STATISTICAL ANALYSIS PLAN

Diabete**S** A**U**toimmu**N**ity Withd**R**awn **I**n New On**SE**t and In Es**t**ablish**e**d Patients

(SUNRISE)

A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety of TOL-3021 in Patients with New Onset or Established Type 1 Diabetes Mellitus

Name of Test Drug/ Investigational Product:	TOL-3021
Indication Studied:	Type 1 Diabetes Mellitus
Protocol:	TOL-3021-231-01
Investigational Phase:	Phase II
Clinicaltrials.gov Study Identifier:	NCT03895437
IND:	018349
Sponsor:	Tolerion, Inc. 131 Oyster Point Blvd South San Francisco, CA 94080
Date:	19 October 2020
Version:	v1.0

This study is performed in compliance with Good Clinical Practice (GCP), according to the ICH Harmonized Tripartite Guideline, including archival of essential study documents.

STATISTICAL ANALYSIS PLAN

Sponsor Name:	Tolerion, Inc.
Protocol No.:	TOL-3021-231-01
Protocol Title:	A PHASE 2 MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE SAFETY OF TOL-3021 IN PATIENTS WITH NEW ONSET OR ESTABLISHED TYPE 1 DIABETES MELLITUS
Prepared by:	The Emmes Company, LLC
SAP Version:	v1.0
Version Date:	19OCT2020

APPROVAL SIGNATURES

The signatures below indicate approval of the Statistical Analysis plan for this study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition/Explanation
ADA	American Diabetes Association
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANA	Anti-nuclear antibody
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
Anti-dsDNA	Anti-double-stranded DNA
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area Under the Curve
BHT	Bayhill Therapeutics
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BW	Body weight
C	Celsius
CBC	Complete Blood Count
CGM	Continuous Glucose Monitoring
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CRF	Case Report Form
CRO	Contract Research Organization
DMT	Diabetes Management Team
DPT	Diabetes Prevention Trial
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECL	Electrochemiluminescence
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GAD65	Glutamic acid decarboxylase
GCP	Good Clinical Practice

Abbreviation or Term	Definition/Explanation
HbA1c	Glycosylated hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hINS	Human proinsulin
HIV	Human immunodeficiency virus
HIPAA	Health Information Portability and Accountability Act of 1996
HLA	Human leukocyte antigen
IA-2	Tyrosine phosphatase-like insulinoma antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IND	Investigational New Drug
IUD	Intrauterine Device
IV	Intravenous
Kg	Kilogram
LTFU	Long Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mITT	Modified Intent to Treat
mL	Milliliter
MMTT	Mixed-Meal Tolerance Test
MOP	Manual of Procedures
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
Ng	Nanogram
PE	Physical examination
PI	Principal Investigator
PP	Per-protocol analysis (i.e., as-treated)

Abbreviation or Term	Definition/Explanation
RBA	Radio-binding assay
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SH	Severe hypoglycemia
SMBG	Self-monitored blood glucose
SOP	Standard Operating Procedures
SUNRISE	Diabete**S** A**U**toimmu**N**ity Withd**R**awn **I**n New On**SE**t and In E**s**tablish**e**d Patients
SUSAR	Serious Suspected Adverse Reaction
T1D	Type 1 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Event
TOL	Tolerion
TNF	Tissue necrosis factor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	United States
WBC	White Blood Cell
WOCBP	Women of childbearing potential
ZnT8	Zinc transporter 8

1 PREFACE

This Statistical Analysis Plan (SAP) for "A Phase 2 Multi-center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Safety of TOL-3021 in Patients with New Onset or Established Type 1 Diabetes Mellitus" (TOL-3021-231-01) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses in the full Clinical Study Report (CSR), to be prepared after the last participant has completed the Week 24 visit, as well as the abbreviated CSR, to be prepared after the last participant has completed the Month 36 visit. Regarding the final analyses and CSRs, this SAP follows the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document details the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety endpoints, and a list of proposed tables and figures. Any deviation from this SAP will be described and justified in both the full and abbreviated CSR, as appropriate. The reader of this SAP is encouraged to also review the current version of the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2 INTRODUCTION

2.1 Overview

The primary goals of the SUNRISE study are to evaluate the safety and the efficacy of TOL-3021 1.0 mg in participants with new onset or established T1D, given the evidence from the previous phase 2a study supporting both safety and efficacy. The SUNRISE study will also provide safety data to enable enrollment of adolescents (aged 12.0 to <18.0 years) in SUNRISE and other TOL-3021 studies. For analytical purposes, all participants 12-<41 will be considered Cohort A, participants aged 12-<18 will considered Cohort B and participants aged 18-<41 will be considered Cohort C.

2.2 Purpose of the Analyses

This SAP describes the statistical methodology and summaries required to assess the endpoints of interest. These analyses will assess the efficacy and safety of the active product TOL-3021 in

comparison with placebo in participants with New Onset or Established Type 1 Diabetes Mellitus and will be included in the full and abbreviated CSRs.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Efficacy Objective

To evaluate the effect of TOL-3021 dosing over 24 weeks on preserving endogenous insulin secretion as reflected by C-peptide secretion, and its effect on other measures of efficacy in patients with Type 1 Diabetes Mellitus (T1D).

3.1.2 Safety Objective

To evaluate the safety of TOL-3021 administered as weekly intramuscular (IM) injections over 52 weeks in patients with Type 1 Diabetes Mellitus (T1D).

3.2 Study Endpoints

3.2.1 Primary Efficacy Outcome

The primary outcome is the TOL-3021 treatment effect as determined by a repeated measures analysis of change from baseline in the log-transformed MMTT C-peptide AUC at 12, 16, and 24 weeks.

3.2.2 Secondary Endpoints

Secondary outcomes will include the treatment effect on:

- Rate of clinically important hypoglycemia, defined as measured glucose value of <54mg/dL (3.0 mM/L) over each approximately 12-week period ending at Weeks 12, 24, 36, and 52:
  - By glucometer, a single blood glucose level.
  - By CGM, ≥15 consecutive minutes with glucose <54mg/dL
- Total daily insulin requirements in units per kilogram (kg) body weight as entered by patients in their Dexcom G6 touch screen receivers.
- HbA1c.
- Time in range 70 - 180 mg/dL

3.2.3 Other Efficacy Endpoints

- The TOL-3021 treatment effect—
  - On a repeated measures analysis of change from baseline in the log-transformed MMTT C-peptide area under the curve (AUC) at Weeks 12, 16, 24, 52.
  - On glucose levels of <70 and <54 mg/dL.

- On a clinical responder analysis defined as no change or an increase in C-peptide AUC from baseline between treatment and placebo at Weeks 12, 16 and 24. Upon completion of Week 52 data, a similar analysis will include the Week 52 data.
- On non-fasting or fasting C-peptide (single test) from baseline at Weeks 12, 16, 24, and 52.
- On proportion of participants in each treatment arm with HbA1c levels less than 6.5% at Week 52.
- On CGM parameters:
  - Time >180 mg/dL
  - Time >250 mg/dL
  - Time <70 mg/dL
  - Mean Glucose Coefficient of Variation
  - Low Blood Glucose Index (LBGI)
  - Glucose below 70 mg/dL Area Over the Curve (AOC_{70})
- On other measures of hypoglycemia:
  - Clinical severe hypoglycemia (SH) events (impaired or loss of consciousness requiring assistance of another).
  - Documented symptomatic hypoglycemia (an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration <70 mg/dl (3.9 mmol/L).
  - Nocturnal hypoglycemia, i.e., severe or documented symptomatic episodes (as defined above) occurring after the participant has retired for the primary sleeping period.

- Immunologic: Immunologic analysis and endpoints, if performed, will be detailed in a separate plan.

