DAIT/Rho STATISTICAL ANALYSIS PLAN
Version 2.0

ITN058AI EXTEND: Preserving Beta-Cell Function with Tocilizumab in New-onset Type 1 Diabetes

VERSION: **2.0**

DATE: **02Oct2020**

SPONSOR: Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases – NIH
[redacted]

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DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

ITN058AI EXTEND: Preserving Beta-Cell Function with Tocilizumab in New-onset Type 1 Diabetes

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
CDC	Centers for Disease Control
CGM	Continuous Glucose Monitoring
CMV	Cytomegalovirus
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events (version 4.0, May 28, 2009)
DAIT	Division of Allergy, Immunology, and Transplantation
DKA	Diabetic ketoacidosis
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
FDA	US Food and Drug Administration
FSIVGTT	Frequently-sampled intravenous glucose tolerance test
HbA_{1c}	Glycosylated hemoglobin
HDL	High-density lipoprotein
Hgb	Hemoglobin

IND	Investigational new drug
IRB	Institutional review board
ITN	Immune Tolerance Network
LDL	Low-density lipoprotein
LFT	Liver Function Test
mAUC	Mean area under the curve
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed-meal tolerance test
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PD	Pharmacodynamics
PK	Pharmacokinetics
RMSE	Root Mean Square Error
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious adverse event
T1D	Type 1 diabetes
T1DM	Type 1 diabetes mellitus
TCZ	Tocilizumab
ULN	Upper limit of normal range
WHO	World Health Organization

1. PROTOCOL SYNOPSIS

Title	Preserving Beta-Cell Function with Tocilizumab in New-onset Type 1 Diabetes
Short Title	TCZ in New-onset T1D
US IND	117725
Sponsor	US and Global Study Sponsor: Division of Allergy, Immunology, and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), USA Local Sponsor in Australia: Pharmaceutical Product Development, Inc. (PPD) for NIAID, NIH
Conducted by	Immune Tolerance Network, an NIH grantee
Protocol Co-Chairs	[redacted]
Accrual Objective	78 eligible pediatric subjects (6-17 years old) and 30-99 eligible adult subjects (18-45 years old) will be enrolled. Only pediatric participants are eligible for randomization after May 15, 2017.
Study Treatment	Tocilizumab or placebo
Study Design	This trial will be conducted in the US and Australia as a multi-center, prospective, double-blind, placebo-controlled, 2:1 randomized, phase 2 clinical trial for individuals with recent-onset T1DM aged 6−45 years, inclusive. All groups will receive standard intensive diabetes management. The subjects will receive IV infusions of either 8.0 mg/kg (body weight ≥30kg) or 10.0 mg/kg (body weight <30kg) tocilizumab or placebo every 4 weeks for 24 weeks. A staggered enrollment plan is being used for this trial. Prior to initiating the study in the pediatric age group (6-17 years old), adults (18-45 years old) were randomized 2:1 to tocilizumab or placebo, respectively. After 30 adult participants completed 12 weeks of treatment, the DSMB and FDA reviewed the available data to weigh potential risks and benefits as well as prospect of benefit before opening the trial to pediatric participants. The result of those reviews was to allow enrollment of children and adolescents 6-17 years old.
Study Duration	Total study duration will be approximately 4-5 years. • The enrollment phase is expected to last up to 42 months. • The study participation phase will be 104 weeks (2 years), which includes a treatment phase of 24 weeks and a follow-up phase of 80 weeks.
Primary Objective	Determine whether tocilizumab will slow the progression of the autoimmune destruction of ß cells and lead to the preservation of C-peptide secretion in T1DM.
Primary Endpoint	MMTT-stimulated mean 2-hour C-peptide AUC at week 52.
Secondary Endpoints	Efficacy: 1. MMTT-stimulated mean 2-hour C-peptide AUC at weeks 12, 24, and 104.

2. MMTT-stimulated mean 2-hour C-peptide AUC assessed longitudinally at weeks 12, 24, 39, 52, 78, and 104.
3. MMTT-stimulated peak and 4-hour C-peptide AUC at weeks 52 and 104 for subjects ≥12 years old.
4. Insulin use (U/kg/day) at weeks 12, 24, 39, 52, 78 and 104; HbA1c levels at weeks 12, 24, 39, 52, 78 and 104.
5. Glycemic control.

Safety:

1. Rate of AEs related to infusion reactions and hypersensitivity.
2. Frequency and severity of all AEs.

Mechanistic:

1. Determine the effect of TCZ on the ratio of Treg and Teff.

Exploratory Endpoints

Mechanistic:

1. Determine effect of TCZ on measures of immune cell number and function such as:
    a. Changes in proportions and phenotype of Treg and Teff.
    b. Changes in sensitivity of Teff to suppression by Treg.
    c. Changes in circulating B cell compartment and activation state of innate immune cells including antigen presenting cells and NK cells.

Metabolic:

1. Explore the relationship between immune responses, metabolic outcomes and clinical variables.
2. Explore the effect of TCZ on insulin sensitivity.

Inclusion Criteria

1. Male or female aged 6-45 years inclusive who meet the American Diabetes Association T1DM criteria.
2. Diagnosis of T1DM within 100 days of enrollment (V0).
3. Positive for at least one diabetes-related autoantibody, including but not limited to:
    a. Glutamate decarboxylase-65 (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).
4. Peak stimulated C-peptide level ≥ 0.2 pmol/mL following a MMTT conducted at least 21 days from diagnosis and within 37 days of randomization (V0).
5. Signed informed consent (and informed assent of minor, if applicable).

