimed at preserving residual β-cell function may allow subjects to more effectively manage their disease and prevent long-term diabetic complications. As reported by the Diabetes Control and Complications Trial (DCCT), current standards of care aim to reduce the incidence and

progression of T1DM- related complications by initiating early, aggressive treatments to maintain a level of HbA1c as close to normal as possible.[13]

5.2.2 The Role of Tregs in T1DM

Efforts to prevent or reverse T1DM have been limited by the absence of tolerogenic drugs that can be used both safely and effectively. Relatively non-specific therapies such as anti-cluster of differentiation 3 (anti-CD3) monoclonal antibodies (mAbs) can be efficacious, but have associated side effects. Two substantial findings have emerged: first, that short-term immune regulation of T-cells can have a long-term effect on disease progression; and second, that immunomodulatory anti-T-cell agents induce a T-regulatory cell subset that is likely to be responsible for the long lived efficacy of T-cells, in both animal and human studies.[14, 15] Recently, Couri and colleagues reported that transplantation of autologous nonmyeloablative hematopoeitic stem cells in participants newly diagnosed with T1DM led to a preservation of β-cell mass and insulin-independence for up to four years.[16] This study demonstrated that immune tolerance can be regained; however, the adverse events associated with the stem cell transplant procedure were considerable. There is mounting evidence that polyclonal Tregs have the potential to alter the course of T1DM relatively safely, as will be detailed below.

Tregs play a central role in the protection from diabetes. Diabetes is accelerated in non-obese diabetic (NOD) mice depleted of $CD4^+CD25^+$ Treg.[17, 18] Similarly, removal of proliferative signals necessary for Treg development or survival, such as IL-2, exacerbates diabetes in NOD mice.[18] Recently, Bettini *et al.*, and Tang *et al.* showed that the number and function of Treg cells were perturbed in NOD mice,[19, 20] and transforming growth factor- β (TGF-β) was reduced.[19] D'Alise *et al.* identified defects in Treg transcripts in locations associated with diabetic pathogenesis in NOD mice (lamina propria and pancreatic lymph node).[21] Experimental work suggests that therapies that augment the number or function of Tregs have beneficial effects on the progression of T1DM. Grinberg-Bleyer *et al.* found that IL-2 reverses established diabetes in NOD mice by a local effect on pancreatic Tregs.[22] Tang *et al.* showed that infusion of Tregs into NOD mice will prevent disease onset and even reverse diabetes in mice with hyperglycemia.[23] Finally, the safety of the polyclonal Tregs—a primary consideration in designing the clinical development plan—has been demonstrated in T1DM,[24, 25] and in graft-versus-host disease (GvHD).[26]

Clinical adoptive transfer of polyclonal expanded Tregs—selected and expanded in a method comparable or similar to the manufacturing process planned for CLBS03—was evaluated in two Phase 1 clinical trials, with one trial in adults with T1DM and one trial in children with T1DM. Doses up to 40 x 10^6 cell/kg body weight (BW) were administered to the adult population, and up to 30 x 10^6 cells/kg BW were administered to children younger than 18 years old. These two clinical trials provided evidence of tolerability and safety of adoptive expanded polyclonal Tregs transfer in both adults and children with T1DM. Given the potential impact of benefit, observed

through efficacy biomarkers, the two clinical trials support further evaluation of CLBS03 in this disease population. Details of the two Phase 1 clinical trials will be discussed in Section 5.4 below, and are also detailed in the CLBS03 Investigator's Brochure (IB).

5.2.3 Description of Investigational Product

[redacted]

5.3 Nonclinical Experience

Extensive nonclinical studies characterizing human Tregs have provided the framework for developing a robust Treg cell therapy product:

[redacted]

A detailed discussion of the nonclinical data outlined above is provided in the CLBS03 IB.

5.4 Clinical Experience

To date, several clinical studies have been conducted with Treg based cell therapies in T1DM, GvHD, and Crohn's disease. The two Phase 1 studies, one study in adults with T1DM and one study in adolescents with T1DM, are discussed in detail below.

5.4.1 US Phase 1 Trial in Adults with T1DM

This was a Phase 1 prospective, open-label, uncontrolled, dose-escalating trial of autologous expanded polyclonal Tregs (investigational product manufacturing process comparable to that planned for CLBS03) in adults with T1DM (Study title: A Phase 1 Safety Trial of $CD4^+CD127^{lo/-}CD25^+$ Polyclonal Treg Adoptive Immunotherapy for the Treatment of Type 1 Diabetes, www.clinicaltrials.gov identifier: NCT01210664) conducted by the University of California, San Francisco (UCSF) and Yale University (Yale). This study evaluated the safety and feasibility of autologous, expanded polyclonal Tregs in treating adults with established T1DM (onset ranging from 4.5 to 23.5 months), and is being evaluated out to 60 months.[27]

Twenty-six patients were screened, 16 met eligibility criteria and were enrolled, and 14 subjects received a single infusion of polyclonal Tregs. After signing the informed consent form (ICF), 400 mL of blood were drawn from each subject followed by separation and expansion of Tregs according the methods prospectively described in the protocol at the UCSF GMP facility. The study involved four dosing cohorts: 1) three subjects were treated in the first dosing cohort with 5×10^6 cells, 2) three subjects were treated in the second dosing cohort with 40×10^6 cells, 3) four subjects were treated in the third dosing cohort (target dose of 320×10^6 cells, average received dose of 360×10^6 cells), and 4) four subjects were treated in the fourth dosing cohort (target dose of 2600×10^6 cells, average received dose of 2700×10^6 cells). The highest dose represents approximately 20% of the total number of Tregs (13×10^9 cells) that are predicted to exist in normal individuals.[28] The mean follow-up at the time of data cutoff for the publication was 124 weeks (cohort 1: 182 weeks; cohort 2: 156 weeks; cohort 3: 104 weeks; and cohort 4: 78 weeks). The two subjects who did not receive expanded Tregs (due to failure of Treg product to meet release criteria) were not included in the data analysis.

5.4.1.1 Safety

To date, (124 weeks follow-up), a total of 144 AEs have been reported of which 4 were reported as serious. Ninety-one events were judged as mild in severity, 42 were judged as moderate, 9 were judged as severe, and 2 were judged as life-threatening. The 11 events judged as severe or life-threatening largely reflected metabolic abnormalities of underlying diabetes. Four serious adverse events in two patients were reported: one patient had three episodes of serious hypoglycemia 14, 248, and 463 days after Treg infusion; and another patient had one episode of diabetic ketoacidosis 67 days after Treg infusion. No opportunistic infections or malignancies were observed. One subject developed grade 2 pharyngitis and had low-copy number CMV detected on day 7, but not detected at day 28, due to a presumed new infection with CMV occurring before receiving Treg cells. There was no apparent relationship between adverse events and Treg dose (refer to table S2 in the Bluestone *et al.* publication[27]). In general, administration of autologous, expanded polyclonal Tregs, comparable to CLBS03, was found to be safe and well tolerated in this Phase 1 dose-escalating trial through the mean follow-up period of 124 weeks.

5.4.1.2 Efficacy

Impact of Treg administration on MMTT-stimulated C-peptide and other indices of metabolic control (HbA1c and daily dose insulin [DDI]) was evaluated. MMTT-stimulated C-peptide levels (measured by 4-hour area under the curve [AUC] for MMTT-stimulated C-peptide) generally remained stable over time and remained unchanged at 1 year and even after 2 years in dose cohorts 1 and 2. Three of four subjects in cohort 3 and three of the fours subjects in cohort 4 showed a decline in MMTT-stimulated C-peptide of more than 50% over 78 weeks of follow-up. DDI also appeared to be stable for almost all subjects over time and there was no apparent decrease in DDI in comparison to baseline values. HbA1c levels appeared to be stable over time (except for one subject whose levels went from 6.2% at screening to 12.6% at week 13), with no clear deterioration in glucose control. Given the small number of subjects in each cohort, the overall changes in MMTT-stimulated C-peptide in this study fall within the expected decline observed in the natural history of the disease. However, the sample size was too small to make a clear statement about stabilization or decay in MMTT-stimulated C-peptide in treated subjects.

A detailed discussion of the clinical data outlined above and a list of all AEs is provided in the CLBS03 IB.

5.4.2 Gdańsk Medical University (GMU) Phase 1 Trial in Children with New Onset T1DM

This was a Phase 1, prospective, open-label, non-randomized, parallel matched group trial of autologous, expanded polyclonal Tregs (IP manufacturing process similar to that planned for CLBS03) in children aged 5-18 years with new onset T1DM, diagnosed within the preceding 2 months.[25] The trial enrolled 12 subjects in the treatment arm, and 10 untreated control subjects matched for age, sex, and disease duration. Twenty-four months follow-up is planned, and 12 months follow-up has been completed and the results published. The trial is being conducted at a single center at Gdańsk Medical University in Poland, and is designed to be a pilot trial to investigate safety and efficacy of Tregs. Three doses were administered based on body weight: single dose of 10 x 10^6 cells/kg for 3 subjects, single dose of 20 x 10^6 cells/kg for 3 subjects, and two doses totaling 30 x 10^6 cells/kg separated by 6-9 months for 6 subjects. In subjects administered 2 doses, the second dose was administered to subjects with good clinical and metabolic response to the first dose of Tregs [fasting C-peptide >0.4 ng/mL and/or DDI <0.5 IU/kg BW], who presented symptoms of disease progression after ≥6 months of follow-up. Protocol predefined release criteria were specified and met for all dosed subjects.[24, 25]

5.4.2.1 Safety and Feasibility

There were no severe or serious AEs reported. There were no AEs suggestive of a transfusion reaction related to the administration of Tregs. In general, administration of autologous, expanded polyclonal Tregs, similar to CLBS03, in this dose escalation trial appeared to be safe

and well tolerated. For feasibility, all planned doses for the treatment cohort met the pre-specified release criteria.

