

STATISTICAL ANALYSIS PLAN

**STUDY TITLE: A T CELL PHENOTYPE SIGNATURE DRIVEN DOSE
FINDING STUDY WITH SIPLIZUMABIN TYPE 1 DIABETES MELLITUS**

PROTOCOL NUMBER: ITN095AI DESIGNATE

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
Ab	Antibody
AD-SCCC	Autoimmune Disease Statistical and Clinical Coordinating Center
AE(s)	adverse event(s)
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CGM	continuous glucose monitoring
CMV	cytomegalovirus
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
eCRF(s)	electronic case report form(s)
FDA	US Food and Drug Administration
HbA1c	hemoglobin A1c or glycated hemoglobin
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA-2	insulinoma antigen-2
ICH	International Conference on Harmonization
IND	Investigational New Drug [application]
IP	investigational product
IRB(s)	institutional review board(s)
ITN	Immune Tolerance Network
mAUC	mean area under the curve
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to treat

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MMTT	mixed meal tolerance test
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PBMC(s)	peripheral blood mononuclear cell(s)
PCR	polymerase chain reaction
PP	per protocol
SAE(s)	serious adverse event(s)
SAP	Statistical analysis plan
SOC	system organ classification
SOE	schedule of events
SQ	subcutaneous
TB	tuberculosis
Tcm(s)	central memory T cell(s)
TEAE(s)	treatment-emergent adverse event(s)
Tem	effector memory T cells
TIGIT	T cell immunoreceptor with Ig and ITIM domains
T1DM	type 1 diabetes mellitus
Tn	T naïve cells
Treg(s)	regulatory T cell(s)
ULN	upper limit of normal
WBC	white blood count
ZnT8	zinc transporter-8

2. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses related to the clinical and safety endpoints in the protocol and to describe the associated data displays to be included in reports for ITN095AI DESIGNATE. This document provides details on study populations, how the variables will be derived, how missing data will be handled and details on statistical methods to be used to analyze the safety and clinical data.

The statistical analysis plan (SAP) is based on ICH guidelines E3 and E9 (Statistical Principles for Clinical Trials).

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Client, and placed on file before database is locked. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Deviations from the final approved plan will be noted in the clinical study report.

3. PROTOCOL SUMMARY

Title	A T cell phenotype signature driven dose finding study with sipilizumab in type 1 diabetes mellitus
Short Title	Siplizumab in T1DM
Clinical Phase	Ib
Planned Number of Sites	Approximately 20 US sites
IND Sponsor Number	DAIT/NIAID IND 154719
Study Objectives	The primary objective is to identify a safe, metabolically favorable, dosing regimen for sipilizumab in patients with type 1 diabetes that induces changes in T cell phenotypes observed with alefacept therapy in new onset T1DM. The secondary objectives are to: 1. Assess the safety profile of sipilizumab in recently diagnosed T1DM. 2. Assess the effects of sipilizumab on residual beta cell function in recently diagnosed T1DM participants.
Study Design	This is a multi-center, open label study in individuals aged 8-45 years with a T1DM diagnosis within 18 months of V0. Participants will be randomized 1:1:1:1 to one of four possible sipilizumab dosing arms. All dosing arms will receive weekly sipilizumab doses for a total of 12 weeks. After the completion of treatment, participants will undergo follow-up visits at weeks 12, 24, 36 and 52 which include longitudinal MMTs. If indicated, participants will enter into long-term safety monitoring. Blood samples for mechanistic analyses will be obtained during the treatment phase and thereafter. Initially, an adult cohort will be enrolled with the aim to collect safety and metabolic data during sipilizumab therapy in type 1 diabetes participants between the ages of 18 and 45 years that suggests a prospect of benefit and supports the enrollment of pediatric participants between the ages of 8 and 17 years. To evaluate the effects of sipilizumab administration on the circulating Tem and Treg cell populations, flow cytometry analysis of the T cell phenotype signature will be assessed at weeks 2, 4, 8, and 12 to determine if participants meet the definition of an acceptable T cell phenotype signature as follows: 1. A 75% increase or greater from baseline in the Treg/Tem ratio in blood and 2. A 20% increase or greater from baseline in the proportion of circulating PD1+TIGIT+ cells with the CD4 Tem population In each age cohort, an interim analysis of flow parameters and safety data will be conducted after the 5th per protocol participant in each dosing arm reaches the week 12 visit. An individual who achieves both T cell markers at any time point between week 2 and week 12 is considered to have met the T cell phenotype signature criteria. However, both criteria do not need to be achieved at the same time point to be considered in meeting the definition. Unless

