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

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A Member of the ROCHE GROUP

CLINICAL STUDY PROTOCOL

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

Investigational Product: CT-868

Protocol Number: CT-868-004

Sponsor:

Carmot Therapeutics, Inc.
740 Heinz Avenue
Berkeley, CA 94710
United States
Telephone: 888-402-4674

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CONTACT INFORMATION

Sponsor's Medical Expert:	[redacted], MD, PhD [redacted] Carmot Therapeutics, Inc. 740 Heinz Avenue Berkeley, CA 94710 United States [redacted]

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SIGNATURE PAGE

STUDY 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

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signed by: [redacted]

[redacted] MD, PhD

Carmot Therapeutics, Inc.

7/29/2024

Date

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document, and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Carmot Therapeutics, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Carmot Therapeutics, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Carmot Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.

I agree to conduct this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regional regulations.

Investigator's Signature	Date

Investigator's Printed Name

SYNOPSIS

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 No.	CT-868-004
Investigational **Product:**	CT-868 Pen Injector, [redacted] mg/mL (CT-868)
Phase:	2
Indication:	Type 1 diabetes mellitus (T1DM)

Objectives and Endpoints:

The study objectives and endpoints are as follows:

Primary Objective	**Primary 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
Key Secondary Objectives	**Key Secondary 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
• 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 <7.0%, ≤6.5%, and <5.7% at Week 16	• Participant status of achieving HbA1c of <7.0% (Yes/No) • Participant status of achieving HbA1c of ≤6.5% (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 at Day 1 to Weeks 8 and 16
Other Secondary Objectives	**Other Secondary Endpoints**
• To assess the effect of CT-868 relative to placebo on the following parameters: o CGM metrics (TIR, time in	• Change from baseline at Day 1 to Weeks 8 and 16 in the following CGM parameters: o Mean sensor glucose (mg/dL) and its SD

hypo- and hyperglycemia, glycemic risk index)	and %CV [both intraday (ie, within 24 hours) and interday (ie, over multiple days)] o Percentage and amount of time (hours and minutes) spent in range (TIR, 70–180 mg/dL) o Percentage and amount of time (hours and minutes) spent in tight range (70-140 mg/dL) o Participants with TIR 70-180 mg/dL with ≥5% points and ≥10% points improvement from Day 1 (Yes/No) o Percentage and amount of time (hours and minutes) spent in Level 1 hypoglycemia (54-69 mg/dL) and Level 2 hypoglycemia (<54 mg/dL) o Percentage and amount of time (hours and minutes) spent in Level 1 hyperglycemia (>180–250 mg/dL) and Level 2 hyperglycemia (>250 mg/dL) o 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) o 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) o 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) o Participants with TBR <70 mg/dL for <4% of each day (Yes/No) o 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) ○ Glycemic risk index
○ 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
○ Percentage of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss	○ Participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss at Week 16 (Yes/No)
○ Proportion of participants experiencing one or more Level 1, 2, 3 hypoglycemia events (incidence rate) and total number of Level 1, 2, 3 hypoglycemia events/total patient-years of exposure (event rate)	○ Proportion of participants experiencing 1 or more Level 1, 2, or 3 hypoglycemia event(s) over the study duration ○ Total patient years of exposure (event rate) at each hypoglycemia level over the treatment period of 16 weeks
○ Incidence of DKA	Participants with "definite" DKA events as defined in Section 5.2 (Kitabchi et al. 2009; ADA 2024) 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 safety and tolerability of CT-868 versus placebo administered QD via Pen over 16 weeks	• AEs/ADEs, physical examinations, vital signs, ECGs, and safety laboratory measurements (urinalysis, hematology, chemistry, BHB, amylase, lipase, calcitonin) over the period of 16 weeks • Change from baseline at Day 1 to Week 8 and Week 16 in systolic/diastolic blood pressure and heart rate
• To evaluate CT-868 plasma concentration	• Plasma drug concentrations at the Weeks 2, 4, 6, 8, 12, and 16 visits

• 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
Exploratory Objectives	**Exploratory 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 Day 1 baseline with: o Improvement in HbA1c ≥0.5% points and <1% TBR <54 mg/dL o Mean glucose <154 mg/dL and <1% TBR <54 mg/dL o ≥70% TIR 70-180 mg/dL and <4% TBR <70 mg/dL o ≥70% TIR 70-180 mg/dL and <1% TBR <54 mg/dL o Either HbA1c improvement ≥0.5% points or ≥70% TIR 70-180 mg/dL, with <1% TBR <54 mg/dL, and without requiring significant increase in daily insulin use [ie, >10% increase in total (bolus + basal) insulin (units/kg/day)]
	• Participants with at least 1 Level 2 (CGM value <54 mg/dL) or Level 3 hypoglycemia event during the 16-week treatment period (Yes/No)
• 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 fasting plasma glucose, insulin, C-peptide, glucagon, GLP-1 (total and active), GIP, HOMA-IR, and QUICKI • 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 at Day 1 to Week 16 in total lean mass and total fat mass as determined by DEXA
• [redacted]	• [redacted]

[redacted] • [redacted] • To assess the percentage of participants at the 4.1 mg, [redacted] mg, and 6.6 mg doses at the end of Week 16 and the time to achieve their final dose (Arm 4 only) • 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)	• [redacted] • [redacted] • Number of participants maintained at the 4.1 mg, [redacted] mg, and 6.6 mg doses at the end of Week 16 (Arm 4 only) • Time (weeks) to achieve the final planned dose (Arm 4 only) • Change in HbA1c values and percent change in body weight at Week 16
Objectives Related to Pharmacokinetics and Immunogenicity • To assess the CT-868 concentration-time profile over 24 hours (in a subset of the T1DM study population) • To evaluate correlation between CT-868 plasma exposure and relevant efficacy parameters • To evaluate treatment-emergent anti-drug antibodies to CT-868 (Arms 2, 3, 4 only)	**Endpoints Related to Pharmacokinetics and Immunogenicity** • CT-868 PK parameters (C_{max}, T_{max}, C_{trough}, C_{last}, T_{last}, AUC_{0-24}, AUC_{0-last}, and $t_{½}$) • Treatment-emergent anti-drug antibodies to CT-868 on Day 1 and Week 16 (Arms 2, 3, and 4 only)

[redacted] ADE = adverse device effect; AE = adverse event; ALT = alanine aminotransferase; 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; CTX-1 = C-terminal telopeptide of type 1 collagen; DEXA=dual energy X-ray absorptiometry; DKA = diabetic ketoacidosis; [redacted] ECG=electrocardiogram; eGFR = estimated glomerular filtration rate; FFA = free fatty acids; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein cholesterol; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; LDL-C = low density lipoprotein cholesterol; MCP-1=monocyte chemoattractant protein-1; PAI-1=plasminogen activator inhibitor-1; PK=pharmacokinetic [redacted] $t_{1/2}$ = half-life; TBR=time below range; TIR=time in range; T_{last}=time to last quantifiable plasma concentration; 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

Inclusion Criteria	Participants must meet all of the following criteria in order to be eligible to participate in the study: 1. Male or female participants, age ≥18 to ≤65 years at the time of signing informed consent. 2. Have a documented clinical diagnosis of T1DM for ≥1 year before the Screening Visit. Clinical diagnosis requires the participant to have been insulin-deficient with the absolute requirement of insulin therapy starting at diagnosis or shortly after the end of the honeymoon period, either with multiple daily injections (MDIs, ie, basal insulin plus bolus insulin injections for meals) or maintained on continuous subcutaneous insulin infusion (CSII with manual pumps or automated insulin delivery [AID] pump devices, except for the iLet Bionic Pancreas). NOTE: Participants with a diagnosis of T1DM and a fasting C-peptide of >0.6 ng/mL at the Screening Visit should be discussed with the study medical monitoring team prior to enrollment/ randomization. 3. Body mass index ≥27.0 kg/m^2. 4. Glycated hemoglobin (HbA1c) level between 7.0% and 10.0%, inclusive, at the Screening Visit. 5. Treated with insulin either by means of an insulin pump for CSII, or by means of MDIs of insulin for ≥12 months prior to the Screening Visit. Participants with insulin pump treatment are eligible if the pumps are manually operated or are AID devices, except for the iLet Bionic Pancreas.

	6. Must be on stable insulin formulation, dose (ie, within 10% of total daily basal dose), and devices (ie, not switching from MDI to manual or automated pump or vice versa) for ≥2 months prior to the Screening Visit and stable during the entire study, as judged and documented by the Investigator. In addition, participant's insulin requirement must be ≥0.6 U/kg per day. 7. Must have some experience using a CGM device (with replacing sensors) within 3 months before the Screening Visit and be willing to wear a study-provided CGM device for the duration of the study. 8. Must be willing and able to be adherent to prescribed diabetes regimen and perform all prescribed diabetes self-management tasks (glucose and ketone monitoring/ testing, change CGM sensors, adjust insulin doses if applicable, etc.). 9. Must be a non-smoker (ie, never smoked cigarettes or used any tobacco or nicotine containing products) or ex-smoker (ie, not smoked cigarettes or used any tobacco or nicotine-containing products during the last 6 months prior to the Screening Visit). 10. Female participants who engage in sex with men and female partners of male participants must use highly effective forms of contraception with either complete abstinence from sexual intercourse or double barrier contraception (including both male and female participants) during the entire duration of the study (ie, up to Week 18) or until at least 2 weeks after the last dose of CT-868. Male participants must refrain from sperm donation from start of study and for at least 2 weeks after the last dose of CT-868. Double barrier contraception is defined as a condom with spermicide and 1 other form of the following: a. Oral contraceptive pills b. Diaphragm with spermicide c. Intrauterine device d. Birth control patch (eg, Ortho Evra) e. NuvaRing®

	f. Documented evidence of surgical sterilization at least 6 months prior to screening, (ie, tubal ligation or hysterectomy for women or vasectomy for men) NOTE: Rhythm methods will not be considered highly effective methods of birth control and are not acceptable. NOTE: implanted/injectable contraceptives may be allowed provided participants have been on a stable dose and regimen of such contraceptives for ≥9 months prior to the Screening Visit. NOTE: Exception to double barrier contraceptive requirements may be considered if participants are with a same-sex partner and do not participate in bisexual activities where there is any risk of pregnancy.
	11. Female participants of childbearing potential must have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test on Day 1 prior to randomization.
	12. Female participants not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level >40 mIU/mL and estradiol ≤30 pg/mL at the Screening Visit or have documented evidence of having had a hysterectomy, bilateral oophorectomy, tubal ligation, or medically documented primary ovarian insufficiency. NOTE: In cases where female participants are peri- or post-menopausal and are undergoing hormone replacement therapy (HRT), either systemic or in the form of patches, the prescribed laboratory limits for FSH and estradiol levels may not accurately reflect their hormonal status. In such instances, the Investigator should consider the participant's clinical history and medical documentation, including the use of HRT, when assessing eligibility.
	13. Testosterone use (prior and current) will be allowed if testosterone has been used for hormonal replacement (similar concept to that of thyroid hormone replacement) as long as the participant’s dose has been stable within the last 6 months and no significant changes in testosterone dose (>25%) are anticipated during the course of the study along with corresponding stable weight (ie no increase or decrease ≥5%).