5.4.2.2 Efficacy

In addition to safety, the primary efficacy endpoints of the trial were remission as defined as DDI ≤0.5 IU/kg, and fasting C-peptide > 0.5 ng/mL 1 year after enrollment. One year after inclusion in the study, 8 out of 12 subjects (66%) still met the protocol predefined criteria of clinical remission (DDI ≤0.5 IU/kg BW) and fasting C-peptide levels > 0.5 ng/mL. In addition, compared to the non-treated control individuals, insulin doses (DDI/kg BW) were significantly lower in Treg-treated individuals at 4 months (intermediate efficacy point) and one year after commencing the trial (primary endpoint) (p=0.04 and p=0.02, respectively).

Fasting C-peptide levels were significantly higher in Treg-treated individuals (4 months: p=0.01 and 1-year: p=0.01). HbA1c levels were the lowest in subjects treated with two doses of Tregs, intermediate in those treated with one dose and the highest in untreated individuals (p=0.01). In addition, when data for the treated and untreated subjects were analyzed together after 4-month and one-year follow-up, it was observed that C-peptide levels correlated with percentage of Tregs in peripheral blood (4 months, p=0.04; 1 year, p=0.01).

This Phase 1 trial provides preliminary evidence supporting the safety, efficacy and biologic activity of single and multiple doses of Tregs in children with new onset T1DM, in comparison with concurrent matched controls. A detailed discussion of the clinical data outlined above is provided in the CLBS03 IB.

6. STUDY DESIGN

6.1 Overview

This will be a double-blinded, multi-center, exploratory trial assessing a single infusion of one of 3 treatments: CLBS03 [redacted] and placebo. The study will include adolescent subjects (aged 8 to less than 18 years old) with recent onset of T1DM.

[redacted]

A screening visit will be conducted to determine eligibility. Subjects who continue to be eligible will be randomized [redacted]

Approximately 111 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio:

- [redacted]
- [redacted]
- Placebo

Randomization will be done centrally [redacted]

Safety, diabetes control, β-cell function, and immune function will be assessed over the course of the study. All subjects are expected to be on intensive diabetes management (refer to Section 9.6) consistent with the American Diabetes Association (ADA) standard of care. Study participants' planned visit schedule is outlined in Section 4, Schedule of Assessments.

6.1.1 Justification for Dose

CLBS03 will be administered in a single dose administration to study subjects, [redacted]

The lowest tested doses in the Phase 1 studies, in adults and children with T1DM, were approximately 0.1 x 10^6 cells/kg BW and 10 x 10^6 cells/kg BW, respectively. These were based on semi-quantitative allometric scaling of animal data, accumulated safety information from preceding clinical studies in other populations, and quantitative understanding of the Treg population in humans (Section 5.4 Clinical Experience). Using an IP comparable or similar to CLBS03, up to 38.9 x 10^6 cell/kg BW, were evaluated in adults, and 20 x 10^6 cells/kg BW in

children in a single administration. Additionally, 30 x 10^6 cells/kg BW were evaluated in children administered 2 separate doses, 6-9 months apart. In both studies all doses tested were well-tolerated, and appear to be safe, based on AE and safety laboratory analyses. As discussed above, preliminary mechanistic analyses from the cohorts in the above mentioned adult Phase 1 study showed no significant changes in T helper (Th) subsets, $CD4^+$ or $CD8^+$ effector cell differentiation, T-cell activation, B-cell subsets or monocytes. Deuterium labeling utilized for a subset of subjects in the same study also confirmed the lineage stability of infused Tregs. Taken together, it appears that all doses tested were not associated with manifestations of Treg effector transdifferentiation that can pose a clinical safety concern. [redacted]

From an efficacy perspective, the high dose is supported by the Gdańsk Medical University Phase 1 study that was conducted in children less than 18 years old, the relevant population for this study. In comparison to concurrent controls, children administered with Tregs were able to maintain higher fasting C-peptide levels, but despite some preliminary evidence pointing to efficacious dose response, the relatively small sample size rules out any robust conclusions. In this study, two children achieved clinical remission (as defined by DDI ≤0.5 IU/kg, and fasting C-peptide > 0.5 ng/mL 1 year after enrollment) in the higher dose group, in comparison to one child in the lower dose group, but the small sample number prohibits a meaningful dose dependency assessment. Additionally, 5 of those receiving two doses of Tregs (for a total of 30 x 10^6 cells/kg BW) achieved remission. In summary, 8 of those in the active treatment arms achieved remission while 2 subjects in the concurrent control groups achieved remission.

[redacted]

6.1.2 Justification for Study Population

Adolescent subjects aged 8 to less than 18 years old with recent onset T1DM will be eligible for enrollment in this study. Details of the inclusion and exclusion criteria are included in Sections 6.4.1 and 6.4.2.

T1DM most commonly presents in childhood with incidence rates increasing from birth, and peaking between 5-7 years of age and at or near puberty.[4, 29, 30] The increasing incidence of T1DM throughout the world is especially marked in young children.[31] Registries in Europe suggest that recent incident rates of T1DM were highest in the youngest age-group (0-4 years).[32] Incidence rates decline after puberty and appear to stabilize in young adulthood (15-29 years). Those under the age of 18 are most often afflicted,[33] but an approximately equal number of adults over 18 are thought to develop the disease, though incidence in older people receives less media or research attention.[34]

The T1DM disease course varies from adolescents to adults. Beta-cell destruction in adults appears to occur at a much slower rate than in young T1DM cases, often delaying the need for insulin therapy after diagnosis.[35] Younger adolescents in particular appear to have a more robust and aggressive autoimmune process with more rapid progression to disease and a shorter remission (or honeymoon) phase.[36] Not surprisingly, there have been suggestions of efficacy differences in younger vs. older subjects in clinical studies of anti-CD3 and anti-CD20 mAbs, with higher efficacy trends observed in younger cohorts.[37, 38] According to a statement from the ADA, adolescents with T1DM have characteristics and needs that dictate different standards of care from adults with T1DM. The management of diabetes in adolescents must take into account the major differences between adolescents of various ages and adults.[39] For example, insulin doses based only on body size are likely to be incorrect; the consequences of hypoglycemic events are distinctly different between adults and adolescents; and risks for diabetic complications are likely influenced by puberty.[40] The rationale for studying childern and adolescents is detailed in the Caladrius Biosciences authored document titled "Prospect of Direct Benefit" (reference on file) that was submitted to the FDA in support of the Investigational New Drug (IND) #[redacted].

As discussed above, there is sufficient evidence from the two Phase 1 studies that autologous *ex vivo* expanded polyclonal Treg therapy (manufactured comparably or similar to CLBS03) is safe and well tolerated in adults with established T1DM, and in adolescents with new onset T1DM. Additionally, Treg therapy appears to be potentially efficacious especially in adolescents.

Taken together, the critical yet unmet medical need in adolescents with new onset T1DM, underpinned by a more aggressive autoimmune process, and with evidence for safety, tolerability, and potential for efficacy in adolescents, support studying the safety and efficacy of CLBS03 in a prospective, randomized, placebo-controlled, exploratory Phase 2 clinical study.

6.2 Objectives

6.2.1 Primary Objective

The primary objective of this study is to assess the safety and potential efficacy of CLBS03 (either of the two doses [redacted] to modify the T1DM disease course,

including preservation of β-cell function and improvements in measures of disease severity, as compared with placebo in adolescents with recent onset T1DM.

6.2.2 Secondary Objective

The secondary objective is to assess the efficacy of CLBS03, including additional measures of T1DM severity, and to evaluate the effect of CLBS03 on the pathologic autoimmune response underlying T1DM and on the general immune responsiveness through 104 weeks.

6.3 Study Endpoints

6.3.1 Primary Efficacy Endpoint

The primary study endpoint is the 4-hour MMTT-stimulated C-peptide AUC mean at 26 and 52 weeks.

6.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the 2-hour MMTT-stimulated C-peptide AUC mean at 13, 26, 52 and 78 weeks and the 4-hour MMTT-stimulated C-peptide AUC mean at 104 weeks. Additional metabolic evaluations will include a comparison between the study treatment groups in DDI, severe hypoglycemia, HbA1c, fasting and post-prandial blood glucose levels, and proportion of subjects who achieve partial or complete remission. Additional information on the secondary efficacy endpoints can be found in Section 12.2.2.

6.3.3 Safety Endpoints

Adverse events, including SAEs and events of special interest (see Section 11), will be assessed in both treatment arms through week 104. Proportion of subjects in which the infusion was prematurely stopped or paused because of adverse events will also be assessed for each treatment arm.

6.3.4 Continuous Glucose Monitoring

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4 Study Population

6.4.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Male and female subjects between the ages of 8 to less than 18 at the time of screening.
2. [redacted]
3. [redacted]
4. [redacted]
5. Weight of ≥30 kg at the time of screening.
6. Body mass index (BMI) z-score less than 2.25 at the time of screening (see Appendix 17.3).

[redacted]

* Visit 4 was removed with protocol version 6.0
† To be performed on specimens from a subset of subjects

7. For females of childbearing potential, a negative urine pregnancy test is required at Screening and prior to the blood draw for Treg collection at Visit 2. A negative pregnancy test is also required prior to infusion of the treatment at Visit 3.
8. Females of child bearing potential (i.e., females who have reached puberty or have had their first menstrual bleeding) must: a) be surgically sterile, or b) be willing to practice an acceptable method of birth control for the duration of their participation in the study. Acceptable methods of birth control are: oral contraceptive tablets, hormonal implant device, hormonal patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, or abstinence.
9. Males must agree to use a reliable and acceptable method of contraception for the duration of their participation in the study. Acceptable methods of contraception are: condom with spermicide, or abstinence.
10. [redacted]
11. Subject signing the study ICF. As the subject will be a minor at the time of consent, the subject must provide written assent with the parent or legally authorized representative signing the ICF.
12. Able to comply with and undergo procedures as required for the study.