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	there are safety concerns, recruitment will not be paused during the flow cytometry interim analysis. If at least 3 of the first 5 per protocol participants in a dosing arm achieve the T cell phenotype signature as defined above, the dosing arm will be expanded to recruit a total of 15 participants. A dosing arm will not be expanded if it fails to meet the 3 of 5 participant criteria described above or any safety concerns are identified. Participants in closed dosing arms will continue to be followed through week 52 for safety, collection of mechanistic samples and assessment of insulin secretion. If no adult dosing arm meets interim analysis criteria, and no safety concerns are observed, study enrollment will be paused for review of the safety and mechanistic data. This will be followed by a protocol amendment updating the dosing regimen and study design. In the adult age cohort, if dosing arms are closed for safety reasons or after an interim analysis does not meet specific flow parameters, additional participants may be added to remaining dosing arms so that a minimum of 30 participants across all dosing arms are enrolled. Data from these adult participants will be used to determine if siplizumab has a prospect of direct benefit that justifies opening the study to pediatric participants. After the 30th adult participant reaches week 12, the Data and Safety Monitoring Board (DSMB) and US Food and Drug Administration (FDA) will review the available data to weigh the potential risks, as well as the prospect of direct benefit. If there are no concerns raised by the DSMB and FDA after review of the safety and insulin secretory data from the siplizumab treated adult participants, enrollment in the pediatric cohort (8-17 years old) will be initiated. Enrollment will continue in the adult cohort during this first safety review unless there are safety concerns.
Dosing Arms	1. 0.08 mg/kg/dose SQ 2. 0.12 mg/kg/dose SQ 3. 0.18 mg/kg/dose SQ 4. 0.22 mg/kg/dose SQ
Primary Endpoint	1. Change from baseline of PD1+TIGIT+ frequency within circulating CD4 Tem cells during the first 12 weeks and 2. Change from baseline in the CD4 Treg/Tem ratio during the first 12 weeks in blood.
Secondary Endpoints	1. Frequency of AEs in all siplizumab dosing arms. 2. MMTT-stimulated mean 2-hour C-peptide AUC at Weeks 12, 24, 36 and 52. The mean 2-hour C-peptide AUC, measured in nmol/L, is computed by dividing the total AUC by 120 minutes. 3. Insulin use (U/kg/day) at Weeks 12, 24, 36 and 52.
Accrual Objective	Target enrollment: 120
Study Duration	The target enrollment duration is approximately 24 months. Participants will be followed for 52 weeks. If long term safety monitoring is indicated, participants may be followed for an additional 48 weeks.
Treatment Description	Four dosing regimens of siplizumab.

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Inclusion Criteria	1. Ability to provide informed consent (parental permission and informed assent of minor, if applicable). 2. Male or female between 8 to 45 years of age. 3. Diagnosis of T1DM within 18 months (550 days) of enrollment (V0). 4. Positive for at least one diabetes-related autoantibody, including: a. Glutamate decarboxylase (GAD-65), b. Insulin, if obtained within 10 days of the onset of exogenous insulin therapy, c. Insulinoma antigen-2 (IA-2), or d. Zinc transporter-8 (ZnT8). 5. Peak stimulated C-peptide level > 0.15 nmol/L following a MMTT conducted $\geq$ 21 days from diagnosis and within 37 days of enrollment (V0). 6. Completion of SARS-CoV-2 vaccination, according to current CDC recommendations and FDA approval(s) or emergency use authorization(s). If the participant requires administration of vaccine(s) to meet eligibility requirements, they must complete the vaccination series at least 10 days prior to enrollment (V0).
Exclusion Criteria	Use of investigational drugs within 24 weeks of participation with the exception of any vaccine for the prevention of SARS-CoV-2 infection and emergency use authorization medications for treating SARS-CoV-2. Severe reaction or anaphylaxis to humanized monoclonal antibodies. Inability to complete a mixed meal tolerance test: a. History of significant allergy (e.g., anaphylaxis) to milk or soy proteins, b. Inability to disable hybrid closed loop system. History of recent (within 180 days of V0) or ongoing uncontrolled bacterial, viral, fungal or other opportunistic infections, including: a. Human immunodeficiency virus (HIV), b. Current or prior infection with hepatitis B (HBV), as indicated by positive HBsAg or positive HBcAb, c. Current or prior hepatitis C (HCV), unless treated with anti-viral therapy with achievement of a sustained virologic response (undetectable viral load 12 weeks after cessation of therapy), d. Positive QuantiFERON-TB Gold or QuantiFERON-TB Gold Plus tests. PPD or T-SPOT®.TB may be substituted for the QuantiFERON-TB Gold or QuantiFERON-TB Gold Plus tests, e. Active infection with EBV as detected by PCR or serology at the screening visit (V-1), f. Active infection with cytomegalovirus (CMV) as detected by PCR or serology at the screening visit (V-1),

	Positive molecular testing of SARS-CoV-2 within 30 days of V-1. Any of the following laboratory abnormalities, confirmed by repeat tests at least 1 week apart: - White blood count (WBC) $< 3 \times 10^3/\mu\text{L}$, - CD3+ CD4+ T cell count below the lower limit of normal, - Platelet count $< 150,000/\mu\text{L}$, - Hemoglobin $< 10 \text{ g/dL}$, - ALT $\geq 2\times$ upper limit of normal (ULN), - AST $\geq 2\times$ ULN, - Serum creatinine $>1.5\times$ ULN in adults or $>\text{ULN}$ in pediatrics, - Absolute lymphocyte count (ALC) below the LLN. Prior or current treatment that is known to alter the natural history of T1DM or immunologic status, including high dose inhaled, extensive topical or systemic glucocorticoids. Current or prior (within last 14 days of the V-1 MMTT) use of any medication known to influence glucose tolerance (e.g., atypical antipsychotics, diphenylhydantoin, thiazide, or other potassium-depleting diuretics, β-adrenergic blockers, niacin). Current or prior (within the last 30 days of the V-1 MMTT) use of non-insulin medications to treat insulin resistance or elevated glucose levels. Previous or current diagnosis of malignancy. History of bone marrow transplantation, solid organ transplantation, or primary immunodeficiencies. History or diagnoses of other autoimmune diseases with the exception of stable thyroid or celiac disease. History of significant cardiovascular disease. Vaccination with a live attenuated vaccine (e.g., varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette- Guérin, and smallpox) within 30 days of V0. Women of child-bearing potential who are unwilling to use a medically acceptable form of contraception from 14 days prior to V0 until study Week 52. Women who are pregnant, lactating, or planning on pregnancy during the study. Current, diagnosed mental illness (e.g., severe depression), current diagnosed or self-reported drug, or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
Study Stopping Rules	Any death or Grade 4 AE except asymptomatic AE and those assessed as not related to siplizumab treatment on review by the DAIT/NIAID Medical Monitor and the ITN Clinical Trial Physician.