	14. Must have unimpaired cognition (ie, without history of any cognitive deficits) and able to communicate well with the Investigator to understand and comply with all the requirements of the study (including maintaining their usual lifestyle patterns throughout the study). 15. Willing and able to understand, provide, and sign the written informed consent. NOTE: Use of lipid lowering and/or antihypertensive medications are allowed, provided the dosage/regimen of these medications have remained stable within the last 2 months prior to the Screening Visit.
Exclusion Criteria	Participants who meet any of the following criteria will be excluded from participation in the study: 1. Diagnosis of type 2 diabetes mellitus (T2DM) or any other types of diabetes (for example latent autoimmune diabetes in adults or maturity-onset diabetes of the young forms), except T1DM. 2. Experienced diabetic ketoacidosis (DKA) within 3 months prior to the Screening Visit. 3. Experienced severe hypoglycemia (Level 3 as defined in the ADA Standards of Medical Care in Diabetes (ADA 2024) within 3 months prior to the Screening Visit. 4. [redacted] 5. Use of any insulin preparation that is not delivered through CSII or MDI (eg, inhaled insulin). 6. Significant changes in diet or exercise regimen within 3 months prior to the Screening Visit or plans to undertake any of these during the study duration (eg, very low calorie, low carbohydrate, very high protein, ketogenic diets, time restricted eating/intermittent fasting, or other nutritional intervention, or initiating a new exercise program). 7. Prior use (ie, within 6 months prior to the Screening Visit) or current use of any of the following: a. Any medication (except insulin) that could interfere with glycemic control (eg, monoamine oxidase inhibitors, growth hormone, bromocriptine)

	b. Any adjunctive treatments for diabetes (eg, pramlintide, metformin, glucagon-like peptide-1 [GLP-1] analogs [eg, exenatide], GLP-1 receptor agonists (GLP-1RAs) [eg, semaglutide, liraglutide, or dulaglutide], GLP-1/GIP RA (Mounjaro™), sodium-glucose cotransporter-2 inhibitors, sulfonylureas, or dipeptidyl peptidase 4 inhibitors) c. Any prescription medication(s), and/or any over-the-counter product(s) including herbal and/or dietary supplements for weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone-bupropion, semaglutide, liraglutide, garcinia cambogia extract, Hydroxycut®, or glucomannan), or for weight gain (eg, testosterone, growth hormone, anabolic steroids, or amino acid supplements) d. Are receiving or have received within 3 months prior to the Screening Visit chronic (>14 consecutive days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (eg, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the Investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) during the study participation e. Any prescribed or non-prescribed drugs that are known to interfere with gut motility including, but not limited to chronic opioids, anticholinergics, antispasmodics, linaclotide, or dopamine antagonists 8. History of treatment intolerance, allergic reactions, or lack of efficacy (ie, non-responders) with prior use of any GLP-1 analogs, GLP-1RAs, or GLP-1/GIP RAs. 9. Any self-reported body weight gain or loss of ≥5% within 3 months prior to the Screening Visit. 10. Have had or is planning to have during the study duration any surgical treatment for obesity (of any type) or with a weight loss device or any other weight loss procedure (eg, Lap-Band®, intragastric balloon, duodenal sleeve, resurfacing).

	NOTE: Liposuction and/or abdominoplasty may be allowed based on the Investigator's discretion, if performed >1 year before the Screening Visit, provided all other eligibility criteria are met.
	11. Have obesity induced by other endocrinologic disorders (eg, Cushing syndrome, acromegaly, or inadequately treated hypothyroidism) or diagnosis of monogenetic or syndromic forms of obesity (eg, melanocortin 4 receptor deficiency or Prader-Willi syndrome).
	12. A diagnosis and/or history of clinically significant gastroparesis, gastric motility, gastric emptying abnormalities, malabsorption disorders (eg, celiac disease), chronic constipation, chronic diarrhea, inflammatory bowel disease, bowel resection, irritable bowel syndrome, or severe gastroesophageal reflux disease.
	13. Any of the following within 6 months prior to the Screening Visit: myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (including participants who may have percutaneous transluminal coronary angioplasty [PTCA] planned and/or anticipated during the study period, such as participants with prior angiographic evidence that may require PTCA); transient ischemic attack, cerebrovascular accident, hospitalization for congestive heart failure, or presenting at Screening with high-risk factors (eg, high blood lipid values). predisposing to cardiovascular events.
	14. Current New York Heart Association Class III or IV heart failure.
	15. Presence of clinically significant electrocardiogram (ECG) findings at the Screening Visit (eg, corrected QT interval using Fridericia's formula [QTcF] >450 msec for males, QTcF >470 msec for females, left bundle branch block), or any other ECG findings considered to be indicative of active cardiac disease or with abnormalities, in the opinion of the Investigator, that are expected to interfere with the interpretation of ECG changes over the study duration or may present a safety issue to the participant.

	16.	Uncontrolled hypertension (ie, mean seated systolic blood pressure ≥160 mm Hg and/or mean seated diastolic blood pressure ≥100 mm Hg) at the Screening Visit (Investigator has the discretion to repeat at least once based on their clinical judgment).
	17.	Any clinically significant change in ophthalmologic examination within 12 months prior to the Screening Visit, including history and/or presence of clinically significant proliferative retinopathy, macular edema, or other diabetes-related eye disease. The ophthalmological examination must be documented in the medical record, not just patient reported. This examination is expected to be part of usual standard of care for their T1DM management and is not a protocol-defined assessment. If an appointment is available, this examination can be performed during the Screening Period.
	18.	History of any hematologic conditions that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle cell disease, other hemoglobinopathies).
	19.	Uncontrolled thyroid disease, defined as having active symptoms (eg, palpitations, lethargy, weight gain, or weight loss) and/or having a thyroid-stimulating hormone (TSH) value <0.4 or ≥4.5 mIU/L ± 10% as the upper normal range at the Screening Visit. If TSH is below or above normal, free T3 and T4 are automatically measured (ie, by reflex testing from the same blood sample). NOTE: Participants receiving adequate treatment for hypothyroidism may be included, provided they are clinically asymptomatic, TSH is within normal reference ranges, and their thyroid hormone replacement dose has remained stable for ≥2 months prior to the Screening Visit.
	20.	Have had an organ transplantation or are awaiting an organ transplantation.
	21.	Have had any major surgery/medical procedure within 12 months of the Screening Visit, or plan to undergo any major surgeries or major procedures during the study.

	22. History or diagnosis of major depressive disorder within 2 years of the Screening Visit, or any history or diagnosis of other severe psychiatric conditions (eg, schizophrenia; bipolar disorder, eating disorder, or other serious mood, anxiety, or hyperactivity disorder). NOTE: Participants with depression or anxiety whose disease state, in the opinion of the Investigator, is considered stable and expected to remain stable throughout the study, may be considered for inclusion only if they are adequately controlled by stable doses of selective serotonin reuptake inhibitors (other than paroxetine) for ≥6 months prior to the Screening Visit, and are expected to continue the same doses for the entire study duration. Participants controlled by other types of anti-depressants or mood stabilizers (see Table 6) are excluded from this study, since many anti-depressants and mood stabilizers are associated with body weight/composition and glucose changes. NOTE: If a participant has a history of non-serious or non-severe anxiety or mood disorder, in other words mild forms of these disorders, AND the participant has not been taking or is not planning to take any medications with a potential impact on weight, appetite or gut motility (even if names of such medications are not explicitly stated in the protocol), then the subject may participate in the study, provided other eligibility criteria are fulfilled. 23. History or current diagnosis of acute or chronic pancreatitis, or risk factors for pancreatitis, such as history of alcoholism, cholelithiasis (without cholecystectomy), hypercalcemia, or severe hypertriglyceridemia. 24. Presence of any other clinically relevant medical and/or psychiatric conditions that would constitute a risk to the participant when taking the study drug or confound study endpoints and/or interfere with study assessments, as determined by the Investigator at the Screening Visit. 25. Presence of any one of the following findings during the Screening Period, as determined by the central laboratory: a. Alanine aminotransferase (ALT), or aspartate aminotransferase (AST), or gamma glutamyl transpeptidase (GGT) >3.0× the upper limit of normal (ULN) of the reference range

	NOTE: Participants with prior history of nonalcoholic fatty liver disease are eligible to participate in this study if their ALT level is ≤3.0×ULN of the reference range. b. Alkaline phosphatase (ALP) >1.5×ULN of the reference range c. Total bilirubin >1×ULN of the reference range d. Amylase or lipase level of >2×ULN of the reference range e. Fasting triglycerides level of >500 mg/dL f. Estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease equation of <45 mL/min/1.73 m^2 g. Calcitonin ≥20 ng/L, if eGFR is ≥60 mL/min/1.73 m^2; or calcitonin ≥35 mg/L, if eGFR is <60 mL/min/1.73 m^2 h. History of, or positive hepatitis screen (including hepatitis B surface antigen [HBsAg] and anti-hepatitis C virus) i. Positive HIV antibody screen j. Hemoglobin level of <11 g/dL (male participants) or <10 g/dL (female participants) NOTE: The Investigator has discretion to repeat laboratory assessments once if they believe there is a high likelihood that the results were spurious and do not accurately represent the participant's true values. Repeat assessments (no more than 1 per laboratory parameter) must be within the Screening Period. The reason for repeat assessments should be documented. 26. Unable to abstain from using >1000 mg acetaminophen/paracetamol every 6 hours, per the safety information associated with the study-provided CGM device (eg, [redacted] 27. Unable to tolerate adhesive tape or has any unresolved adverse skin condition/reaction (eg, psoriasis, rash, *Staphylococcus* infection) in areas of CGM sensor placement.

	28.	Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin carcinoma, in situ carcinoma of the cervix, or in situ prostate cancer) <5 years prior to the Screening Visit.
	29.	Have any active or clinically significant infection, including COVID-19 within 14 days prior to Screening, or has a history of long-COVID-19 syndrome. NOTE: Usual symptoms experienced secondary to post-COVID-19 vaccinations are not exclusionary. All participants are required to follow site-specific COVID-19 protocols, if applicable, during the entire study.
	30.	Have personal or family history (first-degree relative) of medullary thyroid carcinoma or a genetic condition that predisposes to medullary thyroid carcinoma (ie, thyroid C-cell hyperplasia or multiple endocrine neoplasia Type 2A or Type 2B).
	31.	History of atopy (severe or multiple allergic manifestations), clinically significant multiple or severe allergies to prescription or nonprescription drugs, intolerance to topical corticosteroids, or history of severe hypersensitivity reactions.
	32.	A known allergy to any component of the study drug formulation or any other condition not listed in this section (eg, hypersensitivity or intolerance) that is a contraindication to GLP-1RAs or GLP-1/GIP RAs
	33.	Planning to or anticipating initiation of any medications that may affect body weight or glucose metabolism during study participation, including current use of any prescribed or non-prescribed agents in the prohibited medication list (see Table 6).
	34.	Women who are pregnant, breastfeeding, intends to become pregnant, or is of childbearing potential and not using a highly effective contraceptive method if engaged in a heterosexual relationship.

