Official Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of CT-868 Administered for 16 Weeks to Overweight and Obese Adult Participants with Type 1 Diabetes Mellitus

NCT Number: NCT06062069

Document Date: Statistical Analysis Plan Version 1: 01-Aug-2025

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of CT-868 Administered for 16 Weeks to Overweight and Obese Adult Participants with Type 1 Diabetes Mellitus
Protocol Number:	CT-868-004
Protocol Version/Date:	V 5.0 / 29 July 2024
Investigational Product:	CT-868
Sponsor:	Carmot Therapeutics, Inc. A member of the Roche Group 740 Heinz Avenue Berkeley, CA 94710 United States Telephone: 888-402-4674
SAP Version/Date:	V 1.0 / 01 August 2025

CONFIDENTIAL

The information in this document is confidential and is not to be disclosed without the written consent of Carmot Therapeutics, Inc. except to the extent that disclosure would be required by law and for the purpose of evaluating and/or conducting a clinical study for Carmot Therapeutics, Inc. The contents of this document may only be disclosed to the Institutional Review Board or Independent Ethics Committee and study personnel directly involved with conducting this protocol. Persons to whom the information is disclosed must be informed that the information is confidential and proprietary to Carmot Therapeutics, Inc. and that it may not be further disclosed to third parties.

SIGNATURE PAGE

Protocol Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of CT-868 Administered for 16 Weeks to Overweight and Obese Adult Participants with Type 1 Diabetes Mellitus
Protocol Number:	CT-868-004
SAP Version/Date:	V1.0 / 01AUG2025

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
[redacted]***, PhD*** [redacted] ***Medpace, Inc.***	
[redacted] [redacted] ***Roche, Inc.***	
[redacted] [redacted] ***Carmot Therapeutics, Inc.***	

VERSION HISTORY

Version	Version Date	Description
1.0	01AUG2025	Original signed version

TABLE OF CONTENTS

1 Introduction 8
2 Study overview 8
2.1 Study Objectives and Endpoints 8
2.1.1 Primary Objective and Endpoints 8
2.1.2 Key Secondary Objectives and Endpoints 8
2.1.3 Other Secondary Efficacy and Safety Objectives and Endpoints 9
2.1.4 Exploratory Objectives and Endpoints 12
2.1.5 Objectives and Endpoints Related to Pharmacokinetics & Immunogenicity 15
2.2 Study Design 15
2.2.1 Overview 15
2.2.2 Randomization and Blinding 16
2.2.3 Study Drug 17
2.2.4 Sample Size Determination 18
3 Statistical Methodology 19
3.1 General Considerations 19
3.1.1 Analysis Day 19
3.1.2 Analysis Visits 19
3.1.3 Definition of Baseline 20
3.1.4 Summary Statistics 21
3.1.5 Handling of Dropouts, Missing Data, or Other Data Issues 21
3.1.6 Adjunct Therapy 22
3.2 Analysis Populations 23
3.2.1 Intent-to-Treat (ITT) Population 23
3.2.2 Modified Intent-to-Treat (mITT) Population 23
3.2.3 Per-Protocol (PP) Population 23
3.2.4 Safety Population 23
3.2.5 Pharmacokinetic (PK) Population 24
3.3 Participant Data and Study Conduct 24
3.3.1 Participant Disposition 24
3.3.2 Protocol Deviations 24
3.3.3 Analysis Populations 25
3.3.4 Demographic and Baseline Characteristics 25
3.3.5 Medical History and Concurrent Medical Conditions 25
3.3.6 Prior and Concomitant Medications and procedures 26
3.3.7 Study Drug Exposure and Compliance 26
3.4 Efficacy Analyses 27
3.4.1 Primary Endpoint Analyses 28
3.4.2 Key Secondary Efficacy Endpoints 32
3.4.3 Other Secondary Efficacy Endpoints 36
3.4.4 Exploratory Efficacy Endpoints 39

3.4.5 Subgroup Analysis 42
3.5 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis 42
3.6 Immunogenicity Assessments 43
3.7 Safety Assessment 44
3.7.1 Adverse Events (AEs) and Adverse Device Effects (ADEs) 44
3.7.2 Adverse Events of special interest (AESIs) 45
3.7.3 Clinical Laboratory Tests for Safety Assessments 46
3.7.4 Vital Signs 46
3.7.5 Hypoglycemia events, DKA, and other vital sign related endpoints 46
3.7.6 Electrocardiograms 48
3.7.7 Physical Examinations 48
3.7.8 eDiary completion by participant 48
[redacted] 48
..... 49
..... 50
4 Safety Review Committee 50
5 Key Changes from Protocol-Specified Statistical Analyses 51
6 Programming Specifications 52
Appendix A: References 53
Appendix B: Schedule of Procedures 54
Appendix C: Laboratory Tests 57
Appendix D: Dose/Titration Adjustment Schema 59
Appendix E: CGM related endpoints derivation 61
Appendix F: Example SAS code 63

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
ADE	Adverse device effect
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
BHB	Beta-hydroxybutyrate
BMI	Body mass index
CGM	Continuous glucose monitoring
CTCAE	Common Terminology Criteria for Adverse Events
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FDA	Food and Drug Administration
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Hemoglobin A1c
HEC	Hyperinsulinemic-euglycemic clamp
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
ITT	Intent-to-Treat
LoPO	List of planned outputs
MAD	Multiple ascending dose
MDI	Multiple daily injection
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures

Abbreviation	Definition
MMTT	Mixed meal tolerance test
NOAEL	No-observable-adverse-effect level
PK	Pharmacokinetic(s)
PP	Per Protocol
PRO	patient-reported outcome
PTCA	Percutaneous transluminal coronary angioplasty
QTcF	corrected QT interval using Fridericia's formula
RA	Receptor agonist
SAD	Single ascending dose
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGLT-2	Sodium-Glucose Transport Protein 2
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TDD	Total daily dose
TEADE	Treatment-emergent adverse device effect
TEAE	Treatment-emergent adverse event
TBR	Time-below-Range
TIR	Time-in-Range
TSH	thyroid-stimulating hormone
UACR	Urinary-albumin-to-creatinine ratio
ULN	Upper limit of normal
[redacted]	

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the planned statistical methods to be implemented for the analysis of data from the study with protocol number CT-868-004 Amendment #5, "A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of CT-868 Administered for 16 Weeks to Overweight and Obese Adult Participants with Type 1 Diabetes Mellitus". The SAP will be approved prior to any database lock and unblinding. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR). The description of layouts for the Clinical Study Report (CSR) outputs, the details about the underlying analysis datasets, the Analysis Data Model (ADaM), programs and CDISC define package, with the linking production outputs to sections in the CSR are not within the scope of this document and will be covered in separate documents.

The analyses described in this SAP will further detail and supersede those specified in Protocol CT-868-004. The differences from the protocol are described in Section 6 "Changes from the Protocol-Specified Statistical Analyses".

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

This section provides information on the study objectives and the corresponding endpoints. The estimand definition of the primary and key secondary objective is detailed in section 3.7.1.

2.1.1 Primary Objective and Endpoints

Primary Efficacy Objective	Primary Efficacy Endpoint
● To compare the effect of CT-868 versus placebo on change in HbA1c (%) from baseline at Day 1 to Week 16	● Change in HbA1c (%) from baseline at Day 1 to Week 16

2.1.2 Key Secondary Objectives and Endpoints

Key Secondary Efficacy Objectives	Key Secondary Efficacy Endpoints
● To assess the effect of CT-868 versus placebo on change in body weight from baseline at Day 1 to Week 16	● Percent (%) Change in body weight from baseline at Day 1 to Week 16
Other Key Secondary Efficacy Objectives	Other Key Secondary Efficacy Endpoints
● To compare the effect of CT-868 versus placebo on change in HbA1c (%) from baseline at Day 1 to Weeks 4, 8, and 12.	● Change in HbA1c (%) from baseline at Day 1 to Weeks 4, 8, and 12
● To assess the percentage of participants achieving HbA1c of	● Participant status of achieving HbA1c of <7.0% at Week 16 (Yes/No)

<7.0%, ≤6.5%, and <5.7% at Week 16	● Participant status of achieving HbA1c of ≤6.5% at Week 16 (Yes/No) ● Participant status of achieving HbA1c of <5.7% at Week 16 (Yes/No)
● To assess the effect of CT-868 versus placebo on change in insulin doses from baseline at Day 1 to Weeks 8 and 16	● Change (absolute and percentage) in basal, bolus, and total daily insulin doses (units/day and units/kg/day) from baseline to Weeks 8 and 16

2.1.3 Other Secondary Efficacy and Safety Objectives and Endpoints

Other Secondary Efficacy Objectives	Other Secondary Efficacy Endpoints
● To assess the effect of CT-868 relative to placebo on the CGM metrics (TIR, time in hypo- and hyperglycemia, glycemic risk index)	● Change from baseline to Weeks 8 and 16 in the following CGM parameters: ○ Mean sensor glucose (mg/dL) and its standard deviation (SD) and %CV [both intraday (i.e., within 24 hours) and interday (i.e., over multiple days)] ○ Percentage of time spent in range (TIR, 70–180 mg/dL) ○ Percentage of time spent in tight range (TITR, 70-140 mg/dL) ○ Percentage of time spent below target range (TBTR, <70–54 mg/dL) and very below target range (TVBTR <54 mg/dL). ○ Percentage of time spent above target range (TATR, >180–250 mg/dL) very above range (TVATR, >250 mg/dL) ○ Number of events with sensor glucose <70 mg/dL lasting at least 120 minutes (event ends when glucose returns to ≥70 mg/dL for ≥15 minutes) ○ Number of events with sensor glucose >250 mg/dL lasting at least 120 minutes (event ends when glucose returns to ≤180 mg/dL for ≥15 minutes)

	○ Participants with TIR 70-180 mg/dL with ≥5% points and ≥10% points improvement from Day 1 (Yes/No) ○ Participants with TIR 70–180 mg/dL for >70% of the 14-day collection interval around the Week 8 Visit and the 14-day interval prior to the Week 16 Visit (Yes/No) ○ Participants with TBR <70 mg/dL for <4% of each day (Yes/No) ○ Participants with TBR <54 mg/dL for <1% of each day (Yes/No) ○ Participants with time above range >180 mg/dL for <25% of each day (Yes/No) ○ Participants with time very above range >250 mg/dL for <5% of each day (Yes/No) ○ Participants with TBR <70 mg/dL for <4% over the 14-day collection interval (Yes/No) ○ Participants with TBR <54 mg/dL for <1% over the 14-day collection interval (Yes/No) ○ Participants with time above range >180 mg/dL for <25% over the 14-day collection interval (Yes/No) ○ Participants with time very above range >250 mg/dL for <5% over the 14-day collection interval (Yes/No) ○ Glycemia Risk Index
● To assess the effect of CT-868 relative to placebo on the change in body weight	● Body weight ○ Percent (%) change in body weight from baseline at Day 1 to Weeks 4, 8, and 12 ○ Absolute change in body weight (kg) from baseline at Day 1 to Weeks 4, 8, 12, and 16

● To assess the effect of CT-868 relative to placebo on the percentage of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss	● Participants achieving ≥5% weight loss at Week 16 (Yes/No) ● Participants achieving ≥10% weight loss at Week 16 (Yes/No) ● Participants achieving ≥15% weight loss at Week 16 (Yes/No) ● Participants achieving ≥20% weight loss at Week 16 (Yes/No)
● To assess the effect of CT-868 relative to placebo on ○ the proportion of participants experiencing one or more Level 1, 2, 3 hypoglycemia events (incidence rate) and ○ the total number of Level 1, 2, 3 hypoglycemia events/total patient-years of exposure (event rate)	● Participants experiencing one or more Level 1 hypoglycemia event(s) [the most extreme case] over the study duration (Yes/No) ● Participants experiencing one or more Level 2 hypoglycemia event(s) [the most extreme case] over the study duration (Yes/No) ● Participants experiencing one or more Level 3 hypoglycemia event(s) [the most extreme case] over the study duration (Yes/No) ● The total number of Level 1 hypoglycemia events/total patient-years of exposure (event rate) ● The total number of Level 2 hypoglycemia events/total patient-years of exposure (event rate) ● The total number of Level 3 hypoglycemia events/total patient-years of exposure (event rate)
● To assess the effect of CT-868 relative to placebo on the incidence of DKA	● Participants with “definite” DKA events as defined in Section 5.2 in Protocol during the study (Yes/No) ● Participants with DKA events that led to hospitalization or emergency room visits during the study (Yes/No)
● To assess the effect of CT-868 versus placebo on number of daily injections from baseline at Day 1 to Weeks 8 and 16 in those on MDIs of insulin	● Change in the number of daily insulin injections (in those on MDIs of insulin) from baseline at Day 1 to Weeks 8 and 16
Other Secondary Safety Objectives	Other Secondary Safety Endpoints

• To assess the safety and tolerability of CT-868 versus placebo administered QD via Pen over 16 weeks	• Safety assessment over the period of 16 weeks ○ AEs/ADEs, including injection site reactions (NOTE: Only TEAEs will be summarized.) ○ AEs/ADEs of special interest (Refer to Protocol Section 9.1.4). ○ Vital signs ○ Physical examinations ○ ECGs ○ Safety laboratory measurements (urinalysis, hematology, chemistry, beta hydroxybutyrate (BHB), amylase, lipase, calcitonin) • Change from baseline at Day 1 to Week 8 and Week 16 in systolic/diastolic blood pressure and heart rate
Other Secondary Objectives	Other Secondary Endpoints
• To evaluate CT-868 plasma concentration	• Plasma drug concentrations at the Weeks 2, 4, 6, 8, 12, and 16 visits

- Experiences a “definite” DKA episode [defined as the presence of acidosis (blood pH <7.3, serum bicarbonate levels <18 mEq/L), and accompanied by symptoms/signs per the ADA consensus statement on diagnosis of DKA (Kitabchi et al. 2009; ADA 2024), or if the DKA episode results in a hospital or emergency room stay. Triggers for SRC adjudication of DKA will include either the presence of symptoms or signs as listed by the ADA consensus statement on diagnosis of DKA (Kitabchi et al. 2009; ADA 2024) or Investigator-reported AEs indicative of DKA. Events will be adjudicated by the SRC with degrees of certainty (definite, possible, unlikely, or as an unclassifiable event), severity (mild, moderate, severe, or not assessable), and outcome (recovered, sequelae, or fatal).

  NOTE: All participants will be provided with ketone meters (in addition to glucometers) with necessary supplies (blood and urine test strips). Participants will be educated on ketone monitoring when feeling unwell and instructed to seek medical care.

  NOTE: Any participant experiencing ADA Level 3 hypoglycemia and/or a “definite” DKA event in the Placebo Run-in Period will be withdrawn from the study and will not be randomized to receive study drug.