3.2.4 Safety Outcomes

The following will be tracked and monitored through the course of the study

- Clinical laboratory tests (hematology, chemistry, urinalysis);
- Urine pregnancy test (UPT) for women of childbearing potential (WOCBP);
- Concomitant medications;
- Collection of adverse events (AEs), SAEs and AEs leading to withdrawal;

- Vital signs;
- Injection site reactions;
- Severe hypoglycemia or hyperglycemia events either clinical or monitored by CGM;
- Events of special interest:
    - Systemic or hypersensitivity reactions associated with injection, which consist of fever, chills, headache, nausea, vomiting, and/or other signs and symptoms, such as anaphylaxis, wheezing dyspnea, urticaria, and hypotension

3.3 Study Definitions and Derived Variables

Study definitions and derived variables are presented in Section 4.4.1

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The SUNRISE study is a prospective, multi-center, randomized, placebo-controlled trial in participants aged 18.0 to <41.0 years diagnosed with T1D, as defined by ADA criteria, and within 5 years of diagnosis. Time of diagnosis is defined as the first day of insulin administration. The study is triple-blinded through the analysis at Week 24, after which the Sponsor will be group unblinded. The study will continue through Week 52 as double-blind with site staff and participants blinded. Participants will be stratified by duration (zero up to 1 year and 1 year up to five years) to ensure balance of disease duration across treatment and placebo groups in each strata. For analytical purposes, all participants 12-<41 will be considered cohort A, subjects aged 12-<18 will considered cohort B and participants aged 18-<41 will be considered cohort C. For participants aged 12-<18 (Cohort B), dosing will be staggered with an initial 6 participants aged 14-<18 being enrolled with the last participant having a minimum of 2 injections with at least 1 week follow-up after the 2nd injection. Safety data from this cohort will be evaluated before opening the study to participants 12 and older. Participants should be randomized no sooner than 6 weeks after diagnosis, unless blood glucose is adequately controlled as indicated by time in range >55% with CGM. Screening assessments will include a physical examination, a fundus photography examination, chemistry and hematology safety labs, urinalysis, urinary protein screen (if positive a 24-hour collection for urine protein and creatinine will obtained), HbA1c, presence of T1D antibodies, and a MMTT. Approximately 99 qualified participants who meet all selection criteria will be randomized in a 2:1 ratio to treatment with TOL-3021 or placebo and treated for 52 weeks. Participants will agree to diabetes management during the study with the goal of maintaining HbA1c levels of approximately 7.0% without frequent episodes of hypoglycemia.

Study drug treatments will be administered via an IM injection into a large muscle every week for 52 weeks. Initial treatments will be administered at the clinical site at randomization and at the Week 1 and Week 2 visits. During those visits, participants and/or a caregiver will be trained

to administer study drug at home in subsequent weeks. Study drug will be dispensed at the Week 2 visit for Week 3 administration at home, and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 for at home administration.

Participants will have screening and randomization visits, followed by regular visits to the clinic, for efficacy evaluations and safety assessments throughout the 52-week study. A 4-hour MMTT will be conducted during screening, as part of a single-day visit or conducted on a separate day. If the screening visit procedures will be conducted in a single day the participant must be using their own CGM, and able to share that data with site coordinator to confirm if time in range has been met for 3 of 5 consecutive or non-consecutive days prior to confirmation of a single screening visit. Participants will be provided with instructions for preparing for the MMTT prior to the visit when it will be conducted. Participants with peak C-peptide during the screening 4-hour MMTT < 0.150 nmol/L will not be enrolled. The randomization visit must be at least 3 days after the screening MMTT. The screening results will be the baseline value for the MMTT. Continuous glucose monitoring (CGM) will be initiated within 5 days prior to the screening MMTT visit and continued through Week 52. If CGM recordings are inadequate during week 50-52, CGM may be continued until the Week 54 visit.

A Data Safety Monitoring Board (DSMB) will be established prior to study initiation to review data throughout the study, including the 12-week data described below.

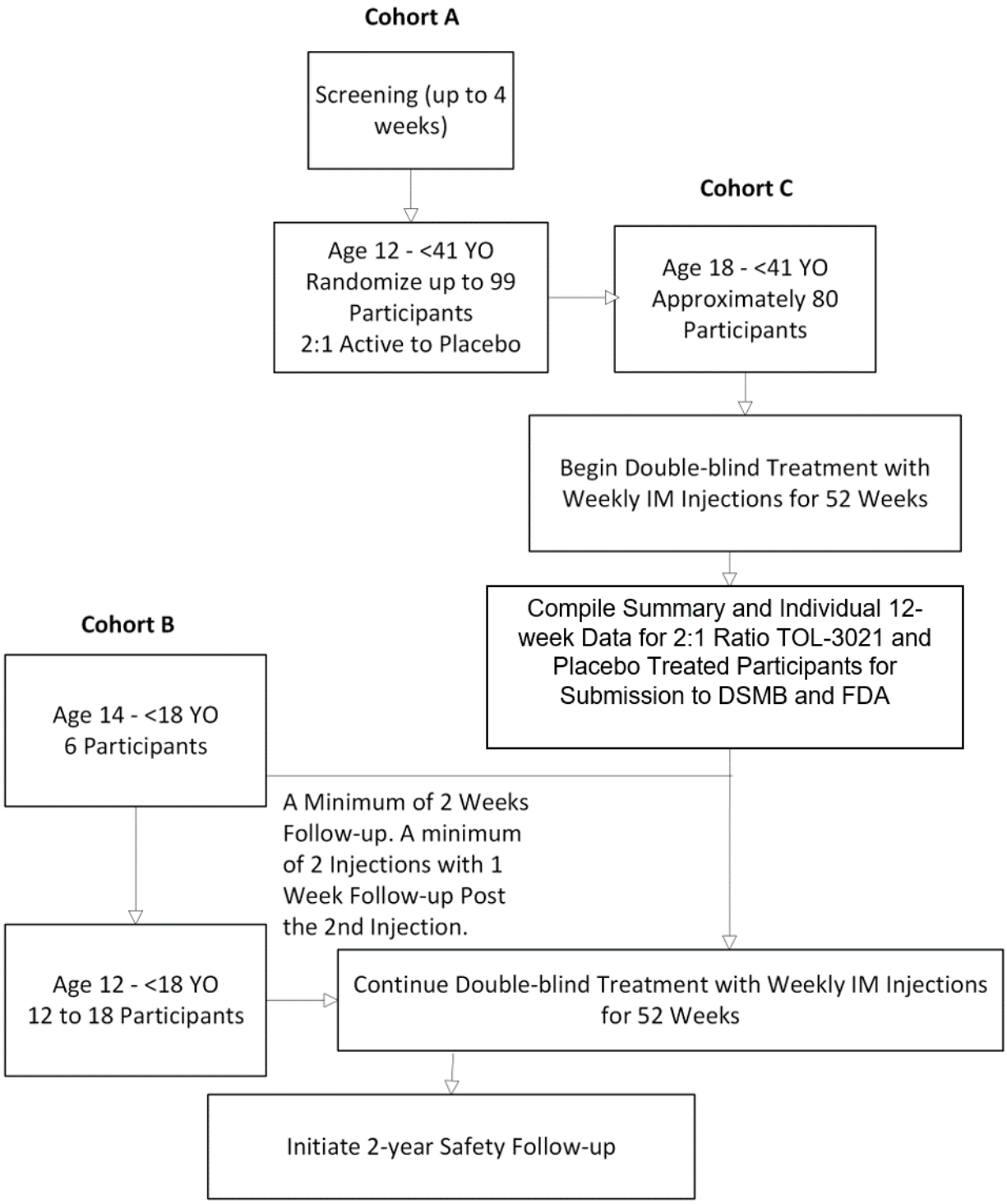
When the first 20 participants treated with TOL-3021 and approximately 10 participants treated with placebo have completed the Week 12 visit, all available data was compiled and provided to the DSMB to consider if the enrollment of adolescent participants in TOL-3021 studies can be recommended. Summary and individual participant data will be provided for DSMB and FDA review. Summary and individual subject data were provided for DSMB and FDA review. The DSMB confirmed that the protocol can be amended to include subjects aged 12 - < 18 years of age and submitted to FDA. If no objection is received from regulators and IRBs, sites will be notified that they may begin enrollment of subjects aged 12 - <18.

In addition, an interim analysis will be performed when the first 30 participants have completed 24 weeks of treatment to evaluate the treatment response.

Participants and investigators will be blinded to treatment assignment throughout the study. Selected Emmes statisticians will have access to treatment assignments. The primary data analysis will be conducted on data collected through Week 24. Unblinded data summaries including safety outcomes and efficacy assessments will be prepared for the sponsor during the study using all data collected through Weeks 24 and 36. Final analysis of the data will be conducted at 52 weeks. Data summaries are unblinded to Sponsor and Emmes, the CRO, only.