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	2. An occurrence of Hy's Law defined as elevations in the AST and/or ALT >3x ULN of the reference range, elevation in total bilirubin >2x ULN of the reference range and no other cause of hepatic injury. 3. Three of the first 10 participants cumulatively across all dosing arms, or 30% of all participants thereafter, require discontinuation of siplizumab treatment for the same or similar serious AE, based on Medical Dictionary for Regulatory Activities (MedDRA) preferred term or at the discretion of the DAIT/NIAID Medical Monitor, except for lymphopenia and CD3+ CD4+ T cell count. This rule will be monitored within and across age cohorts. 4. Five of the first 10 participants cumulatively across all dosing arms, or 50% of all participants thereafter, require discontinuation of siplizumab treatment for AEs except for lymphopenia and CD3+ CD4+ T cell count. This rule will be monitored within and across age cohorts.
Cohort Dosing Arm Stopping Rules	1. Two of the first 5 participants develop a Grade 3 or higher adverse event, except low ALC or low CD3+ CD4+ T cell count, that is at least possibly related to siplizumab treatment. 2. Two of the first 5 participants permanently discontinue siplizumab treatment due to low ALC or low CD3+ CD4+ T cell count. 3. Four out of the 15 planned participants in a dosing arm develop a Grade 3 or higher adverse event, except for low ALC or low CD3+ CD4+ T cell count, that is at least possibly related to siplizumab treatment. 4. Four out of the 15 planned participants permanently discontinue siplizumab treatment due to low ALC or low CD3+ CD4+ T cell count.

4. ANALYSIS SAMPLES

To meet the primary dose-finding objective of this study, we must be able to observe changes in the T cell phenotypes at early time points in participants with exposure to sipilizumab (see per protocol sample definition below). Missing phenotype data will not be imputed. As such, the following PP sample will be used for evaluating the primary objective. Safety and mITT samples are included for evaluation of safety and exploratory endpoints.

Per protocol (PP) sample: All randomized participants who have viable PBMC samples available following two consecutive doses of sipilizumab.

Safety sample (SS): All participants who receive any amount of sipilizumab. The safety analyses will be based on the actual treatment the participants receive.

Modified intent to treat (mITT) sample: All randomized participants who receive any amount of sipilizumab. The impact of sipilizumab on T1DM metabolic endpoints will be based on the mITT sample according to the group to which the participants are assigned.

5. STUDY PARTICIPANTS

5.1. Disposition of Participants

The disposition of all enrolled participants will be summarized in tables and listed.

The numbers and percentages of participants randomized and in each analysis sample, as well as reasons for early termination from the study will be presented. For participants discontinuing study treatment early, the reasons for discontinuing study treatment early will also be presented.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for all randomized and safety sample participants. For assessments that are collected at both Screening and Day 0, data from the Day 0 visit will be used. If data is missing at Day 0 but not Screening, the Screening result will be used. Characteristics to be summarized include:

- Age
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown or Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown or Not Reported)
- Sex (Female, Male, Unknown or Not Reported)
- Weight
- Body Mass Index (BMI)
- Systolic and Diastolic Blood Pressure
- 2-hour C-peptide mAUC
- Insulin use
- Time from diagnosis of T1DM to randomization
- Absolute lymphocyte count
- CD4 count
- NK cells

These data will also be listed by participant.

5.3. Prior and Concomitant Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2022-Sept). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study medication dates. Prior medications will have both the medication

start and stop dates prior to the first dose of study medication date. After medications will have both the medication start and stop dates after the last dose of study medication date. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study medication by at least one day.

The number and percentage of participants receiving prior, concomitant, and after medications will be presented overall and by standardized medication name. When reporting the number of participants receiving the medication, a participant will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of participants in the safety population. Separate data listings will be provided for prior, concomitant, and after medications. The safety sample will be used for all displays.

5.4. Medical History

Medical histories are captured at screening for all enrolled participants on the Medical History CRF. All medical histories or events reported in the Medical History CRF will be listed for all participants in the safety population.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Major protocol deviations occurring throughout the duration of the study are captured on the Major Protocol Deviation and Site Level Major Deviation CRFs.

Major protocol deviations will be summarized and listed. The deviations will be summarized by whether the deviation was site-level or participant-level and by type of deviation.

6.2. Randomization

Participants who sign the informed consent/assent and meet the eligibility criteria will be randomly assigned to available siplizumab dosing arms. The study is open label. Participants are randomized in a 1:1:1:1 fashion to the 4 dosing arms initially. If any dosing arms close temporarily or permanently, participants are randomized in an equal fashion to the open dosing arms.