2.1.4 Exploratory Objectives and Endpoints

Exploratory Efficacy Objectives	Exploratory Efficacy Endpoints
• To assess the effect of CT-868 versus placebo on composite response parameters at Week 16	• Percentage of participants at Week 16 compared with corresponding baseline with improvement (reduction) in HbA1c ≥0.5% points and <1% TBR <54 mg/dL

	● Percentage of participants at Week 16 compared with corresponding baseline with mean glucose <154 mg/dL and <1% TBR <54 mg/dL ● Percentage of participants at Week 16 compared with corresponding baseline with ≥70% TIR 70-180 mg/dL and <4% TBR <70 mg/dL ● Percentage of participants at Week 16 compared with corresponding baseline with ≥70% TIR 70-180 mg/dL and <1% TBR <54 mg/dL ● Percentage of participants at Week 16 compared with corresponding baseline with HbA1c improvement ≥0.5% points, with <1% TBR <54 mg/dL, and without requiring significant increase in daily insulin use [i.e., >10% increase in total (bolus + basal) insulin (units/kg/day) ● Percentage of participants at Week 16 compared with corresponding baseline with ≥70% TIR 70-180 mg/dL, with <1% TBR <54 mg/dL, and without requiring significant increase in daily insulin use [i.e., >10% increase in total (bolus + basal) insulin (units/kg/day) ● Percentage of participants with at least one CGM-detected Level 2 hypoglycemia events during the 16 weeks treatment period. (The following exploratory endpoints will be reported separately from the CSR) ● Percentage of participants at Week 16 achieving ≥70% TIR AND <4% TBR (<70 mg/dL) AND weight loss ≥5% ● Percentage of participants at Week 16 achieving HbA1c <7% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA ● Percentage of participants at Week 16 achieving HbA1c <7% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA AND weight loss ≥5% ● Percentage of participants at Week 16 achieving HbA1c reduction ≥0.5% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA ● Percentage of participants at Week 16 achieving HbA1c reduction ≥0.5% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA AND weight loss ≥5%

	• Percentage of participants at Week 16 achieving ≥70% TIR AND weight loss ≥5% AND insulin total daily dose (TDD) reduction ≥20% • Percentage of participants at Week 16 achieving HbA1c <7% AND weight loss ≥5% AND insulin TDD reduction ≥20%
• To assess the effect of CT-868 versus placebo on daytime and nighttime CGM metrics.	(The following exploratory endpoints will be reported separately from the CSR) • Changes in CGM-based metrics (TIR 70-180 mg/dL, TBR <70mg/dL, TAR >180 mg/dL, mean glucose) during the daytime (6AM-11:59PM) and the nighttime (12AM-5:59PM) from baseline to Week 8 and Week 16.
• To assess the effect of CT-868 versus placebo on blood biomarkers of metabolism, inflammation, and endothelial health	• Change from baseline at Day 1 to Week 8 and Week 16 in glucose, insulin, C-peptide, glucagon, GLP 1 (total and active), and GIP, • Change from baseline at Day 1 to Week 8 and Week 16 in fasting lipid profile (triglycerides, total cholesterol, LDL C, HDL-C, VLDL, FFA, ApoB), adiponectin, leptin, hsCRP, PAI-1 activity, CTX-1, MCP-1, IL-6, endothelin-1, E selectin, VCAM-1, ALT, eGFR, and UACR
• To assess the effect of CT-868 versus placebo on total lean mass and total fat mass by DEXA	• Change from baseline to Week 16 in total lean mass and total fat mass as determined by DEXA
• [redacted]	• [redacted]
• [redacted]	• [redacted]

● To assess percentage of patients who can reach and and/or maintain at different dose levels	● Number of participants completed study treatment and maintained at different dose levels during Week 12 to Week 16 ● Number of participants reached the final planned dose of each cohort, and Time (weeks) to the final planned dose of each cohort.
● To determine correlation between time to attain the highest CT-868 dose and change in HbA1c and % body weight change from baseline to Week 16 (Arm 4 only)	● Time to Highest Dose for patients in Arm 4 ● Change in HbA1c at Week 16 for patients in Arm 4 ● % body weight change from baseline to Week 16 for patients in Arm 4

● [redacted] ADE=adverse device effect; AE=adverse event; ApoB=apolipoprotein B; AUC_{0-24}=area under the plasma concentration time curve from time 0 to 24 hours; AUC_{0-last}=area under the plasma concentration time curve from time 0 to last quantifiable plasma concentration; BHB=beta-hydroxybutyrate; CGM=continuous glucose monitoring; C_{max}=maximum plasma concentration; C_{last}=last quantifiable plasma concentration; C_{trough}=predose trough concentration; DEXA=dual energy X-ray absorptiometry; DKA=diabetic ketoacidosis; [redacted] ECG=electrocardiogram; FFA=free fatty acids; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; HbA1c=hemoglobin A1c; HDL-C=high density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; iAUC=incremental area under the plasma concentration time curve; IL-6=interleukin 6; LDL-C=low density lipoprotein cholesterol; MCP-1=monocyte chemoattractant protein-1; PK=pharmacokinetic; PAI-1=plasminogen activator inhibitor-1; TBR=time below range; TIR=time in range; T_{last}=time to last quantifiable plasma concentration; TWA=time-weighted average; PRO=patient-reported outcome; T_{max}=time to maximum plasma concentration; UACR=urinary-albumin-to-creatinine ratio; [redacted] VCAM-1=vascular cell adhesion protein 1; VLDL=very low density lipoprotein.

2.1.5 Objectives and Endpoints Related to Pharmacokinetics & Immunogenicity

Objectives Related to Pharmacokinetics and Immunogenicity	Endpoints Related to Pharmacokinetics and Immunogenicity
● To assess the CT-868 concentration-time profile over 24 hours (in a subset of the T1DM study population)	● CT-868 PK parameters (C_{max}, T_{max}, C_{trough}, C_{last}, T_{last}, AUC_{0-last}, AUC_{0-last}, and $t_{1/2}$)
● To evaluate treatment-emergent anti-drug antibodies to CT-868 (Arms 2, 3, 4 only)	● Treatment-emergent anti-drug antibodies to CT-868 on Day 1 and Week 16 (Arms 2, 3, and 4 only)

2.2 Study Design

2.2.1 Overview

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of CT-868 in both overweight and obese adult participants with T1DM.

The Protocol Synopsis includes the study objectives and endpoints, study design, inclusion and exclusion criteria, medicinal product administration, and statistical methods as stated in the protocol. For additional details, see the Schedule of Procedures in Appendix B.

The total duration of the study for each participant will be up to ~25 weeks (including the Screening Visit), and include the following:

- Up to 3 weeks of Screening Period to verify eligibility for the study;
- Up to 2 weeks of a discretionary (based on the Investigator's discretion) Insulin Adjustment Period for the Investigator to have an opportunity to assess the adequacy of their existing insulin regimens and discern if participants are within treat-to-target goals (i.e., ≥70% TIR 70-180 mg/dL with <4% TBR <70 mg/dL); instructions on recording daily insulin doses using mobile application would also be provided;
- 2 weeks of mandatory single-blind (participant-blinded) Placebo Run-in Period to collect baseline data and instruct participants on proper administration of study drug using the pen device and reinforcement of other diabetes self-care management tasks (glucose monitoring, ketone testing, changing CGM sensors every 10 days, adjusting insulin doses if needed, etc.);
- 16 weeks of double-blind, randomized Treatment Period to receive either CT-868 or placebo on the background of insulin and other standard-of-care treatments for T1DM; and
- 2 weeks of Safety Follow-up Period after the final dose of CT-868 or placebo is administered.

2.2.2 Randomization and Blinding

2.2.2.1 Randomization

This is a randomized, double-blinded, placebo controlled, multi-center study. Participants were assigned a randomization number associated with the treatment assignment as determined by an Interactive Response Technology (IRT) system. The IRT system was used to manage all aspects of treatment and titration and logistical aspects of study product supply. The master randomization lists were kept by Medpace IRT and confidentially supplied to the PK laboratory, the independent unblinded statistician, or any other unblinded staff as needed. Participants meeting eligibility criteria were randomized at Visit 4 (Day 1) in a [redacted] ratio to 4 treatments arms titrated per protocol and according to the participant's tolerability:

- Arm 1 Volume-matched placebo
- Arm 2 1.8 mg CT-868: [redacted]mg| 1.8 mg
- Arm 3 4.1 mg CT-868: [redacted]mg| [redacted]mg| [redacted]mg| [redacted]mg| 4.1 mg
- Arm 4 CT-868 dosed to tolerability/ up to maximum of 6.6 mg: [redacted]mg| [redacted]mg| [redacted]mg| [redacted]mg| [redacted]mg| [redacted]mg| 6.6 mg

The randomization was stratified based on:

- The HbA1c level measured at Screening (<8.5% or ≥8.5%)
- The method of insulin administration (pump or MDI).

This stratification helped to better understand the effects of CT-868 treatment on glycemic control in both insulin pump and MDI users across different HbA1c levels.

Randomized participants who terminated study participation for any reasons before the first administration of study drug retained their randomization and treatment number. Randomization numbers were not reused. Randomized participants who prematurely discontinued the study were not replaced.

2.2.2.2 Blinding

Due to the titration scheme, participants and study staff were aware of the volume of study drug the participants were receiving; however, they were not aware of whether they were receiving CT-868 or the placebo, as placebo dose is volume-matched to a corresponding dose of CT-868.

Individual treatment assignments may be unblinded when immediate knowledge of the treatment assignment is needed to optimize the clinical management of the participant. In case of medical emergency, the Investigator will have direct access to unblinding of treatment. The Investigator should contact the Medical Monitor as soon as possible to discuss the event. The IRT system allows for immediate emergency unblinding of a participant by the site when determined necessary. Site personnel will be trained by the clinical research associate (CRA) in the unblinding procedures.

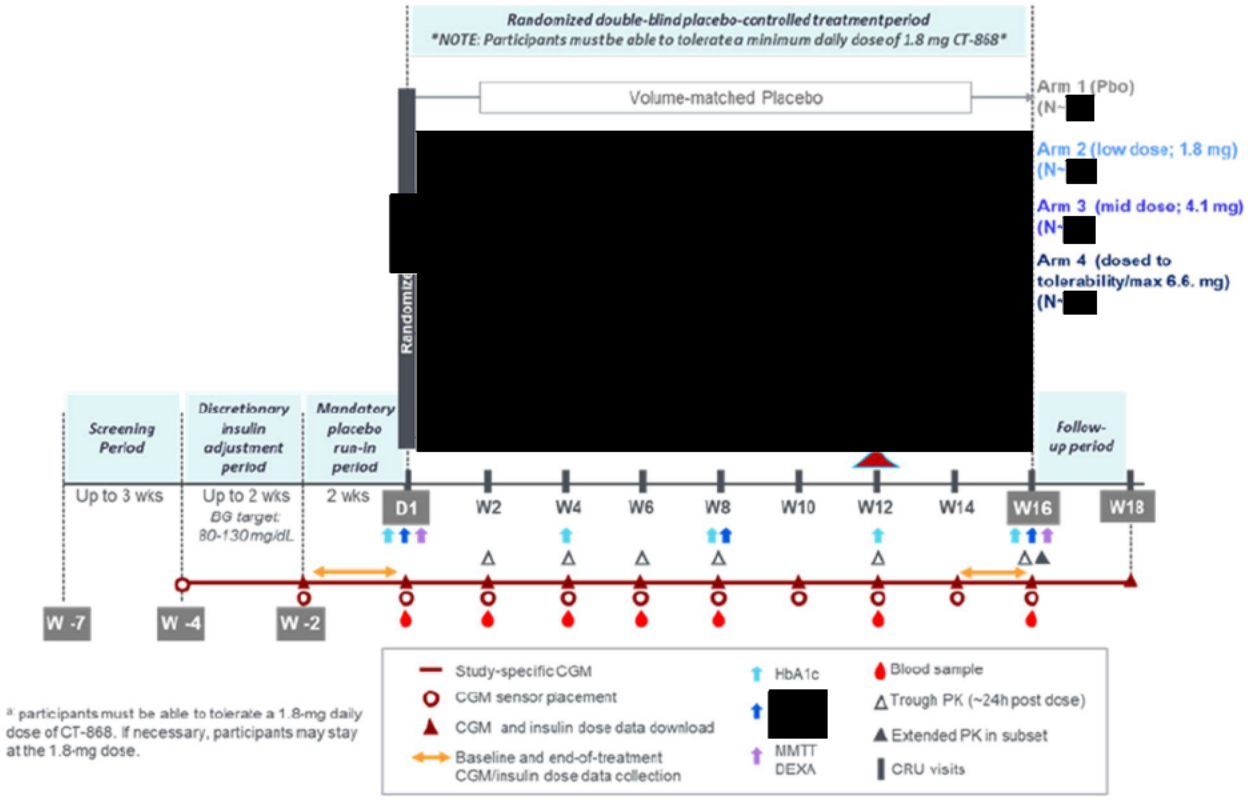
Documentation of the blind break, including the participant's identification, reason for breaking the blind, and the date and time of breaking the blind, must be retained in the participant's source at the site.

2.2.3 Study Drug

CT-868 Injection [redacted] mg/mL and CT-868 Injection placebo solutions will be supplied in a needle based injection system with an integrated non-replaceable [redacted]-mL Type 1 glass cartridge, the CT-868 Pen Injector (Pen). The CT-868 Pen is a multi-dose, single participant, disposable pen designed to deliver [redacted] fixed doses of [redacted] mg ([redacted] mL), 1.8 mg ([redacted] mL), [redacted] mg ([redacted] mL), [redacted] mg ([redacted] mL), and 4.1 mg ([redacted] mL) by SC injection in the [redacted]. The CT-868 Pen contains a clear, colorless, sterile aqueous solution of [redacted] mg/mL CT-868 (active only) in [redacted]

Study Design schematic is presented in Figure S1. Dose escalation may occur at, or after, but not before, the designated time for up-titration.

- Figure S1



- BG=blood glucose; CGM=continuous glucose monitoring; CRU=clinical research unit; D=day; DEXA=dual X ray absorptiometry; HbA1c=hemoglobin A1c; PK=pharmacokinetic; [redacted] W=week; wks=weeks.

The placebo Pen looks identical and contains the same ingredients except CT-868. Each active Pen contains [redacted] mg/[redacted] mL of CT-868. Each Pen is individually packaged in a carton including the Instructions for Use (IFU). Within each dose group, the CT-868 and placebo Pens will be identical in appearance.

CT-868 and placebo are to be titrated per Protocol according to the individual participant's tolerability up to a maximum dose of 6.6 mg CT-868. Adjustments in the dose escalation schedule for participants who experience tolerability issues are allowed; details of the doses and titration scheme for each treatment arm are provided in Appendix D.

2.2.4 Sample Size Determination

Approximately 96 participants were planned to be randomized at a ratio of [redacted] to CT-868 or placebo, to achieve a total of at least [redacted] completed participants at Week 16 (assuming an approximately [redacted] drop out rate).

Based on previously observed treatment effects on HbA1c of [redacted] in a nearly identical T1DM population (Klein et al. 2021), the proposed sample size of [redacted] completed participants per arm is anticipated to provide a meaningful qualitative assessment of outcomes and summary statistics estimates for subsequent pivotal trials. Assuming a standard deviation of [redacted] and a one-sided test at 5% significance level, [redacted] participants per treatment arm would allow for detecting an HbA1c difference of [redacted] with larger than [redacted] power between any 2 arms. In

addition, assuming the difference between any 2 arms is [redacted] and [redacted] in the dropouts and completed participants, respectively, [redacted] participants per arm will provide at least [redacted] power to detect an overall difference of [redacted] between any arm.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of the first dose of randomized study drug (i.e., Day 1). If the date is on or after Day 1, analysis day= date-first dosing date+1; if the date is before, analysis day=date-first dosing day. There will be no Day 0.

3.1.2 Analysis Visits

Analysis Visits will be assigned to the observed values using the corresponding Analysis Day per the Visit Window in tables below. Note that the correct table should be used based on the planned data collection frequency. For example, Table 1.1 of Visit Windows should be used for procedures that are planned to be performed every 2 weeks. Note that for CGM related endpoints and Insulin dose related endpoints refer to Section 3.4.3.1 and Section 3.4.2.2.2, respectively. [redacted]

Unless otherwise specified, in the situation when there are multiple observations falling into the same analysis visit window, the one closest to the Target Analysis Day in the table will be used in the analysis. If two observations are of the equal distance to the Target Analysis Day but one before and one after, the one after the Target Analysis Day will be used.

- **Table 1.1** of Visit Windows for procedures scheduled for every 2 weeks

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Baseline	1	NA	prior to first dosing of the randomized study drug
Week 2	15	9	22
Week 4	29	23	36
Week 6	43	37	50
Week 8	57	51	64
Week 10	71	65	78
Week 12	85	79	92
Week 14	99	93	106
Week 16	113	107	126
Week 18 follow-up	127	127	NA

- **Table 1.2** of Visit Windows for procedures scheduled for every 4 weeks

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Baseline	1	NA	prior to first dosing of the randomized study drug
Week 4	29	16	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	126
Week 18 follow-up	127	127	NA

- **Table 1.3** of Visit Windows for procedures scheduled for every 8 weeks

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Baseline	1	NA	prior to first dosing of the randomized study drug
Week 8	57	30	85
Week 16	113	86	126
Week 18 follow-up	127	127	NA

- **Table 1.4** of Visit Windows for procedures scheduled for every 16 weeks

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Baseline	1	NA	prior to first dosing of the randomized study drug
Week 16	113	86	126
Week 18 follow-up	127	127	NA

3.1.3 Definition of Baseline

For all analyses, unless specified otherwise, “baseline or baseline at Day 1” is defined as the last available non-missing value prior to first dose of the randomized study drug. If no such value exists, the baseline assessment will be set to missing.