Participants will continue in the study for a 2-year safety follow-up period after completion of the 52-week double-blind study. During this 2-year follow-up participants will have clinic visits at 18, 24, and 36 months from their first dose in the double-blind study to evaluate safety. At each of these follow-up visits a MMTT will be administered. Participants may also be offered the opportunity to continue on study medication in a follow-on protocol for one or more years. Any follow-on study will continue to monitor participant safety in line with the requirements of the SUNRISE protocol.

Study Schematic:



4.2 Selection of Study Population

Approximately 99 male or female participants aged 12 to <41 years diagnosed with T1D, as defined by the American Diabetes Association (ADA) criteria and meeting enrollment criteria as

specified in protocol section on eligibility criteria, will be randomized and enrolled in a 2:1 ratio of treatment with TOL-3021 to placebo.

4.3 Investigational Products

4.3.1 Investigational Products Administered

TOL-3021 1.0 mg or placebo will be administered weekly for 52 weeks via an intramuscular (IM) injection into a large muscle.

4.3.2 Identity of Investigational Product(s)

TOL-3021 is formulated in a phosphate-buffered, calcium-containing sterile solution for IM injection. The nominal concentration of TOL-3021 in this solution is 2 mg DNA/mL. TOL-3021 is provided in a sterile single-use 2 mL vial. Placebo is a phosphate-buffered sterile saline solution packaged in a sterile single-use 2 mL vial.

4.3.3 Method of Assigning Participants to IP Groups (Randomization)

Participants will be randomized in a 2:1 ratio of treatment with TOL-3021 to placebo. Randomization will be performed via a secure electronic data capture (EDC) system, Advantage eClinical. Randomization will be stratified by duration of diabetes: 0-<1 year and 1-5 years, to ensure balance of TOL-3021 and placebo within each strata. The randomization code will be prepared by an unblinded statistician at Emmes and will be provided to the designated distributor that will package and ship study drug to the sites. Study drug will be labelled with the blinded numeric code provided by the statistician. The study's Electronic Data Capture system will assign study drug vials to each study participant.

4.3.4 Selection of Doses in the Study

Section 1.1 of the Protocol provides the rationale for the selection of study investigational product dosing. In brief, the 1mg dose from the Phase IIa study was the dose associated with a clinically important treatment response.

4.3.5 Selection of Timing of Dose for Each Participant

The experimental treatment TOL-3021 1.0 mg or placebo will be administered weekly for 52 weeks via an intramuscular (IM) injection into a large muscle.

4.3.6 Blinding

The PI and site staff are blinded to participant treatment throughout the study and do not have access to the randomization code. Unblinding assignments will be maintained by the unblinded statistician at Emmes. The sponsor will be group unblinded after the analysis conducted once all randomized participants have completed Week 24. Participants and site personnel will remain blinded through Week 52.

4.3.7 Prior and Concomitant Therapy

Concomitant medications required for standard care are permitted, except for those specified below as prohibited medications. Use of all concomitant medications must be documented in source documents and reviewed at each visit. Medications taken within the last three months before screening will be documented in an eCRF. Participants will be encouraged to avoid making changes to their concomitant medication regimen during their participation in the study. Any change to a participant's concomitant medication regimen after randomization will be documented in an eCRF. In addition, PIs are encouraged to avoid adding to or changing a participant's medications during study participation unless deemed medically necessary. As clinically indicated, all standard vaccinations are permitted prior, during, and after the treatment period. Preferably, vaccinations should be given in between weekly TOL-3021 dosing and in a muscle that has not been used in the previous 2 weeks for TOL-3021 administration.

Use of the following medications are prohibited from 30 days prior to randomization through the Week 52 final study visit:

- Systemic glucocorticoids or immunosuppressive agents (e.g., cyclosporine, azathioprine, methotrexate, infliximab, or biologic agents). A short course (<21 days) of systemic glucocorticoids for treatment of a transient condition (e.g., asthma) is permitted.
- Medications other than insulin for glycemic control (e.g., metformin, sulfonylureas, glinides, thiazolidinediones, GLP1-RAs, DPP-IV inhibitors, pramlintide, or SGLT-2 inhibitors).
- Verapamil, α-methyldopa.
- Investigational drugs or devices.
- Acetaminophen >4,000 mg per 24-hour period

4.3.8 IP Compliance

Compliance to scheduled study treatment will be tallied by study week for both groups. Weekly and study overall compliance rates will be reported.

4.4 Efficacy and Safety Variables

4.4.1 Efficacy Variables

4-Hour Mixed Meal Tolerance Test

Participants must be fasted for at least 10, and not more than 16, hours prior to the conduct of the MMTT. The 4-hour MMTT will be conducted at the study site with the mixed meal administered between 7:00 AM and 10:00 AM (+ 1 hour), because blood glucose levels will most likely be in the target range of 70-200 mg/dL during those hours. Rapid insulin may be administered 2 hours or short-acting insulin may be administered 6 hours, prior to the MMTT to attain the required glucose levels. Patients using closed-loop insulin pumps must place them in manual mode for the duration of the test. Blood samples will be collected for assay of C-peptide, glucose, and HbA1c at 10 minutes prior to Boost consumption. Immediately prior to Boost consumption (time=0) and

at 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes (± 5 minutes for each timepoint through 60 minutes; ± 10 minutes for each timepoint after 60 minutes) following ingestion of the meal, blood samples will be collected for C-peptide and glucose analysis.

The trapezoidal rule will be applied to each of the C-peptide collection time points through 240 minutes for calculating the 4-hour MMTT C-peptide AUC in units of pmol/mL/min. The AUC will be calculated using all available timepoints for the MMTT.

The timepoints to be analyzed for visits in which MMTT assessments are collected will be derived based on the following visit windows defined around the visit target dates:

- For Week 12, a visit window of -4 weeks (-28 days) to 2 weeks (+14 days) will be used around the Week 12 target date.
- For Week 16, a visit window of -2 weeks (-14 days) to +4 weeks (+28 days) will be used.
- For Week 24, a visit window of -4 weeks (-28 days) to +12 weeks (+84 days) will be used around the Week 24 target date.
- For Week 52, a visit window of -12 weeks (-84 days) to +4 weeks (28 days) will be used around the Week 52 target date.

In general, the time point of an MMTT assessment will be defined according to which window the date of the assessment falls within. For example, an MMTT assessment occurring at Week 11, and thus occurring within the Week 12 visit window, will be analyzed as a Week 12 MMTT assessment. Note, however, that if there are two MMTT assessments that occur within the same visit window, the visit target dates in closest proximity to each MMTT assessment date will be used to define the visit for which the MMTT assessment will be analyzed. Also, MMTT assessments that occur more than 4 weeks prior to Week 12 or more than 4 weeks after Week 52 will not be mapped to Week 12 or Week 52, respectively. In such cases, if there are no other MMTT assessments that fall within the Week 12 or Week 52 visit windows, the Week 12 or Week 52 MMTT outcomes will be considered a missing data point and will be analyzed according to the methods described in Section 6.4.

Glucose Monitoring

Rates of serious and clinically important hypoglycemia comprise key secondary efficacy outcomes in this study. Hypoglycemia symptoms will be recorded in the participant diary. For purposes of study outcomes, hypoglycemia is defined as follows:

- Clinically significant hypoglycemia: measured glucose value of <54 mg/dL (3.0 mM/L) by SMBG, CGM, or laboratory measurement
- Severe hypoglycemia (SH): an event requiring assistance of another to actively administer carbohydrate, glucagon, or other resuscitative actions
- Other measures of hypoglycemia:

- Documented symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration <70 mg/dL (3.9 mmol/L)
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration <70 mg/dL (3.9 mmol/L)
- Nocturnal hypoglycemia: severe or documented symptomatic episodes (as defined above) occurring after the participant has retired for the primary sleeping period

These outcome measures will be derived from Continuous Glucose Monitoring (CGM). Unblinded CGM will be used throughout the 52-week study, beginning at screening. Data from CGM will also be required to ascertain that participants meet the second part of inclusion criterion 3: *time in glycemic range (70-180 mg/dL) >55% by CGM recording over 3 or more consecutive or non-consecutive days.* The sponsor relies on IQVIA and Glooko™ to manage the CGM process from supply of Dexcom G6 CGM units and supplies through data collection.

For CGM efficacy endpoints, the outcome variables are derived based on the recordings on the Dexcom G6 that occur approximately every 5 minutes and that are collected daily within each approximate 12-week interval at Baseline, Week 12, Week 24, Week 36, and Week 52.