	35.	History of alcohol addiction, and/or routinely consumes alcohol in the amount that exceeds 21 units per week (men) and 14 units per week (women) NOTE: 1 unit of alcohol is defined as 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, or 1.5 oz or 45 mL of distilled spirits, as assessed during the Screening Visit.
	36.	History of use of known drugs of abuse within 12 months of the Screening Visit.
	37.	Has a positive alcohol test and/or positive drug test at Screening Visit.
	38.	Prior or current participation in any other study that is evaluating CT-868.
	39.	Participation in any other investigational drug study for any indication in which receipt of an investigational drug product occurred within 5 half-lives or 60 days, whichever is longer, prior to the Screening Visit.
	40.	Participation in any other clinical study within 3 months prior to the Screening Visit, including current enrollment in any other type of clinical research judged not to be scientifically or medically compatible with this study with the exception of investigational vaccines, in which case, participants may be enrolled 3 months after the last dose, regardless of follow-up in another clinical study.
	41.	Inability to comply with daily subcutaneous (SC) injection regimen of study drug or is unwilling to wear and appropriately maintain the study-provided CGM device for the study duration (including the Follow-up Period), or unwilling to maintain their usual lifestyle patterns/regimen throughout the entire study.
	42.	Have donated ≥500 mL of blood, or have received a blood transfusion, or experienced severe blood loss within 3 months of Screening Visit, or have donated blood of any volume within 1 month of Screening Visit, or plan to donate blood during study participation.

	43. Unwilling to adhere to the protocol requirements during the study or unwilling to cooperate or comply with the requirements of this study, or whose T1DM is managed by someone other than the participant (eg, by a caregiver), or is considered by the Investigator or Sponsor to be an unsuitable candidate for the study.
Study Design:	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. While participants' T1DM may be managed with either insulin pump or by means of MDIs of insulin, all participants must have some experience of using a CGM device (with replacing sensors) within the last 3 months before the Screening Visit and must be willing to wear and maintain the study-provided CGM device (eg, [redacted] for the duration of the study. All enrolled participants will be expected to maintain their usual lifestyle pattern during the study (eg, must not initiate a novel diet or new exercise regimen that is different from their normal routines) and follow the usual standards of care for T1DM, including maintaining all other standard-of-care therapies for their other stable chronic conditions, if applicable, throughout the study. After the Screening Period of up to 3 weeks (Weeks -7 to -4), either at the start of Visit 2 (or Visit 3 if the discretionary Insulin Adjustment Period is not undertaken), eligible participants will be [redacted] Following that assessment, participants may enter a <u>discretionary</u> 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% time in range 70-180 mg/dL (3.9-10 mmol/L) and <4% time below range <70 mg/dL (<3.9 mmol/L) (Battelino et al. 2023). The Investigator has the discretion to make adjustments to the participant's insulin regimens, if needed, during this period prior to entering the <u>mandatory</u> 2-week single-blind Placebo Run-in Period (Week -2 to Day 1). At either the start of the Insulin Adjustment Periodor Placebo Run-in Period (if the discretionary Insulin Adjustment Period was not required), participants will be provided with a study-specific CGM device. All participants will be educated and trained in the placement and exchange of [redacted] sensors. CGM metrics and total daily insulin use data, divided into basal and bolus components, are obtained during this mandatory 2-week Placebo Run-in Period (Week -2 to Day 1) will be considered the

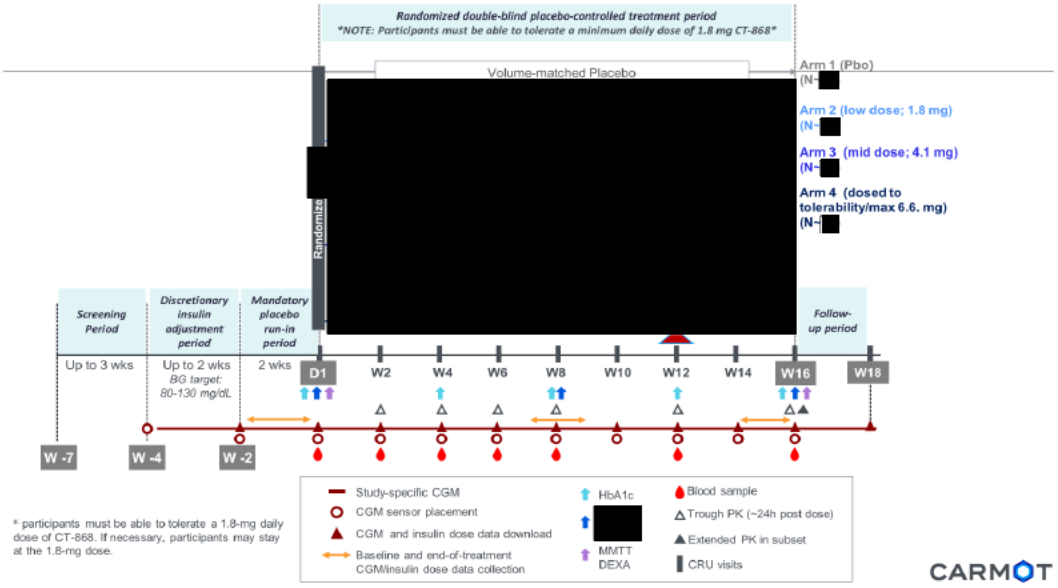
	participant's baseline values for these parameters. During the Placebo Run-in Period, participants are to acclimate to the study drug Pen, and prior to the first dose will receive instruction on proper study drug administration procedures. Before administering the first dose of study drug on Day 1, baseline values will be determined for safety laboratory parameters, HbA1c, fasting glucose, C-peptide, other biomarkers, body weight, DEXA, and [redacted] as detailed in the Schedule of Procedures (Table 7). On Day 1, participants will enter a 16-week double-blind Treatment Period and will be randomized [redacted] to 1 of 4 treatment arms, as depicted in Figure S1. The pooled placebo Arm 1 will consist of 3 sets of ~[redacted] participants to receive the placebo dose volume-matched to a corresponding dose of CT-868. The total number (n [redacted] of placebo participants in Arm 1 will be similar to the number of participants in each of the CT-868 treatment arms (ie, n~[redacted] in each of Arms 2, 3, and 4). At the time of randomization, participants will be stratified by both their [redacted] By stratifying on these two factors, we can better understand the effects of CT-868 treatment on glycemic control in both insulin pump and MDI users across different HbA1c levels. Participants, Investigators, all site personnel, and the Sponsor will be blinded to the treatment code for the duration of the study. Adjustments of insulin doses to minimize risk of [redacted] will be guided by initial HbA1c value and by CGM data (see Table 3). To mitigate risk for [redacted], especially at specified periods of insulin dose reduction, systematic and frequent ketone monitoring with appropriate mitigating measures are recommended (Table 1 and Table 4; see also Study Reference Manual). Just as undertreatment of insulin could lead to [redacted], overtreatment with insulin could lead to [redacted]. Appropriate mitigating measures (Section 3.1 and Table 1) will be undertaken to further minimize risk of [redacted] After randomization on Day 1, the first dose of study drug self-administration will be observed at the clinic after all the necessary baseline assessments have been completed. Participants will once again be instructed to administer study drug by SC injection into the [redacted] at approximately the same time in the morning each day (to the greatest extent possible), for the next 16 weeks. Participants must be able to tolerate a minimum dose of 1.8 mg per day, in order to continue in the study.

	During the Treatment Period, in-person study visits will occur every 2 weeks starting at Week 2, with weekly phone calls from qualified study site staff between the scheduled study visits. All eligible participants will be provided with a study-specific CGM device that should be worn from Week -4 to Week 18 (or at Week -2 for those who do not require the 2-week discretionary insulin-adjustment period). At every in-person study visit from Week -4 through Week 18, CGM data will be uploaded from the respective devices into a vendor data capture system that is compliant with Title 21 of the Code of Federal Regulations Part 11, sensors checked, and adequate CGM-related supplies provisioned for each study participant, including spare sensors/transmitters. As each CGM sensor lasts only 10 days, prompt replacement every 10 days with a new sensor is required to ensure no interruption in glucose data collection; sensors will be replaced by the participant. Participants will manually enter their insulin doses administered into an electronic diary (eDiary) and the data will also be reviewed at each visit. The insulin doses are entered as both the basal and bolus components as well as the total daily doses. On the day of in-person visits, participants will arrive at the study site undosed (ie, their last dose of study drug would have been ~24 hours prior to their visit and following an overnight fast (~8 hours) for collection of blood samples for safety laboratories, biomarkers, CT-868 plasma concentrations, and other assessments, as applicable for each visit. After completion of all their in-person visit assessments, participants will dose themselves with their assigned study drug at the clinic (except at the Week 16 visit, which is their End-of-Treatment Visit). Safety will be monitored throughout the study by a blinded Safety Review Committee comprising the clinical research organization (CRO) Medical Monitor, Principal Investigator, and the Sponsor's medical officer/designee. To characterize the PK profile of CT-868 in T1DM patients, a subgroup of ~[redacted] participants per treatment arm will be asked to participate in an optional 24-hour PK sampling visit at Week 14. The PK sampling time points are detailed in Table 7. After the 16-week double-blind Treatment Period, participants will stop their assigned study drug and have a follow-up safety visit at Week 18 (2 weeks after the last dose of the study drug). During the safety follow-up period, all participants will continue their prescribed insulin treatments and follow usual standard of care for T1DM management.

Dosage Forms and Route of Administration:	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] 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. The CT-868 and placebo Pens must be stored refrigerated and brought to room temperature prior to dosing per the IFU. 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 Table 5. Due to the titration scheme, participants and study staff will be aware of the volume of study drug the participants are receiving; however, they will not be aware of whether they are receiving CT-868 or the placebo (as placebo dose is volume-matched to a corresponding dose of CT-868). Study Design schematic is presented in Figure S1. Dose escalation may occur at, or after, but not before, the designated time for up-titration. It is recommended that the Investigator consult the Sponsor Medical Monitor in case of persistent deviations from the planned escalation regimen, including any questions related to re-initiation of study drug. In case of a whole week of consecutive doses missed for any reason, the participant must re-titrate up from their most recent prior dose level for at least 1 week. Additional details regarding missed doses are provided in Section 6.2. Randomized participants would need to tolerate a minimum dose of 1.8 mg per day to continue participation in the study. If the Investigator believes that the participant will not tolerate the minimum required dose of 1.8 mg despite providing additional time to adjust to that dose level and undertaking all the symptomatic-relief measures to mitigate tolerability issues, then that individual would be discontinued from the study drug; however, they should be

	encouraged to remain in the study for the purpose of collecting additional safety data and undergo all their remaining procedures/assessments.