6.4.2 Exclusion Criteria‡

1. Hemoglobin less than 12.0 g/dL at the time of screening.
2. Leukocytes <3,000/µL; neutrophils <1,500/µL; lymphocytes <800/µL; platelets <100,000/µL at the time of screening.
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. History of malignancy or serious uncontrolled (in the judgement of the investigator) cardiovascular, nervous system, pulmonary, renal, or gastrointestinal disease.
8. Have serologic evidence of current or past viral infection: HIV, hepatitis B, hepatitis C, and HTLV 1/2.

‡ Subjects with exclusionary test results can have the tests repeated for confirmation with approval from the sponsor, or if the clinical picture changes. If the new test results meet study criteria the subject can be enrolled or continue to be enrolled.

[redacted]

12. Diagnosis of liver disease as defined by alanine aminotransferase (ALT) >3x the upper limit of age-determined normal (ULN) or total bilirubin >1.5 x ULN.
13. Pregnant or breast-feeding females.

[redacted]

16. Subjects who have participated in an investigational drug study within 90 days prior to the screening visit.

[redacted]

19. Any other condition which, in the opinion of the investigator, may preclude the subject from safe participation in the study or compromise data integrity.

6.4.3 Protocol Deviations/Violations

Protocol violations and deviations will be summarized with descriptive statistics by category. A listing of all events will also be included.

Protocol deviations include, but are not limited to the following:

- Enrolling subjects in violation of eligibility criteria designed to ensure a specific subject population
- Failing to collect data necessary to interpret primary endpoints
- Subject's refusal to complete scheduled research activities
- Out-of-window study visits or study procedures

6.5 Description of Treatment Groups

This protocol will enroll a total of approximately 111 participants who will be randomly assigned using a 1:1:1 allocation ratio to the two treatment arms of CLBS03 [redacted] or placebo.

6.6 Treatment Assignment and Double Blinding

The study will be conducted as a double blind study. The participants and blinded study personnel will not be informed regarding the treatment assignment until the end of the study (after the end of study database lock), unless required by the DSMB or in case of emergency unblinding for safety reasons (see below). The investigator and investigator site personnel will also be blinded as to subject treatment assignment. Laboratories and other vendors performing assays for this protocol will also be blinded except for the laboratory performing the exploratory

assays. The sponsor personnel, including the study medical monitor or designee, involved in the study conduct will also be blinded to subject treatment assignment.

The final randomization schedule will be generated prior to study enrollment by an unblinded statistician.

In an emergency situation where knowledge of the study treatment is critical to subject safety and will influence choice of treatment, the study treatment for that subject can be unblinded. The Investigator should make all reasonable efforts to notify the medical monitor and/or study manager prior to unblinding. If unable to contact the medical monitor and/or study manager, the investigator must inform the medical monitor and/or study manager as soon as possible after unblinding.

6.7 Investigational Product

Additional information on the handling of investigational product, including instructions for infusion, can be found in the Investigational Product: Collection and Infusion Manual.

6.7.1 Description of IP

The investigational product refers to either dose of CLBS03 or placebo [redacted]

6.7.2 Packaging and Storage

[redacted]

6.7.3 Labeling

Labeling will comply with country-specific requirements for investigational product. The investigational product will be identified as a new drug, limited by federal law to investigational use.

Labels for the investigational product will minimally contain the following:

- Protocol number
- Subject number
- Product name
- Storage temperature
- Expiration date/time
- Caution statement(s) (i.e., "Caution: New Drug—Limited by Federal (or United States) law to investigational use")
- Sponsor information
- Other additional information may be displayed as required by federal laws and regulations.

6.7.4 IP Infusion

The IP infusion procedure is described in detail in the IP Collection and Infusion Manual for the study. [redacted]

All study subjects will be observed at the investigator site on the day of IP infusion (Day 0). Prior to infusion, the investigator will evaluate the subject and ensure that all study assessments are completed (including review of any medical history, laboratory results, and previous/ongoing symptoms that would preclude IP infusion) per the Schedule of Study Assessments (Section 4) and reach a positive decision to proceed with the infusion.

[redacted]

[redacted]

Subjects will be closely monitored for safety during and after the completion of the infusion of the study drug. Clinical monitoring will include monitoring vital signs (see Section 8.3 Vital Signs) prior to IP infusion, and again 2 hours post IP infusion. The investigator may implement additional procedures or increase the time or close monitoring if required for subject's safety. Emergency medical equipment and appropriately trained personnel, including advanced cardiac and life support (ACLS and/or PALS) crash cart, must be immediately available onsite.

6.7.5 Slowing or Pausing the Infusion

No infusion reactions from autologous expanded Treg infusion have been noted to date, in either Phase 1 study (i.e., UCSF or GMU studies). Nonetheless, subjects will be monitored carefully until the resolution of infusion reaction in the case any infusion reaction, such as cytokine release syndrome (CRS) (or individual components including nausea, headache, tachycardia, hypotension, rash, or shortness of breath) occurs. If such an event occurs, it will be handled in the following manner:

6.7.5.1 Mild Reactions (Grade 1)

[redacted]

6.7.5.2 Moderate or More Severe Reactions (Grade 2 or Higher)

[redacted]

6.7.6 Investigational Product Accountability

The investigator will ensure that the IP is stored as specified in the protocol (Section 6.7.2) and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP was received, including the date received, IP identity code, date of manufacture or expiration date, amount received, and disposition. Records will be maintained that include the subject's initials and subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be returned to the sponsor or sponsor's representative or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If the IP is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

6.8 Outcome Measures

During the course of the study, participants will frequently undergo assessments of their insulin production, immunologic status, and overall health and well-being (see Schedule of Assessments, Section 4). Investigator or his/her delegate will be required to review, critically evaluate, and record the amount of insulin subjects have used, as well as glucose levels, during the 3-day period immediately preceding pre-specified study visits (for additional details, see Section 9.6 Intensive Diabetes Management and Section 4. Schedule of Assessments). Diaries will be provided to participants at specified study visits and reviewed and collected at the next visit. Subjects on an insulin pump will provide outputs of their insulin pump activity for the diary days. Depending on the participants' age, a parent or guardian may oversee the collection of data

on the diary or assist with making outputs of insulin pump activity available to the investigator or his/her delegate.

Subjects who volunteer to undergo CGM and with access to a CGM device will provide downloads on a regular basis. Generally, these downloads will occur at the time of diary data collection but downloads may occur at other visits or may occur without a clinic visit either by mailing a used glucose sensor to the clinic for download or by providing a download via the internet. Methods for data transfer will be established with patients and/or a parent or guardian on a case-by-case basis.

6.9 Study Timeline

6.9.1 Study Duration

Total study duration for a subject is approximately 115 weeks, including screening, pretreatment, treatment, and study follow-up visits. All randomized subjects will be followed for safety and efficacy for approximately 104 weeks after treatment.

6.9.2 Visit Windows

All scheduled study visits must occur within the time limits specified in Table 6-1. Visits that occur outside of the specified windows will be considered protocol deviations.

Table 6-1: Visit Windows

	Visit Day(s)	Visit Windows
Visit 1: (screening)	-79 to -23	day -79 to day -23
Visit 2: (pretreatment)	-16 to -15	no window
Visit 3: (treatment)	0	no window
Visit 4:	Removed beginning with Protocol Version 6.0	
Visit 5:	7	±1 day
Visit 6:	14	±3 days
Visits 7 and 8:	28 and 91	±7 days
Visits 9 through 13:	182, 273, 364, 546, and 728	±14 days

7. STUDY VISIT ASSESSMENTS

Additional details on study procedures can be found in Section 8.

7.1 Screening Visit (Visit 1, Day -79 to -23)

- Administer informed consent and assent
- Collect demography: gender, date of birth (age), race, and ethnicity
- Collect medical history (including date of initial type 1 diabetes diagnosis according to ADA criteria [see Appendix 17.1])

- Collect concomitant medications and concurrent procedures
- Perform complete physical examination, including Tanner stage evaluation
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Advise on iron supplementation (recommended to take one week prior to the pretreatment visit and up to visit 7, if eligibility is continued)
- Administer Tdap and inactivated flu vaccine, if required
- Perform urine pregnancy test (on female subjects of childbearing potential)
- Review inclusion and exclusion criteria
- Assess adverse events
- Blood draw for:
    - Safety: Hematology, clinical chemistry
    - [redacted]
- Perform 4-hour MMTT-stimulated C-peptide/glucose (see Section 17.2 Mixed Meal Tolerance Test)
- Collect urine sample for urinalysis
- After the screening visit, randomize the subject once all screening procedure results are available and it's confirmed that the study eligibility requirements are met based on screening. Eligibility requirements will be confirmed at Visit 2 prior to the blood draw for Treg collection/IP manufacture.