For insulin dose related endpoints, the baseline is defined as the average daily insulin dose over a consecutive 7 days period prior to Day 1, provided that at least 4 out of those 7 days have

non-missing daily insulin dose data. If no such 7-day period exists within the 14-day placebo run-in period, the baseline will be considered missing.

CGM metrics data, collected during the mandatory 2-week Placebo Run-in Period (Week -2 to Day 1 predose), will be used to derive the participant's baseline values for the defined CGM endpoints. If less than 70% of the expected readings [redacted] are collected during the Placebo Run-in Period, the baseline will be considered missing. Details of the derivation of each endpoint are provided in Appendix E.

For DEXA scan related endpoints, the baseline is defined as the last available non-missing value prior to Day 1. If such a record doesn't exist, the baseline can then be defined as the first available non-missing value within the +14 days after Day 1 randomization. Otherwise, set to missing.

[redacted]

3.1.4 Summary Statistics

Categorical data will be summarized with counts and percentages of participants. The denominator and the numerator used for the percentage calculation will be clearly defined in the TFLs Programming Specification. Continuous data will be summarized using descriptive statistics including the number of non-missing values (n), mean, median, standard deviation, minimum, and maximum. Data will be presented by participant groups as specified for each analysis. The 3 placebo groups will be pooled prior to analysis for comparison to CT-868 groups.

The unique participant ID collected in the study will be used for analysis.

3.1.5 Handling of Dropouts, Missing Data, or Other Data Issues

For the primary endpoint, the primary efficacy analysis using ANCOVA will impute missing data for HbA1c (%) at Week 16. Missing data will be imputed using the retrieved dropout (RD) approach (Wang et al., 2022; Wang et al., 2023). If the minimum required number of retrieved dropouts is not met, other multiple imputation methods may be considered.

For the key secondary endpoint of percent (%) change in body weight from baseline to Week 16, the missing data will be handled in the similar way as described for the primary endpoint.

For one of the other key secondary endpoints: change (absolute and percentage) in basal, bolus, and total daily insulin doses (total daily insulin doses with non-weight adjusted and weight adjusted), the insulin dose-related endpoint will be based on the median insulin dose over 7 consecutive days prior to the analysis visit. Specifically, it will be calculated from the last 7 consecutive days within a 14-day window prior to the analysis visit, where at least 4 out of those 7 days have non-missing data recorded in the insulin data (Refer to Section 3.4.2.2.2). If the participant does not have any 7 consecutive days with at least 4 non-missing insulin dose entries within the 14 days interval, this will be considered missing. Missing post-baseline data will be imputed implicitly using MMRM.

CGM endpoints at baseline, Week 8, and Week 16 will be derived using a 14-day window before or around the target visit (Refer to Section 3.4.3.1). If less than 70% of the expected readings [redacted] are collected within a 14-day window, CGM metrics for that corresponding target visit will be considered as missing, otherwise, CGM metrics will be computed using all available readings within the 14-day window. As a sensitivity analysis, CGM metrics will be derived regardless of the 70% completeness rule. This would provide a comprehensive view and help determine the impact of missing data on the results. Missing post-baseline data will be imputed implicitly using MMRM. In cases where multiple CGM readings are available at the same timestamp for a participant, the values will be averaged to obtain a single representative measurement.

If there are incomplete start or stop dates for medications (both prior and concomitant medications), dates will be imputed only to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for a missing month. If a medication stop date is incomplete, the last day of the month will be imputed for a missing day and December will be imputed for a missing month. If the imputed end date falls after the data cut date or participants' end of the study date, the data cut date or participants' end of the study date will be assigned as the end date. Incomplete start and stop dates will be reported as collected without imputation.

The above imputation rules also apply to missing onset dates for adverse events to help determine whether an adverse event is a pre-treatment event (if the onset time is prior to the first doing time) or a treatment emergent event (if the onset date and time is on or after the first dosing time). If AE onset time is incomplete, the missing hours will be imputed as 23, and the missing minutes/seconds will be imputed as 59. This should also apply to the imputation of missing AE end date.

In general, if not otherwise specified, missing time imputation (e.g., for vital signs, DEXA, and lab measurements) should follow Roche standards and 23:59:59 will be used. If the date is partially missing, the analysis date is set to be null.

When considering lab and pharmacokinetic result data, values which are including "<" or ">" will be analyzed using the numeric value provided in the result. For PK concentrations, if a concentration is below the limit of quantification (BLQ) the concentration value will be analyzed as 0. If not reportable (NR) then consider the value as missing.

For self-monitoring of blood glucose (sMBG) data entered by participants in the symptom diary, any values < 20 mg/dL will be considered missing. This is because the glucometer issued to study participants has a measuring range from 20 mg/dL to 600 mg/dL as outlined by the user guide of CONTOUR®NEXT blood glucose monitoring system.

3.1.6 Adjunct Therapy

As of the finalization of this SAP, adjunct therapies would include anti-type 1 diabetes therapies approved in the US (Pramlintide) and incretin mimetics (Liraglutide, Dulaglutide, Semaglutide, and Tirzepatide).

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all randomized participants. Analysis using the ITT Population will be done according to the assigned randomized treatment arm. This will be the main population for the analysis of the primary endpoint (change in HbA1c) and the key secondary endpoint (percent change in body weight).

3.2.2 Modified Intent-to-Treat (mITT) Population

The modified Intent-to-Treat (mITT) Population will include all randomized participants who receive at least one dose of study drug. Analysis using the mITT Population will be done according to the assigned randomized treatment arm. This population will be used as the supplementary analysis on the primary endpoint (change in HbA1c) and the key secondary endpoint (percent change in body weight), and as the main analysis population for the remaining efficacy endpoints including other key secondary endpoints, secondary endpoints, and exploratory endpoints

3.2.3 Per-Protocol (PP) Population

The Per Protocol (PP) Population will include all participants in the mITT Population who do not have a major protocol violation i.e. a deviation that would potentially impact the primary efficacy endpoint. Analysis using the PP Population will be done according to the assigned randomized treatment arm. This analysis set will be used for the supplementary analysis for the primary endpoint of change in Hb1Ac and key secondary endpoints of percent (%) change in weight loss only.

Major protocol violations that may impact the primary efficacy assessment may include but are not limited to:

- Failed to meet eligibility criteria
- Took the wrong study drug (i.e., did not take the randomized study drug) or received incorrect dose
- Had study drug compliance <80% or >120%
- Took a restricted concomitant medication (new or dose increase from the highest dose received during Screening) that may affect primary efficacy endpoint
- Baseline fasting C-peptide > 0.6 ng/ml
- Baseline HbA1c<7.0%

A list of participants with major protocol deviations leading to exclusion from the PP Population will be finalized prior to unblinding the randomized treatment assignments.

3.2.4 Safety Population

The Safety Population will include all randomized participants who receive at least 1 dose of randomized study drug. All safety endpoints will be summarized using the Safety Population and participants will be grouped according to their actual treatment received (Placebo or CT-868). Participants receiving at least one dose of CT868 will be grouped into the following three dose groups according to their highest dose received:

- Low dose group (highest dose received: [redacted]mg or 1.8mg)
- Mid dose group (highest dose received: [redacted]mg, [redacted]mg, or 4.1mg)
- High dose group (highest dose received: [redacted]mg or 6.6mg)

As an alternative definition, in the *safety by randomized dose population*, participants will be grouped by their assigned randomized treatment arm, with the exception of:

1. participants randomized to an active arm but only received placebo, who will be grouped in the placebo arm.
2. participants randomized to Placebo but received at least one active dose, who will be grouped by their highest dose received as follows:
    - If highest dose received ≤1.8 mg: assign to Arm 2 (low dose; 1.8 mg)
    - If highest dose received >1.8mg and ≤4.1 mg: assign to Arm 3 (mid dose; 4.1 mg)
    - If highest dose received >4.1mg: assign to Arm 3 (dosed to tolerability/max 6.6mg)

This alternative definition will be used for selected safety outputs as specified in the Safety Assessment Section (Section 3.7)

3.2.5 Pharmacokinetic (PK) Population

The PK Population analysis set will include data from all randomized participants who receive at least 1 dose of study drug and have at least 1 measurable CT-868 concentration. PK summaries and analyses will be conducted using the PK Population.

3.3 Participant Data and Study Conduct

3.3.1 Participant Disposition

Counts and percentages of participants who were screened (signed informed consent), screen failed, and randomized will be summarized in total based on all screened participants. Reasons for screen failures will also be summarized.

A listing and summary table of participants who were screen failures will be provided together with the demographic information (age, sex, race, ethnicity, and last record of weight, BMI and HbA1c prior to screen fail).

Counts and percentages of participants who were randomized, discontinued early from the study drug, discontinued early from the study, the number of participants who actually completed the remaining visits despite discontinuing early from the study drug will be summarized by treatment, CT-868 in total and overall (Placebo and CT-868) based on all randomized participants. Primary reasons for early discontinuation from the study drug and from study will also be summarized.

Additionally, dosing history of each participant up to Week 16 will be displayed using a swimmer plot by randomized treatment groups.

3.3.2 Protocol Deviations

All protocol deviations will be categorized and listed by participant, and major protocol deviations will be summarized. Counts and percentages of participants with at least one major protocol deviation by deviation category will be summarized by treatment, CT-868 in total and

overall (Placebo and CT-868) for all randomized participants by randomized treatment groups. To further investigate sites with particularly high numbers of major protocol deviations, separate summary tables may be generated.

3.3.3 Analysis Populations

Counts and percentages of participants in each analysis population will be summarized by randomized treatment, CT-868 in total and overall (Placebo and CT-868) for all randomized participants. In addition, the HbA1c evaluable population within mITT will also be listed.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Age groups (<65 years or ≥65 years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2), where BMI = Weight/(Height/100)^2, unit of height is cm in data collection.
- BMI categories (<30 kg/m^2 or ≥30 kg/m^2)
- Baseline HbA1c, HbA1c strata (<8.5% or ≥8.5%), and HbA1c categories (<7%, 7% to <7.5%, 7.5% to <8%, 8% to <8.5%, and ≥8.5%)
- Method of insulin administration by the stratification factor (MDI or Pump users), and by further breaking down pump users [MDI or Pump users (AID) or Pump users (non-AID)].

Additional demographic and baseline characteristics might be added.

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of participants, as appropriate, by treatment and CT-868 in total under the ITT Population. If there is more than a 20% difference in the number of participants between the ITT and Safety/mITT (HbA1c)/PP Populations, additional demographic tables will be presented for each defined population.

3.3.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or above.

Medical history refers to any medical condition already stopped by the time of ICF. Concurrent Medical Conditions are those present at the time of ICF, these conditions include any chronic or acute conditions, diseases, past surgeries, and relevant health issues known before the participant enters the study.

Counts and percentages of participants with medical history and concurrent medical conditions by system organ class and preferred term will be summarized by treatment and in total based on the ITT population in two separate tables.

3.3.6 Prior and Concomitant Medications and procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Global B3 March 2023 or above.

For summary purposes, medications will be considered prior medications if they were stopped before the first dose of randomized study drug. Medications will be considered concomitant medications if they were taken prior to and were ongoing at the time of the first dose of the randomized study drug or initiated after the first dose of randomized study drug.

Refer to Section 3.1.5 for incomplete start or stop date of a medication.

Counts and percentages of participants taking prior and concomitant medications by ATC level 2 and preferred terms will be summarized by treatment, CT-868 in total and overall (Placebo and CT-868) based on ITT Population.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to study drugs (treatment duration) will be calculated as date of last dose of study drug – date of first dose of randomized study drug + 1. The first dose date and the last dose date collected in eCRF will be used for the calculation of the exposure. Note that the exposure calculation is intended to describe the length of time a participant was exposed to study drug and therefore does not take study drug interruptions into account.

Days of exposure to study drug will be summarized by treatment based on the ITT Population with descriptive statistics and with counts and percentages of participants with exposure in the following categories:

- <4 weeks (<28 days)
- 4 - <8 weeks (28 – 55 days)
- 8 - <12 weeks (56 – 83 days)
- 12 - <16 weeks (84 – 111 days)
- ≥ 16 weeks

Percent compliance to the study drug regimen will be calculated as 100 x number of doses administered/number of doses planned per Protocol. The number of doses planned per Protocol will be calculated based on study design schematic presented in Figure S1. The number of doses administered will be calculated as the difference between the number of doses planned per Protocol and the number of missed doses collected from eCRF. Percent compliance to the study drug regimen will be summarized based on the ITT Population with descriptive statistics and with counts and percentages of participants with compliance in the following categories:

- <80%
- 80-120%
- >120%

Summary statistics of the number of participants maintained at different dose levels, time stayed on the maintenance dose from Week 12 and up to Week 16 (i.e., treatment completion), number of participants reached final planned dose, and time to achieve the final planned dose of all CT-868 dose cohorts will be provided. ITT Population will be used for these summaries.

- The maintenance dose is defined for completers only (participants who had completed the study treatment based on eCRF). It is defined as the dose level that was administered for the majority of days from Week 12 visit date and up to the last dosing date per eCRF. If the Week 12 visit date is missing, the window for identifying maintenance dose would then start 4 weeks prior to the last dosing date per eCRF, and end on the last dosing date per eCRF. If multiple dose levels were administered for the same number of days, the highest dose level should be selected. Set the maintained dose to be missing if the participant discontinued study treatment early.
- Time spent on the maintenance dose from Week 12 and up to Week 16 is defined as the number of days the maintained dose was administered from Week 12 to treatment completion.
- The final planned dose of Arms 2,3,4 are [redacted], 4.1, and 6.6 mg, respectively.
- Time to achieve the final planned dose is defined as the date of the first time the final planned dose is administered - first dose date +1.

3.4 Efficacy Analyses

Observed values and change from baseline in HbA1c, observed values and percent change from baseline in body weight will be summarized by scheduled visits and treatment groups using the ITT, mITT, and PP Populations, respectively. The other key secondary, secondary, and exploratory endpoints will be summarized using the mITT Population. For continuous variables, observed and change from baseline, if non-missing, will be summarized by treatments and visits; for categorical variables, non-missing values will be counted as the denominator.

For inferential analysis with statistical models (MMRM, ANCOVA, Logistic regression with G-computation, negative binomial, etc), unless otherwise stated, the analysis population should include participants with non-missing data (after imputation if an imputation method is specified) at baseline and at least one post-treatment timepoint (for MMRM) or at the timepoint of interest (the rest of the models).

The stratification factors (HbA1c groups and the insulin administration methods) collected in the IRT system for the efficacy analysis when deemed appropriate.

Unless otherwise stated, the covariance matrix structure used in MMRM will follow the sequence of 1) Unstructured, 2) Autoregressive (1), and 3) Compound Symmetry in the event of non-convergence.

Definition of on-treatment period: For CGM or insulin daily dose related efficacy endpoints, longitudinal measurements up to 24 hours after the last dose or prior to the start of new adjunct therapy, whichever is earlier, may be used. For DEXA related endpoints, measurements up to 14 days after the last dose or prior to the start of new adjunct therapy, whichever is earlier, may be used. ALT and eGFR from the serum chemistry panel are considered as safety endpoints, and longitudinal measurements up to 14 days post-last dose or prior to the start of new adjunct therapy, whichever is earlier, may be used. For other efficacy endpoints, longitudinal measurements up to 7 days post-last dose or prior to the start of new adjunct therapy, whichever is earlier, may be used.