Figure S1. Study Schematic



BG=blood glucose; CGM=continuous glucose monitoring; CRU=clinical research unit; D=day; DEXA=dual energy X-ray absorptiometry; [redacted] HbA1c=glycated hemoglobin; MMTT=mixed meal tolerance test; Pbo=placebo; PK=pharmacokinetic; [redacted] W=week; wks=weeks

Study Duration:	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 (ie, ≥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.
Criteria for Evaluation: **Efficacy:**	Efficacy will be assessed by HbA1c, various CGM metrics, body weight/body composition measurements, and patient-reported outcomes (PROs).
Pharmaco-kinetics:	CT-868 pharmacokinetics will be evaluated via CT-868 plasma concentrations and PK parameters (ie, area under the concentration-time curve from 0 to 24 hours, area under the concentration-time curve from 0 to the last measurable concentration, last measurable concentration, maximum concentration, trough concentration, time to the last measurable concentration, time to maximum concentration, half-life).
Safety:	Safety assessments will include the following: • Adverse events (AEs)/adverse device events (ADEs), including injection site reactions NOTE: Only treatment-emergent AEs (TEAEs)/treatment-emergent ADEs (TEADEs) will be summarized. • AEs/ADEs of special interest [redacted] • Vital signs • Physical examinations • ECGs • Clinical laboratory tests (hematology, chemistry, including beta-hydroxybutyrate, amylase, lipase, calcitonin, and urinalysis)
Statistical Methods:	Details of statistical parameters and methods to be applied will be provided in a Statistical Analysis Plan (SAP) prior to database lock and unblinding. The Intent-to-Treat (ITT) population includes 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 and key secondary endpoints. The modified Intent-to-Treat (mITT) population includes all randomized participants who receive at least 1 dose of study drug and have at least 1 postdose measurement of HbA1c. This population will be used as the supplementary analysis on the primary and key secondary endpoints, as well as the main analysis population for other secondary and exploratory endpoints. The Safety population includes all randomized participants who receive at least 1 dose of study drug. All safety endpoints will be summarized using the Safety population according to the actual treatment assigned. The Per Protocol (PP) population includes all participants in the ITT population who do not have a major protocol violation that would potentially impact the primary efficacy endpoint. This analysis population will be used for the supplementary analysis for the primary and key secondary endpoints only. The PK population includes 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.
Efficacy Analyses	For all analyses, unless specified otherwise as with CGM metrics, baseline is defined as the last available non-missing value prior to the start of treatment on Day 1. The 3 placebo groups will be pooled prior to analysis for comparison to each dose level of CT 868. The ITT population will be the primary population for the analysis of primary and key secondary endpoints. There is 1 estimand of interest in comparing efficacy of CT-868 doses with placebo relative to the primary endpoint of change in HbA1c from baseline to Week 16 – the "treatment regimen" estimand. It represents the efficacy irrespective of adherence to study drug. This will be used to guide the analyses for the primary and key secondary endpoints. The primary and key secondary efficacy endpoints, change in HbA1c (%) and percent change in body weight from baseline to Week 16 will be analyzed using analysis of covariance (ANCOVA) models with treatment as the factor and the baseline, HbA1c strata (<8.5% or ≥8.5%) (for percent change in body weight only), and methods of insulin administration (pump or MDI) as the covariates. The primary efficacy summary measure will be evaluated using the differences in the least squares (LS) means, with 95% confidence intervals and associated 1-sided p-value from this ANCOVA model. Missing data will be imputed using the retrieved dropout (RD) approach (Wang et al., 2022; Wang et al., 2023). Specifically, for participants who discontinue 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 treatment group, (ie, those who discontinued treatment early but have HbA1c measurements at Week 16), using a multiple imputation approach. All statistical tests will be 1-sided and will be performed using a 5% significance level (alpha). Each CT-868 arm will first be compared with the pooled placebo group and then the 3 CT-868 arms with each other. To protect the overall alpha level on the primary endpoint, the hypothesis testing will be performed sequentially. When testing for efficacy, overall treatment effect will be first evaluated. When the overall treatment effect is statistically significant at 5%, Arm 4 will be compared with placebo (Arm 1), then if significant at 5%, Arm 3 will be compared with placebo (Arm 1), and finally, if significant, Arm 2 will be compared with placebo (Arm 1). The primary and key secondary efficacy endpoints will also be analyzed using the PP population (ANCOVA models with RD) and mITT mixed model repeated measures (MMRM) as supplemental analyses. For MMRM, participants with at least 1 non-missing primary and key secondary endpoints will be included. The treatment effect on the change from baseline in HbA1c to Weeks 4, 8, and 12 will be evaluated in this model. Details will be described in the SAP. The impact of actual final doses will be investigated in separate analyses. MMRM models will also be used to analyze continuous endpoints of repeat structure. Binary HbA1c endpoints will be compared between treatments using logistic regression adjusting for treatment, baseline HbA1c, and methods of insulin administration (pump or MDI) as covariates. Similar analyses will be performed for other binary endpoints. Treatment differences will then be expressed as an odds ratio. Number of events will be compared between treatments using a negative binomial regression model, adjusting for baseline, HbA1c strata, and methods of insulin administration (pump or MDI), and using time in study as an offset. The assessment will be expressed as a risk ratio.
Pharmaco-kinetic Analysis	PK data will be analyzed to determine the steady-state trough CT-868 exposure in all enrolled overweight and obese T1DM participants. These data will also be used in a population PK model together with PK data from other CT-868 studies to evaluate the PK of CT-868 in different populations, such as overweight and obese otherwise healthy participants and overweight and obese participants with T2DM. The latter will be covered in a population PK analysis plan for the CT-868 program.

Safety Analyses	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. TEAEs/TEADEs will be coded and summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. TEAEs/TEADEs will be summarized by the number of participants with at least 1 TEAE for overall TEAEs and for each subtype such as related TEAEs/TEADEs, serious TEAEs/TEADEs, discontinuations of treatment due to TEAEs/TEADEs, and TEAEs/TEADEs of different intensity. Observed safety laboratory values, vital signs, ECGs, and changes from baseline will be summarized descriptively by visit and treatment group. Details will be described in the SAP.
Sample Size Determination:	Approximately 96 participants will 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 1-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.
No. of Sites:	Approximately 15 sites in the United States

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AID	Automated insulin delivery
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BHB	Beta-hydroxybutyrate
BMI	Body mass index
CGM	Continuous glucose monitoring
C_{max}	Maximum plasma concentration
CRO	Clinical research organization
CSII	Continuous subcutaneous insulin infusion
CTCAE	Common Terminology Criteria for Adverse Events
DEXA	Dual energy x-ray absorptiometry
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
GCP	Good Clinical Practice
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
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

Abbreviation	Definition
MAD	Multiple ascending dose
MDI	Multiple daily injection
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures
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
RD	Retrieved dropout
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
TEADE	Treatment-emergent adverse device effect
TEAE	Treatment-emergent adverse event
TBR	Time below range
TIR	Time-in-Range
T_{max}	Time to maximum plasma concentration
TSH	thyroid-stimulating hormone
UACR	Urinary-albumin-to-creatinine ratio
ULN	Upper limit of normal
[redacted]	

1.0 INTRODUCTION AND BACKGROUND INFORMATION

Carmot Therapeutics, Inc., is developing CT-868, a unimolecular dual glucagon-like peptide-1 (GLP1)/glucose-dependent insulinotropic polypeptide (GIP) receptor modulator, for treatment of overweight and obese adults with Type 1 diabetes mellitus (T1DM). This is a Phase 2 study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of CT-868 in overweight and obese adult participants with a documented diagnosis of T1DM for ≥1 year, treated with insulin via continuous subcutaneous insulin infusion (CSII) or by means of multiple daily injections (MDIs) of insulin for ≥6 months.

1.1 Background

1.1.1 T1DM Pathology and Epidemiology

In 2017, it was estimated that over 9 million people suffered from T1DM worldwide, with the majority living in high-income countries (Green et al. 2021). Treatment of these patients has typically focused on glycemic control to reduce microvascular complications; however, hyperglycemia is only one of many physiologic abnormalities present in T1DM. Even patients with ideal glycemic control (hemoglobin A1c [HbA1c] <7%) remain at high risk for cardiovascular disease (Lind et al. 2014), are prone to obesity (Minges et al. 2013), and exhibit insulin resistance (Priya and Kara 2018). These issues are exacerbated by insulin therapy.

From the time of diagnosis, patients with T1DM require insulin, which is mostly delivered subcutaneously. This non-physiologic form of delivery results in chronic hyperinsulinemia. Indeed, patients with T1DM have basal insulin concentrations ~2.5-fold higher than people without diabetes (Gregory et al. 2019; Cree-Green et al. 2018; Bergman et al. 2012). This hyperinsulinemia has long been discounted because it was considered necessary to control glucose levels. However, substantial evidence now indicates chronic hyperinsulinemia has multiple deleterious effects that are likely key contributors to the increased cardiovascular disease risk in patients with T1DM. First, hyperinsulinemia induces insulin resistance (Rizza et al. 1985; Marangou et al. 1986; Del Prato et al. 1994). Second, hyperinsulinemia leads to weight gain, peripheral adiposity, and obesity (Van der Schueren et al. 2021). Weight gain can then further exacerbate insulin resistance (Corbin et al. 2018).

Insulin resistance is greatly underappreciated in T1DM. In a recent meta-analysis of 38 hyperinsulinemic-euglycemic clamp (HEC) studies, all patients with T1DM had reduced insulin sensitivity compared with matched, healthy controls (Donga et al. 2015). In these HEC studies, patients with T1DM had 30% to 50% lower peripheral insulin sensitivity than controls. Furthermore, these studies consistently found reduced suppression of endogenous glucose production and lipolysis. These data provide substantial evidence for the presence of insulin resistance in skeletal muscle, adipose, and hepatic tissues in patients with T1DM. Importantly, insulin resistance is recognized as an independent risk factor for cardiovascular disease (Schauer et al. 2011). No therapies currently address this major pathophysiologic abnormality in T1DM.

Although TIDM is often thought of as a disease of "lean" people, the prevalence of obesity in patients with T1DM has increased in the last 2 decades (Corbin et al. 2018). The Diabetes Control and Complications Trial clearly showed that patients treated with intensive insulin therapy were more prone to gain weight (Nathan et al. 1993). While weight gain is viewed as an unfortunate necessity to achieve glycemic control, the deleterious effects of this weight gain are numerous. In patients without diabetes, obesity is associated with higher rates of cardiovascular disease (Afshin et al. 2017), some cancers (Vucenik and Stains 2012), and poor mental health (Avila et al. 2015). In patients with T1DM, rates of cardiovascular disease, hospitalizations for cardiovascular disease, and death resulting from cardiovascular disease increase with increasing body mass index (BMI) (Van der Schueren et al. 2021).

Despite the development of new insulin preparations and diabetes technologies, the state of T1DM care remains suboptimal. The current treatment paradigm, which focuses exclusively on glycemic control via insulin therapy, fails to address, and in fact exacerbates, these issues. In the last decade, a critical paradigm shift has occurred in the treatment of patients with Type 2 diabetes mellitus (T2DM). Specifically, large cardiovascular disease outcome trials using sodium-glucose cotransporter-2 (SGLT-2) inhibitors (Kosiborod et al. 2018; Mahaffey et al. 2018; Neal et al. 2017) and glucagon-like peptide-1 receptor agonist (GLP-1RA) therapies (Marso, Bain, et al. 2016; Marso, Daniels, et al. 2016; Gerstein et al. 2019) have shown a reduction in cardiovascular disease risk that is not attributable to glycemic control alone. Adopting a similar approach that addresses the treatment of overweight and obese patients living with T1DM is overdue.

Numerous medications "adjunctive" to insulin therapy have been studied including metformin, GLP-1RAs, SGLT-2 inhibitors, dipeptidyl peptidase 4 inhibitors, and others (Avgerinos et al. 2021; Holt et al. 2022). However, pramlintide remains the only therapy approved for the use in T1DM patients on insulin therapy in the United States. Pramlintide, an amylin analog, reduces HbA1c and weight (Pullman et al. 2006; Ryan et al. 2005). Unfortunately, the drug requires an additional injection before meals and can cause nausea, which has substantially reduced its clinical viability. Despite its clinical limitations, pramlintide serves as proof that therapies can be developed and used in conjunction with insulin to improve outcomes. Most recently, SGLT-2 inhibitors and GLP-1RAs were studied in patients with T1DM. SGLT-2 inhibitors have been tested in multiple, large, Phase 3 studies (Patoulias et al. 2018). While SGLT-2 inhibitors demonstrated substantial clinical benefits including improving HbA1c, reducing body weight, lowering blood pressure, and improving Time-in-Range (TIR) on continuous glucose monitoring (CGM), they also significantly increased the risk of diabetic ketoacidosis (DKA), and thus, were not approved for use in this patient population in the United States. Liraglutide also underwent Phase 3 trials in T1DM patients and showed only modest efficacy (HbA1c reductions of 0.2% to 0.3%), complicated by clinically significant hypoglycemia (Dejgaard et al. 2021). Thus, there remains an acute need to develop a safe and effective adjunctive therapy for people living with T1DM.