7.2 Pretreatment Visit (Visit 2, Day -16 or -15)

- Collect concomitant medications and concurrent procedures
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Perform urine pregnancy test (on female subjects of childbearing potential)
- Review inclusion and exclusion criteria
- Assess adverse events
- Review diabetes assessments expectations, dispense subject diary, and instruct on how to complete the subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- For subjects using CGM, discuss options for data download
- [redacted]

7.3 Treatment Visit (Visit 3, Day 0)

Prior to IP infusion

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary
- Collect concomitant medications and concurrent procedures
- Perform limited physical examination
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Perform urine pregnancy test (on female subjects of childbearing potential)
- Review inclusion and exclusion criteria
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Blood draw for:
    - Hematology (results must be reviewed prior to IP infusion)
    - HbA1c
    - [redacted]

[redacted]

IP Infusion

- Infuse investigational product (IP dose will be based on the subject's weight at the time of screening (Visit 1).
- Assess adverse events

After IP infusion

- Perform vital signs 2-hours post-infusion: blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events

7.4 Day 1 (Visit 4) - NO LONGER USED BEGINNING WITH PROTOCOL VERSION 6.0

- Collect concomitant medications and concurrent procedures
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Blood draw for:
    - Hematology
    - [redacted]

7.5 Day 7 (Visit 5)

- Collect concomitant medications and concurrent procedures
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events

- Blood draw for:
  - Hematology
  - Clinical chemistry
  - [redacted]
- Collect urine sample for urinalysis
- Download CGM data if applicable

7.6 Day 14 (Visit 6)

- Collect concomitant medications and concurrent procedures
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Dispense subject diary
- Download CGM data if applicable
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology
  - [redacted]

7.7 Day 28 (Visit 7)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Dispense subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology
  - [redacted]

7.8 Day 91 (Visit 8)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform limited physical examination
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature

- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Dispense subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology
  - Clinical chemistry
  - HbA1c
  - [redacted]
- Perform 2-hour MMTT-stimulated C-peptide/glucose (see Section 17.2 Mixed Meal Tolerance Test)
- Collect urine sample for urinalysis

7.9 Day 182 (Visit 9)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform limited physical examination
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Dispense subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology
  - Clinical chemistry
  - HbA1c
  - [redacted]
- Perform 4-hour MMTT-stimulated C-peptide/glucose (see Section 17.2 Mixed Meal Tolerance Test)
- Collect urine sample for urinalysis

7.10 Day 273 (Visit 10)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable

- Dispense subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology
  - HbA1c
  - [redacted]

7.11 Day 364 (Visit 11)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform limited physical examination
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Dispense subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology
  - Clinical chemistry
  - HbA1c
  - [redacted]
- Perform 4-hour MMTT-stimulated C-peptide/glucose (see Section 17.2 Mixed Meal Tolerance Test)
- Collect urine sample for urinalysis

7.12 Day 546 (Visit 12)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform limited physical examination
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Dispense subject diary
- For subjects on an insulin pump, instruct the subject to bring outputs of pump activity for the diary days to the next visit
- Blood draw for:
  - Hematology

  - Clinical chemistry
  - HbA1c
- Perform 2-hour MMTT-stimulated C-peptide/glucose (see Section 17.2 Mixed Meal Tolerance Test)
- Collect urine sample for urinalysis

7.13 Day 728/Early Exit (Visit 13)

- Contact subject approximately 4 days prior to scheduled visit to remind subject to complete subject diary and if using a pump, bring outputs of pump activity for the diary days
- Collect concomitant medications and concurrent procedures
- Perform complete physical examination
- Perform vital signs: height, weight, blood pressure, pulse rate, respiration rate and temperature
- Assess adverse events
- Collect and assess subject diary; download CGM data if applicable
- Blood draw for:
  - Hematology
  - Clinical chemistry
  - HbA1c
  - [redacted]
- Perform 4-hour MMTT-stimulated C-peptide/glucose (see Section 17.2 Mixed Meal Tolerance Test)
- Collect urine sample for urinalysis
- Perform urine pregnancy test (on female subjects of childbearing potential)

In the event that a subject prematurely discontinues the study, site personnel should make all efforts to bring the subject back to the site to compete Visit 13 procedures.

8. STUDY PROCEDURES

See the schedule of assessments (Section 4) for additional information on study procedures performed over the course of the study.

8.1 Medical, Medication, and Non-Drug Therapy-History

At screening, the subject's medical history will be described for the following body systems including past surgeries, and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medical history 30 days prior to screening will be recorded on the eCRFs (refer to the eCRF Completion Guidelines document for additional information). Beyond the 30-day window, the following should be documented, but, not limited to:

- T1DM onset

- Past hospitalizations
- Past surgeries or medically significant procedures
- History of unusual/atypical infections
- History of serious bacterial, viral, fungal or other opportunistic infections
- Allergies (including eczema, asthma, and any food and drug allergies)
- History of other clinically significant diseases/ conditions as deemed by the investigator

All medications taken and non-drug therapies received from 30 days before screening until completion/termination will be recorded on the concomitant medications and non-drug therapies electronic case report forms (eCRFs). Past vaccinations should also be documented.

8.2 Physical Examinations

At screening and subsequent study visits, a physical examination will be performed. A complete physical exam assessment includes general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. Limited physical examinations will be symptom-directed. The physical examinations should be performed by the same investigator each time, whenever possible.

Tanner stage will be evaluated at screening (Visit 1). Tanner stage will be re-evaluated at 12 and 24 months if not already documented as ≥ stage III at a previous exam.

At screening, physical examination abnormalities deemed clinically significant by the investigator, should be recorded as medical history.

At subsequent study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be recorded as an adverse event.

8.3 Vital Signs

Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), height, and weight. Blood pressure and pulse rate measurements will be measured after the subject has rested for at least 5 minutes. Blood pressure should be performed in the same position and measured using the same arm for the duration of the study when possible. On the day of IP infusion, vitals will be taken before infusion and again 2-hours post-infusion (vital signs assessment 2 hours post-infusion will not include height and weight).

BMI z-score will be determined for eligibility using the charts provided in Appendix 17.3. To determine BMI z-score, the subject's BMI, weight and gender must be available. BMI can be derived using the formula below:

BMI = (weight in kg)/(height in m)^2, OR

BMI = (weight in lb)/(height in in)^2 x 703

8.4 Hematology

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet counts, prothrombin time (PT; sec) or international normalized ratio (INR), and activated partial thromboplastin time (APTT; sec). Coagulation assays will only be performed at baseline. A limited hematology assessment will be performed at the treatment visit (Day 0), which will only include the complete blood count (CBC) with differential, and platelet counts. Hematology can be evaluated in either the fed or fasted state.

8.5 Clinical Chemistry

The clinical chemistry panel will consist of C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (e-GRF), creatine kinase (CK), electrolytes (sodium, potassium, chloride, calcium, magnesium, and phosphate), bicarbonate, total protein (T-pro), albumin, ALT, total bilirubin (T-bil), alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), total cholesterol (t-cho), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), and glucose. Clinical chemistry will be evaluated in the fasted state.

8.6 Hemoglobin A1c (HbA1c)

HbA1c can be evaluated in either the fed or fasted state.

8.7 Other tests

At screening, blood may also be collected for the tests described below.

[redacted]

8.8 Mixed Meal Tolerance Test (MMTT)

The MMTT will be performed in the morning, where a mixed meal will be administered and blood collected up to 250 minutes. The 4-hour MMTT should take 250 minutes to perform, and the 2-hour MMTT should take 130 minutes. Refer to the Appendix (Section 17.2 Mixed Meal Tolerance Test) for details on the MMTT.

8.9 Urinalysis

The urinalysis panel will consist of protein, occult blood, glucose, urobilinogen, bilirubin, ketones, and sediments.

8.10 Pregnancy Testing

Urine pregnancy testing for human chorionic gonadotrophin (hCG) will be performed on female subjects of childbearing potential.

9. SUBJECT MANAGEMENT

9.1 Informed Assent/Consent and Enrollment

Subjects will be enrolled when they have provided informed assent/consent to participate in the study, met all inclusion and none of the exclusion criteria, completed the screening visit, and have been randomized.

9.2 Subject Identification Code (SIC)

The subject identification code will be a 3-digit site number-3-digit subject number (e.g., 111-002) reflecting the order in which ICFs were signed. For example, the third subject who signed an informed consent form at study site 002 will be identified as Subject 002-003. All study documents and related material (e.g., electronic case report forms [CRFs], clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC.

9.3 Screening

Enrolled subjects must meet all inclusion criteria and none of the exclusion criteria, and have completed all screening procedures prior to the blood draw for Treg collection at Visit 2. Subjects who have failed the screening process and have not been randomized will be recorded as a screen failure. Re-screening of subjects is allowed, at the discretion of the investigator with prior approval from the study sponsor, unless there are clinical implications that impact the ability of subject to meet selection criteria change.

9.4 Randomization

Subjects will be randomized once all screening procedure results are available and it's confirmed that the study eligibility requirements are met based on screening. Eligibility requirements will be confirmed at Visit 2 prior to blood draw for Treg collection/IP manufacture.

Randomization of eligible subjects will be performed using the Interactive Response Technology (IRT) system. [redacted] to obtain the randomization code

for the subject. The randomization allocation ratio will be 1:1:1. Randomization will be done centrally with stratification by screening MMTT-stimulated C-peptide AUC mean value. Details regarding the randomization assignment will be discussed in the Statistical Analysis Plan (SAP).

9.5 [redacted]

9.6 Diabetes Management

During the study, all participants are expected to be receiving intensive management of their diabetes, and HbA1c will be assessed every 3 months to evaluate metabolic control. The goal of treatment will be to maintain the HbA1c level as close to normal as possible, without frequent occurrence of hypoglycemia. All individuals should strive for targets in accordance with current ADA recommendations, with HbA1c levels of $\leq$7.5% in children under the age of 19 years, and with preprandial glucose levels of 90-130 mg/dL, postprandial levels of less than 180 mg/dL, and bedtime levels of 90-150 mg/dL.[39] All participants will be expected to take a sufficient number of daily insulin injections to meet the glycemic targets. In general, the expectation is that all participants will receive at least four injections of insulin daily, including short- and long-acting insulin preparations, or will utilize continuous subcutaneous insulin infusion. All participants will be expected to manage their diabetes with an insulin pump if possible. Glucose levels should be checked frequently, at a minimum of 4 times per day (before each meal and at bedtime). Subjects who are willing and have access to a continuous glucose monitoring device are strongly encouraged to monitor their blood glucose in this way. The outputs from these devices will occur at regular intervals and will be used in exploratory data analyses. Depending on the participants' age, parent or guardian involvement to obtain these device outputs may be necessary. Subjects will not be permitted to use non-insulin pharmaceuticals for glycemic control.

The primary responsibility for diabetes management will reside with the treating or referring diabetes care provider. The study team will provide close additional support through regular interaction, and records of the glucose levels and insulin dosing will be evaluated by the study team at regularly scheduled study visits.