Exclusion Criteria

1. Severe reaction or anaphylaxis to human, humanized or murine monoclonal antibodies.
2. History of malignancy or serious uncontrolled cardiovascular, nervous system, pulmonary, renal, or gastrointestinal disease, or significant dyslipidemia.
3. Any history of recent serious bacterial, viral, fungal, or other opportunistic infections.
4. Have serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C.
5. Positive tuberculin skin test (PPD) or QuantiFERON TB test, history of tuberculosis, or active TB infection.
6. Active infection with EBV as defined by EBV viral load ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood.
7. Active infection with CMV as defined by CMV viral load ≥ 10,000 IU or copies per mL of whole blood or plasma.

8. Diagnosis of liver disease or elevated hepatic enzymes, as defined by ALT, AST, or both > 1.5 x the upper limit of age-determined normal (ULN) or total bilirubin > ULN.
9. Current or prior treatment that is known to cause a significant, ongoing change in the course of T1D or immunologic status.
10. Current or prior (within last 14 days of screening MMTT visit) use of drugs other than insulin to treat hyperglycemia (e.g. metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, DPP-IV inhibitors, or amylin).
11. Current use of any medication known to significantly influence glucose tolerance (e.g., atypical antipsychotics, diphenylhydantoin, niacin).
12. Any of the following hematologic abnormalities, confirmed by repeat tests:
    a. White blood count <3,000/μL or >14,000/μL;
    b. Lymphocyte count <500/μL;
    c. Platelet count <150,000 /μL;
    d. Hemoglobin <8.5 g/dL; or
    e. Neutrophil count <2,000 cells/μL.
13. Females who are pregnant, lactating, or planning on pregnancy during the 2-year study period.
14. History or diagnoses of other autoimmune diseases, with the exception of stable thyroid or celiac disease.
15. History of alcohol, drug or chemical abuse within 1 year prior to screening (V-1).
16. Any medical or psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
17. Prior participation in a clinical trial that could increase risks associated with this clinical trial.
18. Receipt of live vaccine (e.g. varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette-Guérin, and small pox) in the 6 weeks before randomization (V0).
19. High lipid levels (fasting LDL cholesterol ≥160 mg/dL or ≥4.1mmol/L).
20. History of significant allergy (e.g. anaphylaxis) to milk or soy proteins.

2. INTRODUCTION

This statistical analysis plan (SAP) only includes analyses related to the clinical endpoints outlined in the protocol. Mechanistic analyses will be performed at the Immune Tolerance Network (ITN) and a separate analysis plan will be created to detail the planned analyses. Relevant clinical data from the study will be submitted to the ITN Biomarker and Discovery Research (BDR) and ITN Bioinformatics Groups (BiG) to augment the mechanistic analyses.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analysis and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form “n (%)”.

- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.

- 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 three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as “<0.001.” 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.

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.

4. ANALYSIS SAMPLES

Modified Intent to Treat (mITT) sample will include all randomized participants who received any dose of study treatment. The efficacy analyses will be based on the mITT sample according to the group to which the participants are assigned.

Per protocol samples will be assessed for week 52 (**PP1**) and week 104 (**PP2**), and will include all participants in the mITT sample with no major protocol deviations that impact efficacy assessments, who have completed at least 5 of the 7 monthly infusions of study drug and who received at least 80% of the expected dose in each infusion, and who have the week 52 and week 104 MMTT assessment for C-peptide, respectively. The reported major deviations will be reviewed during a masked data review after the last subject's primary endpoint visit and the end of the study to determine which participants should be excluded from the per-protocol populations.

Safety sample (SS) will be defined as all participants who received any degree of study treatment. Safety analyses will be based on actual treatment the participants receive.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The disposition of all randomized subjects will be summarized in tables by treatment group and age cohort (pediatric and adult) and listed.

The numbers and percentages of subjects randomized, in each analysis sample, and completing the Week 52 and 104 visits will be presented. Additionally, reasons for early termination from the study and reasons for early discontinuation of study treatment will be presented.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for the mITT sample. Data will be summarized by treatment group and age cohort. Demographic and baseline data will include age, race, ethnicity, gender, height, weight, 2-hour C-peptide mAUC, HbA1c, insulin use, and time from diagnosis of T1DM to randomization. BMI will also be presented; for adults BMI will be summarized and for pediatric subjects BMI z-scores based on CDC data will be summarized.[1] Baseline (Visit 0) results will be presented; if a measurement is missing for a subject at baseline, the screening value (Visit -1) will be used.

Some demographic and baseline characteristics will also be presented in data listings by treatment group and age cohort. Auto-antibody status at screening will be listed.

6. STUDY OPERATIONS

6.1. Major Protocol Deviations

Major protocol deviations will be listed by site and subject with information such as category of deviation, date of occurrence, details of the deviation, steps taken to address the deviation, whether the deviation resulted in an AE, whether the deviation met IRB reporting requirements, and whether the deviation led to the subject being excluded from the PP1 or PP2 samples. Additionally, protocol deviations will be summarized in a table and information summarized will include total number of deviations, number of site and subject level deviations, number of subjects with at least one protocol deviation, number of deviations in each category, number of deviations resulting in an AE, and number of deviations leading to exclusion from the PP1 or PP2 samples.

6.2. Treatment Adherence

The subjects will receive IV infusions of either 8.0 mg/kg (body weight ≥30kg) or 10.0 mg/kg (body weight <30kg) tocilizumab or placebo every 4 weeks for 24 weeks, for a total of up to 7 infusions. Study drug is administered intravenously in the clinic over approximately 60 minutes. Since study drug is administered at the study visits, compliance is monitored by the medical staff and documented on the eCRF.

Study drug infusion data will be listed for each subject with information such as number and % of infusions received, date of infusion, whether the infusion was withheld, reason the infusion was withheld, the prescribed dose, and the actual dose. A table and bar chart will be created to summarize the number of infusions received.