Based on the current understanding of disease pathophysiology, an "ideal" adjunctive therapy for T1DM is one that can address the unmet needs in T1DM patients in a safe and well-tolerated fashion. Importantly, adjunctive therapies should improve outcomes that insulin therapy cannot and/or for which it falls short. These characteristics include:

- Reduction of body weight
  A majority (approximately two-thirds) of T1DM patients are overweight and obese. Insulin therapy exacerbates weight gain, which risks precipitating the negative health effects of obesity. Thus, interventions that can decrease adiposity and improve insulin sensitivity and consequently reduce the total daily insulin burden of T1DM patients would be an important component of therapy.
- Reduction of insulin dose needed to maintain glucose control
  Severely obese (BMI of 43 kg/m^2) T1DM patients undergoing bariatric surgery cut their insulin doses by nearly half (118 units/day to 60 units/day), illustrating the benefit of weight loss on the reduction of the required insulin dose (Dessify et al. 2021). Other forms of adjunctive therapy (eg, GLP-1 RA) have reduced the total daily insulin doses while improving control of glucose levels (Dejgaard et al. 2021), suggesting that adjunctive therapy with CT-868 might also allow the reduction of insulin doses while improving HbA1c levels, without exacerbating the risk of hypoglycemia and DKA.
- Improvement of insulin sensitivity and concomitantly addressing several known pathophysiologic defects in T1DM
  Patients with T1DM have insulin resistance in adipose, hepatic, and skeletal muscle tissue; they also have decreased insulin secretion and increased glucagon secretion, both of which exacerbate hyperglycemia. T1DM patients exhibit increased glucose reabsorption by the kidney and accelerated gastric emptying. None of these abnormalities are improved by insulin therapy, whereas CT-868, given its dual mechanism of action, has the potential to address these core defects.
- Reduction of cardiovascular disease risk
  Even those T1DM patients with ideal glucose control still have an increased risk of cardiovascular disease. Evidence suggests this may be induced by hyperinsulinemia and insulin resistance. Therapies that reduce insulin dose and enhance insulin sensitivity are likely to reduce cardiovascular disease risk.
- Improvement of glycemic control
  Despite advances in insulin therapy, delivery, and glucose monitoring, most patients still do not meet current standard-of-care glycemic control goals.

1.1.2 Description of CT-868

GLP-1 and GIP are the 2 primary incretins that are released from the intestine in response to food consumption. Both hormones modulate glucose-dependent insulin secretion (Baggio and Drucker 2007; Frias et al. 2017). GLP-1 also decreases secretion of glucagon, slows gastric emptying, promotes satiety, and reduces food intake (Andersen et al. 2018; WHO 2022). Several GLP-1 mimetics have been approved for the treatment of T2DM. These drugs lower blood

glucose and HbA1c and produce modest weight loss, but their efficacy is limited by gastrointestinal (GI) side effects, predominantly nausea, vomiting, and diarrhea (Marín-Peñalver et al. 2016). The primary action of GIP is the stimulation of glucose-dependent- insulin secretion (Dupre et al. 1973). It also modulates the secretion of glucagon in an inverse glucose-dependent manner to protect against hypoglycemia (Christensen et al. 2011; Meier et al. 2003) and does not delay gastric emptying (Meier et al. 2004). GIP also stimulates glucose uptake in adipocytes (Song et al. 2007) and promotes bone strength (Fulzele and Clemens 2012). Coadministration of long-acting GIP and GLP-1 in animals improves glucose-lowering and body weight reduction compared with either agent alone, and studies with unimolecular dual GLP-1/GIP agonists have shown enhanced anti-hyperglycemic, insulinotropic, and weight loss efficacy relative- to GLP-1 agonists in animal models (Finan et al. 2013). Long-acting dual GLP-1/GIP agonists have been tested in humans and were shown to decrease levels of HbA1c in patients with T2DM with only moderate adverse GI effects (Finan et al. 2013). Co-activation of both GLP-1 and GIP receptors could therefore provide more effective glycemic control and weight loss while minimizing the dose-limiting GI complications associated with specific GLP-1RAs.

CT-868 is distinct from previously tested incretin mimetics in several ways. First, CT-868 does not activate beta-arrestin on either the GLP-1 or GIP receptor, a signaling pathway activated by endogenous GLP-1 and GIP upon binding to its cognate receptor. Beta-arrestin activates kinase signaling pathways but also causes the GLP-1 and GIP receptors to be turned off and internalized (Hsia et al. 2017). Consequently, CT-868 does not cause internalization of the GLP-1 or GIP receptors resulting in enhanced signaling efficacy. The toxicology data show that CT-868 is well tolerated at the highest dose tested, which exceeds the pharmacologically active dose by 100-fold, resulted in weight loss up to 10%, and there were no instances of vomiting observed in the monkeys, an adverse effect commonly reported with several of the other incretin mimetics. Taken together, these observations suggest that CT-868 could be a potent anti-diabetic agent that could safely produce 10% or greater weight loss in humans with acceptable tolerability.

1.1.3 Summary of Nonclinical Studies

CT-868 is a potent GLP-1/GIP receptor modulator that activates production of cyclic adenosine monophosphate (cAMP) as measured by cell-based assays. It activates cAMP at the human GLP-1 and GIP receptors with potencies of 0.17 and 3.3 nM, respectively. CT-868 does not engage the β-arrestin signaling pathways on either GLP-1R or GIP receptor, unlike the endogenous cognate ligands. Protein basic local alignment search tool searches show a high homology between the human GLP-1 and GIP receptors with those of mouse (92% and 81%, respectively), rat (91% and 81%, respectively) and monkey (98% and 97%, respectively). CT-868 modulates insulin secretion and enhances glucose clearance in mouse, rat, and monkey. Therefore, the CD-1 mouse, Sprague-Dawley rat, and cynomolgus monkey were chosen as relevant species for the nonclinical evaluation of CT-868.

1.1.3.1 Pharmacology

Animal studies demonstrated that CT-868 is effective in glycemic control in lean mice and as a weight loss agent in diet and genetic models of obesity. Additionally, CT-868 was able to provide robust glycemic control in a mouse model of T1DM both without insulin, and, as an adjunctive treatment to insulin. In an obese model of T1DM, CT-868 provided significant weight loss benefit in addition to glycemic control further supporting its role as a highly effective adjunctive therapy on a background of insulin treatment.

In vitro, no off-target interactions by CT-868 were seen in a screening assay against 47 human receptors/transporters including the human ether- à-go-go (hERG) receptor, at a concentration of [redacted] µM ([redacted] µg/mL). The concentration used is nearly 100 times the [redacted] mg multiple ascending dose (MAD) Day 14 maximum concentration (C_{max}) at steady state of [redacted] ng/mL observed in the Phase 1 study.

Good Laboratory Practice safety pharmacology studies of CT-868 were performed in the Sprague Dawley rat (dosed once or daily for 28 days by subcutaneous (SC) injection at 0 [vehicle], [redacted] and [redacted] mg/kg) and cynomolgus monkey (dosed once or daily for 28 days SC at 0 [vehicle], [redacted] and [redacted] mg/kg) to evaluate the effects on the respiratory, cardiovascular, and central nervous system function. No significant CT-868 effects after single or repeat dosing were noted on respiratory or central nervous system function in the Sprague Dawley rat, or respiratory, cardiovascular, or central nervous system function in the cynomolgus monkey.

1.1.3.2 Pharmacokinetics and Metabolism in Animals

CT-868 is highly protein bound (>99%) in rat, cynomolgus monkey, and human plasma.

Based on United States Food and Drug Administration (FDA) guidance for drug-drug interactions (CDER 2020) a series of in vitro studies were performed to determine the activity of CT-868 on cytochrome P450 enzymes and on renal (OCT2, OAT1, and OAT3) and hepatic (OATP1B1 and OATP1B3) transporters. CT-868 showed weak or no potential for cytochrome P450 enzyme inhibition. No inhibition of renal transporters OCT2, OAT1, and OAT3 was observed. CT-868 was not a substrate for OATP1B1 and OATP1B3 hepatic transporters. CT-868 at 10 µM concentration inhibited OATP1B1 with half-maximal inhibitory concentration (IC_{50}) of 316 nM (1456 ng/mL) and 7.5 nM (34.58 ng/mL) for OATP1B3, indicating its potential as a weak inhibitor of these hepatic transporters.

The metabolism of CT-868 was evaluated in the Sprague Dawley rat and cynomolgus monkey. The proposed metabolic pathway for CT-868 is mainly by hydrolysis. Eight CT-868 metabolites were identified in rat and monkey plasma and urine. No significant differences in metabolite profile or abundance of the metabolites were observed between males and females. The estimated plasma concentration of CT-868 metabolites at C_{max} in humans for the highest

proposed Phase 2 dose of 6.6 mg is far below the concentration where these metabolites show activity.

The PK profile of CT-868 after a single [redacted]-mg/kg SC dose was similar between male CD-1 mice and Sprague Dawley rats; exposure (C_{max} and area under the plasma concentration time curve [AUC]) was greater in the cynomolgus monkey. In all the species, T_{max} ranged from 3 to 7 hours and the apparent terminal half-life ranged from 5 to 7 hours. Bioavailability of CT-868 for SC administration in CD-1 mouse was 65.9%.

1.1.3.3 Toxicology

In general, CT-868 was well tolerated in both rats and monkeys in repeat-dose Good Laboratory Practice toxicity studies.

Two 28-day repeat-dose toxicity studies were performed with CT-868 in Sprague-Dawley rats (0 [vehicle], [redacted] and [redacted] mg/kg) and cynomolgus monkeys (0 [vehicle], [redacted] and [redacted] mg/kg). In both species, decreased body weight gain and food consumption was noted in the first weeks of dosing. These effects were attributed to the pharmacologic action of CT-868 and were not considered adverse effects. Following this initial period, in general, body weight and food consumption were comparable to controls. The no-observable-adverse-effect levels (NOAELs) for the rat and monkey were [redacted] and [redacted] mg/kg, respectively.

Two 13-week repeat-dose toxicity studies with CT-868 were performed in Sprague-Dawley rats (0 [vehicle], [redacted] and [redacted] mg/kg) and cynomolgus monkeys (0 [vehicle], [redacted], and [redacted] mg/kg). No CT-868 related mortalities were reported. In both species, decreased body weight gain and food consumption during the first weeks of dosing were attributed to the pharmacologic action of CT-868 and were not considered an adverse effect. Following this initial period, in general, body weight and food consumption were comparable to controls. No changes in hematology, coagulation, and urinalysis were noted. In both species, an increase in total bilirubin was noted in males and females at the highest dose ([redacted] and [redacted] mg/kg, respectively); after the recovery period (2 weeks in rat and 4 weeks in monkey), bilirubin levels were within the normal range. The NOAELs for the rat and monkey were [redacted] and [redacted] mg/kg, respectively.