9.7 Subject Diaries

Participants will be required to record the amount and the type of insulin they have used, as well as blood glucose levels during the 3-day period immediately preceding each pre-specified study visit. Subject diaries will be provided to participants at select study visits (see Section 4) and reviewed and collected at the next visit. Subjects will be instructed to document all insulin administrations and glucose assessments during the 3-day period. Depending on the participants' age, a parent or guardian may oversee the collection of data on the diary. Subjects on an insulin pump will bring outputs of their insulin pump activity for the diary days. Subjects using CGM will provide data downloads. Sites will contact the subject for diary completion approximately 4 days prior to the visit. Depending on the participants' age, parent or guardian involvement to obtain these device outputs may be necessary.

9.8 Procedures for Monitoring Subject Compliance

All study procedures are to be performed by the investigator or under his/her designation to a sub-investigator or study team member.

9.9 Withdrawal from Study

Discontinuation of, or partial treatment does not require subject withdrawal from participation in the study. Any subject may voluntarily withdraw consent for continued participation and data collection. Reasons for discontinuation will be reported on the appropriate eCRF, including: screen failure, adverse event (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of discontinuation should be recorded on the appropriate eCRF. The data collected on withdrawn subjects may be used in the analysis and included in the clinical study report.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if judged that continued participation would pose an unacceptable risk for the subject. In the event that the IP cannot be manufactured to meet release criteria, the subject will be terminated from the study prior to receiving treatment.

In the event of subject discontinuation from treatment due to an AE, additional clinical and/or laboratory investigations (that are beyond the scope of the required study observations/assessments) may be performed as part of the event evaluation. These investigations will take place under the direction of the investigator in consultation with the

sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor or its designee.

In the event that a subject prematurely discontinues the study, site personnel should make all efforts to bring the subject back to the site to compete Visit 13 procedures.

10. PARTICIPANT SAFETY

10.1 Risks and Potential Risks from Tregs

The autologous nature of Tregs that constitute CLBS03, and the equivalency in biologic function robustness between the expanded cells and freshly isolated Tregs, diminishes the possibility of a significant toxicity potential. Primary pharmacology animal studies also support this conclusion.

[redacted] Based on this early clinical data, and other biologic and experimental considerations, the following risks outlined in the subsections below are the most relevant to CLBS03 administration.

[redacted]

[redacted]

[redacted]

[redacted]

10.2 [redacted]

[redacted]

10.3 Concomitant and Prohibited Medications

The following medications are not permitted throughout the duration of the study:

1. Use of non-insulin pharmaceuticals that affect glycemic control.

[redacted]

10.4 Expected Side Effects and Adverse Events

- Mild upper respiratory tract infections could be expected since they were commonly observed in the adult Phase 1 study.

- [redacted]

- AEs related to metabolic control of T1DM are to be expected in this subject population, but at comparable rates to that for an age-matched population with new onset T1DM.

11. ADVERSE EVENT REPORTING AND SAFETY MONITORING

11.1 Adverse Event

All AEs will be recorded from the time of consent until study completion or discontinuation. An AE is defined as any untoward medical occurrence in a subject treated with the IP, regardless of a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. Any clinically significant abnormal laboratory finding can be repeated before being reported as an AE. Any medical occurrence that leads to dosing interruption, subject discontinuation, or administration of concomitant medication for treatment will be considered an AE. Each untoward medical occurrence experienced before the first treatment procedure (i.e., from the time of signed informed consent up to but not including the IP infusion) will be described on the AE eCRF. Any untoward medical occurrence that qualifies as an SAE, regardless of study drug administration, will be recorded as an SAE on the eCRF, and reported according to the sponsor as outlined in Section 11.2 below.

As hypoglycemic events are part of the natural course of T1DM, severe hypoglycemia (defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions) will be reported as an AE. Non-severe hypoglycemia deemed clinically significant by the investigator may also be reported as an AE.

11.2 Serious Adverse Event

A serious adverse event is defined as any adverse event resulting in any of the following outcomes:

- Outcome is fatal/results in death
- Is life-threatening (at the time of the event)

- Requires hospitalization or results in prolonged hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is a medically important event that may not be immediately life-threatening or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (e.g., infection, allergic reaction, etc.)

SAEs will be followed until resolution, medically stabilized, or 30 days after the end-of-study visit, whichever comes first. All SAEs are to be reported to INC Research within 24 hours of becoming aware of the event. To report an SAE or event of special interest, fax the report form to 1-877-464-7787 or email it to INCDrugSafety@incresearch.com.

11.3 Events of Special Interest

Events of special interest will be captured for this study and include the following:

[redacted]

11.4 Grading Event Severity and Causality

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below, as recommended by NCI-CTCAE Version 4.03.[42]

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes for example, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. [redacted] The investigator will use his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related (i.e., does not follow a reasonable temporal relationship or has a much more likely alternative etiology).
- Unlikely related (either one or both circumstances are met)
  - Has little or no temporal relationship
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship
  - An alternative etiology is equally or less likely compared to the potential relationship
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship
  - Another etiology is unlikely or significantly less likely

11.5 Preexisting Diseases

Preexisting diseases that are present before entry in to the study (as described in the medical history) will not be recorded as AEs, but will be documented as part of the subject's initial medical history. Preexisting diseases that manifest with the same severity, frequency, or duration after IP exposure also will not be recorded as AEs, but will be documented in the subject initial history. However, when there is an increase in the severity or duration of a preexisting disease, the event must be described as an AE, and recorded on the eCRF.

11.6 Pregnancy

Pregnancy is not considered to be an AE or an SAE, unless a complication occurs that meets the requirements for an AE or SAE, but must be reported on a pregnancy report form. Female subjects who are pregnant or likely to become pregnant are excluded from this study. In the event a subject becomes pregnant during the study, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of notice. For subjects who exit the study prematurely, pregnancies occurring up to 90 days after study treatment should be reported. Any pregnant subject must be followed until the outcome of her pregnancy is known (i.e., normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). The pregnancy (i.e., the mother and the fetus) must be followed through delivery with regard to outcome.

11.7 Adverse Event Reporting and Monitoring

All AEs will be recorded from the time of consent until study completion or discontinuation. For subjects who exit the study prematurely, SAEs occurring up to 90 days after study treatment should be reported. All AEs will be described using the sign, symptom, or medical diagnosis (where available, medical diagnosis is preferred over symptom) on the AE eCRF in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions. Each AE will be defined as a SAE or non-serious AE according to the definitions in Section 11. Both serious and non-serious AEs will be followed until resolution, medically stabilized or 30 days after the end-of-study visit, whichever occurs first. All SAEs are to be reported to the INC Research within 24 hours of becoming aware of the event.

11.8 Assessment of Adverse Events

Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.2
- Severity as defined in Section 11.3
- Causal relationship to IP exposure as defined in Section 11.3

For each AE, the outcome (e.g., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken will also be recorded on the AE

eCRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the end-of-study visit, whichever comes first.

12. STATISTICAL CONSIDERATIONS

[redacted]

The randomization allocation ratio will be 1:1:1 and will be done centrally [redacted]

12.1 Analysis Populations

Several analysis populations will be defined for this trial for the summaries and analyses of the study data.

The Intent-to-Treat (ITT) population will consist of all randomized subjects who receive a study treatment. Subjects will be analyzed according to the treatment to which they were randomized, even if they received a different treatment or less than a full dose of the assigned treatment. The ITT population will be used for subject demographics and efficacy analyses.

The modified Intent-to-Treat (mITT) population will consist of all randomized subjects who receive a study treatment and have at least one post-treatment assessment, with their treatment group designation defined by the actual numbers of Treg cells dosed, which will be further defined in the SAP. This population will be used for efficacy analyses.

The Per-Protocol (PP) population will consist of all randomized subjects who receive the correct dose of the randomized study treatment and have at least one post-treatment assessment, have MMTT-stimulated C-peptide levels assessed at day 182 (week 26), and do not have any major protocol violations. This population will exclude subjects who receive less than the intended treatment dose. The PP population will be used for subject demographics and as a supportive analysis for the primary and secondary efficacy analyses.

The Safety population will consist of all subjects who receive study treatment, analyzed according to the treatment they received.

Further details on the definitions of the analysis populations will be provided in a prospectively developed statistical analysis plan (SAP).

12.2 Study Endpoints

12.2.1 Primary Endpoints

The primary study endpoint is the 4-hour MMTT-stimulated C-peptide AUC mean at 26 and 52 weeks.

12.2.2 Secondary Endpoints

- The 2-hour MMTT-stimulated C-peptide AUC mean at 13, 26, 52, 78 and 104 weeks and the 4-hour MMTT-stimulated C-peptide AUC mean at 104 weeks.
- Additional metabolic evaluations will include a comparison between the study treatment groups in:

  - DDI as measured by U/kg BW at weeks 4, 13, 26, 39, 52, 78 and 104.
  - Severe hypoglycemia, defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions, occurring from the time of treatment through weeks 13, 26, 52, 78 and 104.
  - HbA1c levels measured at 13, 26, 39, 52, 78 and 104 weeks.
  - Fasting blood glucose levels at weeks 13, 26, 52, 78 and 104 (based on MMTT).
  - Post-prandial (2-hour post meal) blood glucose levels at weeks 13, 26, 52, 78 and 104 (based on MMTT).

[redacted]

[redacted]

12.2.5 Safety Endpoints

The primary safety endpoints are treatment emergent adverse events (TEAE), SAEs, and events of special interest. Additional safety and tolerability endpoints include clinical laboratory tests, physical examination findings, concomitant medications, and vital signs.

12.3 Demographic and Baseline Characteristics

Demographic and relevant baseline characteristics will be presented and summarized descriptively by treatment for the various analysis populations.

12.4 Statistical Analysis

12.4.1 General Considerations

Baseline: Baseline refers to the last measurement collected on or prior to study treatment at Visit 3. Subjects with missing baseline data will have their baseline values imputed by the mean baseline value of subjects with baseline values.

Type 1 Error for Multiple Comparisons: This is a Phase 2 exploratory study and thus there will be no adjustment of type 1 errors arising from multiple comparisons. All statistical analyses will be conducted at the 2-sided 0.05 significance levels.