7. ENDPOINT EVALUATION

7.1. Overview of Efficacy Analysis Methods

7.1.1. Timing of planned analyses

Analysis of the primary endpoint (mean 2-hour C-peptide AUC in response to an MMTT at week 52) as well as secondary analyses on secondary efficacy endpoints at week 52 will be performed after all randomized subjects have either completed the week 52 assessment or terminated from the study prematurely, and the primary and key secondary efficacy data in EDC for visits through week 52 are cleaned and locked. Note that some data are subject to change after week 52 and will not be locked at this time; these include data on adverse events, concomitant medications, protocol deviations, and study status. Analysis results and summary tables by treatment group will be created; subject level treatment assignments will not be released.

Additional analyses on week 104 endpoints will be completed after all randomized subjects have either completed the week 104 assessment or terminated from the study. Data for visits through week 104 will be cleaned and locked prior to completing these additional analyses. In order to maintain the mask and ensure the validity of the assessments through week 104, randomized treatment assignments at the subject level will not be available until the last subject's week 104 visit is completed and data have been locked.

7.1.2. Multicenter Studies

Study subjects will be recruited from 19 study sites total (17 in the U.S. and 2 in Australia). Due to the large number of sites, study data will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made.

7.1.3. Efficacy Endpoints

Table 7-2 Table of Efficacy Endpoints and Analysis Methods

Efficacy Endpoint	Method
Primary	
2-hour C-peptide mAUC at week 52 (Sample: mITT)	***Primary Analysis:*** *ANCOVA* ***Covariates:*** *treatment, screening C-peptide mAUC, age*
Sensitivity Analyses for the Primary Endpoint	
Primary endpoint without imputation	*Same as Primary*
Primary endpoint (Sample: PP1)	*Same as Primary*
Primary endpoint with multiple imputation	*Same as Primary*
MANCOVA results at week 52, using C-peptide data through week 52	***Analysis:*** *MANCOVA* ***Covariates:*** *treatment, categorical time, treatment*time, screening C-peptide mAUC, age*
Secondary[1]	
2-hour C-peptide mAUC at weeks 24, 52, and 104	***Analysis:*** *ANCOVA* ***Covariates:*** *treatment, screening C-peptide mAUC, age*
2-hour C-peptide mAUC at weeks 12, 24, 39, 78, 104	***Analysis:*** *MANCOVA* ***Covariates:*** *treatment, categorical time, treatment*time, screening C-peptide mAUC, age*
Longitudinal 2-hour C-peptide mAUC from screening to week 52	***Analysis:*** *Mixed effects model* ***Covariates:*** *treatment, time, age, treatment*time, age*time*
Longitudinal 2-hour C-peptide mAUC from screening to week 104	***Analysis:*** *Mixed effects model* ***Covariates:*** *treatment, time, age, treatment*time, age*time*
4-hour C-peptide mAUC at weeks 24, 52, and 104	***Analysis:*** *ANCOVA* ***Covariates:*** *treatment, screening C-peptide mAUC, age*
Peak 4-hour C-peptide at weeks 52 and 104	***Analysis:*** *ANCOVA* ***Covariates:*** *treatment, peak screening C-peptide, age*

Efficacy Endpoint	Method
Average insulin use per kg at weeks 24, 52, and 104.	***Analysis:*** *ANCOVA* ***Covariates:*** *treatment, baseline insulin use, age*
Average insulin use per kg at weeks 12, 24, 39, 52, 78 and 104	***Analysis:*** *MANCOVA* ***Covariates:*** *treatment, categorical time, treatment*time, baseline insulin use, age*
Longitudinal average insulin use per kg from baseline to week 52	***Analysis:*** *Mixed effects model* ***Covariates:*** *treatment, time, age, treatment*time, age*time*
Longitudinal average insulin use per kg from baseline to week 104	***Analysis:*** *Mixed effects model* ***Covariates:*** *treatment, time, age, treatment*time, age*time*
HbA1c at weeks 24, 52, and 104	***Analysis:*** *ANCOVA* ***Covariates:*** *treatment, baseline HbA1c, age*
HbA1c at weeks 12, 24, 39, 52, 78 and 104	***Analysis:*** *MANCOVA* ***Covariates:*** *treatment, categorical time, treatment*time, baseline HbA1c, age*
Longitudinal HbA1c from baseline to week 52	***Analysis:*** *Mixed effects model* ***Covariates:*** *treatment, time, age, treatment*time, age*time*
Longitudinal HbA1c from baseline to week 104	***Analysis:*** *Mixed effects model* ***Covariates:*** *treatment, time, age, treatment*time, age*time*
Proportion of subjects with a major hypoglycemic event at intervals baseline – week 52, week 52 – week 104, baseline – week 104	***Analysis:*** *Fisher's exact test*

[1] ANCOVA models for C-peptide, HbA1c, and insulin use at week 104 will be repeated with an additional covariate of "days week 104 visit out of window" for the pediatric and pooled cohorts. This sensitivity analysis will be done because some week 104 pediatric subject visits were delayed due to the COVID-19 pandemic.

The sample used for the primary analysis of the primary endpoint will be the mITT sample with pediatric subjects. Both the mITT sample and the appropriate PP sample (depending on if the analysis is at week 52 or 104) will be used for the ANCOVA analyses of 2-hour C-peptide mAUC at weeks 52 and 104. All other endpoints will be analyzed using the mITT sample only. Additionally, all primary and secondary endpoints will be analyzed using the pediatric cohort only, the adult cohort only, and the pooled data consisting of both adults and pediatric subjects.

7.2. Primary Endpoint

The primary endpoint is the mean 2-hour C-peptide AUC in response to a mixed-meal tolerance test (MMTT) at Week 52 in pediatric subjects.

7.2.1. Computation of the Primary Endpoint

The MMTT will be done at screening and weeks 12, 24, 39, 52, 78, and 104. During the MMTT, C-peptide levels are measured at –10, 0, 15, 30, 60, 90, and 120 minutes for a 2 hour MMTT, and additionally at minutes 150, 180, 210, and 240 for a 4 hour MMTT.