Outcomes based on the rate of hypoglycemic events or other time in range events of interest that are based on a single CGM level (e.g., <54 mg/dL, <70 mg/dL, 70-180 mg/dL) will be derived by the total number CGM recordings meeting the threshold condition(s) out of the total number of recordings within each interval. Outcomes based on the proportion of participants experiencing each CGM event of interest based on a single CGM level will be based on a single recording meeting the threshold condition(s) in each interval.

Outcomes defined for events occurring over consecutive minutes or readings (e.g., ≥10 consecutive minutes with CGM < 54 mg/dL) will be derived according to the total number of instances on the CGM for which the event met specific criteria (to be defined below) occurred out of the total number of instances where the event could have occurred. The event criteria for these outcomes are defined below:

- **≥15 consecutive minutes with glucose <54mg/dL:** The first reading of 4 consecutive readings (of at least 15 minutes) for which the CGM is observed at < 54 mg/dL will define the start of this event interval that will end once an observed reading reaches at least 70 mg/dL. In totality, all CGM recordings during this event interval will be considered a single instance of this event. The total number of instances where the event could have occurred will be defined as the sum of the total number of instances (or event intervals) observed to meet the event criteria and the total number of remaining readings that do not meet the event criteria divided by 4.

Insulin Requirements

Total daily insulin dose is an important secondary efficacy outcome and must be recorded in the CGM receiver, regardless of how insulin dose data is collected. Insulin use data is collected by manually entering the amount of insulin administered into the Dexcom receiver through 30OCT2020 or, with Glooko, into the Glooko mobile app beginning 19AUG2020. Note that the primary source for insulin data intended for this study are the doses entered into the Dexcom receiver from the IQVIA system until data becomes available from the Glooko app/transfer, at which point doses entered via Glooko will be considered the primary source. The insulin use data can be collected from an insulin pump or from an InPen™ if the participant is using either of these devices. Additionally, an Insulin dose log eCRF was established for site coordinators to review with participants any intervals with gaps in insulin usage to solicit from the participant the total daily insulin dose. Average monthly insulin usage is also reported on the disease history (DHX) case report form. Below describes the process for how the mean total daily insulin will be derived at each study visit Weeks 12, 16, 24, and 52 and the process for reconciliation of the insulin doses from secondary sources.

Mean total daily insulin will be derived at each visit by first computing the average total daily insulin for each week from the primary source (Dexcom IQVIA receiver or Glooko app). The following scenarios describe the process for reconciliation of the insulin dose data as available for a given week from the insulin eCRF log as the secondary source. This process will be applied for each week for each participant starting with first week during the Baseline interval and proceed in a chronological fashion until a final, reconciled mean total daily insulin dose is derived for each week.

Scenario 1: Insulin data available from the Dexcom IQVIA receiver or Glooko app for at least 4 out of the 7 days of the given week.

a) No secondary source will be used to supplement insulin data. Mean total daily insulin will be derived only from data on the Dexcom IQVIA receiver or Glooko app.

Scenario 2: Insulin data available from the Dexcom IQVIA receiver or Glooko app for <4 days of the given week.

a) If, for the given week, total insulin doses are available on the insulin eCRF log and:
    - If insulin data is available from the Dexcom IQVIA receiver or Glooko app for at least one day of the given week and the mean total daily insulin derived from the Dexcom IQVIA receiver or Glooko app is within 25% of the total insulin doses available on the log then no secondary source will be used to supplement the insulin data. Mean total daily insulin will be derived only from data on the Dexcom IQVIA receiver or Glooko app.
    - If insulin data is available from the Dexcom IQVIA receiver or Glooko app for at least one day of the given week and instead the mean total daily insulin derived

from the Dexcom IQVIA receiver or Glooko app is +/- 25% of the total insulin doses available on the log, then the mean total daily insulin for the given week will be based only on the insulin eCRF log (secondary source).
- If insulin data is not available from the Dexcom IQVIA receiver or Glooko app for any days of the given week, then the mean total daily insulin for the given week will be based only on the insulin eCRF log (secondary source).

b) If, for the given week, only a basal or bolus dose is available on the insulin eCRF log and:
- If insulin data is available from the Dexcom IQVIA receiver or Glooko app for at least one day of the given week and the sum of the mean total daily insulin derived from the Dexcom IQVIA receiver or Glooko app and of the dose on the insulin eCRF log is within 25% of the final (reconciled) mean total daily insulin from the previous week, the mean total daily insulin for the given week will be derived based on the sum of the mean total daily insulin on the Dexcom IQVIA receiver or Glooko app and the dose on the insulin eCRF log.
- If insulin data is available from the Dexcom IQVIA receiver or Glooko app for at least one day of the given week and the sum of the mean total daily insulin derived from the Dexcom IQVIA receiver or Glooko app and of the dose on the insulin eCRF log is +/- 25% of the final (reconciled) mean total daily insulin from the previous week or if no insulin data is available from the previous week (such as during the first week of the Baseline interval), then no secondary source will be used to supplement the insulin data. Mean total daily insulin for the given week will be derived based only on the mean total daily insulin on the Dexcom IQVIA receiver or Glooko app.
- If insulin data is not available from the Dexcom IQVIA receiver or Glooko app for any days of the given week, then the mean total daily insulin for the given week will be based only on the DHX form (secondary source) if available.

c) If no data is available from the insulin eCRF log for the given week and:
- If insulin data is available from the Dexcom IQVIA receiver or Glooko app for at least one day of the given week and if the mean total daily insulin derived from the Dexcom IQVIA receiver or Glooko app is within 50% of the total insulin doses as reported on the diabetes history (DHX) form then no secondary source will be used to supplement the insulin data. Mean total daily insulin for the given week will be derived only from data on the Dexcom IQVIA receiver or Glooko app.
- If insulin data is available from the Dexcom IQVIA receiver or Glooko app for at least one day of the given week and if instead the mean total daily insulin derived from the Dexcom IQVIA receiver or Glooko app is +/- 50% of the total insulin dose as reported on the DHX form then the mean total daily insulin for the given week will be based only on the DHX form (secondary source).

- If insulin data is not available from the Dexcom IQVIA receiver or Glooko app for any days of the given week, then the mean total daily insulin for the given week will be based only on the DHX form (secondary source) if available.

d) If no data is available from any secondary source (insulin eCRF log or DHX) then no secondary source will be used to supplement the insulin data. Mean total daily insulin will be derived only from data on the Dexcom IQVIA receiver or Glooko app if available.

The mean total daily insulin doses through Weeks 12, 24, 36, and 52 will then be based on the final reconciled total daily insulin dose for each week averaged over each week up to and including Weeks 12, 24, 36, and 52.

4.5 Safety Variables

4.5.1 Physical Examination

A complete physical examination will be performed at screening and week 54, including examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, and throat (ENT), cardiovascular system (CVS), respiratory system (RS), gastrointestinal system (GI), lymph nodes, musculoskeletal system, and central nervous system (CNS). A detailed medical history must be obtained at the time of screening. A brief physical exam should be done at Week 12, 24, 36 and 52 visits. The brief physical is defined as palpation/percussion/auscultation of the chest, abdomen and extremities, and follow-up of any interim complaints of specific adverse event that require examination/verification.

4.5.2 Fundus Photography

Standard view (not wide field) fundus photography is required during screening, Week 54 and Months 24 and 36. The report must be signed by an optometrist or an ophthalmologist. If a participant has had fundus photography completed within the 12 months prior to screening and can provide a signed report, the exam will not have to be repeated at screening.

4.5.3 Vital Signs

Vital signs will include body temperature (°C), respiratory rate, sitting radial pulse rates, and sitting systolic and diastolic blood pressures. Sitting recordings are to be made after the participant has been sitting up for 3 minutes or more. Weight will be recorded at each visit. Height will be recorded at screening.

4.5.4 24-Hour Urine Protein and Creatinine

If urinary protein screen is positive during the screening period, a 24-hour urine sample will be collected during the screening period and at Week 54 for analysis of urinary protein and creatinine.

5 SAMPLE SIZE CONSIDERATIONS

Approximately 99 participants aged 18.0 to <41.0 years will be randomized in a 2:1 ratio to receive active or placebo study drug. A minimum of 18 up to a maximum of 24 adolescents aged 12-18 will be enrolled.