All collected data will be listed. A detailed SAP will be written and approved prior to database lock.

12.4.2 Analyses of the Primary Endpoints

The AUC mean of 4-hour MMTT-stimulated C-peptide is defined as the AUC for the 4-hour MMTT-stimulated C-peptide divided by the actual time span the samples are collected during the target 4-hour period. The AUC will be calculated using the trapezoidal rule. Similarly, the AUC mean of 2-hour MMTT-stimulated C-peptide is defined as the AUC for the 2-hour MMTT-stimulated C-peptide divided by the actual time span the samples are collected during the target 2-hour period. The unit for AUC mean is pmol/mL.

[redacted]

[redacted]

12.4.3 Analysis of the Secondary Endpoints

The changes in the secondary endpoints of 2-hour AUC mean of MMTT-stimulated C-peptide from baseline will be analyzed in a similar manner as described above for the analysis of the primary endpoint whereby the response variable and the independent variables will include values at 13, 26, 52, 78, and 104 weeks.

The change in the secondary endpoint of 4-hour AUC mean of MMTT-stimulated C-peptide from baseline will be analyzed in a similar manner as described above for the analysis of the primary endpoint whereby the response variable and the independent variables will include values at 104 weeks.

The daily dose of insulin and HbA1c will be summarized and analyzed similarly as for the primary efficacy endpoints without the log-transformation.

Severe hypoglycemia will be summarized by incidence and event rate adjusted by patient year of observation.

The change from baseline in the secondary endpoints of fasting plasma glucose and the 2-hour post-prandial glucose measured by MMTT at Weeks 13, 26, 52, 78, and 104 will be analyzed in a similar manner as for the analysis of the secondary endpoint of the 2-hour AUC mean C-peptide.

[redacted]

12.4.4 Analysis of the Safety Endpoints

The analysis of safety data will be performed for the Safety Population unless otherwise stated. The primary safety and tolerability endpoints are the incidence of TEAEs.

12.5 Adverse Events

Treatment-emergent adverse events will be defined as those occurring during or after administration of randomized study treatment on Visit 3 or existing prior to the time of and worsening after the time of the dose of randomized study treatment through study termination or early termination. Adverse events prior to the dose of randomized study treatment on Visit 3 will be classified as pretreatment (non-treatment-emergent). Treatment-emergent AEs will be summarized by treatment, system organ class, and preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA®). The number of events, the number of subjects, and the percent of subjects who experienced at least one TEAE will be presented for each system organ class and for each preferred term by treatment group. TEAEs that lead to early withdrawals and serious TEAEs will be summarized in the same manner. Additional details will be provided in the SAP.

12.6 Clinical Laboratory Evaluations

All hematology, clinical chemistry and urinalysis data will be listed by treatment, subject, and visit, including scheduled and unscheduled/repeat measurements. Laboratory assessments that are outside of normal ranges will be flagged.

Baseline values, the values at each visit, and changes from baseline values will be summarized for each of the quantitative laboratory assessments by treatment.

Shift tables of hematology, clinical chemistry, and urinalysis results will be used to summarize changes from baseline to study termination (or early termination).

12.7 Vital Signs and Physical Examinations

Vital signs at baseline, each scheduled visit, and changes from baseline values will be summarized by treatment. Clinical significant physical examination findings will be listed.

12.8 Sample Size and Power Estimation

[redacted]

12.9 [redacted]

[redacted]

13. DATA MANAGEMENT

13.1 Study Documentation and Case Report Forms (CRFs)

The data collection tool for this study will be sponsor defined eCRFs to be completed by study-site personnel. The investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the Institutional Review Board (IRB) and the study monitor/sponsor, screening and consent information, CRFs, SAE reports, laboratory reports, subject diaries, data clarifications requested by the sponsor or designee, and any other documentation deemed relevant and pertinent to the study and the study subjects. Subject data necessary for analysis and reporting will be entered into a validated database or data system in accordance with Title 21 of the Code of Federal Regulations (21 CFR) Part 11. Clinical data management will be performed by a sponsor assigned data management vendor in accordance with applicable data management vendor standards and data cleaning procedures. The investigator is responsible for the procurement of data and for the quality of data recorded on the eCRFs. The eCRF will be electronically signed by the investigator listed on Form FDA 1572.

The handling of data by the sponsor and the data management vendor, including data quality assurance, will comply with regulatory guidelines (e.g., International Council on Harmonisation Guideline for Good Clinical Practice E6 [ICH GCP]) and the standard operating procedures of the sponsor or designee. Data management and control processes specific to the study will be described in the Data Management Plan.

13.2 Document and Data Retention

The investigator will retain study documentation and data (electronic case report forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Data Management Plan or other supporting documents as applicable.

13.3 Direct Access to Source Data/Documents

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the Ethics Committee, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

14. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

14.1 Statement of Compliance

This study will be conducted in accordance with this protocol, the ICH GCP, 21 CFR, and applicable national and local regulatory requirements.

Before enrollment of subjects into this study, the IRB will review and approve/give favorable opinion on the protocol, ICF, any promotional material/advertisements, and any other written information to be provided to the subjects. The IB will be provided to the IRB for review. The IRB's composition or a statement that the IRB's composition meets applicable regulatory criteria will be documented.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the IRB, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

14.2 Participating Centers

Participating clinical sites must have an appropriate IRB governance since they are actively engaged in research and provide informed consent. The protocol and consent/assent forms will be approved for the sponsor by a central IRB review prior to release to participating sites. Health Insurance Portability and Accountability Act (HIPAA) and applicable local regulations will be followed by each participating institution in accordance with each institution's requirements. The participating sites will obtain approval from their corresponding review boards in accordance with their local procedures and institutional requirements.

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented.

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants participating in this study. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits.

14.3 Informed Consent/Assent

Written informed consent will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. Investigators will enroll subjects according to the study eligibility criteria and in compliance with 21CFR50. The investigator will exercise no selectivity so that no bias is introduced from this source.

14.4 Study Subject Confidentiality

The investigator will comply with applicable subject privacy regulations/guidance as described as per HIPAA and any additional local regulations.

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects. When a subject participates in this study at more than one site, sharing of this information is required. Sharing of information obtained during this study between clinical centers and affiliates will be done to assure subject understanding and consent, safety, and adherence to protocol. Medical and research records will be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. Study records with the study subject's information for internal use at the clinical sites will be secured at the study site during the study. At the end of the study, all records will continue to be kept in a secure location for at least 2 years post market approval in the applicable region. There are no plans to destroy the records.

Retained samples including genetic samples could be utilized to learn more about causes of type 1 diabetes, its complications (such as eye, nerve, and kidney damage) and other conditions for which individuals with diabetes are at increased risk, and how to improve treatment (e.g. via biomarker screening). Samples can also be utilized to further evaluate those subjects responsive to therapy to elucidate treatment mechanisms. The results of these future analyses, and any mechanistic studies, will not be made known to the participant.

14.5 Risks and Benefits

The risks of this study are presented in this protocol, the Investigator's Brochure and the informed consent form. There is no guaranteed benefit to subjects for their participation in the study.

14.6 Ethics

The study protocol, along with the required informed consent forms, will be approved by each participating institution's IRB prior to the initiation of any research procedures (at the site). In addition to details described in the sections above (informed consent, confidentiality, and risks and benefits), the investigators should review and consider ethical ramifications in the design and development of this protocol, in accordance with 21 CFR 50. The investigators will make every effort to minimize and monitor risks and discomforts to participants throughout the course of the study.

15. STUDY ADMINISTRATION

15.1 Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

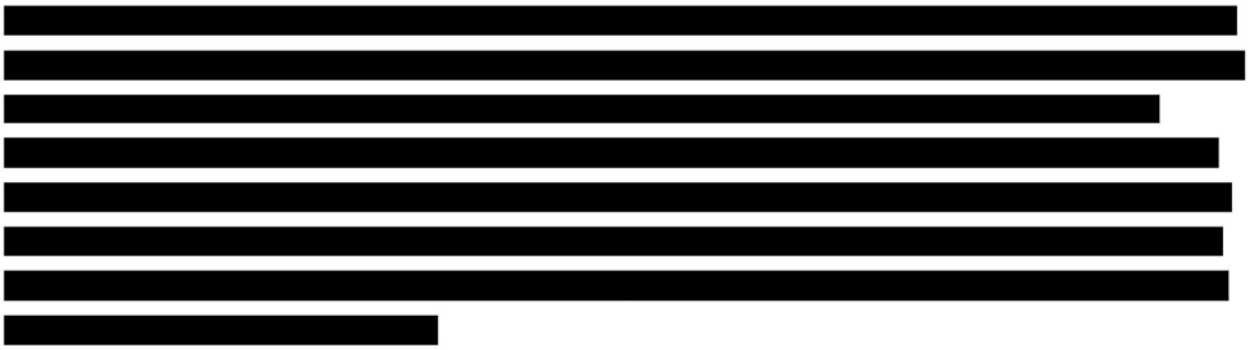
On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

15.2 Medical Monitor and Data Safety Monitoring Board (DSMB)

All adverse events will be recorded on the adverse event forms, and the treatment related SAEs will be sent to the IRB, per their reporting requirements, and to sponsor. The study medical monitor or designee will review all adverse event reports, masked to treatment assignment. Further details are captured in the study medical monitoring plan.

The DSMB is responsible for monitoring the safety of the trial subjects, and data integrity during periodic and ad hoc reviews. Following these reviews, it can recommend to the sponsor and the study executive committee the continuation of study as planned, modification of the protocol, or the stopping of the study.

The sponsor will ensure the timely communication of the safety and efficacy data to the DSMB according to the agreed upon schedules or within reasonable time if requested for an ad hoc analysis. The DSMB will meet periodically during scheduled and ad hoc meetings as specified in its charter.