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:

$$\text{AUC} = \sum_{k=1}^{N}(t_{k+1} - t_k)\ \frac{(0.331 \times f(t_{k+1})\ +\ 0.331 \times f(t_k))}{2}\ ,$$

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 conventional units of ng/mL. 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 ½ the lower limit of detection. Since C-peptide results are typically reported in the International System of Units (SI) unit, pmol/mL, f(t) in **Formula 1** is multiplied by the conversion factor 0.331, which is based on the molecular weight of C-peptide (3020.29 g/mole). By stoichiometry, the derivation is as follows:

$$1\ ng/mL \times 1\ nmol/3020.29\ ng \times 1000\ pmol/1\ nmol = 0.331\ pmol/mL$$

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

Four-hour C-peptide mAUC will be calculated analogously.

For the primary analysis only, for a participant who misses the entire week 52 MMTT assessment, the missing mAUC values will be imputed using the following approach for the primary analysis of the primary endpoint:

- If the subject's last observed C-peptide measurements are less than the lower limit of detection (LLD) at all timepoints, the missing week 52 mAUC will be imputed to the previously calculated mAUC value, where ½ LLD was used at all timepoints to calculate the mAUC.
- If the subject's last observed mAUC value was at week x and at least one C-peptide timepoint was greater than the LLD, then the missing mAUC at week 52 will be imputed using data from subjects in the same arm who had available mAUC values at both week x and week 52. Specifically, a linear regression line will be fit where week 52 mAUC values are regressed on mAUC values at week x (e.g. week 24) and age. In each arm a missing week 52 mAUC value will be imputed as the value predicted from the linear regression line.

7.2.2. Primary Analysis of the Primary Endpoint

The primary analysis of the primary endpoint, change in MMTT-stimulated mean 2-hour C-peptide AUC at week 52, will test the null hypothesis of "no treatment group difference" versus the two-sided alternative using only pediatric participants from the mITT sample. The hypothesis test and screening-adjusted treatment group estimates will be derived from an ANCOVA model with response of change in mean 2-hour C-peptide AUC at week 52 and fixed effects for treatment group, screening mean 2-hour C-peptide AUC, and age. If departures from model assumptions are apparent alternative approaches (such as using a generalized linear model or transformation) will be considered as secondary analyses.

7.2.3. Sensitivity Analyses of the Primary Endpoint

At a minimum, the following sensitivity analyses for the primary endpoint will be performed:

- An analysis analogous to the primary endpoint analysis using only mITT subjects with observed data at week 52 (i.e., without imputing any missing week 52 mAUC values).
- An analysis analogous to the primary endpoint analysis using the PP1 subjects.
- An analysis analogous to the primary endpoint analysis in the mITT sample using multiple imputation to fill in missing C-peptide mAUC values.
- Week 52 results from a MANCOVA model that uses data from screening through week 52 will be presented. More details on the MANCOVA model are in section 7.3.1.

P-values will be considered descriptive and no corrections for multiple tests are planned.

7.3. Secondary Endpoints

The null hypothesis proposes that there is no difference in the secondary endpoint (measured either as means or proportions) between study groups. The alternative hypothesis proposes the opposite; that there is a difference in the secondary endpoints between the treatment and control groups. All secondary inferential analyses are considered supportive; p-values will be presented without adjustment for multiple comparisons. All analyses will be performed on the mITT sample with available data. Additionally, the ANCOVA analyses of 2-hour C-peptide mAUC at weeks 52 and 104 will be performed on the corresponding PP samples. Analyses will be performed on pediatric subjects separately, adult subjects separately, and on all subjects pooled unless otherwise specified.

The original laboratory that processed the C-peptide and HbA1c samples closed before all week 104 pediatric data were analyzed; adult data and pediatric data through the week 52 primary endpoint were not affected. The data will be used as-is with no adjustment for lab. If indicated by the results, exploratory graphs and models will compare results from the 2 labs.

7.3.1. Secondary Analyses: C-peptide

- Summary statistics for 2-hour and 4-hour C-peptide mAUC will be presented in tables and box plots by visit, treatment, and age cohort for the mITT population with available data.

- 2-hour and 4-hour C-peptide mAUC will also be listed by subject, treatment group, and cohort for all visits.
- Analyses similar to those described in Section 7.2.2 *Primary analysis of the primary endpoint*, will be performed for the following endpoints. All non-missing data will be used.
    - 2-hour C-peptide mAUC at weeks 24, 52, and 104 using the mITT sample. The week 52 analysis will additionally use the PP1 sample and the week 104 analysis will additionally use the PP2 sample.
    - 4-hour C-peptide mAUC at weeks 24, 52, and 104 using the mITT population with available data.
    - Peak 4-hour C-peptide at weeks 52 and 104 using the mITT population with available data.
    - For all the ANCOVA models at week 104, a sensitivity analysis will be done where an additional covariate will be added to the models for the pediatric and pooled cohorts only. The additional covariate added to these models will be a variable indicating the number of days the week 104 visit was out of window since some pediatric subjects had their week 104 visit delayed due to the COVID-19 pandemic.
- A MANCOVA-type mixed model will be created using 2-hour C-peptide mAUC as the response. This will coincide with the primary analysis at week 52 and will include assessments at screening and weeks 12, 24, 39, and 52. All subjects with at least 1 C-peptide assessment will be included in the model. The model will include fixed effects for time point (categorical), treatment, and their interaction as well as screening C-peptide mAUC and age, as covariates. For fitting the model, an unstructured covariance matrix for repeated measures within subject is preferred, but alternative simplified matrices will be considered, if necessary. Mean estimates and confidence intervals at each week will be presented.
- Two mixed models will be created using 2-hour C-peptide mAUC as the response. The first will use C-peptide assessments at screening and weeks 12, 24, 39, and 52, and the second will additionally include C-peptide assessments at weeks 78 and 104. All subjects with at least 1 post-screening assessment will be included in these models. The model will include fixed effects for treatment, time, age, and interactions for treatment*time and age*time. The time variable will be continuous variable study week, which will be defined as the MMTT assessment date - treatment start date divided by 7. Piece-wise slopes will be considered for study week by graphing the means across time and checking for rises and falls in the 2-hour C-peptide mAUC. Random within-subject effects for intercept and slopes over time will be included assuming an unstructured covariance matrix. Transformations of data and alternative link functions will be considered if evidence of significant departures from model assumptions are apparent. Alternative covariance structures will be considered if models fail to converge.