3.4.1 Primary Endpoint Analyses

3.4.1.1 Estimand for the primary endpoint

The primary objective of assessing the effect of CT-868 versus placebo on change in HbA1c from baseline to Week 16 is expressed using the estimand framework in accordance with the International Conference for Harmonization (ICH) E9 (R1) statistical principles for clinical trials (ICH 2020) as follows:

Primary objective: Assess the effect of CT-868 versus placebo on change in HbA1c from baseline to Week 16:

Treatment condition: The randomized CT-868 (Arm 2: CT-868 titrated to 1.8 mg/day, Arm 3: CT-868 titrated to 4.1 mg/day, and Arm 4: CT-868 titrated up to 6.6mg/day) or Placebo (Arm 1: pooled placebo dose), following the same dosing schedule without the active ingredient.

Population: Overweight and obese adult participants with Type 1 Diabetes Mellitus who have met the inclusion and not met exclusion criteria.

Endpoint (Variable): Change in HbA1c (%) from baseline to Week 16

Intercurrent events and strategy for handling:

- The maintenance dose is different from the final planned dose. This will be handled by a treatment policy strategy.
- Early discontinuation from study treatment due to any reason.
    - This will be first handled using a treatment policy strategy with RD imputation. Note that the on-treatment period definition contradicts with the treatment policy strategy, and will not be applied to subjects discontinued study treatment early.
    - If the RD imputation does not converge, a hypothetical strategy with MMRM will be used as the primary strategy to handle instead.

Population-level summary: the mean difference in change in HbA1c (%) from baseline to Week 16 between each CT-868 treatment group and placebo.

3.4.1.2 Primary analysis of the primary estimand

As the primary analysis, the change in HbA1c (%) from baseline to Week 16 will be compared between each of the CT- 868 treatment groups and Placebo using an Analysis of Covariance (ANCOVA) model. The ANCOVA model will include treatment, methods of insulin administration (pump or MDI), and baseline HbA1c as model covariates. Analysis will be conducted on the ITT population.

The effect of CT-868 on HbA1c will be evaluated by estimating the differences in the least squares (LS) means between a CT-868 dose group and Placebo, along with 90% two-sided confidence intervals and the associated two-sided p-value from this ANCOVA model. No formal hypothesis testing and no multiple comparison adjustments will be made.

3.4.1.3 Missing data consideration for the primary estimand analysis

For the primary analysis, missing data will be imputed using the retrieved dropout (RD) approach (Wang et al., 2022; Wang et al., 2023). Specifically, for participants who discontinued the study drug early and do not have HbA1c measurements at Week 16, their Week 16 HbA1c values will be imputed based on the data from those retrieved participants in the same randomized treatment group, i.e., those who discontinued treatment early but have HbA1c measurements at Week 16, using a multiple imputation approach. The following steps will be conducted to perform the retrieved dropout MI to impute the missing data for primary endpoint:

1. Intermediate missing data points are imputed using Markov Chain Monte Carlo (MCMC) to achieve a monotone missing data pattern. This process will be repeated $N = 100$ times to generate 100 datasets using SAS PROC MI. The covariates in the model are Baseline HbA1c and method of insulin administration (pump or MDI).
2. For each of the 100 datasets in Step 1, create 2 subsets:
    a. Subset 1: participants classified as off-treatment at the endpoint visit. These participants are either RDs or non-RDs.
    b. Subset 2: on-treatment completers.
3. Imputation for each subset separately
    a. Within each Subset 1 from Step 2, perform monotone regression imputation once for those with missing data to create one complete subset.
    b. In case there is missing at Week 16, within each Subset 2 from Step 2, perform imputation for those with missing data at Week 16 to create one complete subset
4. Combine each of the completed subsets from Step 3 with the on-treatment completers (Subset 2 if non-missing) to form one complete dataset.
5. Apply an Analysis of Covariance (ANCOVA) model as described above on each of the 100 complete datasets to calculate the estimates and standard errors of LS means, the difference in LS means and CI for comparison between treatment groups.
6. Use Rubin's rules to combine and synthesize the N=100 sets of results from Step 5 to estimate an overall treatment effect and corresponding variability using SAS PROC MIANALYZE.

Example SAS code for performing this analysis is in Appendix F.

Although the RD approach is the preferred method that aligns with the MNAR assumption of the missingness and a treatment policy estimand, this is a phase 2 trial with a limited sample size. We may not have a sufficient number of retrieved dropouts to implement this approach. With such a small sample size, ANCOVA with RD may lead to estimators with inflated variance and a small, unstable effect size. As recommended by Wang et al. (2022), a minimum of 24 retrieved dropouts are needed to have a robust imputation when there are 10 or more early dropouts. Therefore, the RD imputation method will be triggered only when there are at least 24 retrieved dropouts in the Placebo arm and also in the pooled CT-868 arm.

In instances where the number of retrieved dropouts does not meet the above criteria, the secondary hypothetical estimand with MMRM (Section 3.4.1.4) will be considered as the primary analysis.

No sensitivity analysis is planned for the primary estimand.

3.4.1.4 Secondary estimand

As a secondary estimand, a hypothetical strategy will be used to handle the intercurrent event of early discontinuation from study treatment, where observations after the last dose for participants who discontinued treatment early will be deleted.

An MMRM model will be used to estimate the treatment difference. In addition to the factors and covariates used in the ANCOVA model described in Section 3.4.1.2, all visits with pre-planned data collection (Weeks 4, 8, 12, and 16) and the treatment-by-visit interaction will be included as additional factors in the MMRM model. Analysis will be conducted on the ITT population.

The model will incorporate a common unstructured variance-covariance matrix for the random error terms in each arm. If the MMRM model with unstructured covariance matrix does not converge (under the default SAS setting for MMRM using PROC MIXED), it will be replaced with firstly Autoregressive (1) covariance matrix, and then a Compound Symmetry covariance matrix. Parameters will be estimated with the use of restricted maximum likelihood, and the Kenward-Roger method will be used for calculating the denominator degrees of freedom. Marginal effect will be estimated via MMRM.

Missing data will be handled implicitly via the MMRM model based on the missing at random (MAR) assumption. That is, MMRM assumes that given the statistical model and given the observed values of the endpoint, the missing data are independent of the unobserved values (O'Kelly and Ratitch 2014). Correlation between successive observations on a participant allows data from participants who dropped out to make a contribution to the estimation of the effects at the final time point. Additional sensitivity analyses (Section 3.4.1.5) will be performed to assess the impact on missing data handling.

As described in Section 3.4.1.3, this analysis will be run as the *primary analysis* in the instance where the number retrieved dropouts does not meet the minimum requirement.

3.4.1.5 Sensitivity Analysis under a hypothetical estimand

The following sensitivity analyses under a hypothetical estimand will be performed in the ITT population. Observations after the last dose for participants for discontinued treatment early will be deleted. The change from baseline in HbA1c to Week 16 between each of the CT-868 treatment groups and Placebo will be analyzed using the following statistical model:

- Use the ANCOVA model as described in section 3.4.1.2, and the Last observation (on treatment) carry forward (LOCF) to impute the missing HbA1c measurement at Week 16. Note that for patients without any observations after the first dose, LOCF will not be performed.
- Use the ANCOVA model as described in section 3.4.1.2, including only the participants with complete HbA1c measurement at Week 16. No imputation will be done for the missing HbA1c measurement at Week 16.

3.4.1.6 Supplementary Analyses

The primary estimand (treatment policy with ANCOVA model and RD imputation, if reaching the minimum required number of retrieved dropouts) and/or the supplementary estimand (hypothetical strategy with MMRM including the two sensitivity analyses with ANCOVA) will be repeated as supplementary analysis in the following population:

- The mITT population and among participants with baseline and at least one post-treatment measurement of the corresponding endpoint. This analysis will be performed if this population is different from the ITT.
- The PP population and among participants with baseline and at least one post-treatment measurement of the corresponding endpoint.

Summary statistics of observed and change in HbA1c from baseline at Day 1 to each scheduled visit with planned HbA1c measurement will be provided.

- **Table 2**: Primary and Secondary Estimand for the Primary Endpoint

Intercurrent Event	Handling Strategy	Estimation/Missing data imputation	Sensitivity Analysis	Analysis population for primary and sensitivity analysis	Supplementary analysis [3]
Early discontinuation from treatment	Primary: Treatment Policy	ANCOVA with RD imputation	- None	- ITT	- mITT - PP
	Secondary [1]: Hypothetical [2]	MMRM	- ANCOVA with LOCF - ANCOVA by excluding participants with missing data	- ITT	- mITT - PP
Maintenance dose is different from the final planned dose	Treatment Policy	Treatment effect will be quantified regardless of being able to maintain at the final planned dose.			

[1] If the minimum requirement for the RD imputation is not met, the hypothetical estimand will be treated as the primary estimand.

[2] Under a hypothetical estimand, observations after the last dose for participants who discontinued treatment early will be deleted.

[3] For the treatment policy estimand, supplementary analysis in mITT and PP will only be performed if the minimum requirement for RD imputation has been reached; For the hypothetical estimand, such supplementary analysis will be performed not only for the MMRM analysis, but also for the two sensitivity analyses with ANCOVA.

3.4.2 Key Secondary Efficacy Endpoints

3.4.2.1 Key secondary efficacy endpoint of percent change in body weight from baseline to week 16

3.4.2.1.1 Estimand for the key secondary efficacy endpoint

The estimand for the key secondary objective of assessing the effect of CT-868 versus placebo on percent (%) change in body weight from baseline to Week 16 is as follows:

The key secondary endpoint: Assess the effect of CT-868 versus placebo on percent (%) change in body weight from baseline to Week 16.

Treatment condition: The randomized CT-868 (Arm 2: CT-868 titrated to 1.8 mg/day, Arm 3: CT-868 titrated to 4.1 mg/day, and Arm 4: CT-868 titrated up to 6.6mg/day) or Placebo (Arm 1: pooled placebo dose), following the same dosing schedule without the active ingredient.

Population: Overweight and obese adult participants with Type 1 Diabetes Mellitus who have met the inclusion and not met exclusion criteria.

Endpoint (Variable): Percent (%) change in body weight from baseline to Week 16

Intercurrent events and strategy for handling:

- The maintenance dose is different from the final planned dose. This will be handled by a treatment policy strategy.
- Early discontinuation from study treatment due to any reason.
    - This will be first handled using a treatment policy strategy with RD imputation. Note that the on-treatment period definition contradicts with the treatment policy strategy, and will not be applied to subjects discontinued study treatment early.
    - If the RD imputation does not converge, a hypothetical strategy with MMRM will be used as the primary strategy to handle instead.

Population-level summary: The mean difference in percent (%) change in body weight from baseline to Week 16 between each CT-868 treatment group and placebo.

3.4.2.1.2 Primary analysis of the key secondary endpoint

The key secondary efficacy endpoint, percent (%) change in body weight from baseline to Week 16, will be evaluated using the same approaches described above for the primary endpoint. There will be no formal hypothesis testing performed, and no adjustment for multiplicity.

3.4.2.1.3 Sensitivity analysis and Supplementary analysis of the key secondary endpoint

The same sensitivity and supplementary analyses described for the primary endpoint will be performed for the percent (%) change in body Weight from baseline to Week 16.

For the MMRM model and the ANCOVA model, baseline body weight will be added as a model covariate, and baseline HbA1c measurement will be replaced by baseline HbA1c strata (<8.5% or ≥8.5%). Note that due to more frequent data collection for body weight, all visits with pre-planned weight measurements (i.e., Weeks 2, 4, 6, 8, 10, 12, 14, and 16) will be included in the MMRM model.

Summary statistics of observed and change in body weight from baseline at Day 1 to each scheduled visit with planned body weight measurement will be provided.

3.4.2.1.4 Other Key secondary efficacy endpoint

The analysis of the other key secondary efficacy endpoints will be done on the mITT population. If not otherwise specified, a hypothetical strategy will be used to handle the intercurrent event of early discontinuation from treatment, that is, observations after participants' last dose will be deleted for those who discontinued treatment early. No hypothesis testing and no multiple comparison adjustments will be made. Difference of treatment effect and corresponding 95% two-sided confidence intervals and associated two-sided p-values will be reported descriptively unless otherwise stated.

3.4.2.1.5 HbA1c related endpoints

Change from baseline in HbA1c (%) to Week 4, 8, and 12: results will be obtained from the same MMRM model as described above for the primary endpoint, and therefore, 90% 2-sided confidence intervals and associated 2-sided p-value will be reported.

Percentage of participants achieving HbA1c of <7.0%, ≤6.5%, and <5.7% at Week 16:

Descriptive tables reporting the frequency and percentage of participants achieving HbA1c below 7.0%, 6.5%, and 5.7% by visits will be presented. The effect of each CT-868 arm over the placebo arm on the probability of achieving HbA1c below 7.0%, 6.5%, or 5.7% at Week 16 and improved from baseline (i.e., HbA1c value at Week 16 is less than the baseline value) will be evaluated using the G-computation method as outlined by Steingrimsson et al. (2017) and Freedman (2008): et al. (2017) and Freedman (2008):

1. Fit a working logistic regression model with treatment, the methods of insulin administration (pump or MDI), baseline HbA1c values, and baseline HbA1c strata as model covariates on all patients with complete observations. The model should include an intercept term.
2. For each participant with non-missing baseline covariates, regardless of treatment group assignment, compute the model-based prediction of the probability of response under placebo by setting the treatment variable to "Placebo", and using participant's specific values for other baseline covariates.
3. Estimate the average response under placebo by averaging the probabilities estimated in Step 2.
4. Repeat Steps 2 and 3 for each CT-868 treatment arm (i.e., by setting the treatment variable to CT-868 1.8mg, CT-868 4.1mg, or CT-868 6.6mg) and obtain the average response for each treatment arm.
5. The estimates of average response rates in the placebo arm and all CT-868 treatment arms from Steps 3 and 4 can be used to estimate an unconditional treatment effect in terms of odds ratio between any CT-868 treatment arm and the placebo arm.

The standard error can be estimated using a bootstrap approach with a random seed 111111:

1. Obtain a bootstrap sample of the original analysis population. The sampling will be done with replacement and stratified by randomized treatment arms, methods of insulin administration (pump or MDI), and baseline HbA1c strata. The sample size of the bootstrap sample is the same as the original analysis population.
2. Perform the G-computation method (Step 1-5 above) on the bootstrap sample obtained in Step (1) and calculate the treatment effect of interest.

3. Repeat Steps (1) and (2) for 5000 times, The unconditional treatment effect between any CT-868 arm and the placebo arm will be estimated by the median of the bootstrap distribution, and the 95% confidence interval of the unconditional treatment effect will be constructed using the empirical 2.5%- and 97.5%- quantiles of the bootstrap distribution.
4. The standard error of the estimated treatment effect can be obtained as the standard deviation of the bootstrap distribution. By assuming asymptotic normality of the natural log of odds ratio, a p-value can then be obtained from a Wald test.

Missing Week 16 HbA1c data will be handled using the retrieve dropout method. In case of not meeting the minimum required number of RDs, the same alternative methods specified in Section 3.4.1.5 will be used to handle the missing data.

3.4.2.1.6 Daily Insulin Dose

Daily Insulin doses (Basal, Bolus, and Total daily) are reported by the participants in units/day in eDiary or reported in the EDC by sites. The weight-adjusted daily insulin doses (Units/kg/day) will be calculated with the derived daily insulin doses (units/day) divided by the participant's weight in kilograms at the corresponding visit. Total daily insulin dose is only to be calculated when daily bolus and daily basal are both present. Otherwise set to missing.

Note: Pump user's daily basal insulin is captured in EDC from midnight to midnight, MDI daily basal insulin and all daily bolus insulin are captured in eDiary.