6.3. Measurement of Treatment Compliance

Starting on Day 0, all participants will be administered weekly SQ doses and will receive one of the four doses for 12 weeks based on the randomization assignment. Siplizumab is administered at the study visits by site personnel. Compliance, therefore, will be monitored by the site and documented on the electronic case report form (eCRF). A listing will be created of all siplizumab injections for each participant using the safety sample. At each study week it will be indicated if the injection was received, the date, dose level, and whether the full dose was administered. The total number of injections received for each participant will also be displayed.

7. GENERAL ANALYSIS AND REPORTING CONSIDERATIONS

The following is a list of general analysis and reporting conventions to be applied for this study:

- Categorical variables will be summarized using counts (n) and percents (%) and will be presented in the form n (%).
- Moment statistics including mean will be reported at 1 more significant digit than the precision of the original data. The standard deviation will be reported at 2 more significant digits than the precision of the original data. The level of precision may be modified on specific displays based on clinical judgement.
- Order statistics including median, min, and max will be reported to the same level of precision as the original observations. If any values are calculated to have more significant digits, then the value should be rounded so that it is the same level of precision as the original data.
- Following SAS default rules, the median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including t and z test statistics will be reported to two decimal places.
- P-values will be reported to 3 decimal places if greater than 0.001. If less than 0.001, then report '<0.001'. P-values and significant levels will be reported as 0.05 rather than .05. A p-value can be reported as "1.000" only if it is exactly 1.000 without rounding. A p-value can be reported as "0.000" only if it is exactly 0.000 without rounding.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider the digit to the right of last significant digit: if < 5 then round down, if ≥5 then round up.
- In general, listings will be sorted in the order that columns are displayed, starting with the first column on the left.
- All analyses will be performed using the SAS System version 9.4 or higher.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

7.1.1. Multicenter Studies

Study participants will be recruited from up to 20 study sites in the United States. Analysis will not consider site as a stratification factor or covariate.

7.1.2. Assessment Time Windows

Visit windows for each scheduled visit are provided in Table 2.

Table 2: Visit Windows

Visit	Time Point	Visit Window
Screening: Visit -1	Must occur no more than 37 days prior to V0	

Baseline: Visit 0	Day 0/Week 0	n/a
Visits 1 to 11	Every week through Week 11	+/- 1 day
Visit 12	Week 12	+/- 3 days
Visits 13 to 15	Weeks 24, 36, and 52	+/- 14 days
Visits 1SM to 4SM	Weeks 64, 76, 88, and 100	+/- 14 days

All data will be included in analyses, regardless of time of assessment, unless explicitly stated.

7.1.3. Timing of Analyses

Analysis of the primary, secondary, and exploratory endpoints will be completed after all participants completed the study and the corresponding data are frozen or locked. Ad-hoc analyses of the primary endpoint mechanistic data may be conducted as samples are processed for this open label phase 1b study.

7.1.4. Multiple Comparisons/Multiplicity

This is a small dose finding study, and no prespecified analyses will report p-values. Due to the large number of sites (up to 20), study data will be analyzed as a whole and no formal accommodation for site-to-site variation will be made.

8. ENDPOINT EVALUATION

8.1. Primary Endpoint

The primary endpoint is:

1. Change from baseline in PD1+TIGIT+ frequency within circulating CD4 Tem cells during the first 12 weeks **and**
2. Change from baseline in the CD4 Treg/Tem ratio during the first 12 weeks in blood.

8.1.1. Computation of the Primary Endpoint

The PD1+TIGIT+ frequency within circulating CD4 Tem cells and CD4 Treg/Tem ratio will be derived using a qualified flow cytometry assay at Weeks 0, 2, 4, 8, and 12. The % change from baseline at each study week for each participant will be calculated for CD4 Treg/Tem ratio and PD1+TIGIT+ frequency. The following 2 criteria comprise the estimand for the primary endpoint and will be used to evaluate whether a participant meets the T cell phenotype signature:

1. A 75% increase or greater from baseline in the CD4 Treg/Tem ratio in blood and
2. A 20% increase or greater from baseline in PD1+TIGIT+ frequency within circulating CD4 Tem.

An individual who achieves both signature criteria at any timepoint on or before Week 12 is counted as having the signature response. Both criteria do not need to be achieved at the same time point.

All PP sample participants will be included in analyses on the primary endpoint regardless of intercurrent events. Potential intercurrent events are treatment discontinuation, missed doses of sipilizumab, use of prohibited medications, and missed or unavailable T cell phenotype data.

8.1.2. Primary Analysis of the Primary Endpoint

The original goal of the study was to identify dosing arms where at least 80% of per protocol participants in an age cohort achieve the T cell phenotype signature. This study was stopped early after only 7 participants had initiated treatment. Therefore, for the primary endpoint the PD1+TIGIT+ frequency within circulating CD4 Tem cells and CD4 Treg/Tem ratio will be graphed over time for each PP sample participant from baseline to Week 12, and a table will report the number and percent of participants achieving the T cell phenotype signature by dosing arm. Data will also be listed for each participant. All displays of primary endpoint data will only include PP sample participants.

8.1.3. Sensitivity Analyses of the Primary Analysis

If the mITT and PP samples are not equivalent, the displays described in section 8.1.2 will be created for the mITT sample.