7.3.2. Secondary Analyses: Insulin

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 subject'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 subject's weight is not collected or is missing at the study visit where insulin use was collected, the subject's weight for that visit will be derived as the average of the subject's weight at the visits before and after the visit in question.

Analyses of total insulin use will use the mITT population with available data.

- Average insulin use per kg will be summarized by visit, treatment, and age cohort in a table and boxplot for each scheduled visit. Change from baseline summary statistics will also be included in the table.
- Insulin use and administration information will be listed by subject, treatment group, and age cohort.
- ANCOVA models adjusting for baseline insulin use and age will be used to analyze average insulin use per kg at weeks 24, 52, and 104.
    - For the ANCOVA models at week 104, a sensitivity analysis will be done where an additional covariate will be added to the models for the pediatric and pooled cohorts only. The additional covariate will be a variable indicating the number of days the week 104 visit was out of window since some pediatric subjects had their week 104 visit delayed due to the COVID-19 pandemic.
- A MANCOVA model will be created and an analysis analogous to that described in section 7.3.1 will be performed. The response will be average insulin use per kg and the covariates will be treatment, categorical time, age, baseline average insulin use per kg, and an interaction for treatment*time.
- Two mixed models will be created and an analysis analogous to that described in section 7.3.1 will be performed. The response will be average insulin use per kg and the covariates will be treatment, continuous time, age, and interactions for treatment*time and age*time.

Basal insulin use will be analyzed separately. All analyses listed above will also be performed using basal insulin, using the pediatric cohort only.

7.3.3. Secondary Analyses: HbA1c

HbA1c will be collected at each study visit. Analyses of HbA1c will use the mITT population with available data.

- HbA1c will be summarized by visit, treatment, and age cohort in a table and boxplot for each scheduled visit. Change from baseline summary statistics will also be included in the table.
- HbA1c will be listed by subject, treatment group, and age cohort.
- ANCOVA models adjusting for baseline HbA1c and age will be used to analyze HbA1c at weeks 24, 52, and 104.
    - For the ANCOVA models at week 104, a sensitivity analysis will be done where an additional covariate will be added to the models for the pediatric and pooled cohorts only. The additional covariate will be a variable indicating the number of days the week 104 visit was out of window since some pediatric subjects had their week 104 visit delayed due to the COVID-19 pandemic.
- A MANCOVA model will be created and an analysis analogous to that described in section 7.3.1 will be performed. The response will be HbA1c and the covariates will be treatment, categorical time, age, baseline HbA1c, and an interaction for treatment*time.

- Two mixed models will be created and an analysis analogous to that described in section 7.3.1 will be performed. The response will be HbA1c and the covariates will be treatment, continuous time, age, and interactions for treatment*time and age*time.

7.3.4. Secondary Analyses: Major Hypoglycemic Events

Information on major hypoglycemic events will be collected at each study visit and reported on the *Adverse Events* eCRF. Data from the glucometers will be reviewed for blood glucose values < 40 md/dL. For each subject, the number of major hypoglycemic events will be tabulated from baseline to week 52 and from week 52 to week 104 (or last study visit).

- For each time period (i.e. baseline-week 52, week 52-week 104/last study visit, and baseline-week 104/last study visit), the number and percent of subjects experiencing hypoglycemic events and the total number of events will be summarized by treatment and age cohort. The proportion of subjects experiencing a major hypoglycemic event during each time period (i.e. baseline-week 52, week 52-week 104, and baseline-week 104) in each treatment group will be analyzed using Fisher's exact test by age cohort. Additionally, Fisher's exact test will be used on the combined cohorts.
- Major hypoglycemic event information will be listed.

7.4. Exploratory Analyses

7.4.1. Continuous Glucose Monitor (CGM)

Subjects are given the option to use a continuous glucose monitor (CGM) for clinical care. CGMs were provided by the study, but a subject could also provide data from a personal CGM if they were not using the study CGM. CGM use was added to the protocol in v4.0 (May2016), which is after over half of adult subjects had been randomized. Therefore, many adult subjects will not have CGM data at baseline available. Furthermore, this is an optional device for all subjects.

Sites were instructed to download CGM data from the 14 days prior to weeks 0, 12, 24, 52, 78, and 104; these contain readings of a subject's glucose values in frequent intervals, typically every 5 minutes. In all summaries, CGM data collected the 14 days prior to the visit will be used. There must be data for at least 70% of the expected times over the 14 days or else the data will not be used in the tabular summaries. 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 subject and visit. Each of these metrics will be summarized in a table by visit, treatment group, and age cohort. Additionally, time in key ranges will be summarized in box plots.
- Hypoglycemic events from CGM data will be defined using the following definition[2]:

  15 consecutive minutes with a sensor glucose value below 70 mg/dL. At least two sensor values <70 mg/dL that are 15 or more minutes apart plus no intervening values ≥ 70 mg/dL are required to define an event. The end of the event will be defined as at

least two sensor values ≥ 70 mg/dL that are 15 or more minutes apart with no intervening values < 70 mg/dL.