The definition of baseline insulin endpoint is provided in Section 3.1.3. For Week 8 and Week 16, as stated in Section 3.1.5, insulin endpoints will be calculated from the last 7 consecutive days within an analysis window (usually with a length of 14-days except for when the actual visit date for Week 8 or Week 16 visit is missing, the length of the window may be shorter than 14-days. See below for detail.) prior to an analysis visit, where at least 4 out of those 7 days have non-missing data recorded in the insulin data. If such a 7-day window cannot be identified, or if the length of the analysis window is less than 7 days, insulin endpoints are considered missing for that corresponding analysis visit. The analysis window prior to Week 8 or Week 16 should be determined as follows:

- For participants who complete treatment: use the actual visit date for Week 8 (or Day 60 when missing) and min (last dosing date per eCRF, Week 16 actual visit date [or Day 116 when missing]) for Week 16, respectively, as the anchor day and count 14 days back.
- For participants who discontinued treatment early:
    - If their last dosing date per eCRF is on or after the Week 8 visit (or Day 60 when missing), use the actual visit date for Week 8 (or Day 60 when missing) as the anchor day and count 14 days back. If their last dosing date per eCRF is on or after the Week 16 visit (or Day 116 when missing), use the actual visit date for Week 16 (or Day 116 when missing) as the anchor day and count 14 days back.
    - If their last dosing date per eCRF falls within 14 days before the actual Week 8 visit date (for Week 8), or within 14 days before the actual Week 16 visit date (for Week 16), their last dosing date per eCRF should be used as the anchor day and count 14 days back. However,
        - If Week 8 visit date is missing but Week 7 phone call date present,
            - If the last dosing date per eCRF is on or after the Week 7 phone call date and before Day 60, use the last dosing date per eCRF as

the end day, and use max (Day 40, last dosing date per eCRF - 14 days) as the start day, of the analysis window for Week 8.
- Otherwise, insulin endpoints would be considered missing for Week 8.

- If Week 8 visit date and Week 7 phone call date are both missing,
  - If the last dosing date per eCRF is within Day 40 and Day 60, use the last dosing date per eCRF as the end day, and use max (Day 40, last dosing date per eCRF - 14 days) as the start day, of the analysis window for Week 8.
  - Otherwise, insulin endpoints would be considered missing Week 8.
- Similarly for Week 16, If Week 16 visit date is missing but Week 15 phone call date present,
  - If the last dosing date per eCRF is on or after the Week 15 phone call date and before Day 116, use the last dosing date per eCRF as the end day, and use max (Day 96, last dosing date per eCRF - 14 days) as the start day, of the analysis window for Week 16.
  - Otherwise, insulin endpoints would be considered missing for Week 16.
- If Week 16 visit date and Week 15 phone call date are both missing,
  - If the last dosing date per eCRF is on or after Day 96 and before Day 116, use the last dosing date per eCRF as the end day, and use max (Day 96, last dosing date per eCRF - 14 days) as the start day, of the analysis window for Week 16.
  - Otherwise, insulin endpoints would be considered missing Week 16.

- If their last dosing date per eCRF is prior to 14 days before the actual Week 8 visit day (or Day 40 if the actual Week 8 visit day is missing), or prior to 14 days before the actual Week 16 visit day (or Day 96 if the actual Week 16 visit day is missing), no anchor day should be defined and insulin endpoints would be considered missing for the corresponding analysis visit.

For calculating weight-adjusted daily insulin doses within the above defined analysis window, the body weight record that is the closest to the anchor day should be used.

The total daily insulin doses (basal, bolus and total), weight and non-weight adjusted, will be summarized by treatment at Baseline, Week 8, and Week 16. Change and %change from baseline will also be calculated at these visits. The descriptive statistics (n, mean, SD, %CV, minimum, median, and maximum) will be calculated for each parameter mentioned above and summarized by treatment and by visit. The summaries will also be provided by pump users (yes/no).

The change (absolute and percentage) in basal, bolus, and total daily insulin doses (weight and non-weight adjusted daily insulin dose) from baseline to Weeks 8 and 16 will be analyzed using an MMRM model with treatment, visits (Week 8 and 16), treatment by visit interaction, methods of insulin administration (pump or MDI), the baseline HbA1c (%) strata, and baseline insulin daily dose as covariates.

Summary statistics of observed and change in the number of daily insulin injections (in those on MDIs of insulin) from baseline at Day 1 to Weeks 8 and 16 will be provided.

3.4.3 Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints will be analyzed in the mITT Population. If not otherwise specified, a hypothetical strategy will be used to handle the intercurrent event of early discontinuation from treatment, that is, observations after participants' last dose will be deleted for those who discontinued treatment early. When applicable, difference in treatment effect and corresponding 95% two-sided confidence intervals and associated two-sided p-values will be reported.

3.4.3.1 CGM metrics related endpoints

CGM is performed from Day -14 to Week 18 using [redacted] The device measures glucose values every 5 mins, with a total of 288 values expected over a 24-hour interval, and a total of 4032 values expected over a 14 consecutive days interval.

The definition of the baseline for CGM related endpoint is provided in section 3.1.3.

CGM endpoints will be derived at Baseline, Week 8 and Week 16. Analysis windows for these visits are defined as:

- For baseline, a 14-consecutive day interval up to Day 1 dosing time will be used. If Day 1 dosing time is missing, set to 8:00am.
- For Week 8,
    - The standard 14-day window should be derived as
        - Anchor time: dosing time of the actual Week 8 visit, set to 8:00am if missing
        - Start time: anchor time - 7*24 hours
        - End time: anchor time + 7*24 hours
        - Start day: date part of start time
        - End day: date part of end time
    - If a participant completed all treatment, or the last dosing date/time per eCRF is after the *End time* of the Week 8 standard 14-day window, the standard window should be used.
    - For participants who discontinue treatment early:
        - If their last dosing date/time per eCRF is within the start time to the end time of the standard 14-day window for Week 8 (or within Day 48 at last dosing time to Day 67 at last dosing time if the actual Week 8 visit day is missing), the analysis window ends at the last dosing date/time as per eCRF (or set as 8:00am if the actual dosing time is missing), and starts at 7*24 hours before the Week 8 visit date with the last dosing time in eCRF. If Week 8 visit date is missing, the analysis window should start at max (the same dosing time on Day 48, the last dosing time/day - 14*24 hours).
        - If their last dosing date/time per eCRF is before the start time of the standard 14-day window for Week 8 (or before Day 48 at the last dosing time if the actual Week 8 visit date is missing), no analysis window can be defined and CGM parameters will be set as missing.
- For Week 16,
    - The standard 14-day window should be derived as

        - Anchor time/End time: The date part is min (the last dosing date per eCRF, actual Week 16 visit date [or Day 116 if the Week 16 visit is missing]). The time part is the last dosing time of the day per eCRF.]
        - Start time: Anchor time - 14*24 hours
        - Start day: day part of start time
    - If a participant completes all treatment, the standard 14-day window for Week 16 should be used.
    - For participants who discontinue treatment early,
        - If their last dosing date/time per eCRF is prior to 14*24 hours before the actual Week 16 visit (using actual visit date as the date, and last dosing time per eCRF as the time of the day) (or prior to Day 97 at the last dosing time if the actual Week 16 visit date is missing), no analysis window can be defined and CGM parameters will be set as missing.
        - If their last dosing date/time per eCRF is on or after 14*24 hours before the actual Week 16 visit (using actual visit date as the date, and last dosing time per eCRF as the time of the day) (or on or after Day 97 at the last dosing time if the actual Week 16 visit date is missing), the analysis window should end at min(the last dosing date/time as per eCRF, the actual Week 16 visit date with last dosing time of the day per eCRF). Set as 8:00am if the actual dosing time is missing, and use Day 116 if the Week 16 visit date is missing. The analysis window should start at 14*24 hours before the same dosing time on the actual Week 16 visit date. If the Week 16 visit date is missing, the analysis window should start at max (same dosing time on Day 97, the last dosing date/time - 14*24 hours).

In each of these three time windows, if a participant has less than 70% of the expected readings (number of actual readings/[redacted]*100<70), all CGM parameters for this participant at the specific visit will be set as missing. Participants with missing baseline value will be excluded from the analysis as per the analysis population requirement. An exploratory analysis will be performed by ignoring the 70% data completeness threshold. When summarizing CGM parameters by intra-day, each of the three 14-day time windows will be divided into 14 consecutive, non-overlapping 24-hour periods (or “days”). The detail of the algorithm that will be used for the derivation of the CGM related endpoints is provided in Appendix E.

The effect of CT-868 on the change from baseline to Week 8 and week 16 in CGM endpoints will be evaluated using an MMRM model. The response variable will be the change from baseline, with treatment, visit (Weeks 8 and 16), the treatment-by-visit interaction, methods of insulin administration (pump or MDI), the baseline HbA1c strata (<8.5% or ≥8.5%), and baseline CGM parameter values as model covariates. The change from baseline for the following CGM endpoints will be analyzed using this MMRM model, and treatment effect will then be expressed as difference in ls means from placebo with confidence interval and associated p-value.

- Mean sensor glucose (mg/dL) over the 14-day interval
- Its standard deviation (SD) and %CV [both intraday (i.e., within 24 hours) and interday (i.e., over 14-consecutive days)]
- Percentage of time spent in range (TIR, 70–180 mg/dL)
- Percentage of time spent in tight range (TITR, 70-140 mg/dL)

- Percentage of time spent below target range (TBTR, <70–54 mg/dL) and very below target range (TVBTR <54 mg/dL) as defined further in Section 3.1 in Protocol.
- Percentage of time spent above target range (TATR, >180–250 mg/dL) and very above target range (TVATR >250 mg/dL)
- Glycemia Risk Index

Figures of the mean CGM parameters +/-SD will be presented by treatment and visits. In particular, figures of daily mean glucose values from Day -14 to Week 16 will be provided for each treatment group. Raw CGM daily means provided by the vendor will be used for this plot.

The following CGM endpoints at Week 8 and Week 16 will be compared between each of the CT-868 treatment groups and placebo using the G-computation procedure as described in Section 3.4.2.1.1. The working logistic regression adjusts for treatment group, methods of insulin administration (pump or MDI), baseline HbA1c strata (<8.5% or ≥8.5%) and corresponding endpoints baseline values. Treatment effect will then be expressed as an odds ratio (CT-868/Placebo) with a 95% two-sided confidence interval and associated two-sided p-value.

- Participants with TIR 70-180 mg/dL with ≥5% points and ≥10% points improvement from baseline (Yes/No)
- Participants with TIR 70–180 mg/dL for >70% of the 14-day collection interval around the Week 8 Visit and the 14-day interval prior to the Week 16 Visit (Yes/No)
- Participants with TBR <70 mg/dL for <4% of each day (Yes/No)
- Participants with TBR <54 mg/dL for <1% of each day (Yes/No)
- Participants with time above range >180 mg/dL for <25% of each day (Yes/No)
- Participants with time above range >250 mg/dL for <5% of each day (Yes/No)
- Participants with TBR <70 mg/dL for <4% over the 14-day collection interval (Yes/No)
- Participants with TBR <54 mg/dL for <1% over the 14-day collection interval (Yes/No)
- Participants with time above range >180 mg/dL for <25% over the 14-day collection interval (Yes/No)
- Participants with time above range >250 mg/dL for <5% over the 14-day collection interval (Yes/No)

The following CGM endpoints will be compared between treatment groups using two negative binomial regression models (Week 8 and Week 16, respectively), adjusting for treatment groups, methods of insulin administration (pump or MDI), baseline number of events, and using the ratio of number of actual readings to number of expected readings, i.e., calculated as number of actual readings/ [redacted] as an offset. The assessment will be expressed as a risk ratio with confidence interval and associated p-value.

- Number of events with sensor glucose <70 mg/dL lasting at least 120 minutes and without gaps ≥30 minutes between consecutive CGM readings (event ends when glucose returns to ≥70 mg/dL for ≥15 minutes)
- Number of events with sensor glucose >250 mg/dL lasting at least 120 minutes and without gaps ≥30 minutes between consecutive CGM readings (event ends when glucose returns to ≤180 mg/dL for ≥15 minutes)

The summary statistics for observed and change from baseline in continuous CGM parameters will be calculated and summarized by treatment groups and by visit for all the above CGM parameters. Frequency tables will be provided for categorical CGM parameters.

A CGM disposition table will be provided to summarize the following endpoint by treatment at Baseline, Week 8, and 16 based on mITT Population:

- Percentage of time CGM is active:
    - ≥70%,
    - ≥ 50% and <70%,
    - ≥ 30% and <50%, or
    - <30%,
- summary statistics of percentage of actual CGM readings over the expected readings.

3.4.3.2 Body weight related endpoints

The following other secondary body weight related efficacy endpoints will be compared between treatments using a MMRM model, with all visits with pre-planned body weight measurements (Weeks 2, 4, 6, 8, 10, 12, 14, and 16), the treatment-by-visit interaction, methods of insulin administration (pump or MDI), the baseline HbA1c strata (<8.5% or ≥8.5%), and baseline weight as model covariates. Treatment effect will then be expressed as the difference in LS means between CT-868 and placebo with confidence intervals as well as associated p-values.

- Percent (%) change in body weight from baseline at Day 1 to Weeks 4, 8, and 12. These endpoints will be by-products from the same MMRM model under a hypothetical estimand as described in Section 3.4.2.1.3. Therefore, results in ITT, mITT (if applicable), and PP population will be available.
- Absolute change in body weight (kg) from baseline at Day 1 to Weeks 4, 8, 12, and 16. As an "other secondary efficacy endpoint", this analysis will only be performed in the mITT population and under a hypothetical strategy for handling early treatment discontinuation

Descriptive tables reporting the frequency and percentage of participants achieving following weight loss thresholds by visits will be presented. The percentage of participants meeting the following weight loss thresholds will be compared between treatment groups using the G-computation procedure as described in Section 3.4.2.1.1. The working logistic regression adjusts for methods of insulin administration (pump or MDI), baseline HbA1c strata (<8.5% or ≥8.5%), and baseline weight. The working logistic regression adjusts for treatment group, methods of insulin administration (pump or MDI), baseline HbA1c strata (<8.5% or ≥8.5%), and baseline weight. Treatment differences will be expressed as an odds ratio (CT-868/placebo) with 95% confidence intervals and associated p-values. The number and proportion of participants achieving each weight loss threshold at each visit will also be provided for each scheduled visit by treatment groups (mITT).

- Percentage of participants achieving ≥5% weight loss at week 16
- Percentage of participants achieving ≥10% weight loss at week 16
- Percentage of participants achieving ≥15% weight loss at week 16
- Percentage of participants achieving ≥20% weight loss at week 16

3.4.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are based on mITT Population. If not otherwise specified, a hypothetical strategy will be used to handle the intercurrent event of early discontinuation from treatment, that is, observations after participants' last dose will be deleted for those who

discontinued treatment early. When applicable, difference in treatment effect and corresponding 95% two-sided confidence intervals will be reported unless otherwise stated.

The counts and percentage by treatment arm for the following exploratory efficacy endpoints will be provided. For CGM related endpoints, similar to the main analysis of other CGM related endpoints (Section 3.4.3.1), only time windows with ≥ 70% of the expected readings (number of actual readings/ [redacted] *100<70) will be included.

- Participants at Week 16 with improvement (reduction) in HbA1c ≥0.5% points (compared with corresponding baseline) and <1% TBR <54 mg/dL
- Participants at Week 16 e with mean glucose <154 mg/dL and <1% TBR <54 mg/dL
- Participants at Week 16 with ≥70% TIR 70-180 mg/dL and <4% TBR <70 mg/dL
- Participants at Week 16 with ≥70% TIR 70-180 mg/dL and <1% TBR <54 mg/dL
- Participants at Week 16 with HbA1c improvement (reduction) ≥0.5% points (compared with corresponding baseline), with <1% TBR <54 mg/dL, and without requiring significant increase in daily insulin use [i.e., >10% increase in total (bolus + basal) insulin (units/kg/day) compared with baseline]
- Participants at Week 16 with ≥70% TIR 70-180 mg/dL, with <1% TBR <54 mg/dL, and without requiring significant increase in daily insulin use [i.e., >10% increase in total (bolus + basal) insulin (units/kg/day) compared with baseline]
- Participants with at least one CGM-detected Level 2 hypoglycemia events (events starts when there is ≥15 consecutive minutes with a CGM censor value <54 mg/dL and without gap ≥30 minutes between consecutive CGM readings; event ends when there is ≥15 consecutive minutes with a CGM sensor value of ≥54 mg/dL) during the 16 weeks treatment period (from first dose per eCRF and up to 24 hours after last dose per eCRF) (Yes/No).