A 26-week repeat-dose toxicity study with CT-868 was performed in Sprague Dawley rats (at [redacted] and [redacted] mg/kg) and a 39-week repeat-dose toxicity study with CT868 was performed in cynomolgus monkeys (at [redacted] and [redacted] mg/kg) to determine the potential toxicity and to help justify the maximum recommended dose of CT-868 for the Phase 2 studies in humans. No test article-related mortalities were reported. In both species, decreased body weight gain and food consumption were noted in the first weeks of dosing. These effects are the result of the pharmacologic action of CT868 and were not considered an adverse effect. Following this initial period, in general, the animals resumed a normal growth pattern and food consumption (ie, lower, or comparable to those of the control group). In the Sprague Dawley rat decreases in body weight and food consumption were substantial but not deemed adverse as they were among the intended effects of drug treatment. Total protein, albumin, and total bilirubin

increased in the [redacted] and/or [redacted] mg/kg/day males and females. Total bilirubin, total protein, and albumin recovered during the recovery phase. The changes in these clinical chemistry parameters were not considered adverse or dose-limiting toxicities because they were moderate in magnitude and recovered during the recovery phase and did not correlate with any other clinical chemistry parameter. No test article-related organ weight changes were considered directly attributable to the test article in either the dosing or recovery phases.

In the cynomolgus monkey, a significant decrease in body weight was noted in both males (Days 7 to 42) and females (Days 7 to 91) at [redacted] mg/kg. At terminal sacrifice, body weight decreases of 5.0% were noted in females at [redacted] mg/kg; however, body weights of males at all doses were no different from controls. The decrease in body weight was considered related to the pharmacologic effect of the test article but not adverse or a dose-limiting toxicity. No significant changes in hematology or urinalysis were noted. Clinical chemistry changes included increased total bilirubin in males and females at [redacted] mg/kg; by the end of the 4-week recovery period, total bilirubin levels were within normal ranges for males but still increased in females (81.31%). The changes in these parameters were not considered adverse or a dose-limiting toxicity. The NOAELs for the rat and monkey were [redacted] and [redacted] mg/kg/day, respectively.

Toxicokinetic analysis was performed as part of the repeat-dose toxicity studies in the Sprague Dawley rat and cynomolgus monkey. Median T_{max} values were observed between 1 and 8 hours postdose. The systemic exposure increased dose proportionally in both sexes as the dosage increased. No marked drug accumulation for CT-868 was observed after 14 or 28 days of repeat daily dosing in the Sprague-Dawley rat or cynomolgus monkey. In the Sprague-Dawley rat and cynomolgus monkey, antiCT868 antibodies were detected, but their presence did not affect the exposure to CT-868 (C_{max} and AUC).

Local tolerance was evaluated in the repeat-dose toxicity studies. Microscopic changes associated with injection site trauma and not due to the test article were present in all groups in the repeat-dose toxicity studies in Sprague-Dawley rat at a solution concentration up to [redacted] mg/mL and in repeat-dose toxicity studies in the cynomolgus monkey at a solution concentration up to [redacted] mg/mL.

In vitro genotoxicity studies (Ames test and micronucleus assay) and in vivo micronucleus assay in the Sprague Dawley rat indicated no genotoxic potential.

No carcinogenicity or developmental and reproductive toxicity studies with CT-868 have been performed.

Overall, the nonclinical package for CT-868 supports the safety and design of the Phase 2 clinical studies.

See the CT-868 Investigator's Brochure (Version 5.0) for additional information on these and other nonclinical studies.

1.1.4 Summary of Clinical Studies

Two clinical studies with CT-868 are completed to date (CT-001 and CT-868-003). A third study (CT-868-002) is still in progress and interim analysis results are summarized in Section 1.1.4.2.

1.1.4.1 CT-001

The CT-001 study was a Phase 1 randomized, double-blind, placebo controlled, dose-escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of CT-868 when administered as single and multiple doses in healthy, lean participants (BMI of 20–25 kg/m^2) and in overweight/obese and otherwise healthy participants (BMI of 27–45 kg/m^2), and as multiple doses in patients with T2DM. The study was to be conducted in 3 parts: Part 1-single ascending dose (SAD) and Part 2–MAD in overweight/obese otherwise healthy participants, and Part 3 - multiple doses in patients with T2DM. The Sponsor terminated the study upon completion of Part 2 due to the COVID-19 outbreak.

In Part 1 (SAD), 56 overweight/obese and otherwise healthy adult participants and 8 lean, healthy adult participants were sequentially enrolled in 8 cohorts (64 total, 8 participants per cohort; 6 active:2 placebo).

In Part 2 (MAD), 23 overweight/obese and otherwise healthy adult participants were sequentially enrolled into 1 of 3 cohorts (8 participants per cohort; 6 active:2 placebo). A total of 3 MAD cohorts were dosed once daily for 14 days where all doses were given without an up-titration regimen: MAD Cohort 1 at [redacted] mg, MAD Cohort 2 at [redacted] mg, and MAD Cohort 3 at [redacted] mg.

CT-868 was safe and generally well tolerated in overweight/obese and otherwise healthy participants. No severe adverse events (AEs) or serious AEs (SAEs) were reported, and no [redacted] was observed. Most AEs were mild and [redacted] AEs such as [redacted] are a consequence of the mechanism of action of CT-868 and may also be related to confinement in a clinical research unit over an extended period. Other GI events, such as decreased appetite and increased satiety, are desirable effects of CT-868. Injection site reactions (ISRs) occurred in only 4 of 89 (4.5%) participants, were mild, and resolved quickly.

Half-life was ~24 hours consistent with once-daily dosing. Systemic exposure to CT-868 is dose-related (higher C_{max} and AUC with higher dose) but appears to be greater than dose-proportional in the examined dose ranges. With repeat daily dosing, plasma concentrations increased over time to a greater extent than would be predicted based on the PK profile after the first dose. With daily CT-868 dosing, plasma concentrations appeared to reach a plateau after a few days. The plasma concentrations reached after 14 days of dosing were again dose-related and greater than dose proportional, especially between [redacted] mg and [redacted] mg doses. The steady-state C_{max} observed following 14 daily doses of [redacted] mg/day (the highest dose tested in Part 2- MAD) was [redacted] ng/mL, which is >50-fold lower than the C_{max} at the NOAEL in the 39-week repeat-dose toxicity study in cynomolgus monkeys (NOAEL=[redacted] mg/kg; C_{max}=[redacted] ng/mL).

1.1.4.2 CT-868-002

Study CT-868-002 is a multiple-center evaluation of CT-868 in a randomized, double-blind, placebo-controlled, parallel-group study when administered once daily for 26 weeks as a SC injection to assess the HbA1c-lowering effect of CT-868 in overweight and obese participants with inadequately controlled T2DM (defined as HbA1c between 7.0% to 10.0%, inclusive) and were either on a diet/exercise regimen and/or on metformin monotherapy for at least 3 months prior to their Screening Visit (ie, no other oral or injectable T2DM therapy was allowed). Several participants were also stably maintained on anti-hypertensive and/or lipid-lowering medications (eg, statins) during the course of the trial.

Participants entered a 1-week Lead-in Phase, which served as a period to monitor glucose stability (ie, for persistent hypo- or hyperglycemia) and to acclimatize participants to standardized lifestyle guidance that was to be adhered to throughout the study. Those who completed the Lead-in Phase entered the study at Day 1. On Day 1, participants were randomized 1:1:2 into one of the following 3 treatment arms, respectively:

- Treatment Arm 1: Placebo (n ~[redacted])
- Treatment Arm 2: CT-868 1.75 mg (n ~[redacted])
- Treatment-Arm 3: CT-868 dosed to tolerability/up to maximum of 4.0 mg (n ~[redacted])

Participants were stratified evenly across each treatment arm based on baseline HbA1c (<8.5%, ≥8.5%) and BMI (<35, ≥35 kg/m^2). CT-868 was suppled in a prefilled syringe intended to deliver up to [redacted] mL for self-administered SC injection in the [redacted] Dosage for each participant in Treatment Arm 3 was titrated based on that individual's tolerability. Titrations were performed once every 4 weeks.

It is important to note that treatment assignments in Study CT 868-002 remain blinded and all data described herein are preliminary interim data. This summary is included since this interim analysis provides the safety data for 12-weeks of study drug administration, which is the longest duration of exposure to date with CT-868. It is also important to emphasize that in Arm 3, at the time of this interim analysis, dose titration had only reached 3.25 mg, ie, the target dose of 4 mg had yet to be initiated.

Preliminary interim analyses for Study CT-868-002 have been completed through Week 12 in about 35 participants. At Week 12, most participants (17 [94.4%]) were successfully up-titrated to 4 mg; however, at the time of the interim analysis, the dose level was 3.25 mg in Arm 3. The tolerability and safety profile revealed mostly mild [redacted] There were no serious treatment-related treatment-emergent adverse events (TEAEs) or deaths, and only 1 treatment-related discontinuation to date. While the favorable tolerability profile seen in CT-868-002 may be attributable to the gradual monthly titrations, a more optimal titration regimen for CT-868 may be somewhere in between weekly and monthly, such as over a 2-week period (proposed in Study CT-868-004, and with allowance for adjustments in the dose

escalation schedule at earlier timepoints for participants who experience tolerability issues). Of note, no clinically significant changes in bilirubin levels (or liver enzyme levels or other relevant safety laboratory, electrocardiogram [ECG], or vital sign parameters) have been observed to date. Several patients in this trial were maintained on stable doses of statins and blood pressure medications without any safety-related concerns requiring dose adjustments. Clinically meaningful reductions in fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and body weight were observed at Week 12 in the CT-868 treatment arms relative to the placebo treated group.

1.1.4.3 CT-868-003

Study CT-868-003 was a single-site crossover study conducted in 2 parts. Part 1 was conducted in obese but otherwise healthy participants. Part 2 was conducted in overweight and obese participants with T2DM. Each part was conducted as a 3-period crossover study that included either CT-868 or placebo in Periods 1 and 2 and the active comparator, liraglutide, in Period 3. In Parts 1 and 2, all participants received a graded glucose infusion assessment on Day 3. In Part 2, participants also had a fourth day (Day 4) of assessments for each crossover period that included a mixed meal tolerance test (MMTT) to examine glucose handling and an acetaminophen absorption test to assess gastric emptying. Participants were also asked to consume ad libitum a lunch meal to measure their food intake (total grams and calories) while assessing several parameters on a [redacted]

The safety and tolerability findings for CT-868 in this study indicate a similar profile to that seen for Studies CT-868-001 and CT-868-002. There were no SAEs, no deaths, and no suspected unexpected serious adverse reaction (SUSARS). One participant each discontinued due to an adverse event (AE); One participant in the CT-868 group developed anemia and 1 participant in the placebo group had an abnormal coagulation test. The tolerability findings have been mostly [redacted] consistent with the general AE profile of the incretin-based class of drugs.

Although this was a small study, significant information was gleaned supporting the weight-independent pharmacologic effects of CT-868 on glucose homeostasis. Effects on beta cell activity were assessed using a graded glucose infusion assessment performed after starting CT-868, placebo, or liraglutide. Results from the graded glucose infusion assessment confirmed that CT-868 relative to placebo can robustly stimulate insulin secretion rate at any given glycemic level (ie, a strongly positive slope of insulin secretion rate/glycemic level), which was comparable to that of liraglutide.