When the first 20 participants treated with TOL-3021 and approximately 10 participants treated with placebo have completed the Week 12 visit, an analysis of all available data on selected outcomes on this cohort will be conducted and provided to the DSMB to consider if the enrolment of adolescent participants in TOL-3021 studies can be recommended. An interim analysis will also be performed when the first 30 participants complete 24 weeks of treatment for administrative purposes. See Section 6.5 for additional details on the interim analyses.

Participants will be asked to continue in the study for a 2-year safety follow-up period after completion of the 52-week double-blind study. During this 2-year follow-up participants will have clinic visits at 18, 24, and 36 months from their first dose in the double-blind study to evaluate safety. At each of these follow-up visits a MMTT will be administered.

6 GENERAL STATISTICAL CONSIDERATIONS

6.1 General Principles

Data from Cohorts B (participants aged 12-<18) and C (participants aged 18-<41) will be analyzed and presented separately for all interim reports that are prepared prior to the full clinical study report at Week 24. Once all randomized participants have reached Week 24, the data from Cohort A (participants aged 12-<41) will be analyzed together in the full clinical study report. Data will also be analyzed together in Cohort A for the abbreviated clinical study report once all participants have completed Month 36. All continuous variables at baseline and in terms of changes from baseline will be summarized using the following notation (unless otherwise noted) and descriptive statistics: N (total number of participants in the population), n (total number of participants in the population with a given condition, mean, and standard deviation. The frequency and proportion of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, IP assignment, strata (age and diabetes status), and participant, and by visit number within participants when appropriate. All summary tables will be structured with a column or row for each IP assignment in the order (TOL-3021, Placebo). Descriptive summaries of study endpoints across each visit will be presented in tables by Treatment group. Inferential summaries of study endpoints in which formal statistical testing is implemented will be performed and presented. Descriptive graphical summaries of study endpoints will be presented by Treatment group, strata, and visit, as appropriate to blinding and the type of table or chart.

Timing of analyses. When the first 20 participants treated with TOL-3021 and approximately 10 participants treated with placebo have completed the Week 12 visit, a data base freeze will

be implemented and summary and individual safety data will be submitted to the DSMB for review to support expanding enrollment in TOL-3021 studies to adolescent participants aged 12.0 to <18 years of age. Blind will be maintained except for members of the DSMB and specified unblinded personnel as described in the study Unblinding Plan.

An interim analysis will be performed after the first 30 participants have completed the Week 24 visit for administrative purposes based on an interim data base freeze.

Data base freezes will also be conducted once all randomized participants have completed Weeks 24 and 36, at which point group-unblinded analyses including safety outcomes and efficacy assessments will be prepared for the Sponsor. Note that the Week 24 analysis is the primary efficacy analysis for the study for which a full clinical study report will be prepared (once all randomized participants in Cohorts B and C have completed Week 24). A database freeze will also be conducted once all randomized participants have completed Week 54, at which point a final analysis of all the data will be conducted (which will include Week 52 efficacy and safety data through Week 54 safety data).

Additional primary efficacy and safety summaries will be prepared at 18 Months, 24 Months and 36 Months. A final database lock will be conducted at Month 36, at which point an abbreviated CSR will be prepared.

6.2 Analysis Populations

6.2.1 Intention-to-Treat Analysis Population

All efficacy analyses will be performed on the intention-to-treat (ITT) population. The ITT population will consist of all participants randomized to treatment and who have received at least one injection of IP.

6.2.2 Per Protocol Population

Efficacy analyses for the primary and key secondary endpoints will be performed on the per protocol (PP) population only if the percentage of participants in the ITT population with major protocol deviations exceeds 5%. The per protocol population will consist of all participants who are in ITT with no major protocol violations (note violations as a result of COVID will be reported separately to other violations), have complete MMTT data for at least one visit at Weeks 12, 16, and 24. Protocol deviations are classified into major and minor categories are conducted during blinded data reviews. See Section 7.2 for additional details.

6.2.3 Safety Population

The safety population will consist of all participants who receive one or more doses of TOL-3021 or placebo and have any follow-up safety data

6.3 Covariates and Subgroups

Models for primary and secondary endpoint analyses will generally include IP group, age group (12-<18 vs. 18-41 years), duration group (<1 year vs. 1-5 years), as well as the baseline response

of the specified outcome variable (e.g., baseline log-transformed 4-hour C-peptide AUC for the primary endpoint). Additionally, type of insulin intervention may be included as a covariate in models for the analysis of total daily insulin.

Subgroup analyses of insulin and HbA1C endpoints may be carried out based on the baseline median insulin use and HbA1c percentage, respectively. A sensitivity analysis may be conducted as well on the analyses of insulin endpoints among only participants with pumps. Sensitivity analyses will also be carried out for all CGM endpoints according to whether CGM readings were collected during the day (defined as 7AM to 11PM based on the user's local time) or during the night (defined as 11PM to 7AM based on the user's local time).

6.4 Missing Data

Every attempt will be made to collect data per the protocol and to avoid missing data. As such, dropouts and missing data are expected to be minimal, but can inevitably occur. Any visit with a missing record for which an assessment is intended to be collected, including, but not limited to, participant termination or discontinuation of IP, will be considered a missing data point.

For participants with complete MMTT visits at two visits and missing MMTT visits at one visit during Weeks 12, 16, or 24, linear interpolation will be utilized to perform a single imputation of the missing MMTT based on the line connecting the MMTT C-Peptide AUCs at the two visits with complete data.

Available case analysis based on maximum likelihood estimation will be used for missingness in the primary endpoint with at least 2 visits with missing MMTTs and in all secondary endpoints (including key secondary endpoints) such that all data observed for a participant across time will be included in the analysis.

Any data point in the primary or key secondary efficacy endpoints that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

6.5 Interim Analyses and Data Monitoring

A Data Safety Monitoring Board (DSMB) will be established prior to study initiation to review data throughout the study, including the Week 12 data review described below.

When the first 20 participants treated with TOL-3021 and approximately 10 participants treated with placebo have completed the Week 12 visit, all available data will be compiled and provided to the DSMB to consider if the enrolment of adolescent participants in TOL-3021 studies can be recommended. Summary and individual participant data will be provided for DSMB and FDA review.. Summary and individual subject data were provided for DSMB and FDA review. The

DSMB confirmed that the protocol can be amended to include subjects aged 12 - < 18 years of age and submitted to FDA. If no objection is received from regulators and IRBs, sites will be notified that they may begin enrollment of subjects aged 12 - <18. This analysis will include blinded and unblinded summaries of safety, primary efficacy, and key secondary efficacy endpoints data. As described in the Unblinding Plan, the unblinded statistician will distribute the unblinded report to the DSMB.

When the first 30 participants complete 24 weeks of treatment, an interim analysis will be performed on the primary efficacy endpoint. The interim analysis will include a formal statistical test for the difference in treatment groups on the primary endpoint (change from baseline in log-transformed MMTT C-peptide AUC), that will be assessed using two-sided significance level, alpha, of 0.0052 based on the O'Brien-Fleming alpha-spending function. This analysis will be conducted only on the first 30 participants in the ITT population expected to complete 24 weeks of treatment as of the interim data base freeze using the primary analysis model specified in Section 8.1, except that the covariate for age group will be omitted from the model since all 30 participants are expected to be of the same age group (18-41). Linear interpolation will be used for MMTT measures that are missing at a given visit if there are at least 2 visits (at Weeks 12, 16, or 24) with complete MMTT data using the methods described in Section 6.4. Note, however, that 95% confidence intervals will be reported based on an unadjusted two-sided alpha of 0.05. The interim analysis will also include descriptive analyses on the key secondary endpoints and safety data. As described in the DSMB Charter, based on review of this interim analysis, the DSMB may make recommendations to the Sponsor concerning continuation or modifications of the study on the basis of safety. There is no provision to halt this trial prematurely for lack of efficacy or for clearly demonstrated efficacy. Any decision regarding the continuation or halting of the trial on the basis of safety by the Sponsor will be agreed with the DSMB. Blinded and unblinded interim analysis reports will be prepared by the unblinded statistician at the Coordinating Center. The blinded report will be distributed to the Sponsor and DSMB. The unblinded report will be distributed by the unblinded statistician to the DSMB and a designated group of Sponsor representatives for administrative purposes. As described in the study Unblinding Plan, the unblinded Sponsor representatives are not permitted to share data from the interim analysis report with the blinded study team until the formal unblinding of the Sponsor (when all participants complete Week 24).