  (The following composite endpoints will be reported separately from the CSR)

- Percentage of participants at Week 16 achieving ≥70% TIR AND <4% TBR (<70 mg/dL) AND weight loss ≥5%
- Percentage of participants at Week 16 achieving HbA1c <7% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA
- % of participants at Week 16 achieving HbA1c <7% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA AND weight loss ≥5%
- Percentage of participants at Week 16 achieving HbA1c reduction ≥0.5% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA
- Percentage of participants at Week 16 achieving HbA1c reduction ≥0.5% AND no severe hypoglycemia (Level 3 hypoglycemia by ADA) or DKA AND weight loss ≥5%
- Percentage of participants at Week 16 achieving ≥70% TIR AND weight loss ≥5% AND insulin total daily dose reduction ≥20% from baseline
- Percentage of participants at Week 16 achieving HbA1c <7% AND weight loss ≥5% AND insulin TDD reduction ≥20% from baseline

The summary statistics for the following exploratory efficacy endpoints (observed and change from baseline) will be provided. Change from baseline will be analyzed using an MMRM model, with baseline value, treatment, week of the visit, the treatment-by-week interaction, baseline HbA1c strata (<8.5% or ≥8.5%), and methods of insulin administration (pump or MDI) as model covariates.

- Change from baseline at Day 1 to Week 8 and Week 16 in serum glucose, insulin, C-peptide, glucagon, GLP 1 (total and active), GIP.
- Change from baseline at Day 1 to Week 8 and Week 16 in fasting lipid profile (triglycerides, total cholesterol, LDL C, HDL-C, VLDL, FFA, ApoB, non-HDL-C [calculated by subtracting HDL-C from Total Cholesterol]), other blood biomarkers (adiponectin, leptin, hsCRP, PAI-1 activity, CTX-1, MCP-1, IL-6, endothelin-1, E-selectin, VCAM-1), ALT (from serum chemistry), eGFR (from serum chemistry, calculated by CKD-EPI formula), and UACR
- [redacted]
- Change from baseline at Day 1 to each scheduled visit in vital sign results: systolic blood pressure, diastolic blood pressure, and heart rate.

(The following composite endpoints will be reported separately from the CSR)

- Changes from baseline at Day 1 to Week 8 and Week 16 in CGM-based metrics (TIR 70-180 mg/dL, TBR <70mg/dL, TAR >180 mg/dL, mean glucose) during the daytime (6AM-11:59PM) and the nighttime (12AM-5:59PM). These CGM-based metrics will be calculated based on all individual records from the 14 daytime (or nighttime) intervals at each analysis visit, treating each record equally.

The summary statistics for the following endpoints (observed and change from baseline) will be provided. An ANCOVA model with baseline value, treatment, baseline HbA1c strata (<8.5% or ≥8.5%), and methods of insulin administration (pump or MDI) as model covariates will be used to model the following endpoints. Same as for the primary estimand analysis, missing data will be imputed using the RD method. In the events when RD imputation cannot be triggered, other alternative sensitivity analysis as described for the primary endpoint will be explored.

- [redacted]
- [redacted]
- Change and percent change from baseline to Week 16 in total lean mass as determined by DEXA
- Change and percent change from baseline to Week 16 in total fat mass as determined by DEXA

The following correlation coefficients will be provided:

- Correlation coefficient between time to attain the highest dose of CT-868 and change in HbA1c from baseline to Week 16 for patients in Arm 4
- Correlation coefficient between time to attain the highest dose of CT-868 and percentage change in body weight from baseline to Week 16 for patients in Arm 4
- Correlation coefficient between change in HbA1c from baseline to Week 16 and percentage change in body weight from baseline to Week 16 for patients in each treatment arm (according to mITT) separately.

Pearson's correlation will be reported if both variables are continuous and normally distributed. Otherwise, Spearman's rank association will be reported. The results of a normality test (with p-value) will be provided.

3.4.5 Subgroup Analysis

The following exploratory subgroup analysis may be performed:

- Absolute change in HbA1c, and percent change in body weight will be assessed in the following subgroups (provided there are at least 10 participants in each treatment group) using an MMRM model with baseline value, treatment, visit with pre-planned data collection, treatment-by-visit interaction, baseline HbA1c strata (<8.5% or ≥8.5%, for non-HbA1c endpoints), and methods of insulin administration (pump or MDI, which will not be included when the subgroup is defined by baseline pump types) as model covariates. Since this is an exploratory analysis, mITT population will be used, and a hypothetical strategy will be used for handling early discontinuation from treatment. Missing data imputation will be done implicitly by the MMRM model.
    - Baseline pump types (All pump users vs. Auto pump vs. Manual pump vs. MDI)
    - An alternative baseline HbA1c strata (<7.5% vs, ≥7.5%)
    - Baseline HbA1c < 8% only
    - Baseline BMI (<30 kg/m2 vs, ≥30 kg/m2)
- Absolute change in HbA1c, and percent change in body weight, absolute change in selected CGM endpoints (mean sensor glucose and %CV, TIR, TBR, and TBVR) will be analyzed using an MMRM model as described above.
    - Baseline C-peptide category (<0.02 ng/ml vs. ≥0.02 ng/ml and ≤0.6 ng/ml). Note that C-peptide values reported as "<0.02" ng/ml will be categorized to the "<0.02 ng/ml" group. For other summaries of C-peptide, the general guidance in Section 3.1.5 should be followed, and values which are including "<" or ">" will be analyzed using the numeric value provided in the result

3.5 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis

For all participants in the PK Population (Section 3.2.5), plasma concentrations of RO7795074 at each sampling time point will be presented descriptively by dose level, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. Individual and mean plasma concentrations by dose level versus time data will be plotted on linear and semi-logarithmic scales.

For the participants participated in the week 14 optional 24-hour PK sampling visitvisitsubpopulation, plasma PK parameters for RO7795074 will be estimated according to the internal guiding principles for "Calculation and Analysis of Non-Compartmental pharmacokinetic (PK) Parameters", Version 4 (July 2015), using non-compartmental methods with validated Phoenix WinNonlin Version 8.1 or higher (Certara, L.P.). Descriptive statistics (N, arithmetic mean, median, minimum, maximum, standard deviation, CV%, geometric mean [Cmax and AUCs], and geometric CV% [Cmax and AUCs]) will be calculated for PK parameters per dose level, as appropriate and permitted by the data.

Nonlinear mixed-effects modeling will be used to analyze the concentration-time data for RO7795074 in plasma following SC administration. A covariate analysis will be conducted to evaluate the effect of covariates such as body weight, age, sex and immunogenicity (as applicable) on RO7795074 exposure.

Population and individual estimates of primary PK parameters (e.g., clearance, distribution volume) and secondary PK parameters (e.g., area under the plasma concentration-time curve, average trough plasma concentration) will be computed and, if appropriate, used to explore exposure-response relationship on primary and key secondary endpoints, as well as safety measures. The data from this study may be pooled with data from other studies conducted with RO7795074 to support the population PK/PD modeling.

Details of this mixed-effects modeling and exploration of exposure-response analysis and results will be described and reported in a document separate from the SAP and Clinical Study Report.

Prior to completion of the study (a) separate PK cutoff date(s) may be established to allow expedient sample analyses and early PK/antidrug antibody data access. The PK cutoff date will be applied when there is sufficient PK sample data available to adequately characterize PK. For PK/PD analysis, for the PD data (a) separate cutoff date(s) may be applied.

3.6 Immunogenicity Assessments

The anti-drug antibody assessments will be performed at visits specified in the Schedule of Procedures and in case of severe ISRs and hypersensitivity reactions. Blood samples for anti-drug antibody will be collected approximately 24 hours after the preceding dose.

Analysis will include all participants with at least one ADA assessment and grouped according to the Safety Population. Participants will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

ADA evaluable participant: Participant with a non-missing ADA result at baseline AND at least one non-missing ADA result after drug administration.

ADA positive participant: A participant with at least one treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment or follow-up observation period. Per Shankar et al. (2014), a treatment-induced ADA-positive sample refers to a sample where anti-drug antibodies (ADAs) are detected in participants who were previously ADA-negative (i.e., did not have pre-existing antibodies) before the initiation of the treatment with the therapeutic protein. A treatment-boosted ADA-positive sample refers to a situation where anti-drug antibodies are detected at increased levels in participants who had pre-existing ADAs at baseline. Essentially, the treatment has caused a noticeable increase in the antibody levels compared to the baseline levels.

ADA negative participant: Participants without a treatment-induced or treatment-boosted ADA-positive sample during the treatment or follow-up observation period.

ADA prevalence: The proportion of all individuals having drug-reactive antibodies (including pre-existing antibodies) at any point in time.

ADA incidence: The proportion of the study population found to have either treatment-induced ADA or treatment-boosted ADA (an increase in pre-existing ADA levels by at least 0.60 titer unit greater than the titer of the baseline sample) during the study period.

ADA prevalence at baseline and ADA incidence will be summarized with counts and percentage by treatment arm.

The relationship between ADA status and safety, efficacy and biomarker endpoints may be analyzed and reported using descriptive statistics.

3.7 Safety Assessment

Analyses of safety will be performed based on the Safety population and consist of descriptive analysis for each safety variable. Safety will be analyzed by actual treatment received.

Observed safety laboratory values, vital signs, ECGs, and changes from baseline will be summarized descriptively by visit and treatment arm.

3.7.1 Adverse Events (AEs) and Adverse Device Effects (ADEs)

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this study drug. An ADE is defined as an AE related to the medical device. This includes any event that is the result of incomplete user manual information or of incorrect use of the medical device. AEs and ADEs will be captured from the date of informed consent through study completion. Verbatim descriptions of treatment-emergent AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or above in effect at the time of analysis database lock.

Treatment Emergent Adverse Events (TEAEs), and Treatment Emergent Adverse Device Effects (TEADEs) will be summarized for this study. They are defined as AEs that start after the first dose of a randomized study drug, and up to 30 days after the last dose or prior to the initiation of new adjunct therapy, whichever is earlier.

A participant experiencing multiple TEAEs under the same PT (SOC) will be counted only once for that PT (SOC) by worst severity. If a participant experiences the same AE more than once with more than one relationship to study drug, the worst causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and classified as ‘Missing’. TEAEs/TEADEs will be summarized by treatment, Counts and percentages of participants (and event counts) will be reported.

The following summaries in Safety Population will be presented:

- Overview of Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Emergent Adverse Events (TEAEs) by Preferred Term
- Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, and Preferred Term
- Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and CTCAE Grade.
- Serious Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, and Preferred Term
- Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, and Preferred Term.
- Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) with CTCAE Grade ≥3 by System Organ Class, and Preferred Term
- Treatment-Emergent Adverse Events (TEAEs) Leading to Permanent Study Treatment Discontinuation by System Organ Class, and Preferred Term
- Treatment-Emergent Adverse Events (TEAEs) Leading to Dose Interruption by System Organ Class, and Preferred Term

- Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) Leading to Dose Interruption by System Organ Class, and Preferred Term
- Treatment-Emergent Adverse Events (TEAEs) Leading to Dose Reduction by System Organ Class, and Preferred Term
- Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) Leading to Dose Reduction by System Organ Class, and Preferred Term
- Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and CTCAE Grade
- Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) System Organ Class, Preferred Term, and CTCAE Grade (may not be summarized in a table format due to low incidence)
- [redacted]
- Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Relationship
- Treatment-Emergent Adverse Events (TEAEs) Leading to Death by System Organ Class, and Preferred Term

In addition, the following safety summaries will also be provided using the *safety by randomized dose population* (Section 3.2.4)

- Overview of Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Emergent Adverse Events (TEAEs) by Preferred Term

Drug-Related is defined as possibly related, probably related, definitely related to study drug.

3.7.2 Adverse Events of special interest (AESIs)

The following would be considered as adverse events of special interest (AESIs) for this study (many of these are generally associated with GLP-1, GLP-1/GIP receptor agonists, and the broader incretin drug class):

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

During the course of the study, additional AESIs may be identified by the Sponsor.

The number and percentage of participants with AESIs will be summarized by AESI category, System Organ Class, and Preferred Term. Overview Tables will also be generated for AESIs.

3.7.3 Clinical Laboratory Tests for Safety Assessments

Clinical laboratory tests (serum chemistry, hematology, amylase and lipase, urinalysis, and calcitonin) will be performed at visits specified in the Schedule of Procedures. Before blood collection, participants must be in a fasted state defined as ~8 hours of fasting. See Appendix B for a complete list of laboratory analytes.

For each laboratory test, measurements up to 14 days after the last dose or prior to the initiation of adjunct therapy, whichever is earlier, may be included in the analysis. Descriptive statistics for observed lab values and changes from baseline will be presented at each scheduled visit grouped according to the safety population.

The incidence of abnormalities (as defined by normal ranges) not present at baseline and present after the first dose of study drug with directions will be summarized with counts and percentages of participants using the Safety Population. A laboratory result is defined as abnormal if the value is outside of the normal range in either direction; it is defined as Low if it is below the lower limit of normal, or High if it is above the upper limit of normal. Shift tables of laboratory data (lipid profile, endocrinology, blood biomarkers, standard safety chemistry panel) from baseline to worst grade (high/low) by each scheduled visit during treatment will be presented separately.

A by- participant listing will be provided for each laboratory parameter.

A by-participant listing will be provided for positive pregnancy test results.

3.7.4 Vital Signs

Vital signs (weight, BMI, temperature, heart rate, blood pressure, respiratory rate) will be measured at visits specified in the Schedule of Procedures.

Vital sign parameters to be analyzed as safety endpoints including temperature [C], heart rate [beats/min], systolic blood pressure [mmHg], and diastolic blood pressure [mmHg]. Measurements up to 7 days after the last dose or prior to the initiation of new adjunct therapy, whichever is earlier, may be included in the analysis. Descriptive statistics for vital sign values and changes from baseline will be presented at each scheduled visit grouped according to the safety population. Incidence of abnormal vital sign measurements will be summarized descriptively by visit. Shift tables for vital signs will be provided.

Vital sign assessments will also be provided in a by- participant listing with flagging of values outside the normal ranges and flagging of marked abnormalities.

3.7.5 Hypoglycemia events, DKA, and other vital sign related endpoints

Endpoints in this section will be analyzed in the Safety Population (Section 3.2.4).

The summary statistics for the following hypoglycemia related endpoints will be provided. Level 1 and level 2 hypoglycemia events will be derived based on serum glucose data, sMBG data, as well as hypoglycemia AEs reported in the eCRF, whereas level 3 hypoglycemia events will be

derived based solely on hypoglycemia AEs reported in the eCRF. Hypoglycemia events occurred pre-treatment (from Day -14 to prior to the first dose of study treatment) or occurred on-treatment (between the first study treatment and up to the last dosing time as per eCRF + 24 hours) will be reported separately.

- Proportion of participants experiencing 1 or more Level 1 (as worst severity) hypoglycemia (<70–54 mg/dL) event(s) over the study duration
- Proportion of participants experiencing 1 or more Level 2 (as worst severity) hypoglycemia (<54 mg/dL) event(s) over the study duration
- Proportion of participants experiencing 1 or more Level 3 (as worst severity) hypoglycemia event(s) as worst severity over the study duration

In above summaries, the total number of hypoglycemia events will be presented.
The following endpoints on hypoglycemia event rate will also be reported separately for pre-treatment period and on-treatment period. For on-treatment period, the endpoints are defined as:

- Hypoglycemia event rate over the treatment duration will be calculated as (the total number of events) / (sum of the person-time exposed to the study drug after randomization + 24 hours (in weeks)).
- The event rate per patient-year will also be estimated as (the total number of events) / (sum of the person-time exposed to study drug after randomization + 24 hours (in years). Considering the short treatment duration of 16 weeks, the inference of the event rate per patient-year is limited.

For pre-treatment period, the above two endpoints will be derived using 2 weeks (or 14/365.25 years) as the exposure time for each participant in the denominator. All event rates will be presented for Level 2 only, Level 3 only, and Level 2 or 3, respectively.