- Additionally, these hypoglycemic events will be separated into level 1 and level 2 events[3]. Level 1 hypoglycemic events are those in a range of 54-<70 mg/dL and level 2 hypoglycemic events are those <54 mg/dL.

- All CGM data received will be used for the following analysis. A longitudinal poisson regression model will be created with number of CGM hypoglycemic events as the response and covariates of treatment and study visit. Additionally, a treatment by study visit interaction will be considered if these are indicated after reviewing graphs of the data and they improve the fit of the model. The amount of time of CGM data provided by each subject prior to each visit will be used as an offset. The offset will subtract out any time that is part of a hypoglycemic event. Separate models using data through week 52 and data through week 104 will be created and separate models will be created for each age cohort.

7.4.2. Frequently-sampled Intravenous Glucose Tolerance Test (FSIVGTT)

A frequently-sampled intravenous glucose tolerance test (FSIVGTT) will be offered to subjects age >= 15 at baseline, week 24, and week 52. Subjects may decline to participate in this aspect of the protocol.

Minimal model analysis will be used to calculate insulin sensitivity from the FSIVGTT results. Summary descriptive statistics for insulin sensitivity will be reported. Of particular interest is the change in insulin sensitivity from baseline to Week 24 and from Week 24 to Week 52 in each treatment group. Additionally, the relationship between insulin sensitivity and C-peptide mAUC will be investigated and correlations will be provided if appropriate.

8. SAFETY EVALUATION

8.1. 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 analyzed in each treatment group 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 age cohort, treatment, subject identifier (ID), and date/time of assessment.

8.2. 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 17.1). The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 4. 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.

AEs will be collected from screening (Visit -1) until the participant completes the study, or prematurely withdraws from the study. Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication. If the start of the AE in relation to

the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent. All data tabulations will be of only treatment-emergent events while non-treatment-emergent AEs will be listed separately.

COVID-19 adverse events will be collected in the following manner: any cases of COVID-19 that have been confirmed by a positive PCR test or serology will be called “COVID-19 confirmed”. For other adverse events that are not confirmed cases of COVID-19, typical reporting procedures will be used to describe a diagnosis if available, or a list of symptoms if no diagnosis is available. A listing of confirmed COVID-19 cases will be created if any occur.

An overall summary table by treatment group and age cohort will be developed to report the number of events and the number and percentage of subjects 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, probably, or definitely related) to study drug
- AEs reported by severity
- Infections
- Infusion reactions
- 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 treatment group 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 subjects experiencing the events. If a subject 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 subjects experiencing the events, a subject 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 subjects in the safety population.

In addition, the following specific AEs will be summarized by treatment group and overall. Fisher’s exact test will be used to compare proportions of subjects experiencing the events:

- Infusion reactions
- Hypersensitivity

Additionally, an analysis analogous to section 7.3.4 (Major Hypoglycemic Events) will be done using the safety sample, if this sample differs from the mITT sample.

8.3. Deaths and Serious Adverse Events and AEs of Special Interest

Serious adverse events (SAEs) will be summarized in the overall AE summary table and also in a separate table by SOC and preferred term. A listing showing all SAEs and AEs of special

interest (AESIs) will be created. Separate displays listing and summarizing death, including time to death and cause of death, will be created if a death occurs.

8.4. Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry, hematology, lipid panel, EBV and CMV viral load, and urinalysis. Lab results are reported as AEs if they are symptomatic, or if they meet grade 3 or higher criteria if they are asymptomatic. Lab results are provided by a central lab, and sites are also able to enter local lab results when necessary. For results from local labs, results will be converted to standardized units where possible. Summary data by visit will only include central lab results, but listings will include all lab (central and local) results.

For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each treatment group and age cohort. For categorical laboratory results, the number and percentage of subjects reporting each result will be presented for each treatment group and age cohort. A listing will also be created that shows all lab results that met a dose modification criteria or Grade 3+ criteria.

Laboratory data will be plotted to show patterns over time. Summary statistics including 25th percentile, median, and 75th percentile will be plotted for each visit by treatment group and age cohort. Lines connecting individual subject results from subjects with grade 3 or higher values will be overlaid on each figure. For lab results that are not gradable, results from subjects with values outside of 2*upper limit of normal or 0.5*lower limit of normal will be overlaid. Tests with qualitative results (such as “present” or “positive”) will not be plotted.

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

8.5.1. Vital Signs

Vital signs of height, weight, BMI, temperature, heart rate, respiratory rate, and blood pressure will be obtained at all visits. These vital signs and their grade per the NCI-CTCAE will be displayed in a listing. Also, vital signs will be summarized in a table by treatment group and age cohort for each scheduled visit. Regarding BMI, BMI z-scores based on CDC data will be presented for pediatric subjects only.

Vital signs of BMI, temperature, heart rate, respiratory rate, and blood pressure will be plotted to show patterns over time. Summary statistics including 25th percentile, median, and 75th percentile will be plotted for each visit by treatment group and age cohort. Lines connecting individual subject results from subjects with grade 3 or higher values will be overlaid on each figure.

Infusion vital signs will be displayed in a separate listing.

8.5.2. Physical Examinations

Either a comprehensive or directed physical examination will be performed at each scheduled study visit. A data listing will be provided for physical examination results and sorted by age cohort, treatment group, subject, and body system. A separate listing of only abnormal physical exam results will also be provided.

8.5.3. Other Safety Measures

8.5.4. Pregnancy

A listing of any pregnancies that occur in a study participant or their partner will be created. Information provided will include: whether the pregnancy was in the participant or their partner, outcome of the pregnancy, and description of any abnormalities.

9. OTHER ANALYSES

9.1. Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2015.01). 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 subjects receiving prior, concomitant, and after medications will be presented overall and by standardized medication name. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of subjects in the safety population. Separate data listings will be provided for prior, concomitant, and after medications.