Multi-center Studies

Data will be pooled across all clinical sites for all analyses.

6.6 Multiple Comparisons/Multiplicity

Two-sided significance levels (alpha) of 0.0052 and 0.048 will be used for the statistical testing of the primary endpoint at the interim (when 30 participants have completed 24 weeks of treatment) and final analyses, respectively. Note, however, confidence intervals reported in both

the interim and the final analyses will be presented based on an unadjusted two-sided alpha of 0.05.

Given the exploratory aim of this pilot study, no adjustment will be made to the significance levels for statistical testing of the secondary endpoints; all tests for secondary endpoints will be evaluated at a two-sided alpha of 0.05.

7 STUDY PARTICIPANTS

7.1 Disposition of Participants

The number of participants screened and of those, the number and percentage who were screen failures will be presented in the full clinical study report. The number and percentage of participants in each analysis population (ITT, PP, safety) will be presented by treatment group and overall. The number and percentage of participants among those in the ITT population attending each clinic visit will be summarized by treatment group and overall .The number and percentage of participants in the ITT population who completed the study, who withdrew prematurely from the study and who reported each primary and sub-reason for withdrawal will be presented for each treatment group and overall. A listing of participants who terminate the study for any reason and the given reasons will be produced.

7.2 Protocol Deviations

Protocol deviations identified here are those considered to affect the primary outcome of the study. Prior to the final data base lock, a blinded data review will be conducted with the Sponsor and Coordinating Center to classify each protocol deviation into major or minor severity categories. In general, a major protocol deviation includes conditions, practices or processes that could adversely affect the rights, safety, or wellbeing of the participants and/or the quality and integrity of the data. All decisions on whether to exclude a participant or a participant's data from analysis will be made prior to breaking the blind, with the exception of participants receiving incorrect treatment container. If, after breaking the blind, the container was found to have contained the correct randomized treatment, no data will be excluded from analyses.

Summaries and listings of protocol deviations will be reported by deviation category, severity, and IP group, as well as whether they are related to COVID-19. The number and percentage of participants in the ITT population who failed each inclusion or exclusion or criterion will be presented, by treatment group and overall.

8 EFFICACY EVALUATION

All efficacy variables will be listed by participant and site. Data will be summarized descriptively by visit and treatment group. Note that data from Cohorts B (participants aged 12-<18) and C (participants aged 18-<41) will be analyzed and presented separately for all interim reports that are prepared prior to the full clinical study report at Week 24. Once all randomized

participants have reached Week 24, the data from Cohort A (participants aged 12-<41) will be analyzed together in the full clinical study report. Data will also be analyzed together in Cohort A for the abbreviated clinical study report once all participants have completed Month 36. Continuous efficacy variables will be summarized at baseline and at each visit in terms of the raw score and change from baseline score using the following metrics and notation unless otherwise noted: N (total number of participants in the population), n (total number of participants in the population with a given condition), mean, and standard deviation. Categorical variables will be summarized using number and percent.

Inferential analysis of efficacy measures will be conducted using model-based approaches, from which two-sided 95% confidence intervals for overall treatment effects and p-values will be derived. The next subsections provide further details on the model-based analyses for the primary, secondary, and exploratory endpoints appropriately.

8.1 Primary Efficacy Analysis

A linear mixed model for repeated measures (MMRM) will be used to model the change from baseline in log-transformed MMTT-stimulated 4-hour mean C-peptide AUC at Weeks 12, 16, and 24. The model will include fixed effect terms for IP group, baseline log-transformed 4-hour C-peptide AUC, age group (Cohort A), T1D-duration disease group, week along with the IP group by week interaction term. Note that age group will be omitted as a covariate for data analyzed in Cohort B or Cohort C only. Model and analysis details are specified below.

Let Y_{ij}, $i = 1,\ldots,N$, $j = 1,2,3$ denote the change from baseline in log-transformed MMTT C-peptide AUC for the i^{th} participant and the j^{th} visit over Weeks 12, 16, and 24, with N denoting the total number of participants. Let $GROUP_i$ indicate the IP group assignment (with placebo specified as the reference level), $BASE_i$ be the baseline log-transformed 4-hour C-peptide AUC, $WEEK_{ij}$ be the week the change from baseline in log MMTT C-Peptide AUC is obtained, AGE_i denote the age group (12-<18 vs. 18-41 years), DUR_i denote the T1D duration disease group (<1 year vs 1-5 years), all for the i^{th} participant. Note that $WEEK_{ij}$ will be considered continuous in the model. The primary analysis model can be expressed as

$$Y_{ij} = \beta_0 + \beta_1 BASE_i + \beta_2 GROUP_i + \beta_{3j} WEEK_{ij} + \beta_4 AGE_i + \beta_5 DUR_i + \beta_{5j} GROUP_i * WEEK_{ij} + \beta_{6j} DUR_i * WEEK_{ij} + \beta_7 DUR_i * GROUP_i + \beta_{8j} GROUP_i * DUR_i * WEEK_{ij} + \epsilon_{ij}, i = 1,\ldots,N, j = 1,2,3$$

where $\boldsymbol{\epsilon_i} = (\epsilon_{i1}, \epsilon_{i2}, \epsilon_{i3})'$, $\boldsymbol{\epsilon_i} \sim MVN(\mathbf{0}, \mathbf{V_i})$ is the vector of repeated errors for the i^{th} participant. The within-participant correlations due to the repeated measures over time will be addressed via the specification of the within-participant covariance matrix, $\mathbf{V_i}$. An unstructured correlation structure will be specified for $\mathbf{V_i}$, unless the model with the unstructured covariance matrix does not converge, in which case a compound symmetry correlation structure will be utilized.

The models will be fit using the PROC MIXED procedure in SAS version 9.4. The METHOD=ML option will be specified in the PROC MIXED statement to perform maximum likelihood.

The DDFM= KR option will be specified in the MODEL statement for computing the denominator degrees of freedom for the tests of fixed effects. Options in the REPEATED statement will include SUBJECT to identify correlated observations of the same participant and TYPE=UN to specify the unstructured (or compound symmetry if the model does not converge) correlation structure. A LSMESTIMATE statement will be utilized to generate tests and confidence intervals for the treatment group difference.

Note that a linear mixed model using a random effect, i.e., RANDOM statement instead of a REPEATED statement will also be implemented as a sensitivity analysis. For this analysis, participant ID will be specified on the RANDOM statement and will be considered nested within IP group, and days from randomization at which the MMTT was conducted will be used instead of week. The same covariates will be used in this model as those included in the above MMRM.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. Should distributional violations appear for the primary endpoint, the alternative log(mean AUC+1) as suggested by Lachin (PLoS 2011) will be evaluated.

8.2 Secondary Efficacy Analyses

The rate for which the CGM level falls below 54 mg/dL over the approximate 12-week intervals at Weeks 12, 24, 36, and 52 will be modeled using a Poisson regression model. Specifically, the total number of CGM readings within each approximate 12-week interval for which the value falls below 54 mg/dL will be modeled at each visit using a Poisson generalized estimating equation (GEE) with the log of the total number of CGM readings in each interval used as the offset term. The model will include fixed effect terms for IP group, total number of CGM readings below 54 mg/dL at baseline, age group (Cohort A), T1D-duration disease group, week along with the IP group by week interaction term. An unstructured working correlation structure will be specified in the model unless the model does not converge, in which case an exchangeable correlation structure will be utilized. PROC GENMOD with DIST=POISSON specified as an option in the model statement will be used to fit the GEE model. Options in the REPEATED statement will include SUBJECT to identify correlated observations of the same participant and TYPE=UN (EXCH) to specify the unstructured (or exchangeable if the model does not converge) correlation structure. A LSMESTIMATE statement with the EXP option will be utilized to generate tests and confidence intervals for the estimated treatment group risk ratios.

Note that if there is evidence of overdispersion in the Poisson model, a negative binomial model will be used for this analysis by setting DIST=NEGBIN. Evidence of overdispersion will be determined based on whether the deviance statistic divided by its degrees of freedom in the Poisson model is 2 or greater.