8.1.4. Secondary Analyses of the Primary Endpoint

Not applicable

8.2. Secondary Endpoints

The secondary endpoints for the DESIGNATE study and the analyses to evaluate them are provided in this section. Planned analyses described in the subsections below will be performed for the safety and/or mITT sample. Missing data will not be imputed and will be left as missing. All analyses are descriptive, and no hypothesis testing is planned.

8.2.1. Secondary Endpoint 1: Frequency of AEs in all siplizumab dosing arms

The frequency of AEs and SAEs will be tabulated by MedDRA Preferred Term and System Organ Class for all 4 dosing arms. Additionally, AEs will be tabulated by maximum severity. Section 9.2 describes further how adverse events will be summarized. The safety sample will be used for all summaries of adverse events.

8.2.2. Secondary Endpoint 2: MMTT-stimulated mean 2-hour C-peptide AUC at Weeks 12, 24, 36, and 52.

During the MMTT, C-peptide levels are measured at –10, 0, 15, 30, 60, 90, and 120 minutes. The 2-hour C-peptide mean AUC (mAUC) will be calculated using the trapezoidal rule over the 2-hour period as shown in **Formula 1**.

Formula 1: Calculating AUC:

$$AUC = \sum_{k=0}^{N-1} (t_{k+1} - t_k) \frac{(f(t_{k+1}) + f(t_k))}{2},$$

where t represents the time point (e.g. $t_0 = 0$, $t_1 = 15$, etc.), and $f(t)$ is the C-peptide result at time t in units of nmol/L. For this computation, the “time 0” C-peptide value will be taken as the average of C-peptide values measured at time points -10 and 0 minutes. The AUC calculation will be based on the time points available from the MMTT. The actual time points (e.g. 14 minutes) will be used for calculating the AUC. If the actual time is not provided, the prescribed time point (e.g. 15 minutes) will be used. Results reported as less than the lower limit of detection will be imputed as $\frac{1}{2}$ the lower limit of detection.

Since the quantity $(t_{k+1} - t_k)$ is in minutes, the final unit for AUC is (nmol*min/L). The mean 2-hour C-peptide AUC (mAUC) = AUC/120 minutes (or, the actual length of the MMTT); the unit for mAUC is nmol/L.

Using the mITT sample, C-peptide mAUC and the change in C-peptide mAUC from baseline will be summarized in a table by visit and siplizumab dosing arm. C-peptide mAUC will also be displayed in a spaghetti plot and listed.

8.2.3. Secondary Endpoint 3: Insulin use at Weeks 6, 12, 24, 36, and 52

The amount (basal, bolus, and total units) of insulin used per day will be reported for the five days prior to each study visit along with the primary route of administration (injection vs. pump). The participant’s weight will also be collected at every study visit. At each scheduled visit, average insulin use per kg will be computed as the average number of units per day (over the five-day period) divided by weight in kilograms. If a participant’s weight is not collected or is

missing at the study visit where insulin use was collected, the participant's weight for that visit will be derived as the average of the participant's weight at the visits before and after the visit in question.

Average insulin use per kg and the change from baseline in average insulin use per kg will be summarized in a table by visit and siplizumab dosing arm using the mITT sample. Average insulin use per kg will also be displayed in a spaghetti plot and listed; listings will also include the daily total units.

8.3. Exploratory Endpoints

8.3.1. Exploratory Endpoint 1: Continuous glucose monitoring (CGM)

Participants will be encouraged to use a personal CGM during the study, but one will not be provided to them. In all summaries, CGM data collected the 14 days prior to the visit will be used¹. There must be data for at least 70% of the expected times over the 14 days or else the data will not be used to derive CGM metrics. Due to the exploratory nature of this data, alternative thresholds will be considered depending on data availability². The following analyses will be performed using glucose data from the CGMs for the mITT population with available data:

- The mean, SD, coefficient of variation (CV), and proportion of time in key ranges (<54, 54-<70, < 70 mg/dL, 70-180 mg/dL, >180 mg/dL) will be computed for each participant and visit. These metrics will be graphed for each participant. Graphical comparisons of these metrics to other study endpoints, such as C-peptide mAUC, may be explored.
- The CGM metrics listed above may also be explored separately during nocturnal (midnight to 6am) and diurnal hours.

8.3.2. Exploratory Endpoint 2: HbA1c

HbA1c will be summarized in a table by visit and siplizumab dosing arm. HbA1c will also be displayed in a spaghetti plot and listed. The mITT sample will be used.

8.4. Examination of Subgroups

Not applicable

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed.

Safety will be described in all 4 dosing arms through the reporting of adverse events (AEs), vital signs, physical examination findings, and changes in routine laboratory values.

Listings will be prepared for all safety measurements. All listings will be sorted in order of dosing arm, site, participant identifier (ID), and time of assessment (e.g., visit, date).

9.2. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 25.1). The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0, except for the grading of liver chemistry abnormalities, which is described in protocol section 12.3.2, the grading of allergic reactions, which is described in protocol section 12.3.1, and the grading of glycemic events, which is described in protocol section 12.3.3. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. As such, no additional data manipulation is needed to identify events.