The summary statistics (% participants with at least one event during the treatment period and the total number of events) for the following DKA related endpoints will be provided. If there are ≥10 participants with at least one DKA event, the endpoints will be analyzed using the G-computation procedure as described in Section 3.4.2.1.1. The working logistic regression adjusts for treatment, baseline HbA1c strata (<8.5% or ≥8.5%), and methods of insulin administration (pump or MDI) as covariates. Treatment differences will then be expressed as an odds ratio (CT-868/placebo) with 95% confidence intervals and associated p-values.

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]

The summary statistics for the following vital signs endpoints (observed and change from baseline) will be provided. Change from baseline in these endpoints will be analyzed using an MMRM model, with baseline value, treatment, all scheduled visit with preplanned data collection of a corresponding endpoint, the treatment-by-week interaction, baseline HbA1c strata (<8.5% or ≥8.5%), and methods of insulin administration (pump or MDI) as model covariates. Treatment effect will then be expressed as difference in mean with 95% confidence interval and associated p-value.

- Change from baseline at Day 1 to Week 8 and Week 16 in systolic blood pressure
- Change from baseline at Day 1 to Week 8 and Week 16 in diastolic blood pressure
- Change from baseline at Day 1 to Week 8 and Week 16 in heart rate

3.7.6 Electrocardiograms

ECGs (12-lead) will be performed at visits specified in the Schedule of Procedures. All ECGs are performed with the participant in the supine position. Standard 12-lead ECGs will be recorded prior to drawing blood samples with the participant resting supine for at least 5 minutes.

Measurements up to 7 days after the last dose or prior to the initiation of new adjunct therapy, whichever is earlier, may be included in the analysis. Descriptive statistics for ECG values and changes from Baseline will be presented at each scheduled visit grouped according to the safety population. A listing of participants with ECGs showing clinically significant abnormalities will be produced. Incidence of abnormal ECG measurements will be summarized descriptively by visit. Shift tables for ECG will be provided.

3.7.7 Physical Examinations

Full and brief physical examinations will be performed at visits specified in the Schedule of Procedures. During study drug dosing period, physical examination will include inspection of injection site(s).

All data collected from physical examinations assessments will be available in the source documents but will not be added to the analysis database. A listing of physical examinations by visit will be provided.

3.7.8 eDiary completion by participant

The eDiary will be used daily by participants to keep diaries to document hypoglycemic, hyperglycemic, and DKA events, insulin dose, and study drug administration as outlined in the Schedule of Procedures.

[redacted]

[redacted]

[redacted]

4 SAFETY REVIEW COMMITTEE

Safety will be monitored throughout the study by a blinded SRC comprising the CRO Medical Monitor, a selected Principal Investigator, and the Sponsor's medical officer. A blinded data manager and statistician will support the SRC by providing needed blinded study data (tables, figures, and listings).

Details of the composition, roles and responsibilities, and processes of the SRC will be documented in the Medical Data Surveillance Plan.

No interim analysis is planned. If it is determined to conduct the interim analysis (IA), an external Independent Data Monitoring Committee (IDMC) will be established with further details provided in the IDMC charter.

5 KEY CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Changes to CGM related endpoints:

- The amount of time spent in various ranges will not be summarized as it provides limited information on glycemia control.
- Level 1 or Level 2 hypo-/hyperglycemia will not be derived from CGM data. Instead, the following terminology/endpoints will be used:
    - Percentage of time spent below target range (TBTR, <70–54 mg/dL) and very below target range (TVBTR <54 mg/dL).
    - Percentage of time spent above target range (TATR, >180–250 mg/dL) very above range (TVATR, >250 mg/dL)

The following CGM related endpoint is modified to follow the definition in Battelino et al. (2023), and the summary of all levels of hypoglycemia events is removed because it is covered by another endpoint.

- Participants with at least one Level 2 (CGM values <54 mg/dL) or Level 3 hypoglycemia events during the 16 weeks treatment period (Yes/No)

In the protocol V5 Table 2, there is a typo in the endpoint definition of event rate for hypoglycemia events. The correct definition should read: total number of Level 1, 2, 3 hypoglycemia events/total patient-years of exposure (event rate) at each hypoglycemia level over the treatment period of 16 weeks.

Added endpoints to assess drug tolerability:

- Number of participants completed study treatment and maintained at different dose levels during Week 12 to Week 16
- Number of participants reached the final planned dose of each cohort, and Time (weeks) to the final planned dose of each cohort.

A hypothetical estimand with MMRM is proposed as the choice of an alternative estimand to treatment policy with ANCOVA and retrieved dropout imputation if the number of retrieved dropouts does not meet the minimum requirement.

Although ANCOVA with retrieved dropouts (RD) was specified in the protocol for the primary analysis of the primary estimand, this method can lead to estimators with inflated variance and a small, unstable effect size in the presence of a limited number of retrieved dropouts. Therefore, MMRM was chosen as an alternative to ANCOVA to better handle the data.

Other alternative methods were explored but ultimately deemed not appropriate due to the mechanism of action of CT-868 and the nature of the disease. Washout and return to reference were considered as they align with the treatment policy estimand and are recommended in

Wang 2023. However, these methods were thought to be too conservative and could potentially penalize CT-868, risking the possibility of missing its effect in this phase 2 study.

Furthermore, the copy-increments-in-reference (CIR) method was evaluated but found to be less defensible in this context, as it is known that participants usually start regressing to placebo once they stop treatment. Additionally, while the copy reference (CR) method was seen as a less conservative alternative to joint reference (JR), it was also not deemed ideal, as it might assume participants progress faster to placebo than is realistic.

Given these considerations, the best alternative method of using the MMRM model was selected. The MMRM approach provides a balanced and plausible method for analyzing the data while addressing the limitations posed by the small sample size and the difficulties associated with retrieved dropout data.

PK parameters:

- AUCtau was used instead AUC_{tau} because the profile was measured at steady state
- $t_{1/2}$ was removed from the list of pharmacokinetic (PK) parameters as it could not be appropriately determined by non-compartmental analysis (NCA) due to the sampling duration.
- The analysis of the correlation between PK and efficacy parameters was removed from the Statistical Analysis Plan (SAP) as it is beyond the scope of the SAP; this analysis will be documented separately.

The definition of mITT Population was updated to be, the mITT will include all randomized participants who receive at least one dose of study drug.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in participant data listings which will be sorted by participant and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

1. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes–2022. Diabetes Care 2022;45(Suppl 1):S17-S38.

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

3. Freedman DA, 2008, Randomization Does Not Justify Logistic Regression, Statistical Science, 23(2):237-249.

4. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1335–43.

5. Klein KR, Freeman JLR, Dunn I, et al. The SimpliciT1 Study: a randomized, double-blind, placebo-controlled Phase 1b/2 adaptive study of TTP399, a hepatoselective glucokinase activator, for adjunctive treatment of Type 1 diabetes. Diab Care 2021;44(4):960–8.

6. Wang, S., Hu, H. Impute the missing data using retrieved dropouts. BMC Medical Research Methodology, 22, 82 (2022). https://doi.org/10.1186/s12874-022-01509-9

7. Wang Y, Tu W, Kim Y, et al. Statistical methods for handling missing data to align with treatment policy strategy. Pharmaceutical Statistics. 2023;22(4):650-670. doi:10.1002/pst.2299

8. CONTOUR®NEXT blood glucose monitoring system user guide, https://www.contournextone.com/siteassets/pdf/web85688006_cntrnxtone_ug_r01-17.pdf.

9. Steingrimsson, JA, DF Hanley, and M Rosenblum, 2017, Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions, Contemporary Clinical Trials, 54:18-24.

APPENDIX B: SCHEDULE OF PROCEDURES

	Screening	Discretionary Insulin Adjustment [a]	Mandatory Placebo Run-In[v]	Randomized Double-Blind Treatment Period									ET Visit	EOS Follow-Up Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	Any	14
Week	-7 to -4	-4 to -2	-2 to -1	Day 1	2	4	6	8	10	12	14	16	Any	18
Day (±Visit Window)	-49 to -29 (±3)	-28 to -15 (±3)	-14 (±3) to 1	1 (NA)	15 (±3)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	99 (±3)	113 (±3)	Any	127 (±3)
Informed consent [b]	X													
Inclusion/exclusion criteria	X	X	X	X										
Demographic information	X													
Medical/psychiatric/surgical history	X	X	X	X										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [d]	X			X	X	X	X	X	X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [f]	X			X	X	X	X	X	X	X	X	X	X	X
Estradiol and FSH [g]	X													
Hematology	X			X				X				X	X	X
Urinalysis	X			X								X	X	X
Thyroid-stimulating hormone	X							X				X	X	
Amylase and lipase	X							X				X	X	
Calcitonin	X							X				X	X	
Lipid profile [h]	X			X				X				X	X	
Serum chemistry panel [i]	X			X		X		X		X		X	X	X
Hepatitis and HIV screen	X													
HbA1c	X			X		X		X		X		X	X	

	Screening	Discretionary Insulin Adjustment [a]	Mandatory Placebo Run-In[v]	Randomized Double-Blind Treatment Period									ET Visit	EOS Follow-Up Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	Any	14
Week	-7 to -4	-4 to -2	-2 to -1	Day 1	2	4	6	8	10	12	14	16	Any	18
Day (±Visit Window)	-49 to -29 (±3)	-28 to -15 (±3)	-14 (±3) to 1	1 (NA)	15 (±3)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	99 (±3)	113 (±3)	Any	127 (±3)
[redacted]														
Blood biomarkers [j]	X			X		X		X		X		X	X	X
UACR			X	X				X				X	X	
12-lead ECG [k]	X			X				X			X[w]	X	X	X
Urine drug screen/ alcohol breath test	X											X	X	
Randomization				X										
Study drug dosing diary entry			←				X					→		
Insulin doses eDiary entry		←				X						→		X
Hypoglycemic, hyperglycemic, and DKA events entry		←				X						→		X
Assess diary for completeness		←				X						→		X
Insulin adjustments [l]		←				X						→		X
CGM sensor placement [m]		←				X						→		
CGM data upload [m]			X	X	X	X	X	X	X	X	X	X	X	X
Telephone call visit [n]					←			X				→	X	X
Provide blood glucose and ketone meters with test strips and supplies [o]			X											
Study drug self-administration IFU initially provided [p]			X											

	Screening	Discretionary Insulin Adjustment [a]	Mandatory Placebo Run-In[v]	Randomized Double-Blind Treatment Period									ET Visit	EOS Follow-Up Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	Any	14
Week	-7 to -4	-4 to -2	-2 to -1	Day 1	2	4	6	8	10	12	14	16	Any	18
Day (±Visit Window)	-49 to -29 (±3)	-28 to -15 (±3)	-14 (±3) to 1	1 (NA)	15 (±3)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	99 (±3)	113 (±3)	Any	127 (±3)
Study drug administration [p]				X	X	X	X	X	X	X	X	X		
DEXA [q]				X								X	X	
[redacted]														
Study drug plasma concentration [s]					X	X	X	X	X	X	X	X	X	
Antidrug antibody assessment [s]				X[x]								X	X	
PK profile (optional) [t]											X			
AEs/ADEs [u]	X	X	X	←					X				→	

[redacted]ADE = adverse device effect; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoB = apolipoprotein B; AST =aspartate aminotransferase; BHB = beta-hydroxybutyrate; BUN = blood urea nitrogen; CGM = continuous glucose monitoring; CTX-1 = C-terminal telopeptide of type I collagen; DEXA = dual energy X-ray absorptiometry; DKA = diabetic ketoacidosis; [redacted] ECG = electrocardiogram; eCRF = electronic case report form; EDC = electronic data capture; eDiary = electronic diary; eGFR = estimated glomerular filtration rate; EOS = End of Study; ePRO = electronic patient-reported outcome; ET = Early Termination; FSH = follicle-stimulating hormone; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HDLC = high density lipoprotein cholesterol; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; hsCRP = high-sensitivity C-reactive protein; IFU = instructions for use. IL6 = interleukin 6; LDLC = low density lipoprotein cholesterol; MCP-1 = monocyte chemoattractant protein 1; NA = not applicable; PAI-1 = plasminogen activator inhibitor-1; PK = pharmacokinetic; QUICKI = Quantitative Insulin Check Index; SC = subcutaneous; TBR = time below range; TIR = time in range; T_{max} = time to maximum plasma concentration; UACR = urine albumin-creatinine ratio; [redacted] VCAM1 = vascular cell adhesion protein 1; VLDL = very low-density lipoprotein

[a]Either at the start of Visit 2 (or Visit 3 if the discretionary Insulin Adjustment Period is not undertaken), eligible participants will be administered diabetes-related quality of life and treatment satisfaction questionnaires. Following that assessment, participants may enter a discretionary Insulin Adjustment Period for up to 2 weeks (Weeks -4 to -2) where the Investigator has an opportunity to assess the adequacy of their existing insulin regimens and discern if participants are within treat-to-target goals, ie, ≥70% TIR 70-180 mg/dL (3.9-10 mmol/L) and <4% TBR <70 mg/dL (<3.9 mmol/L).

[b]Obtain signed informed consent before any study-related procedures are performed.
[c]Collect height at the Screening Visit only for use in calculating body mass index. Assess body weight at every visit.
[d]Perform a full physical examination at Screening (and Visits 4 [Day 1] and 12 [Week 16]). Perform a brief physical examination at the other visits. During the study drug dosing period, include inspection of injection site(s) in the physical examination.
[e]Vital signs include temperature, heart rate, and blood pressure. Participants should not drink coffee for 1 hour prior to collection and should be seated for ≥10 minutes prior to collection.
[f]For female participants of childbearing potential, perform a serum pregnancy test during Screening and at Visits 4 (Day 1) and 12 (Week 16) and perform a urine pregnancy test at all the other visits.
[g]For female participants whose menopausal status needs to be determined.
[h]Includes triglycerides, total cholesterol, LDL-C, HDL-C, ApoB, free fatty acids, and VLDL. Before blood collection, participants must be in a fasted state defined as ~8 hours of fasting.
[i]Complete metabolic panel, including blood glucose, total bilirubin, ALP, ALT, AST, BUN, creatinine, and eGFR. Before blood collection, participants must be in a fasted state defined as ~8 hours of fasting.
[j]Includes adiponectin, leptin, glucagon, C-peptide, insulin, glucose, HOMA-IR, QUICKI, GLP-1, GIP, hsCRP, PAI-1 activity, CTX-1, MCP-1, IL-6, endothelin-1, E selectin, VCAM-1, and beta-hydroxybutyrate. Before blood collection, participants must be in a fasted state defined as ~8 hours of fasting.
[k]Standard 12-lead ECGs will be recorded prior to drawing blood samples with the participant resting supine for at least 5 minutes.
[l]A participant's insulin doses may be adjusted weekly based on their CGM readings to maintain their treat-to-target ranges (ie, ≥70% TIR 70-180 mg/dL and <4% TBR <70 mg/dL). Adjustments may be made during the in-person visit, remotely during phone calls from study staff on alternate weeks from the scheduled in-person visits, and/or when deemed necessary by the Investigator or qualified clinic staff to maintain glycemic targets. All changes in insulin doses from Week -4 to Week 16 will be documented in the eCRF.
[m]Participants will be provided with study-specific CGM device and have sensor placement overseen by the clinic staff. Participants will be given instruction on changing their sensors at home every 10 days (ie, a new sensor should be placed by the participant on the 10th day following the last sensor placement) and all participants will be provisioned with adequate CGM-related supplies.
[n]Starting at the end of Week 1, participants will be contacted by telephone on alternate weeks between in-person visits. These telephone visits are intended to be check-in visits, not a comprehensive review of all CGM and insulin data. That is expected during the in-clinic visits, during which insulin adjustments can be made. During the telephone visits, site personnel will have access to participant-reported events verbally and through ePRO; insulin data will be available through ePRO, and CGM data will be participant-reported. All this information may be used to make appropriate insulin dose adjustments via telephone to minimize [redacted] risk for a given participant. Any insulin dose adjustments made telephonically would still need to be captured in the EDC. If a complete review of the last week's CGM data is desired based on participant-reported events/values, either an Unscheduled Visit should be scheduled so that the full CGM data can be downloaded and reviewed, or participants (if they elect to do so) will have the option of being able to upload their CGM data for remote site review.
[o]Provide participants with glucometer and blood ketone meter with necessary supplies (blood and urine test strips) for additional self-monitoring for the duration of the study. Instruct participants to report any symptoms of hypoglycemia and/or symptoms consistent with DKA.
[p]Instruct participants to self-administer the study drug dose by SC injection in the [redacted] daily at the same time each morning, whenever possible.
[q]Baseline DEXA assessment may be performed up to +3 days from Day 1. In case of early withdrawal, DEXA may be repeated only if the participant participated for at least 10 weeks.
[redacted]
[s]Blood samples to assess study drug plasma concentration and antidrug antibodies will be collected ~24 hours post dose at the indicated visits following an overnight fast of ~8 hours.