16. REFERENCES

1. Lachin JM, McGee PL, Greenbaum CJ, Palmer J, Pescovitz MD, Gottlieb P and Skyler J. Sample size requirements for studies of treatment effects on beta-cell function in newly diagnosed type 1 diabetes. PLoS One. 2011;6:e26471.
2. National Diabetes Data Group. Diabetes in America, Second edition. http://diabetes.niddk.nih.gov/dm/pubs/america/index.aspx. 1995.
3. National Diabetes Statistics Report. Centers for Diease Control, National Center for Cronic Disease Prevention and Health Promotion, Division of Diabetes Translation. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. 2014.
4. Maahs DM, West NA, Lawrence JM and Mayer-Davis EJ. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am*. 2010;39:481-497.
5. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, Lawrence JM, Liese AD, Liu LL, Mayer-Davis EJ, Rodriguez BL and Standiford D. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes care*. 2012;35:2515-2520.
6. Atkinson MA and Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med*. 1994;331:1428-1436.
7. Harrison LC, Chu SX, DeAizpurua HJ, Graham M, Honeyman MC and Colman PG. Islet-reactive T cells are a marker of preclinical insulin-dependent diabetes. *J Clin Invest*. 1992;89:1161-1165.
8. Roep BO. The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. *Diabetologia*. 2003;46:305-321.
9. O'Meara NM, Sturis J, Herold KC, Ostrega DM and Polonsky KS. Alterations in the patterns of insulin secretion before and after diagnosis of IDDM. *Diabetes care*. 1995;18:568-571.
10. Eisenbarth GS, Srikanta S, Jackson R, Rabinowe S, Dolinar R, Aoki T and Morris MA. Anti-thymocyte globulin and prednisone immunotherapy of recent onset type 1 diabetes mellitus. *Diabetes Res*. 1985;2:271-6.
11. Herold KC, Gitelman SE, Masharani U, Hagopian W, Bisikirska B, Donaldson D, Rother K, Diamond B, Harlan DM and Bluestone JA. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes*. 2005;54:1763-1769.
12. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P and Skyler JS. C-Peptide Is the Appropriate Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve β-Cell Function Report of an ADA Workshop, 21–22 October 2001. *Diabetes*. 2004;53:250-264.
13. Nathan DM, Zinman B, Cleary PA, Backlund J-YC, Genuth S, Miller R, Orchard TJ and Trial C. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Archives of Internal Medicine*. 2009;169:1307.
14. Chatenoud L and Bluestone JA. CD3-specific antibodies: a portal to the treatment of autoimmunity. *Nat Rev Immunol*. 2007;7:622-632.

15. Herold KC, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, Boyle KD, Keyes-Elstein L, Aggarwal S, Phippard D, Sayre PH, McNamara J and Bluestone JA. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes*. 2013;62:3766-3774.
16. Couri CE, Oliveira MC, Stracieri AB, Moraes DA, Pieroni F, Barros GM, Madeira MIA, Malmegrim KC, Foss-Freitas MC and Simões BP. C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *Jama*. 2009;301:1573-1579.
17. Salomon B and Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. *Annu Rev Immunol*. 2001;19:225-252.
18. Salomon B, Lenschow DJ, Rhee L, Ashourian N, Singh B, Sharpe A and Bluestone JA. B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. *Immunity*. 2000;12:431-440.
19. Bettini ML, Pan F, Bettini M, Finkelstein D, Rehg JE, Floess S, Bell BD, Ziegler SF, Huehn J, Pardoll DM and Vignali DAA. Loss of epigenetic modification driven by the Foxp3 transcription factor leads to regulatory T cell insufficiency. *Immunity*. 2012;36:717-730.
20. Tang Q, Adams JY, Penaranda C, Melli K, Piaggio E, Sgouroudis E, Piccirillo CA, Salomon BL and Bluestone JA. Central role of defective interleukin-2 production in the triggering of islet autoimmune destruction. *Immunity*. 2008;28:687-697.
21. D'Alise AM, Ergun A, Hill JA, Mathis D and Benoist C. A cluster of coregulated genes determines TGF-beta-induced regulatory T-cell (Treg) dysfunction in NOD mice. *Proc Natl Acad Sci U S A*. 2011;108:8737-8742.
22. Grinberg-Bleyer Y, Baeyens A, You S, Elhage R, Fourcade G, Gregoire S, Cagnard N, Carpentier W, Tang Q, Bluestone J, Chatenoud L, Klatzmann D, Salomon BL and Piaggio E. IL-2 reverses established type 1 diabetes in NOD mice by a local effect on pancreatic regulatory T cells. *J Exp Med*. 2010;207:1871-1878.
23. Tang Q, Henriksen KJ, Bi M, Finger EB, Szot G, Ye J, Masteller EL, McDevitt H, Bonyhadi M and Bluestone JA. In vitro-expanded antigen-specific regulatory T cells suppress autoimmune diabetes. *J Exp Med*. 2004;199:1455-1465.
24. Marek-Trzonkowska N, Myśliwiec M, Dobyszuk A, Grabowska M, Derkowska I, Juścińska J, Owczuk R, Szadkowska A, Witkowski P and Młynarski W. Therapy of type 1 diabetes with CD4(+)CD25(high)CD127-regulatory T cells prolongs survival of pancreatic islets - results of one year follow-up. *Clinical Immunology*. 2014;153:23-30.
25. Marek-Trzonkowska N, Mysliwiec M, Dobyszuk A, Grabowska M, Techmanska I, Juscinska J, Wujtewicz MA, Witkowski P, Mlynarski W, Balcerska A, Mysliwska J and Trzonkowski P. Administration of CD4+CD25highCD127- regulatory T cells preserves beta-cell function in type 1 diabetes in children. *Diabetes care*. 2012;35:1817-20.
26. Trzonkowski P, Bieniaszewska M, Juscinska J, Dobyszuk A, Krzystyniak A, Marek N, Mysliwska J and Hellmann A. First-in-man clinical results of the treatment of patients with graft versus host disease with human ex vivo expanded CD4+CD25+CD127- T regulatory cells. *Clin Immunol*. 2009;133:22-26.
27. Bluestone JA, Buckner JH, Fitch M, Gitelman SE, Gupta S, Hellerstein MK, Herold KC, Lares A, Lee MR, Li K, Liu W, Long SA, Masiello LM, Nguyen V, Putnam AL, Rieck M,

Sayre PH and Tang Q. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. *Sci Transl Med*. 2015;7:315ra189.

28. Tang Q and Lee K. Regulatory T-cell therapy for transplantation: how many cells do we need? *Curr Opin Organ Transplant*. 2012;17:349-354.
29. Dabelea D, Bell RA, D'Agostino RB, Imperatore G, Johansen JM, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ and Waitzfelder B. Incidence of diabetes in youth in the United States. *JAMA*. 2007;297:2716-2724.
30. Harjutsalo V, Sjoberg L and Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. *Lancet*. 2008;371:1777-1782.
31. DIAMOND_Project_Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabet Med*. 2006;23:857-66.
32. Eurodiab A. Variation and trends in incidence of childhood diabetes in Europe. *Lancet*. 2000;355:873-876.
33. Haller MJ, Atkinson MA and Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. *Pediatric Clinics of North America*. 2005;52:1553-1578.
34. Bluestone JA, Herold K and Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature*. 2010;464:1293-1300.
35. Leslie RDG, Williams R and Pozzilli P. Clinical review: Type 1 diabetes and latent autoimmune diabetes in adults: one end of the rainbow. *J Clin Endocrinol Metab*. 2006;91:1654-1659.
36. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steinrauf H, Skyler JS and Sosenko JM. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes*. 2012;61:2066-2073.
37. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, McGee PF, Moran AM, Raskin P, Rodriguez H, Schatz DA, Wherrett D, Wilson DM, Lachin JM and Skyler JS. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N Engl J Med*. 2009;361:2143-2152.
38. Sherry N, Hagopian W, Ludvigsson J, Jain SM, Wahlen J, Ferry RJ, Bode B, Aronoff S, Holland C, Carlin D, King KL, Wilder RL, Pillemer S, Bonvini E, Johnson S, Stein KE, Koenig S, Herold KC and Daifotis AG. Teplizumab for treatment of type 1 diabetes (Protege study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. 2011;378:487-497.
39. American_Diabetes_Association. Standards of Medical Care in Diabetes. Chapter 12. Children and Adolescents. *Diabetes care*. 2017;40:S105-s113.
40. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA and Clark N. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28:186-212.
41. American_Diabetes_Association. Standards of Medical Care in Diabetes. Chapter 2. Classification and Diagnosis of Diabetes. *Diabetes care*. 2017;40:S11-s24.
42. The US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Published May 28, 2009 (Version 4.03, June 14, 2010). 2010.
43. Bugelski PJ, Volk A, Walker MR, Krayer JH, Martin P and Descotes J. Critical review of preclinical approaches to evaluate the potential of immunosuppressive drugs to influence human neoplasia. *International journal of toxicology*. 2010;29:435-466.

44. Corthay A. Does the immune system naturally protect against cancer? *Frontiers in immunology*. 2014;5.
45. Grulich AE, van Leeuwen MT, Falster MO and Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *The Lancet*. 2007;370:59-67.

17. APPENDICES

17.1 ADA Criteria for Diabetes Diagnosis

The following criteria are taken from the 2017 ADA publication on classification and diagnosis of diabetes:[41]

*Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.**

OR

*2-h plasma glucose (PG) ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.**

OR

*A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the DCCT assay.**

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Per ADA Standards of Medical Care-2017, blood glucose rather than A1c should be used to diagnose acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia.

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

17.2 Mixed Meal Tolerance Test

The mixed meal tolerance test (MMTT) measures the level of C-peptide (an amino acid which is released by the pancreas in amounts equal to insulin) and glucose. The level of C-peptide in the blood indicates how much insulin the pancreas is producing. A beverage called Boost® High Protein (HP) Nutritional Drink (a milkshake-like drink containing carbohydrate, fat and protein) will be administered. Boost HP will raise blood glucose levels and cause the body to release insulin, as a meal would. In general, if a participant has a known food allergy to one or more components of Boost HP, the participant should not be enrolled and the site should notify the Sponsor/designee immediately.