The total number of instances (or rate) for which the CGM level falls below 54 mg/dL for 10 consecutive minutes (defined by the event criteria in Section 4.4.1) over the approximate 12-week intervals at Weeks 12, 24, 36, and 52 will be modeled using a Poission generalized estimating equation (GEE). The log of the total number of instances meeting the event criteria defined in Section 4.4.2 will be used as the offset term. The model will include fixed effect terms for IP group, and total number instances for whether CGM fell below 54 mg/dL for 10 consecutive minutes during the baseline interval, age group (Cohort A), T1D-duration disease group, week along with the IP group by week interaction term. An unstructured working correlation structure will be specified in the model unless the model does not converge, in which case an exchangeable correlation structure will be utilized. PROC GENMOD with DIST=POISSON specified as an option in the model statement will be used to fit the GEE model. Options in the REPEATED statement will include SUBJECT to identify correlated observations of the same participant and TYPE=UN (EXCH) to specify the unstructured (or exchangeable if the model does not converge) correlation structure. A LSMESTIMATE statement with the EXP option will be utilized to generate tests and confidence intervals for the estimated treatment group odds ratios.

The total daily insulin used over approximate 12-week intervals at Weeks 12, 24, 36 and 52 will be modeled using a linear mixed model for repeated measures, using similar model structure as the MMRM specified for the primary analysis. Specifically, the model will include fixed effect terms for IP group, baseline total daily insulin usage, age group (Cohort A), T1D-duration disease group, insulin intervention type, week along with the IP group by week interaction term. An unstructured correlation structure will be specified, unless the model with the unstructured covariance matrix does not converge, in which case a compound symmetry correlation structure will be utilized. SAS procedures and statements for performing this analysis will be similar to those specified for the MMRM model in the primary efficacy analysis.

The percentages for hemoglobin A1c at Weeks 12, 24, 36 and 52 will be modeled using a linear mixed model for repeated measures, using similar model structure as the MMRM specified for the primary analysis and for the key secondary analysis for total daily insulin. Specifically, the model will include fixed effect terms for IP group, baseline hemoglobin A1c percentage, age group (Cohort A), T1D-duration disease group, week along with the IP group by week interaction term. An unstructured correlation structure will be specified, unless the model with the unstructured covariance matrix does not converge, in which case a compound symmetry

correlation structure will be utilized. SAS procedures and statements for performing this analysis will be similar to those specified for the MMRM model in the primary efficacy analysis.

The rate for which the CGM level is within the glycemic range (70-180 mg/dL) the approximate 12-week intervals at Weeks 12, 24, 36, and 52 will be modeled using a Poisson regression model. Specifically, the total number of CGM readings within each approximate 12-week interval for which the value falls within the glycemic range will be modeled at each visit using a Poisson generalized estimating equation (GEE) with the log of the total number of CGM readings in each interval used as the offset term. The model will include fixed effect terms for IP group, total number of CGM readings in the glycemic range at baseline, age group (Cohort A), T1D-duration disease group, week along with the IP group by week interaction term. An unstructured working correlation structure will be specified in the model unless the model does not converge, in which case an exchangeable correlation structure will be utilized. PROC GENMOD with DIST=POISSON specified as an option in the model statement will be used to fit the GEE model. Options in the REPEATED statement will include SUBJECT to identify correlated observations of the same participant and TYPE=UN (EXCH) to specify the unstructured (or exchangeable if the model does not converge) correlation structure. A LSMESTIMATE statement with the EXP option will be utilized to generate tests and confidence intervals for the estimated treatment group risk ratios. Note that if there is evidence of overdispersion in the Poisson model, a negative binomial model will be used for this analysis by setting DIST=NEGBIN. Evidence of overdispersion will be determined based on whether the deviance statistic divided by its degrees of freedom in the Poisson model is 2 or greater.

As discussed in section 6.5, available-case analysis based on maximum likelihood estimation will be used to account for missing data in all secondary endpoints.

8.3 Other Secondary Efficacy Analyses

The analyses for the other secondary efficacy endpoints will generally follow the analysis models specified for the primary and key secondary endpoints according to the type and scale of the other secondary outcome measures. MMRM analyses similar to the analysis described for the primary analysis will be used to analyze the following continuous secondary endpoints:

- Change from baseline in the log-transformed MMTT C-peptide AUC at Weeks 12, 16, 24, 52.
- Change from baseline in fasting C-peptide at Weeks 12, 16, 24, and 52
- Mean glucose coefficient of variation at Weeks 12, 24, 36, and 52
- Mean glucose at Weeks 12, 24, 36, and 52
- Low Blood Glucose Index (LBGI) at Weeks 12, 24, 36, and 52
- Area over the curve for which CGM reading is < 70 mg/dL at Weeks 12, 24, 36, and 52.

In general, the same fixed effect terms as the primary analysis will be specified in the model except that the baseline log MMTT C-peptide will be replaced the baseline response of the given

outcome measure in each model for continuous secondary endpoints. Note that the analysis model for the change from baseline in log MMTT C-peptide AUC at Weeks 12, 16, 24, and 52 will be the same as the model specified for the primary analysis except that it will also include MMTT data at Week 52.

Poisson GEE-type analyses similar to the analyses described for secondary endpoints in Section 8.3 will be used for the following secondary endpoints according to rates the CGM reported values:

- < 70 mg/dL at Weeks 12, 24, 36, and 52
- ≥54 and <70 mg/dL at Weeks 12, 24, 36, and 52
- > 180 mg/dL at Weeks 12, 24, 36, and 52
- >180 and ≤250 mg/dL at Weeks 12, 24, 36, and 52
- > 250 mg/dL at Weeks 12, 24, 36, and 52
- CGM < 70 mg/dL for at least 10 consecutive minutes during each 12 week interval at Weeks 12, 24, 36, and 52 (meeting the event criteria defined in Section 4.4.1).
- CGM < 80 mg/dL for at least 10 consecutive minutes during each 12 week interval at Weeks 12, 24, 36, and 52 (meeting the event criteria defined in Section 4.4.1).
- Days CGM events were recorded at Weeks 12, 24, 36, and 52.
- Time CGM is active (based on the number of observed readings out of total number of readings possible) at Weeks 12, 24, 36, and 52.

In general, the same fixed effect terms as the Poisson GEE models in Section 8.2 will be specified in the models here except that total number of CGM readings in the given outcome range at baseline will be used as the baseline response. Note that if there is evidence of overdispersion in a given Poisson model, a negative binomial model will be used instead by setting DIST=NEGBIN. Evidence of overdispersion will be determined based on whether the deviance statistic divided by its degrees of freedom in the given Poisson model is 2 or greater.

Binomial GEE-type analyses similar to the analyses described for secondary endpoint in Section 8.3 will be used for the following secondary endpoints according to the proportion of participants with:

- At least one clinically severe hypoglycemia event (i.e., impaired or loss of consciousness requiring assistance of another) during each 12 week interval at Weeks 12, 24, 36, and 52.
- At least one episode of documented symptomatic hypoglycemia (an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of <70 mg/dl (3.9 mmol/L)) during each 12 week interval at Weeks 12, 24, 36, and 52.

- At least one episode of nocturnal hypoglycemia (i.e., severe or documented symptomatic episodes) occurring after the participant has retired for the primary sleeping period during each 12 week interval at Weeks 12, 24, 36, and 52.
- CGM < 54 mg/dL during each 12 week interval at Weeks 12, 24, 36, and 52.
- CGM < 70 mg/dL during each 12 week interval at Weeks 12, 24, 36, and 52.
- CGM in the glycemic range for at least 70% of each 12 week interval at Weeks 12, 24, 36, and 52.
- CGM < 54 mg/dL for less than 1% of each 12 week interval at Weeks 12, 24, 36, and 52.
- Positive responder outcome defined as no change or an increase in C-peptide AUC from baseline between treatment and placebo at Weeks 12, 16, 24 and 52.
- HbA1c levels less than 6.5% at Week 52.
- Glycemic variability in terms of % CV ≤ 35% at Weeks 12, 24, 36, and 52.

In general, proportions of participants experiencing the above events will be modeled using Binomial generalized estimating equations (GEE). The model will include fixed effect terms for IP group, indicator for whether event was experienced during the baseline interval, age group, T1D-duration disease group, week along with the IP group by week interaction term. An unstructured working correlation structure will be specified in the model unless the model does not converge, in which case an exchangeable correlation structure will be utilized. PROC GENMOD with DIST=BINOMIAL specified as an option in the model statement will be used to fit the GEE model. Options in the REPEATED statement will include SUBJECT to identify correlated observations of the same participant and TYPE=UN (EXCH) to specify the unstructured (or exchangeable if the model does not converge) correlation structure. A LSMESTIMATE statement with the EXP option will be utilized to generate tests and confidence intervals for the estimated treatment group odds ratios. As discussed in section 6.5, available-case analysis based on maximum likelihood estimation will be used to account for missing data in all secondary endpoints.