All adverse events will be collected from the time the participant signs informed consent until the participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study. All symptomatic AEs and all Grade 2 or higher asymptomatic AEs will be recorded on the appropriate AE eCRF for this study, except for non-major glycemic events (protocol section 12.3.3). For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, or an electrocardiogram), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events if related to a study-mandated procedure or if they are deemed serious. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result. All data tabulations will be of only treatment-emergent events while non-treatment emergent AEs will be included in a separate listing.

An overall summary table will be developed to report the number of events and the number and percentage of participants in each dosing arm having at least one event in the following categories:

- All AEs
- AEs indicated as serious
- AEs of special interest

- AEs that were reported as being related (possibly related or related) to study drug
- AEs reported by severity
- AEs that lead to hospitalization
- AEs that lead to study drug discontinuation
- AEs with an outcome of death

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each dosing arm and overall for each of the following:

- All AEs
- AEs by maximum severity
- AEs by relationship to study drug

Summary tables will present the total number of events as well as the number and percentage of participants experiencing the events. If a participant experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of participants experiencing the events, a participant will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of participants in the safety sample.

9.3. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Serious adverse events (SAEs) will be summarized in the overall AE summary table and also in a separate table by SOC and preferred term if any occur. A listing showing all SAEs and AEs of special interest (AESIs) will be created if any occur. Separate displays listing and summarizing death, including time to death and cause of death, will be created if a death occurs.

9.4. Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry, hematology, lymphocyte subset count, viral load testing, HbA1c, and hepatic function panel. Laboratory results will be reported from a central lab. However, sites can additionally report results performed locally in the electronic data capture (EDC) system. Local results will be converted to standardized units where possible. Changes in laboratory parameters that represent increases in NCI-CTCAE severity grade over time (Grade 2 or higher or symptomatic) are captured as AEs and summarized as described in section 9.2 Adverse Events.

Laboratory data will be plotted to show patterns over time. For chemistry, hematology, lymphocyte subset count, and the hepatic function panel, spaghetti plots showing each participant's trajectory for each lab test over time will be created. Grade 2 or higher results will be annotated on the figures. Both local and central lab results will be included. If a local and central lab draw for a lab test occurred on the same date, the central result will be presented on the figure. Additionally, separate spaghetti plots will be created for absolute lymphocyte count

(ALC) and CD4 over time. These figures will be paneled by treatment group that will additionally indicate thresholds for when siplizumab should be suspended and resumed, as well as when siplizumab doses were given.

Viral load testing results will be listed. Section 8.3.2 describes the displays that will be created for HbA1c.

9.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1. Vital Signs

Vital signs of weight, temperature, pulse, respiratory rate, and blood pressure will be obtained at all in-person visits. Additionally, height is collected at the screening visit only. These vital signs will be displayed in a listing. The grade will be included in the listing for vital signs with NCI-CTCAE grading criteria. Injection vital signs will be displayed in a separate listing.

9.5.2. Physical Examinations

Either a comprehensive or limited physical examination will be performed at each scheduled in-person study visit. A listing will be created for physical examination results that is sorted by dosing arm, site, participant, body system, and visit. A separate listing of only abnormal physical exam results will also be created.

10. OTHER ANALYSES

Not applicable

11. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The joint NIDDK and NIAID ACE/ITN/TrialNet DSMB will review safety data and make recommendations regarding the continuation, termination, or modification of the study. The DSMB shall review safety data at least yearly during planned DSMB Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs. The DSMB will also review C-peptide results at Week 12 by dosing arm and age cohort to monitor for an unexpected drug-induced worsening of T1DM.

In each age cohort, an interim analysis of flow parameters and safety data will be conducted after the 5th per protocol (PP) participant in each dosing arm reaches the week 12 visit. An individual who achieves both T cell markers at any time point between week 2 and week 12 is considered to have met the T cell phenotype signature criteria. However, both criteria do not need to be achieved at the same time point to be considered in meeting the definition. Unless there are safety concerns, recruitment will not be paused during the flow cytometry interim analysis. If at least 3 of the first 5 PP participants in a dosing arm achieve the T cell phenotype signature as defined above, the dosing arm will be expanded to recruit a total of 15 participants. A dosing arm will not be expanded if it fails to meet the 3 of 5 participant criteria described above or any safety concerns are identified, as referenced in Protocol Section 11.6. Participants in closed dosing arms will continue to be followed through week 52 for safety, collection of mechanistic samples and assessment of insulin secretion. Participants who meet criteria for long-term safety monitoring will be followed through week 100.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

This study was stopped early, and therefore none of the dosing arms will be fully enrolled. The protocol states that the goal for the analysis of the primary endpoint (protocol section 13.4.2) is to identify dosing arms where at least 80% (12 of 15) PP participants in an age cohort achieve the T cell phenotype signature with no safety concerns. While the number of participants meeting the T cell phenotype signature will be calculated (section 9.1.2), dosing arms that meet this 80% threshold cannot be identified.

Additionally, since the study was stopped early there is no possibility of the study opening to a pediatric cohort.

For the secondary endpoint of AE evaluation, incidence rates of AEs will not be calculated due to the small sample size.