The MMTT should be performed by study staff adequately trained and authorized by the PI to perform the procedure including the PI, sub-investigators, or study nurses/coordinators trained in the performance of IV procedures. The MMTT should be performed in the morning, with the first blood draw (time point) between 7:00 am and 10:00 am (when blood glucose is more likely to be within the target range). The 4-hour MMTT should take 250 minutes to perform, and the 2-hour MMTT should take 130 minutes.

The table below outlines the time points at which the blood sample will be taken from the subject for MMTT-stimulated C-peptide/glucose measurement.

Time	2-hour MMTT	4-hour MMTT
–10	X	X
0	X	X
Participant drinks Boost®		
15	X	X
30	X	X
60	X	X
90	X	X
120	X	X
150		X
180		X
210		X
240		X

In preparation for the visit, each participant should:

- Fast for at least 10 hours (but not more than 16 hours) before the test. Participants should not eat or drink anything except water. This means no coffee, tea, soda, cigarettes, alcohol, or chewing gum during the fasting period.
- Refrain from vigorous exercise during the fasting period.
- Refrain from working the night before the morning of the test.
- Discontinue taking any prescription medications that must be taken daily (guidelines on insulin use are provided below).

Carbohydrates should not be restricted from the diet before the test. As a general guideline, for each of the 3 days prior to the visit where a MMTT will be done, it is recommended that adolescent subjects should consume at least 150 grams of carbohydrates. Most diets include greater amounts of carbohydrates and there is no need to alter the participant's diet unless he/she has been on a carbohydrate-restricted diet. Participants should also be instructed to drink plenty of liquids during the 3 days prior to the test.

Target Glucose Level at the Start of the MMTT

The target glucose level at the start of the test is between 70 and 200 mg/dL. Regular insulin or short acting insulin analogues may be used up to 6 and 2 hours before the test, respectively (see below), to achieve the desired glucose level. The principal investigator and the study participant should discuss the individual situation for insulin administration to attain the goal of meter capillary glucose values within the range of 70-200 mg/dL at the start of the test.

Subjects should be instructed to check their blood glucose by meter at home 2 hours before the start of the test so that marked hyperglycemia can be treated with a short-acting insulin analogue. Alternatively, participants who arrive at the research unit with elevated blood glucose can receive additional short-acting insulin analogues at the time of their arrival, if the test itself does not start until at least 2 hours after insulin administration and occurs before 10 a.m.

If a subject's blood glucose is below the limit (70 mg/dL) prior to performing the MMTT, the participant should be treated according to local practice, and the MMTT should be rescheduled (within the allowed visit window).

Insulin Before the Test

- Short-acting insulin analogues (such as lispro or aspart) may be administered up to 2 hours before the test.
- Regular insulin may be administered up to 6 hours before the test.
- Intermediate-acting insulin (such as neutral protamine Hagedorn [NPH]) may be administered on the evening before the MMTT, but not on the morning of the test. Participants managed with intermediate-acting insulin (NPH or Lente) should administer their usual dose on the evening before the MMTT, but not on the morning of the test.
- Long-acting basal (such as glargine) insulin or continuous subcutaneous insulin infusion may be administered before, during and after the test as usual. Participants on glargine may take their usual injection at the appropriate time, and those on continuous subcutaneous insulin infusion may continue with their usual basal settings.

IV Placement During the Test

- The IV should be in place for the duration of the test and must be flushed after each draw with saline solution or heparin flush.
- The participant should remain sitting or resting in bed quietly throughout the test until the test is completed. However, he or she may engage in quiet, nonstrenuous activities, such as reading, playing cards, or watching TV. The participant may walk to the bathroom between blood draws if necessary.

Boost HP to be Administered

Calculate the amount of Boost HP to be administered using the formula below. To convert from pounds to kilograms: pounds ÷ 2.2 = kg. There is no need to calculate after 60 kg, as this meets the minimum weight requirement for the full volume of 360 mL.

Boost HP dose= 6 kcal/kg body weight, at 1 kcal/mL to a max of 360 kcal (360 mL)

Amount of Boost HP to be administered = 6 mL x ___kg = ___ mL

Testing Procedure

1. Confirm that all prerequisite requirements of the test as detailed above are met prior to starting the test (i.e. participant has fasted, that fasting glucose is between 70 mg/dL and 200 mg/dL (will also be verified by in clinic by finger stick prior to testing), and that any insulin use prior to the test meets the specified guidelines).
2. Please refer to the Laboratory Manual for instructions on sample processing.
3. Check blood glucose level by finger stick and proceed with test if within range.
4. Establish IV line (after each blood draw, saline lock IV or run saline drip to keep open).
5. The first sample should be taken at least 10 minutes after establishing the IV line (this is the '–10 minute' sample).
6. After at least 10 minutes, the second sample should be taken just before the participant drinks the Boost HP (this is the '0 minute' sample). Immediately administer the Boost HP and instruct the participant to consume within 5 minutes (keep the Boost HP out of the reach of the participant so that you can control the start time). Start timer at beginning of the Boost HP drink. Patient can drink water after finishing the Boost HP and freely throughout the remainder of the test.
7. The remaining samples should be drawn per the collection schedule based on the start time of the Boost HP drink.
8. It is critical to adhere to the collection schedule as closely as possible and to accurately record the collection times. However, it will not be considered a protocol deviation if a specimen is collected at an incorrect time.
9. At the conclusion of the test, check blood glucose and administer insulin as per participant's standard insulin plan.
10. Discontinue IV.

17.3 BMI z-score

Age (months)	BMI z-score +2.25 SD Males	BMI z-score +2.25 SD Females
95.5	23.69	24.62
96.5	23.85	24.76
97.5	24.00	24.89
98.5	24.15	25.03
99.5	24.31	25.17
100.5	24.46	25.31
101.5	24.61	25.45
102.5	24.77	25.59
103.5	24.92	25.73
104.5	25.07	25.86
105.5	25.22	26.00
106.5	25.37	26.14
107.5	25.52	26.28
108.5	25.67	26.42
109.5	25.82	26.56
110.5	25.97	26.70
111.5	26.11	26.84
112.5	26.26	26.98
113.5	26.40	27.12
114.5	26.55	27.26
115.5	26.69	27.39
116.5	26.83	27.53
117.5	26.97	27.67
118.5	27.11	27.81
119.5	27.24	27.94
120.5	27.38	28.08
121.5	27.51	28.22
122.5	27.64	28.35
123.5	27.77	28.49
124.5	27.90	28.63
125.5	28.03	28.76
126.5	28.16	28.89
127.5	28.28	29.03
128.5	28.40	29.16
129.5	28.52	29.30
130.5	28.64	29.43
131.5	28.76	29.56
132.5	28.88	29.69
133.5	28.99	29.82
134.5	29.10	29.95
135.5	29.21	30.08
136.5	29.32	30.21
137.5	29.43	30.34

Age (months)	BMI z-score +2.25 SD Males	BMI z-score +2.25 SD Females
138.5	29.53	30.47
139.5	29.64	30.60
140.5	29.74	30.72
141.5	29.84	30.85
142.5	29.93	30.98
143.5	30.03	31.10
144.5	30.12	31.23
145.5	30.22	31.35
146.5	30.31	31.47
147.5	30.39	31.60
148.5	30.48	31.72
149.5	30.57	31.84
150.5	30.65	31.96
151.5	30.73	32.08
152.5	30.81	32.20
153.5	30.89	32.32
154.5	30.96	32.44
155.5	31.04	32.56
156.5	31.11	32.68
157.5	31.18	32.79
158.5	31.25	32.91
159.5	31.32	33.03
160.5	31.38	33.14
161.5	31.45	33.26
162.5	31.51	33.37
163.5	31.57	33.49
164.5	31.63	33.60
165.5	31.69	33.72
166.5	31.75	33.83
167.5	31.80	33.94
168.5	31.86	34.05
169.5	31.91	34.17
170.5	31.96	34.28
171.5	32.01	34.39
172.5	32.06	34.50
173.5	32.11	34.61
174.5	32.15	34.72
175.5	32.20	34.84
176.5	32.24	34.95
177.5	32.29	35.06
178.5	32.33	35.17
179.5	32.37	35.28
180.5	32.41	35.39

	BMI z-score +2.25 SD	**BMI z-score +2.25 SD**
Age (months)	**Males**	**Females**
181.5	32.45	35.50
182.5	32.49	35.61
183.5	32.53	35.72
184.5	32.57	35.83
185.5	32.61	35.94
186.5	32.64	36.06
187.5	32.68	36.17
188.5	32.72	36.28
189.5	32.75	36.39
190.5	32.79	36.51
191.5	32.82	36.62
192.5	32.86	36.73
193.5	32.89	36.85
194.5	32.93	36.96
195.5	32.96	37.08
196.5	33.00	37.20
197.5	33.03	37.31
198.5	33.07	37.43
199.5	33.11	37.55
200.5	33.14	37.67
201.5	33.18	37.79
202.5	33.22	37.92
203.5	33.26	38.04
204.5	33.29	38.16
205.5	33.33	38.29
206.5	33.37	38.42
207.5	33.42	38.54
208.5	33.46	38.67
209.5	33.50	38.81
210.5	33.55	38.94
211.5	33.59	39.07
212.5	33.64	39.21
213.5	33.69	39.35
214.5	33.74	39.49
215.5	33.79	39.63
216.5	33.85	39.77

17.4 [redacted]

[redacted]

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A Prospective Randomized Placebo-Controlled Double Blind Clinical Trial to Evaluate the Safety and Efficacy of CLBS03 (Autologous *Ex Vivo* Expanded Polyclonal [redacted] Regulatory T-cells [Tregs]) in Adolescents with Recent Onset Type 1 Diabetes Mellitus (T1DM)

Protocol Number: CLBS03-P01

Version: 7.0

Original Protocol Date: 27-Oct-2014

Revision Date: 17-Jan-2017

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Investigator Signature Date

Print Name and Title of Investigator