Sensitivity analyses will also be carried out for all CGM endpoints according to whether CGM readings were collected during the day (defined as 7AM to 11PM based on the user's local time) or during the night (defined as 11PM to 7AM based on the user's local time). Sensitivity analyses may also be implemented to analyze the total number of instances of CGM events (e.g., < 54 mg/dL, CGM < 70 mg/dL, < 80 mg/dL) that occur for ≥ 10 consecutive minutes or 3 readings based on the event criteria defined in Section 4.4.1. These analyses will be conducted using similar models (Poisson GEE) as those described above for the events based on 15 consecutive minutes.

Evaluation of Composite Endpoints

The following composite endpoints will be evaluated as exploratory endpoints based on the proportions of participants experiencing both factors in each composite endpoint at Weeks 12, 24, 36, and 52.

1) Total daily insulin <0.5U/kg/day and HbA1c <7%
2) No change or an increase in C-peptide AUC from baseline and insulin <0.5u/kg/day
3) No change or an increase in C-peptide AUC from baseline C-peptide and HbA1C<7%
4) No change or an increase in C-peptide AUC from baseline C-peptide and Symptomatic hypoglycemia
5) No change or an increase in C-peptide AUC from baseline C-peptide and Severe hypoglycemia
6) No change or an increase in C-peptide AUC from baseline C-peptide and CGM < 54 mg/dL

These analyses will be conducted using similar models (Binomial GEE) as those described above for the analyses of proportions. The models will include fixed effect terms for IP group, indicator for whether event was experienced during the baseline interval, age group (Cohort A), T1D-duration disease group, week along with the IP group by week interaction term. An unstructured working correlation structure will be specified in the model unless the model does not converge, in which case an exchangeable correlation structure will be utilized.

9 SAFETY EVALUATION

All safety data will be reported among participants in the safety population. Percentages for all safety-related events will be calculated based on the total number of participants in the safety population.

9.1 Baseline Characteristics

9.1.1 Primary and Concurrent Medication Conditions

A pre-existing medical condition is one that is present prior to the start of the study and is to be reported as part of the participant's medical history. It will be reported as an AE only if the frequency, intensity, or the character of the condition worsens during the study.

9.1.2 Prior and Concomitant Medications

A listing of medication, dose, unit, route, reason for administration, type (Diabetic/non-Diabetic) will be produced.

Classification of a concomitant medication as being taken pre-treatment, on-treatment or post-treatment will be made with reference to the study treatment and medication start and stop dates. For medications with partial start and stop dates, the medication will be classed in every period of the study in which it could have been taken.

9.2 Measurements of IP Compliance

Compliance with both in-clinic and self-administered injection of study investigational product will be described as percent of visits for which study treatment was dispensed with injection reported.

9.3 Adverse Events

Adverse events will be coded to a Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later. Classification of an AE as pre-treatment or treatment-emergent will be made with reference to the study treatment start and stop dates and the AE onset date. All treatment-emergent adverse events will be those reported from the time of the first IP administration through the last scheduled follow-up visit. AEs reported by participants prior receiving treatment will be considered pre-treatment. Participants who experience SAEs that are ongoing at time of last scheduled follow-up visit will be followed to resolution or stabilization. Non-serious AEs that are ongoing at a participant's closeout visit are to be reported as "not recovered/not resolved" with no end date reported. SAEs that are ongoing at the participant's closeout visit should continue to be followed by the site until resolution, patient withdrawal of consent for follow up, or the database lock. If a serious SAE is still ongoing upon the withdrawal of consent or the database lock, the event is to be reported as "not recovered/not resolved" with no end date reported. Participants who experience pregnancy during the study will also be followed to completion of pregnancy. An overall summary of AEs, related AEs, SAEs and deaths will be reported by treatment group, age group, and T1D duration group. The numbers and proportions of participants, experiencing adverse as well as the total number events will be summarized by MedDRA System Organ Class (SOC), Preferred Term (PT), IP group, age group and T1D duration group. Verbatim description, the MedDRA SOC, and PT for all adverse events will be contained in the participant data listings.

9.4 Deaths, Serious Adverse Events and other Significant Adverse Events

A listing of serious adverse events will be reported. The numbers and proportions experiencing SAEs and the total number of SAEs will be summarized by MedDRA SOC, PT, Cohort, and IP Group.

9.5 Pregnancies

Any pregnancies reported during the study will be listed.

9.6 Clinical Laboratory Evaluations

The laboratory assessments performed are listed in Section 10.8 of the protocol.

The proportions of participants for each visit with abnormal (outside normal range) laboratory results and with shifts from normal lab results at baseline to abnormal at post-baseline will be presented by laboratory panel (e.g., chemistry, hematology, urinalysis), visit, and IP group. Change from baseline values will also be summarized by treatment group for parameters with observed shifts from normal at baseline to abnormal at post-baseline visits.

All laboratory data for participants who have any values outside the normal range will be listed; normal ranges will be included in this listing.

9.7 Vital Signs

Body temperature (°C), respiratory rate, sitting radial pulse rates, and sitting systolic and diastolic blood pressure values will be summarized by treatment group at different scheduled visits.

Change from baseline values after the start of treatment will be summarized by treatment group similarly.

All vital sign data will be listed.

9.8 Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary once all participants have completed Week 24 prior to the generation of the first clinical study report. Concomitant medications taken during the study will be recorded on the CRFs. A by-participant listing of concomitant medication use will be presented.

9.9 Other Safety Measures

Other safety measures (injection site reactions, severe hypoglycemia or hyperglycemia events monitored by CGM) will be summarized by treatment group, based on the number and percent of participants who experienced each event, and listed. For injection site reactions, the number and percent of injections with an observed reaction will also be summarized.

10 REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to three decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and other statistics will be reported to one decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients), will be reported to three significant figures.

Data collected at unplanned (i.e. unscheduled) time points will not be included in the summaries unless otherwise stated. Unscheduled or unplanned readings will be presented in the listings.

In all data displays, planned and actual relative times will be relative to the study drug dosing time of the relevant dosing session.

11 TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings. Additional statistical packages will be utilized as needed.

12 SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes in the conduct of the study or planned analyses will be applied at this time, except that the key secondary endpoint defined in protocol v1.07 as the rate of clinically important hypoglycemia, based on a measured glucose value of <54 mg/dL (3.0mM/L) for at least 10 consecutive minutes over each approximately 12-week period ending at Weeks 12, 24, 36, and 52, was redefined in this SAP as based on glucose <54 mg/dL for at least 15 consecutive minutes. Deviations from the analyses in the SAP will be identified in the final clinical study report

13 REFERENCES

Seaman, S. R. and R. A. Hughes (2018). "Relative efficiency of joint-model and full-conditional-specification multiple imputation when conditional models are compatible: The general location model." Stat Methods Med Res **27**(6): 1603-1614.

Estimating the parameters of a regression model of interest is complicated by missing data on the variables in that model. Multiple imputation is commonly used to handle these missing data. Joint model multiple imputation and full-conditional specification multiple imputation are known to yield imputed data with the same asymptotic distribution when the conditional models of full-conditional specification are compatible with that joint model. We show that this asymptotic equivalence of imputation distributions does not imply that joint model multiple imputation and full-conditional specification multiple imputation will also yield asymptotically equally efficient inference about the parameters of the model of interest, nor that they will be equally robust to misspecification of the joint model. When the conditional models used by full-conditional specification multiple imputation are linear, logistic and multinomial regressions, these are compatible with a restricted general location joint model. We show that multiple imputation using the restricted general location joint model can be substantially more asymptotically efficient than full-conditional specification multiple imputation, but this typically requires very strong associations between variables. When associations are weaker, the efficiency gain is small. Moreover, full-conditional

specification multiple imputation is shown to be potentially much more robust than joint model multiple imputation using the restricted general location model to mispecification of that model when there is substantial missingness in the outcome variable.

14 LISTING OF TABLES, FIGURES, AND LISTINGS

The organization and structure of unblinded table, figure, and listing shells, as intended for the full clinical study report and final abbreviated clinical study report will be finalized separate from this SAP prior to the database lock of the clinical study report.

APPENDICES