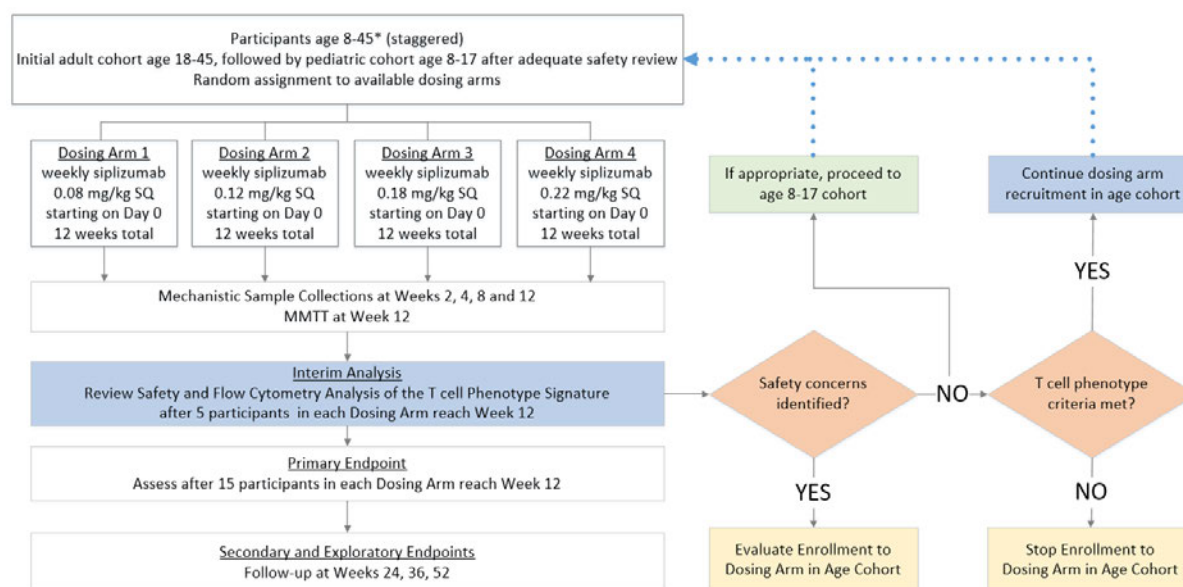
13. REFERENCES

¹ Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care*. 2017;40(12):1631-1640. doi:10.2337/dc17-1600

² Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol*. 2023;11(1):42-57. doi:10.1016/S2213-8587(22)00319-9

14. APPENDICES

14.1. Study Flow Chart



14.2. Schedule of Events

PHASE OF TRIAL	SCR	DOSING												FOLLOW-UP				WD	U
DAY	--	0	7	14	21	28	35	42	49	56	63	70	77	84	168	252	364	WD	U
WEEK	--	0	1	2	3	4	5	6	7	8	9	10	11	12	24	36	52	WD	U
VISIT WINDOW (DAYS)	37	+/-1												+/-3	+/-14				
VISIT	V-1	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	WD	U ¹
GENERAL ASSESSMENTS																			
Informed consent/assent	X																		
Eligibility criteria	X																		
Randomization ²		X																	
Demographics	X																		
Medical history	X																		
T1DM history	X																		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EBV-associated disease evaluation ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMV-associated disease evaluation ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive physical examination ⁵	X					X				X				X	X	X	X	X	
Directed physical examination ⁵		X	X	X	X		X	X	X		X	X	X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CENTRAL LABORATORY ASSESSMENTS ⁶																			
Serum Chemistries	X	X		X		X		X		X		X		X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte subset counts ⁷	X	X		X		X		X		X		X		X	X	X	X	X	X
Viral load CMV (PCR) ⁴	X																	X	X
Viral load EBV (PCR) ³ for seropositive	X	X				X				X				X ⁸	X ⁸	X ⁸	X ⁸	X	X
Viral load EBV (PCR) ³ for seronegative	X	X		X		X		X		X		X		X ⁸	X ⁸	X ⁸	X ⁸	X	X
Infectious disease serology ^{3,4}	X																		X
SARS-CoV-2 molecular test	X	X ⁹																	
SARS-CoV-2 antibody test		X												X					
Serum βhCG ¹⁰	X																		
TSH	X																		
HbA1c	X													X	X	X	X	X	
LOCAL ASSESSMENTS																			

¹ Unscheduled assessments are at the discretion of the site investigator but should include glucose meter and CGM downloads if available.

² May occur up to 1 business day prior to V0.

³ Symptoms of EBV are listed in Protocol Section 8.3.1. After the screening visit, EBV serology will be repeated if participants show clinical signs of infection. See Appendix 3 for additional details of EBV monitoring.

⁴ After the screening visit, CMV PCR and serology will only be collected at study visits where CMV is suspected clinically based on symptoms in Protocol Section 8.3.1 or if the participant's most recent CD3+ CD4+ T cell count is <200 cells/μL. Management and follow up of a positive CMV PCR assay will be determined after discussion with the DAIT/NIAID Medical Monitor, Protocol Chair, and ITN Clinical Trial Physician.

⁵ During the dosing phase, physical exams must be conducted prior to study drug administration.

⁶ Verify prior visit's lab values before study drug administration. The PoR must review ALC and CD3+ CD4+ T cell count prior to dispensing study drug. Notify study team if prior visit's central lab values are not available.

⁷ May be increased to at least weekly if study drug administration is paused. See Appendix 2 if CD3+ CD4+ T cell count is <400 cells/μL at V15 (week 52).

⁸ See Appendix 3 for additional details of EBV monitoring after the dosing period.

⁹ SARS-CoV-2 molecular test results must be available prior to V0. If run locally, performed within 3 days of V0. If run centrally, performed within 5 days of V0.