9.2. COVID-19 Listing

All visits affected by the COVID-19 pandemic and a description of how they were affected (e.g. out of window, visit done remotely) will be listed.

10. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The joint NIAID/NIDDK TrialNet DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

The FDA put the IND on a partial clinical hold prior to initiating enrollment in the INT058AI EXTEND trial, and stated that a “prospect of benefit” needed to be shown in adult subjects before enrolling pediatric subjects. After at least 30 adults completed 12 weeks of treatment, the unblinded safety and efficacy data were reviewed in an interim report by the FDA and DSMB to evaluate prospect of benefit. The interim analysis was submitted to the DSMB in December 2017. The FDA removed the partial clinical hold and opened the trial to pediatric participants (children and adolescents 6-17 years old). The interim analysis plan is attached.

The primary efficacy analysis in the pediatric cohort of 2-hour C-peptide mAUC in response to an MMTT at Week 52 will be performed upon completion of data collection and verification for all week 52 assessments (prior to end of study) (see section 7.1.1 for more details).

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

- Regarding missing data for the primary analysis of C-peptide mAUC (section 7.2.1):
  - The protocol stated that if a subject's mAUC was zero at the last observed visit, future mAUC values will be imputed to zero. However, when calculating mAUC, if C-peptide is less than the lower limit of detection (LLD), ½ the LLD is used to calculate mAUC. Therefore, the mAUC will never be exactly 0. Language in the SAP was updated to state that if at the last observed visit all of the subject's C-peptide measurements are less than the LLD, then the week 52 mAUC will be imputed to have this same value.
  - The method of imputing missing values if at least one C-peptide time point was greater than the LLD was updated. For the linear regression model to impute missing values, age was added as a covariate. Additionally, the SAP has clarified that this imputation method is only planned to be used for the primary analysis of the primary endpoint (i.e. ANCOVA analysis at week 52 for pediatric subjects).

- Under secondary endpoints for C-peptide, HbA1c, and insulin use: a MANCOVA model will be created instead of creating separate ANCOVA models at all specified study weeks. ANCOVA models will still be created for weeks 24, 52, and 104.

- Updates to secondary endpoints for C-peptide, HbA1c, and insulin use due to the COVID-19 pandemic:
  - Sensitivity analyses for the ANCOVA models through week 104 were added. These analyses will include an additional covariate of "days week 104 visit out of window" for the pediatric and pooled cohorts.
  - The MANCOVA-type models will no longer be created for visits through week 104. Only a longitudinal model using continuous study week will be created for data through week 104.

12. REFERENCES

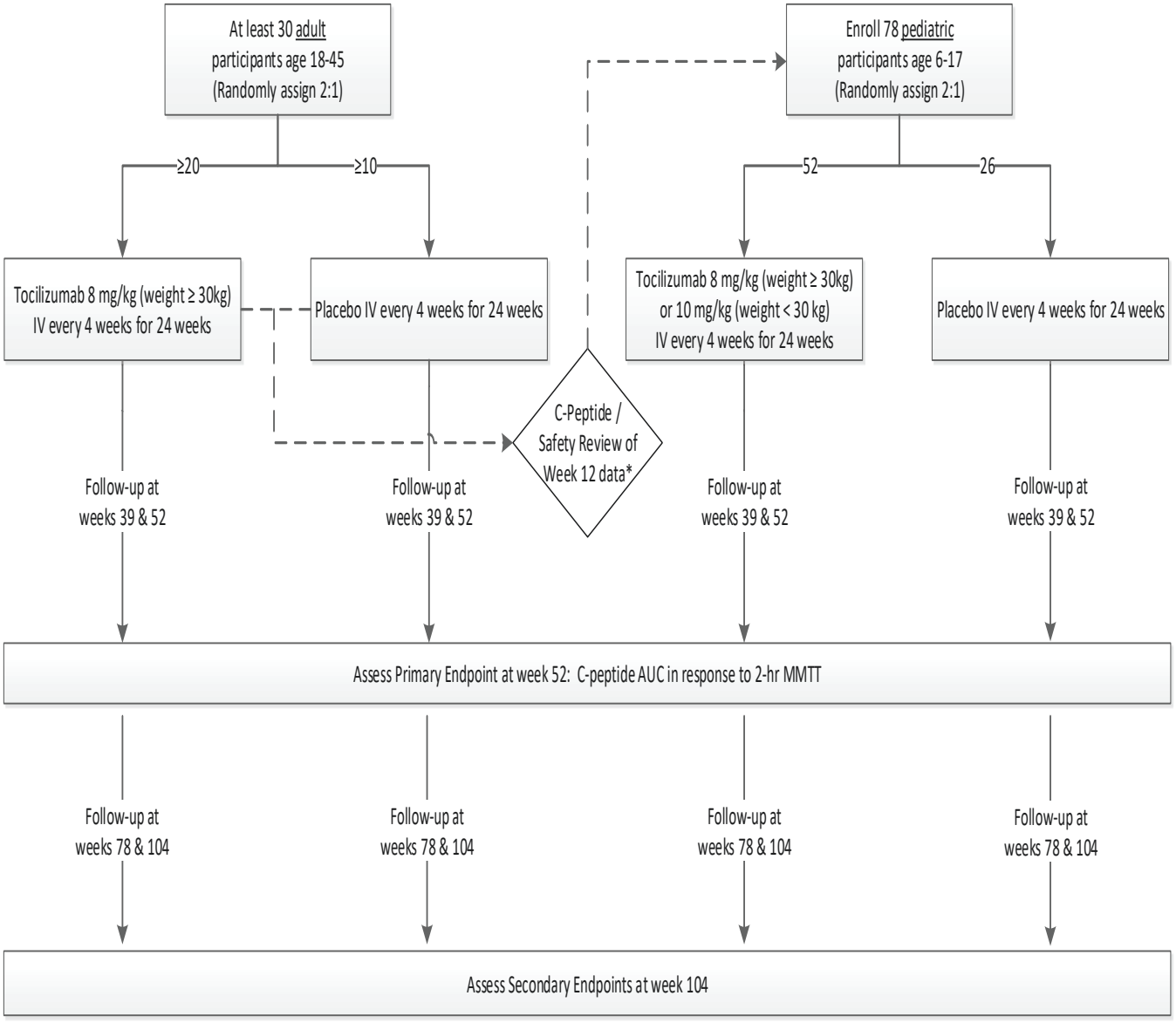
[1] A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years); https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

[2] Russell SJ, Beck RW. Designs Considerations for Artificial Pancreas Pivotal Studies. Diabetes Care. 2016;39:1161-1167.