To better understand glucose disposition, an MMTT was performed in participants with T2DM on Day 4 of treatment with CT-868, placebo, or liraglutide. CT-868 demonstrated robust reduction in glucose AUC during the MMTT accompanied by lower insulin excursion (ie, product of insulin x glucose AUC was substantially lower versus both placebo and liraglutide). While gastric emptying (assessed via acetaminophen absorption) was delayed after CT-868 treatment relative to placebo, it was generally similar to that of liraglutide treatment.

Therefore, the lower insulin x glucose observed after CT-868 treatment versus liraglutide treatment in the same participants most likely is indicative of enhanced glucose disposal and/or decreased endogenous glucose production. Further studies (such as with an isotopic tracer clamp) are required to confirm and elucidate the tissues/organs responsible for the enhanced insulin sensitivity.

Additionally, in contrast to liraglutide treatment, the same participants treated with CT-868 demonstrated lesser suppression of glucagon during the MMTT. These findings are consistent with activity of CT-868 at the GIP receptor, which is known to enhance/maintain glucagon secretion in contrast to GLP-1RAs, which lower glucagon. Thus, the combined profile of enhanced disposal of glucose with less/minimal suppression of glucagon seen with the fully biased CT-868 (versus unbiased liraglutide) has the potential to substantially lower [redacted] risk, especially in patients with T1DM, who are highly susceptible to such risk.

[redacted] prior to drug administration as well as after starting CT-868, placebo, or liraglutide. A composite appetite score derived from the above parameters was also calculated. [redacted] Consistent with these findings, in the setting of an ad libitum meal test, both food intake (grams of food) and total calories consumed following CT-868 treatment were significantly lower compared with the same participants treated with placebo.

See the CT-868 Investigator's Brochure (Version 5.0) for additional detailed information on CT-868 studies.

1.2 Rationale

1.2.1 Overall Approach

This is a dose-ranging Phase 2 study to evaluate the efficacy, safety, tolerability, and PK of CT-868 over 16 weeks. Doses are gradually escalated using a titration regimen based on an individual's tolerability to study drug or up to a maximum dose of 6.6 mg per day (thereby optimizing tolerability). The treatment duration of 16 weeks will provide a clinically meaningful understanding of the potential of CT-868 to lower HbA1c and body weight reduction in overweight and obese adults with T1DM, while providing sufficient time for a gradual up-titration to the proposed maximum dose of 6.6 mg to optimize tolerability. The safety observations and the efficacy evaluations will inform on doses, titration regimens, and design for a subsequent Phase 3 program.

1.2.2 Justification of Proposed Doses

As is the norm with nearly all incretin-based therapies, a gradual up-titration regimen is also applied in this study. In addition, dose escalations are guided by an individual's tolerability

profile and subsequent adjustments in insulin doses, as appropriate, are guided by an individual's preceding CGM data.

The lowest dose of 1.8 mg proposed in this study (Arm 2) is expected to be well tolerated given the preceding information at this exposure, especially from both Studies CT-001 and CT-868-002. In the latter study, while the 1.75 mg dose produced glucose lowering effects, the impact on weight loss was minimal (placebo-adjusted weight loss -0.9%) at Week 12. Hence, a dose of 1.8 mg is chosen as the minimally efficacious dose to interrogate effects on both glycemia and weight loss in a population of overweight and obese T1DM patients.

Systemic exposure anticipated in Arm 3 (4.1 mg) has also been studied and shown to be generally well tolerated across a broad population from overweight/obese otherwise healthy participants (Study CT-001) to overweight/obese participants with T2DM (Studies CT-868-002 and CT-868-003). Thus far, no participant who has been progressively up-titrated to their maximal dose in Study CT-868-002 has required dose reduction or has discontinued due to an AE. Nonetheless, the current study given it is in a different population (T1DM), provides sufficient flexibility to provide the Investigator full discretion to adjust doses downward to [redacted] mg and maintain at that dose, if needed, based on the individual's tolerability profile. In Study CT-868-002, a dose of 3.25 mg produced glucose-lowering effects as well as some weight loss (placebo-adjusted weight loss -2.2%) at Week 12. It is anticipated that a dose of 4 mg when given over the subsequent 12 weeks (total duration of Study CT-868-002 is 26 weeks), would likely produce a placebo-adjusted weight loss of ~5%. Hence, a dose of 4.1 mg (anticipated to be well tolerated given the preceding experience to date at this dose) is chosen as the proposed mid-dose to interrogate effects on both glycemia and weight loss in a population of T1DM patients.

The planned approach and dose level in Arm 4 (ie, dosed to tolerability or up to maximum of 6.6 mg gradually escalated over 10 weeks with flexibility to extend by another 2 weeks to Week 12), is also expected to be well tolerated based on the nonclinical safety margin data established in Sprague Dawley rat and cynomolgus monkey (anticipated to be >15-fold at the maximum recommended high dose of 6.6 mg). Importantly, Arm 4 is designed to be titrated based on the individual's tolerability. In other words, escalation to doses beyond 4.1 mg in Arm 4 will be performed with ample flexibility in the protocol to provide the Investigator full discretion to adjust doses downward and/or maintain at a given dose level based on the individual's tolerability profile even allowing to continue at a level of 1.8 mg if the Investigator and participant see this as necessary.

All participants in this study are required to attend the study site/clinic every 2 weeks and dose escalations are guided by the participant's preceding CGM recordings, both of which provide additional safety oversight with continuous and almost real-time monitoring of every participant in the study before any dose escalation decision. If a dose of 6.6 mg is well tolerated (ie, with manageable [redacted] it is very likely that such a dose might provide an optimal benefit:risk to achieve both glycemic control and clinically meaningful weight loss (ie, placebo-adjusted weight loss ≥10%) to impact clinical

outcomes in overweight/obese patients living with T1DM. Hence, a dose of 6.6 mg is chosen as the proposed high dose to interrogate effects on both glycemia and weight loss in a population of T1DM patients.

1.3 Benefit/Risk

Although the clinical experience with the dual GLP-1/GIP agonists is still limited, it draws on the large safety database available for the GLP-1 mimetics. Multiple GLP-1RAs have been approved since 2005 for human use for indication of treatment of obesity and/or T2DM (eg, exenatide, liraglutide, semaglutide, dulaglutide, and lixisenatide) with highly favorable benefit:risk profiles in these participants, where the most frequently reported AEs are [redacted] have also been associated with GLP-1RAs. Large, prospective cardiovascular outcome studies have been conducted with all the above agents, some showing neutrality or no harm (exenatide), and several others showing a significant cardiovascular benefit (liraglutide, semaglutide, and dulaglutide).

Additional data have been collected with the dual incretin agonist tirzepatide (Mounjaro™). The recent FDA approval of this drug for the treatment of T2DM suggests that glycemic control can be accomplished with significant weight loss, as clinical trials indicated that marked weight loss (37% of patients on [redacted] mg reached or exceeded 15% weight loss after 52 weeks of treatment) can accompany improved glycemic control in T2DM patients with incompletely controlled blood glucose levels (Del Prato et al. 2021). In November 2023, the FDA approved tirzepatide injection (Zepbound™) for chronic weight management in adults with obesity or overweight with at least 1 weight-related condition, for use in addition to a reduced-calorie diet and increased physical activity (November 8, 2023 - FDA Approves New Medication for Chronic Weight Management).

The use of GLP-1RAs or dual incretin agonists such as CT-868 in patients with T1DM presents different issues regarding the risk:benefit ratio. Because these patients are dependent on insulin administration to maintain glycemic control, they remain at risk of hypo- or hyperglycemia. The GLP-1RA liraglutide was studied extensively in the T1DM population (Mathieu et al. 2016; Ahrén et al. 2016). Although it significantly improved glycemic control, reduced daily insulin requirements, and led to clinically meaningful weight loss, the drug appeared to be associated with an increased risk of [redacted] Liraglutide has not been approved in the United States as adjunctive therapy for patients with T1DM.

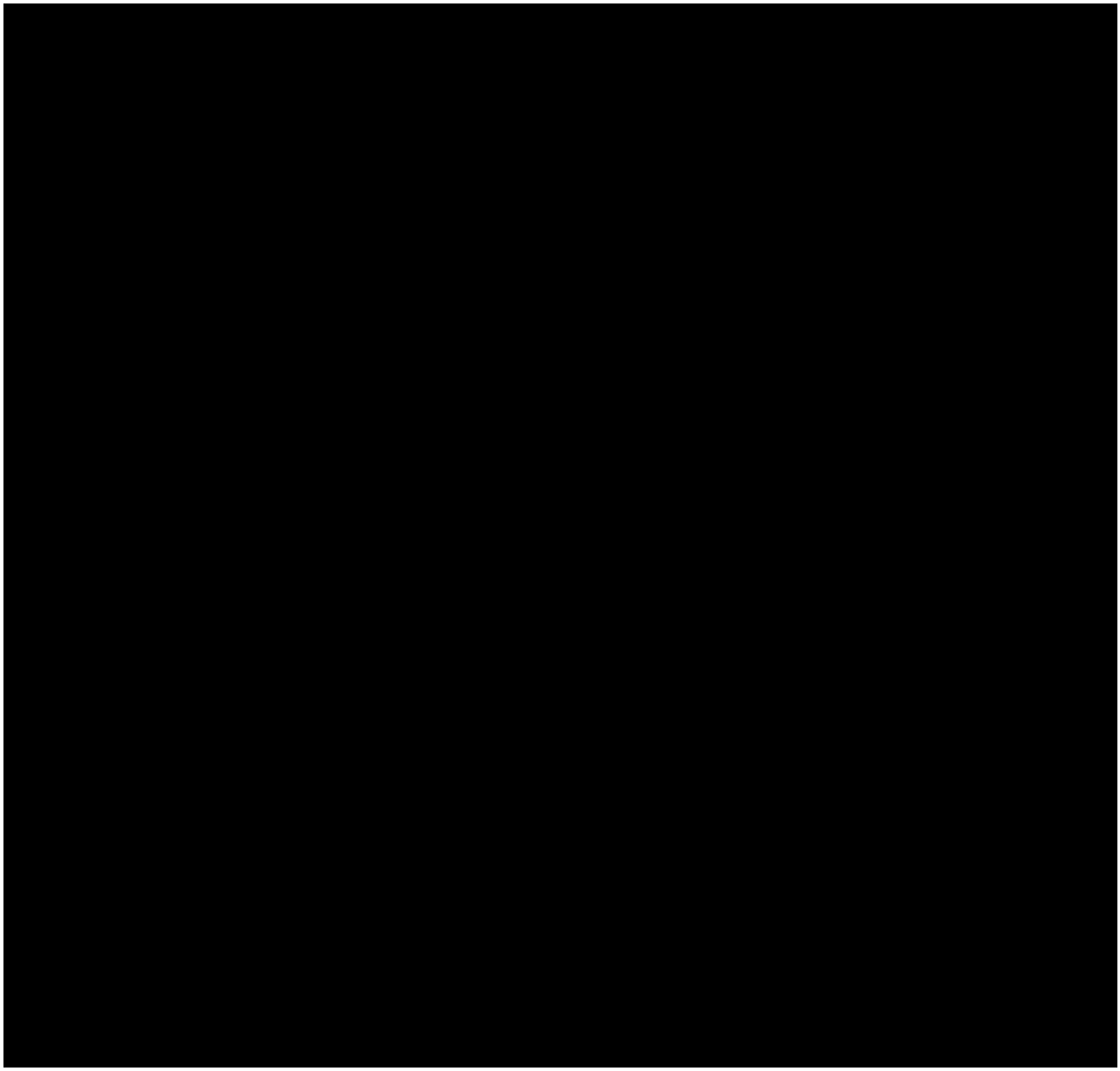
Notably, the use of CGM in the management of T1DM was not prevalent at the time these studies were conducted. In 2022, CGMs are routinely used in both clinical practice and trial settings, and indeed, their use is now considered standard of care for glucose management in patients living with type 1 diabetes (ADA 2024). The use of the CGM devices continuously throughout the study drug treatment period in the current study offers potential protection from [redacted] through the alerts when glucose levels are not in the target range. Furthermore, as CT-868 also modulates the GIP receptor, it could provide a counterregulatory defense against