¹⁰ Female participants with reproductive capacity will be monitored for pregnancy.

DAIT NIAID
Statistical Analysis Plan – ITN095AI DESIGNATE

PHASE OF TRIAL	SCR	DOSING												FOLLOW-UP				WD	U
DAY	--	0	7	14	21	28	35	42	49	56	63	70	77	84	168	252	364	WD	U
WEEK	--	0	1	2	3	4	5	6	7	8	9	10	11	12	24	36	52	WD	U
VISIT WINDOW (DAYS)	37		+/-1												+/-3	+/-14			
VISIT	V-1	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	WD	U ¹
Urine hCG ¹⁰		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis test ¹¹	X																		
STAT CBC with differential ¹²			X	X	X	X*	X*	X*	X*	X*	X*	X*	X*						
STAT SARS-CoV-2 antigen test ¹³			X	X	X	X	X	X	X	X	X	X	X						
SARS-CoV-2 molecular test		X ⁹																	
DISEASE SPECIFIC ASSESSMENTS																			
2-hour MMTT (C-peptide & glucose)	X													X	X	X	X	X	
Diabetes-related autoantibodies	X																		
Glucometer data review ¹⁴	X	X				X				X				X	X	X	X	X	X
CGM data review ¹⁵	X	X				X				X				X	X	X	X	X	X
Insulin use	X	X						X						X	X	X	X	X	X
Hypoglycemic/hyperglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY DRUG ADMINISTRATION AND DRUG RELATED ASSESSMENTS																			
SQ Study drug administration ¹⁶		X	X	X	X	X	X	X	X	X	X	X	X						
Pre- and post-administration vitals		X	X	X	X	X	X	X	X	X	X	X	X						
PK ¹⁷		X		X		X		X		X		X		X	X	X	X		
Anti-siplizumab antibodies ¹⁷		X		X		X				X				X	X	X	X		
MECHANISTIC ASSESSMENTS ¹⁸																			
Serum ¹⁹	X	X		X		X		X		X		X		X	X	X	X	X	
Cellular Assays (PBMCs)	X	X		X		X				X				X	X	X	X	X	
Gene Expression (whole blood)		X		X		X				X				X	X	X	X	X	
DNA (whole blood) ²⁰		X																	

¹¹ QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, T-SPOT®.TB test or equivalent assay. A PPD tuberculin test may substitute.

¹² Required within 24 hours of V1, V2, and V3. *Only to be done if the prior week's ALC is <800 cells/mL or if participant has recovered or is recovering from a SARS-CoV-2 infection.

¹³ Only if participant has recovered from a SARS-CoV-2 infection. See Protocol Section 6.4.8 for additional details.

¹⁴ If available, reviewed by site staff for diabetes management. Data is not sent to CDSMC.

¹⁵ If available, reviewed by site staff for diabetes management. Data is uploaded by the site and sent to CDSMC.

¹⁶ Siplizumab treatment must be suspended if the participant develops a signs or symptoms that suggest an EBV or CMV infection (see Protocol Section 8.3.1), has a high risk exposure to SARS-CoV-2, or has a confirmed SARS-CoV-2 infection. Additional guidance on suspending siplizumab is provided in Table 6.

¹⁷ During the dosing phase (V0, V2, V4, V6, V8 and V10), PK and anti-siplizumab antibodies samples are collected before SQ administration. For the follow-up phase (V12-15), these samples are collected before the MMTT administration.

¹⁸ The schedule for these assessments may vary as appropriate. At no time will the blood draw volume exceed what is allowable according to the participant's age and body weight per country specific requirements.

¹⁹ Includes diabetes-related autoantibodies, PK and anti-siplizumab antibodies samples.

²⁰ If there are blood volume limits, this specimen may be collected at another time point (e.g., V12).

Schedule of Events – Long Term Safety Monitoring

PHASE OF TRIAL	LONG TERM SAFETY MONITORING ¹				
DAY	444	532	616	700	U
WEEK	64	76	88	100	U
VISIT WINDOW (DAYS)	+/- 14 DAYS				
VISIT	1SM	2SM	3SM	4SM	U
GENERAL ASSESSMENTS					
Adverse events	X	X	X	X	X
EBV-associated disease evaluation ²	X	X	X	X	X
CMV-associated disease evaluation ³	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Directed physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
LABORATORY ASSESSMENTS ⁴					
Hepatic function panel	X	X	X	X	X
Hematology	X	X	X	X	X
Lymphocyte subset count	X	X	X	X	X

1. If the participant is unable to return for a visit, telephone follow up and remote assessments will be performed.
2. EBV PCR and serology will be collected when EBV is suspected clinically based on symptoms listed in Section 8.3.1. Management and follow up of a positive EBV PCR assay will be determined after discussion with the DAIT/NIAID Medical Monitor, Protocol Chair, and ITN Clinical Trial Physician.
3. CMV PCR and serology will be collected when CMV is suspected clinically based on symptoms in Section 8.3.1. Management and follow up of a positive CMV PCR assay will be determined after discussion with the DAIT/NIAID Medical Monitor, Protocol Chair, and ITN Clinical Trial Physician.
4. The list of laboratory assessments is for participants with CD3+ CD4+ T cell count <400 cells/μL; it may be modified for other AEs by the DAIT/NIAID Medical Monitor.

15. ATTACHMENTS

Not applicable