[3] Danne T, Nimri R, Battelino T. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-1640.

13. APPENDICES

13.1. Study Flow Chart



13.2. Schedule of Events

SCHEDULE OF EVENTS[1]

Phase of Trial	Dosing								Follow Up				Unsch.
Week	-1	0	4	8	12	16	20	24	39	52	78	104	U
Visit	V-1	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10[2]	U[3]
GENERAL ASSESSMENTS													
Informed consent	X												
Eligibility criteria	X												
Randomization		X											
Medical history	X												
Adverse events	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
Comprehensive physical examination	X							X[4]		X		X	
Directed physical examination		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X		X		X
Additional vital signs (during infusion)		X	X	X	X	X	X	X					
CENTRAL LABORATORY ASSESSMENTS													
Serum Chemistries (includes liver panel and CRP)	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
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid Panel	X		X					X		X	X	X	X
Viral load (PCR)[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Infectious disease serology[5]	X												
Serum ßHCG[6]	X												
QuantiFERON TB test[7]	X												
LOCAL LABORATORY ASSESSMENTS													
Urine HCG[6]		X	X	X	X	X	X	X	X	X	X	X	X
TB test[7]	X												
DISEASE-SPECIFIC ASSESMENTS													
2-Hour MMTT[8]					X			X	X		X		

[1] With approval of study sponsor (DAIT, NIAID) and after informed consent, study procedures and/or sample collections may be performed at a location convenient for the participant as described in the Manual of Operations (MOP).

[2] Participants who terminate early from the study should complete all procedures listed for this visit (see sections 4.3 and 5.3).

[3] Assessments for unscheduled visits will be at the discretion of the principal investigator.

[4] Physical exam should be conducted prior to study drug administration.

[5] Serology will be repeated after screening for CMV and EBV if participants show clinical signs of infection; *or* if viral load testing shows that the EBV viral load is ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood or the CMV viral load is ≥ 10,000 IU or copies per mL whole blood or plasma.

[6] Female participants with reproductive capacity will be monitored for pregnancy.

[7] Sites may perform a PPD skin test in place of a QuantiFERON TB test.

[8] A 2-hour MMTT is to be performed at weeks 12, 24, 39, and 78. MMTT should be performed prior to study drug infusion for weeks 12 and 24.

Phase of Trial	**Dosing**								**Follow Up**				**Unsch.**
Week	**-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**39**	**52**	**78**	**104**	**U**
Visit	**V-1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10[2]**	**U[3]**
4-Hour MMTT[9]	X									X		X	
FSIVGTT[10]		X						X		X			
Diabetes-related autoantibodies	X												
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	
Glucometer Readings	X	X	X	X	X	X	X	X	X	X	X	X	
CGM Readings[11]		X			X			X		X	X	X	
Insulin use	X	X	X	X	X	X	X	X	X	X	X	X	
Hypoglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	
STUDY DRUG ADMINISTRATION AND DRUG-RELATED ASSESSMENTS													
Study drug infusion		X	X	X	X	X	X	X					
Pharmacokinetics (PK)		X[12]	X[13]				X[12]	X[13]					
IL-6 and IL-6sR	X				X			X	X	X	X	X	
Anti-TCZ antibodies[14]	X												
MECHANISTIC ASSESSMENTS[15]													
Serum	X	X	X	X	X	X	X	X		X	X	X	
Cellular Assays		X	X	X	X	X	X	X		X		X	
Gene Expression		X			X			X		X		X	
DNA		X			X			X		X		X	

[9] A 4-hour MMTT is to be performed at weeks -1 (screening), 52, and 104 for subjects ≥12 years old (for subjects <12 years old, a 2-hour MMTT will be performed instead).

[10] FSIVGTT will be offered to subjects age ≥15. Week 0 visit may be done on the same day before the first infusion or within 2 weeks prior to week 0. Week 24 and week 52 visits will be done on a separate day than the MMTT visits; the window for these two visits are +/- 2 weeks of target date.

[11] Randomized participants will be invited to use a commercially available FDA approved CGM system and its components for a 14 day period at weeks 0, 12, 24, 52, 78, and 104; the window for the CGM will be ± 3 weeks. Participants may repeat the 14 day period once during these widows if less than 10 days of data is evaluable from initial wearing.

[12] Pharmacokinetics (PK) samples for week 0 and week 20 will be collected before, 10 minutes after, and 7 (±3) days after the infusions (see section **Error! Reference source not found.**).

[13] Pharmacokinetics (PK) samples for week 4 and week 24 will be collected before the infusions (see section **Error! Reference source not found.**).

[14] Baseline anti-TCZ antibodies samples will be collected for all participants and will only be analyzed in event of specified adverse event (defined as anaphylaxis, serious hypersensitivity, or study treatment discontinuation due to hypersensitivity, whether serious or non-serious). Additional anti-TCZ antibodies samples will be collected at the time of an adverse event and then again at least 6 or 8 weeks after the last TCZ dose.

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

14. ATTACHMENTS

Attachment 1: Interim Analysis Plan