[t]Blood samples for extended PK analysis will be collected at Visit 11 (Week 14) from a subset of participants predose (-0.5 hours), at the time of dosing (t=0), and at 0.5, 1, 2, 4, 8, 12, and 24 hours postdose. Additional plasma samples for CT-868 metabolite assessment will be collected predose (-0.5 hours), and 4, 12, and 24 hours postdose. A baseline sample for antidrug antibodies will be collected on Day 1 predose.
[u]AEs/ADEs will be collected throughout the study starting at Visit 1.
[v]All attempts should be made to have a 14-day Mandatory Placebo Run-in Period, or as close to 14 days as possible. The minimum Placebo Run-in Period is 11 days.
[w]At Week 14 – ECGs will only be performed in the subgroup of participants who are participating in the optional 24-hour PK assessment at Week 14. The ECG measurement will be performed at the approximate T_{max} of the study drug (~ 10 hours postdose).
[x]On Day 1, a blood sample to assess antidrug antibodies will be collected in the fasting state prior to the first study drug administration.

APPENDIX C: LABORATORY TESTS

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Creatinine	Chloride
Gamma-glutamyl transpeptidase	Estimated glomerular filtration rate
Inorganic phosphorus	Glucose
Lipase	Lactate dehydrogenase
Sodium	Potassium
Total protein	Total bilirubin
Uric acid	

Blood Biomarkers

Adiponectin	beta-hydroxybutyrate
C-peptide	Leptin
E-selectin	Endothelin-1
Glucose-dependent insulinotropic polypeptide	Glucagon-like peptide-1
High-sensitivity C-reactive protein	Hemoglobin A1c
Monocyte chemoattractant protein-1	Interleukin 6
Vascular cell adhesion molecule 1	

Endocrinology

Estradiol[a]	Follicle-stimulating hormone [1]
Glucagon	Insulin
Thyroid stimulating hormone	Calcitonin
Free T4/T3 in case of abnormal TSH	C-peptide

[a] Estradiol and follicle-stimulating hormone should be analyzed for females whose menopausal status needs to be determined.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential[a]	

[a] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Hepatitis and HIV Screen

Hepatitis B surface antigen
Hepatitis C virus antibody (HCV-RNA, Qualitative)
HIV

Lipid Profile

Free fatty acids	High density lipoprotein cholesterol
Lactate	Low density lipoprotein cholesterol
Total cholesterol	Triglycerides
Very low-density lipoprotein	Apolipoprotein-B

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy[a]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

[a]Microscopy is performed only as needed based on positive dipstick test results.

Urine, Other

Urinary Creatinine
Urinary Albumin
Urinary Creatinine to Albumin Ratio

Urine Drug Screen

3,4-methylenedioxy-methamphetamine	Amphetamines
Barbiturates	Benzodiazepines
Cocaine	Methadone
Methamphetamine	Opioids
Oxycodone	Phencyclidine
Tetrahydrocannabinol	Tricyclic antidepressants

Alcohol Breath Test

Ethyl alcohol

Pregnancy Test

Serum and urine pregnancy test[a]

[a] For female participants of childbearing potential, perform a serum pregnancy test during Screening and at Visits 4 (Day 1) and 12 (Week 16) and urine pregnancy test at all other visits.

APPENDIX D: DOSE/TITRATION ADJUSTMENT SCHEMA

Treatment Arm	Dose and Duration	Dose/Titration Adjustment
Arm 1 Volume-matched placebo (n ~[redacted])	[redacted]	[redacted]
Arm 2 1.8 mg CT-868 (n ~[redacted])		
Arm 3 4.1 mg CT-868 (n ~[redacted])		

Treatment Arm	Dose and Duration	Dose/Titration Adjustment
Arm 4 CT-868 dosed to tolerability/ up to maximum of 6.6 mg (n ~[redacted])	[redacted]	

[1] Administered as [redacted] doses of [redacted] mg each.

[2] Administered as [redacted] doses of [redacted] mg each.

[3] No up-titrations in dose will be allowed after Week 12 (i.e., whichever is the dose that the participant is able to tolerate at the Week 12 visit will be the dose that would be maintained for the remainder of the dosing period without further dose increases). However, doses may continue to be down-titrated after Week 12 to their previously tolerated dose if the final re-challenge/up-titration dose at Week 12 was not tolerated.

- The actual received dose of the study drug will be recorded on the eCRF each week during the study.

Participants randomized to Arm 2, Arm 3, or Arm 4 must tolerate a minimum of 1.8, [redacted], or 4.1 mg/day, respectively, of the study drug to continue participation in the study. If the Investigator believes that the participant will not tolerate the required minimum doses stipulated for each study arm despite undertaking all the symptomatic relief measures to mitigate tolerability issues, the participant will discontinue administration of their assigned study drug but will be encouraged to remain in the study for the purpose of collecting additional safety data and undergoing the remaining procedures and assessments.

APPENDIX E: CGM RELATED ENDPOINTS DERIVATION

Only 14 consecutive days of CGM data with at least 70% of data collected during the study period of interest will be used in the derivation. Analysis visit windows of Baseline, Week 8 and Week 16 are defined as analysis day [-14, -1], [50, 63], [106,119], respectively. For each parameter of interest, the Change from Baseline at Week 8 or 16 = Value at Week 8 or 16 − Value at Baseline.

	Endpoints	Derivation	Comments
Intraday (ie, within 24 hours)	Mean sensor glucose (mg/dL)	$\bar{x}_i = \frac{1}{j}\sum_j x_{ij}\ (i = 1, \ldots, 14,\ j\ in\ \{1, 2, \ldots, 288\})$ x _i,j is the glucose value at timepoint i on day j i is the day index (total 14 days), j is the measurement index within a day (total 288 measurements per day, since we have 1 measurement every 5 minutes).	This formula computes the mean of glucose levels for each day. Intraday mean within 14 days in the study period of interest is the mean of the mean of each day.
	SD of Mean sensor glucose (mg/dL)	$SD_i = \sqrt{\frac{1}{J-1}\sum_j (x_{ij} - \bar{x}_i)^2}\ (i = 1, \ldots, 14, j\ in\ \{1, 2, \ldots, 288\})$	This formula computes the standard deviation of glucose levels for each day. Intraday SD within 14 days in the study period of interest is the mean of the SD of each day.
	%CV of sensor glucose (mg/dL)	$\%CV_i = 100 * SD_i\ /\ \bar{x}_i\ (i = 1, \ldots, 14)$	This formula computes the %CV of glucose levels for each day. Intraday %CV within 14 days in the study period of interest is the mean of the %CV of each day.
Interday (ie, over multiple days)	Mean sensor glucose (mg/dL)	$\bar{x}' = \frac{1}{k}\sum_k x_k\ (k\ in\ \{1, 2, \ldots, 4032\})$ x _k is the glucose value at timepoint k k is the measurement index within 14 days (total 4032 measurements in 14 days, since we have 1 measurement every 5 minutes).	Mean of values of measurements within 14 days in the study period of interest. This formula computes the mean of glucose levels for multiple days.
	SD of Mean sensor glucose (mg/dL)	$SD' = \sqrt{\frac{1}{k-1}\sum_k (x_k - \bar{x}')^2}(k\ in\ \{1, 2, \ldots, 4032\})$	
	%CV of sensor glucose (mg/dL)	$\%CV' = 100 * SD'/\bar{x}'$	

	Endpoints	Derivation	Comments
Percentage of time spent in range	70–180 mg/dL	100% * # Readings in the specific range / All # readings in the study period period of interest. Only >= 15 consecutive min in the range will be counted in numerator.	Percentage of Time in Range (PTIR)
	70-140 mg/dL		Percentage of Time in Tight Range (PTITR)
	<70-54 mg/dL		Percentage of Level 1 hypoglycemia, or Time below Range 1 (PTBR1)
	<54 mg/dL		Percentage of Level 2 hypoglycemia, or Time below Range 2 (PTBR2)
	>180–250 mg/dL		Percentage of Level 1 hyperglycemia, or Time above Range 1 (PTAR1)
	>250 mg/dL		Percentage of Level 2 hyperglycemia, or Time above Range 2 (PTAR2)
Time spent in range	70–180 mg/dL	Readings in the range in the study period period of interest * 5 mins, unit Hour or Minutes Only >= 15 consecutive min in the range will be counted in numerator.	Time in Range (TIR)
	70-140 mg/dL		Time in Tight Range (TITR)
	<70-54 mg/dL		Level 1 hypoglycemia, or Time below Range 1 (TBR1)
	<54 mg/dL		Level 2 hypoglycemia, or Time below Range 2 (TBR2)
	>180–250 mg/dL		Level 1 hyperglycemia, or Time above Range 1 (TAR1)
	>250 mg/dL		Level 2 hyperglycemia, or Time above Range 2 (TAR2)

	Endpoints	Derivation
Proportion of participants with time in range	70–180 mg/dL with >= 5% points improvement at Week 8 from Baseline at Day 1	Number of participants with (PTIR at Week 8 - PTIR at Baseline) > 5%/ Number of participants
	70–180 mg/dL with >= 5% points improvement at Week 16 from Baseline at Day 1	Number of participants with (PTIR at Week 16 - PTIR at Baseline) > 5%/ Number of participants
	70–180 mg/dL with >= 10% points improvement at Week 8 from Baseline at Day 1	Number of participants with (PTIR at Week 8 - PTIR at Baseline) > 10%/ Number of participants
	70–180 mg/dL with >= 10% points improvement at Week 16 from Baseline at Day 1	Number of participants with (PTIR at Week 16 - PTIR at Baseline) > 10%/ Number of participants
	70–180 mg/dL for >70% of the 14-day collection interval around the Week 8 Visit	(Number of participants with PTIR at Week 8 > 70%) / Number of participants
	70–180 mg/dL for >70% of the 14-day collection interval prior to the Week 16 Visit	(Number of participants with PTIR at Week 16 > 70%) / Number of participants
	<70 mg/dL for <4% of each day	Number of participants with (PTBR1 + PTBR2) < 4% of each day in the study period period of interest / Number of participants
	<54 mg/dL for <1% of each day	Number of participants with PTBR2 < 1% of each day in the study period period of interest / Number of participants
	>180 mg/dL for <25% of each day	Number of participants with (PTAR1+PTAR2) < 25% of each day in the study period period of interest / Number of participants
	>250 mg/dL for <5% of each day	Number of participants with PTAR2 < 25% of each day in the study period period of interest / Number of participants
Number of events with sensor glucose	<70 mg/dL lasting at least 120 minutes	Number of events with sensor <70 mg/dL lasting at least 120 minutes in the study period period of interest. event ends when glucose returns to ≥70 mg/dL for ≥15 minutes
	>250 mg/dL lasting at least 120 minutes	Number of events with sensor >250 mg/dL lasting at least 120 minutes in the study period period of interest. event ends when glucose returns to ≤180 mg/dL for ≥15 minutes
	Glycemic risk index	100 * (3.0 * PTBR2)+(2.4 * PTBR1)+(1.6 * PTAR2)+(0.8 * PTAR1) with a maximum permissible value of 100

APPENDIX F: EXAMPLE SAS CODE

```
/*
Note:
        USUBJID  = unique participants identifier
        TRT01PN  = planned analysis treatment Placebo (Arm 1) = 0, CT-868 arm = 1 (overall
treatment i.e. pooled Arms 2, 3 and4)
        STRAT1RN = methods of insulin administration (pump or MDI)
        BASE     = Baseline HbA1c value
        CHG = change in HbA1c (%) from Baseline to Week 16
     Week12 - Week16 = HbA1c (%) at Week 12, Week 16

        Competed Status = 1 (on-treatment completers); 0 (missing assessment at Week 16 for
non-RDs); 999 (RDs with non-missing assessment at Week 16)
        tr_dataImp_MCMC_2a = subsets 2 with repeating N=100 times with _IMPUTATION_ = 1
to 100
        _IMPNUM_ = 1 to 100 imputation iteration
*/


**-------------------------------------**;
** Step 1: Intermediate missing data **;
**-------------------------------------**;

PROC MI DATA = tr_data1 (where(BASE^=.)) SEED = 20241658 OUT = tr_dataImp_MCMC
NIMPUTE = 100;
    VAR BASE STRAT1RN TRT01PN Week12 - Week16CHG     ;
    MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE;
    RUN;

**-------------------------------------**;
** Step 2: Create subsets for Off-Treatment and On-Treatment Completers **;
**-------------------------------------**;

DATA tr_dataImp_MCMC_1;
    SET tr_dataImp_MCMC;
    IF Completed Status in (0, 999);  /* Assuming '0' for non-RDs with missing data, '999' for
RDs */;
    RUN;

DATA tr_dataImp_MCMC_2;
    SET tr_dataImp_MCMC;
    IF Completed Status = 1; /* On-treatment completers */
    RUN;

**-------------------------------------**;
** Step 3.1: Monotone Regression MI for Off-Treatment Subset **;
**-------------------------------------**;
```

```
PROC MI DATA = tr_dataImp_MCMC_1 SEED = 6354351 OUT = tr_dataImp_MCMC_1a
NIMPUTE = 1;
    BY _IMPUTATION_;
    CLASS STRAT1RN TRT01PN ;
    MONOTONE REGREGRESSION (CHGWeek12 = TRT01PN STRAT1RN BASE);
    MONOTONE REGRESSION (Week16 = Week12 TRT01PN STRAT1RN BASE);

    VAR BASE STRAT1RN TRT01PN CHGWeek12 Week16;
    RUN;

**-----------------------------------**;
** Step 3.2: MI for on-Treatment Subset if it is missing at Week 16**;
**-----------------------------------**;
PROC MI DATA = tr_dataImp_MCMC_2 (where(BASE^=.)) SEED = 6354654 OUT =
tr_dataImp_MCMC_2a NIMPUTE = 1;
    BY _IMPUTATION_;
    VAR BASE STRAT1RN TRT01PN Week16;
    RUN;


**-----------------------------------**;
** Step 4: Combine the completed subsets with On-Treatment Completers **;
**-----------------------------------**;

DATA Imputed_data;
    SET tr_dataImp_MCMC_1a (IN=a drop = Week12)
       tr_dataImp_MCMC_2a (IN=b);
    BY _IMPNUM_; /* Ensure datasets are merged by the imputation number */
    RUN;

**-----------------------------------**;
** Step 5: ANCOVA model **;
**-----------------------------------**;
PROC MIXED DATA= Imputed_data METHOD=REML  ;
        BY _IMPNUM_;
        CLASS STRAT1RN TRT01PN  (ref='0');
        MODEL CHG = TRT01PN STRAT1RN BASE / SOLUTION CL DDFM= KR ;

        LSMEANS TRT01PN / ALPHA=0.1 CL DIFF= CONTROLU ('0');

        ODS OUTPUT
                LSMEANS= lsm01 DIFFS= diff01;
RUN;

**-----------------------------------**;
** Step 6: MIANALYZE to combine imputations using Rubin’s Rules **;
**-----------------------------------**;
PROC MIANALYZE DATA= LSM01 ALPHA= 0.1;
        BY TRT01PN;
        MODELEFFECTS ESTIMATE;
        STDERR STDERR;
```

```
        ODS OUTPUT
                PARAMETERESTIMATES= LSM02;
RUN;

PROC MIANALYZE DATA= DIFF01 ALPHA= 0.1;
        BY TRT01PN;
        MODELEFFECTS ESTIMATE;
        STDERR STDERR;
        ODS OUTPUT
                PARAMETERESTIMATES= DIFF02;
RUN;
```