hypoglycemia consistent with its known actions of modulating glucagon in an inverse glucose-dependent manner while enhancing insulin-independent glucose disposal via the stimulation of glucose uptake in adipocytes. As demonstrated in Study CT-868-003, treatment with CT-868 produced minimal glucagon suppression versus liraglutide, consistent with CT-868's activation of the GIP receptor. Effects of CT-868 to concomitantly lower blood glucose with minimal excursion of insulin, thereby leading to a reduced insulin x glucose product in the setting of MMTT, suggests a likely insulin-sensitizing effect of CT-868, consistent with CT-868's activation of the GIP receptor to enhance peripheral glucose disposal, an effect that would be highly beneficial in overweight and obese patients with T1DM. Taken together, the cumulative mechanism of action of CT-868 combined with the implementation of state-of-the-art technology such as CGMs to further mitigate against hypoglycemia along with close safety monitoring of study participants offers the potential for a robust benefit:risk for T1DM patients.

Because CT-868 is an investigational drug, it is possible that unforeseen, unknown, or unanticipated drug reactions and toxicities may occur. Nonetheless, both identified and potential risks based on findings in nonclinical studies and clinical trials to date with the broader GLP-1RA and dual GLP-1/GIP RA class, taken together, are summarized in Table 1.

This clinical protocol is designed to mitigate some of these risks to participants through a detailed plan for careful safety monitoring, systematic review of AEs, adverse device effects (ADEs), AEs of special interest (AESIs), ADEs of special interest, vital signs, physical examinations, ECGs, clinical laboratory tests, and active pharmacovigilance review to assess for safety signals or trends.

[redacted]



In summary, chronic toxicity studies and the clinical experience to date with CT-868, coupled with the robust precedented multi-decade clinical experience with GLP-1RAs and extensive studies with dual GLP-1/GIP RAs, has not revealed any safety concerns that would preclude the administration of CT-868 once daily over 16 weeks in a relatively stable and closely monitored population of overweight and obese adults with T1DM. Necessary precautions have been implemented in the design and planned conduct of this trial to further minimize any potential risk and inconveniences to the participants. Cumulative data of incretin mimetics overwhelmingly support substantial and clinically meaningful glycemic control and weight loss that translates to improved clinical outcomes. Thus, the overall potential risk to participants in this study is considered low and outweighed by the anticipated potential benefits that CT-868 would provide for the participants enrolled in this study. More details about known and expected risks and benefits and reasonably anticipated AEs of CT-868 are detailed in the Investigator's Brochure.

2.0 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are displayed in Table 2.

Table 2. Study Objectives and Endpoints

Primary Objective	**Primary 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
Key Secondary Objectives	**Key Secondary 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
• 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 <7.0%, ≤6.5%, and <5.7% at Week 16	• Participant status of achieving HbA1c of <7.0% at Week 16 (Yes/No) • 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 at Day 1 to Weeks 8 and 16
Other Secondary Objectives	**Other Secondary Endpoints**
• To assess the effect of CT-868 relative to placebo on the following parameters: CGM metrics (TIR, time in hypo- and hyperglycemia, glycemic risk index)	• Change from baseline at Day 1 to Weeks 8 and 16 in the following CGM parameters: o Mean sensor glucose (mg/dL) and its SD and %CV [both intraday (ie, within 24 hours) and interday (ie, over multiple days)] o Percentage and amount of time (hours and minutes) spent in range (TIR, 70–180 mg/dL) o Percentage and amount of time (hours and minutes) spent in tight range (70-140 mg/dL)

	○ Participants with TIR 70-180 mg/dL with ≥5% points and ≥10% points improvement from Day 1 (Yes/No) ○ Percentage and amount of time (hours and minutes) spent in Level 1 hypoglycemia (<70–54 mg/dL) and Level 2 hypoglycemia (<54 mg/dL) ○ Percentage and amount of time (hours and minutes) spent in Level 1 hyperglycemia (>180–250 mg/dL) and Level 2 hyperglycemia (>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 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) ○ Glycemic risk index
○ Change in 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
○ Percentage of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss	○ Participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss at Week 16 (Yes/No)

○ Proportion of participants experiencing one or more Level 1, 2, 3 hypoglycemia events (incidence rate) and total number of Level 1, 2, 3 hypoglycemia events/total patient-years of exposure (event rate)	Proportion of participants experiencing 1 or more Level 1, 2, or 3 hypoglycemia event(s) over the study duration Total patient-years of exposure (event rate) at each hypoglycemia level over the treatment period of 16 weeks
○ Incidence of DKA	○ Participants with "definite" DKA events as defined in Section 5.2 (Kitabchi et al. 2009; ADA 2024) 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 safety and tolerability of CT-868 versus placebo administered QD via Pen over 16 weeks	• AEs/ADEs, physical examinations, vital signs, ECGs, and safety laboratory measurements (urinalysis, hematology, chemistry, BHB, amylase, lipase, calcitonin) over the period of 16 weeks • Change from baseline at Day 1 to Week 8 and Week 16 in systolic/diastolic blood pressure and heart rate
• To evaluate CT-868 plasma concentration	• Plasma drug concentrations at the Weeks 2, 4, 6, 8, 12, and 16 visits
• 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
Exploratory Objectives	**Exploratory 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 Day 1 baseline with: ○ Improvement in HbA1c ≥0.5% points and <1% TBR <54 mg/dL ○ Mean glucose <154 mg/dL and <1% TBR <54 mg/dL ○ ≥70% TIR 70-180 mg/dL and <4% TBR <70 mg/dL

	○ ≥70% TIR 70-180 mg/dL and <1% TBR <54 mg/dL ○ Either HbA1c improvement ≥0.5% points or ≥70% TIR 70-180 mg/dL, with <1% TBR <54 mg/dL, and without requiring significant increase in daily insulin use [ie, >10% increase in total (bolus + basal) insulin (units/kg/day)]
	• Participants with at least 1 Level 2 (CGM value <54 mg/dL) or Level 3 hypoglycemia event during the 16-week treatment period (Yes/No)
• 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 fasting plasma glucose, insulin, C-peptide, glucagon, GLP-1 (total and active), GIP, HOMA-IR, and QUICKI • 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 at Day 1 to Week 16 in total lean mass and total fat mass as determined by DEXA
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• To assess the percentage of	• Number of participants maintained at the 4.1 mg,

participants at the 4.1 mg, [redacted]mg, and 6.6 mg doses at the end of Week 16 and the time to achieve their final dose (Arm 4 only) • 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)	[redacted]mg, and 6.6 mg doses at the end of Week 16 (Arm 4 only) • Time (weeks) to achieve the final planned dose (Arm 4 only) • Change in HbA1c values and percent change in body weight at Week 16
Objectives Related to Pharmacokinetics and Immunogenicity • To assess the CT-868 concentration-time profile over 24 hours (in a subset of the T1DM study population) • To evaluate correlation between CT-868 plasma exposure and relevant efficacy parameters • To evaluate treatment-emergent anti-drug antibodies to CT-868 (Arms 2, 3, 4 only)	**Endpoints Related to Pharmacokinetics and Immunogenicity** • CT-868 PK parameters (C_{max}, T_{max}, C_{trough}, C_{last}, T_{last}, AUC_{0-24}, AUC_{0-last}, and $t_{½}$) • Treatment-emergent anti-drug antibodies to CT-868 on Day 1 and Week 16 (Arms 2, 3, and 4 only)

[redacted]ADE = adverse device effect; AE = adverse event; ALT = alanine aminotransferase; 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; CTX-1 = C-terminal telopeptide of type 1 collagen; DEXA = dual energy X-ray absorptiometry; DKA=diabetic ketoacidosis; [redacted]ECG = electrocardiogram; eGFR = estimated [redacted]se-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein cholesterol; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; LDL-C = low density lipoprotein cholesterol; MCP-1 = monocyte chemoattractant protein-1; PAI-1=plasminogen activator inhibitor-1; PK = pharmacokinetic; [redacted] $t_{1/2}$ = half-life; TBR=time below range; TIR=time in range; T_{last}=time to last quantifiable plasma concentration; 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

3.0 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, tolerability, and PK of CT-868 in overweight and obese adult participants with T1DM. The overall study design is shown in Figure 1. As indicated in the study design, participants must be able to tolerate a minimum daily dose of 1.8 mg of CT-868.

While participants' T1DM may be managed with either insulin pump or by means of MDIs of insulin, all participants must have gained some experience in the use of CGM devices (with replacing sensors) within the last 3 months before the Screening Visit and must be willing to wear and maintain the study-provided CGM device [redacted] for the duration of the study. Standard of care for CGM targets in adults with T1DM and guidelines for insulin adjustments are summarized in Table 3.

All enrolled participants will be expected to maintain their usual lifestyle pattern during the study (eg, must not initiate a novel diet or new exercise regimen that is different from their normal routines) and follow the usual standards of care for T1DM, including maintaining all other standard-of-care therapies for their other stable chronic conditions, if applicable, throughout the study.

After the Screening Period of up to 3 weeks (Weeks -7 to -4), either at the start of Visit 2 (or Visit 3 if the discretionary Insulin Adjustment Period is not undertaken), [redacted]

Following the administration of the questionnaires, participants may enter a discretionary Insulin Adjustment Period lasting from a few days up to 2 weeks (Weeks -4 to -2). In this period, the Investigator has an opportunity to assess the participants' existing insulin regimens on MDI or with manual or AID pumps and evaluateif participants are within treat-to-target goals, ie, ≥70% time in range 70-180 mg/dL (3.9-10 mmol/L) and <4% time below range <70 mg/dL (<3.9 mmol/L) (Battelino et al. 2023). The Investigator has the discretion to make adjustments to the participant's insulin regimens, if needed, during this period prior to entering the mandatory 2-week single-blind Placebo Run-in Period (Week -2 to Day 1). At either the start of the Insulin Adjustment Period or Placebo Run-in Period (if the preceding discretionary Insulin Adjustment Period was not required), participants will be provided with the study-specific CGM device. All participants will be educated and trained in the placement and exchange of [redacted] sensors, 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.

Participants who are entering the study with their AID devices should discuss with the Investigator whether to use 2 sensors during the study. One is the study-specific [redacted] which is used for downloading CGM data via the [redacted] at every visit to the clinic to evaluate glycemic control with the Investigator or designee. The other sensor may be connected to the participant's AID device to provide continuous real-time glycemic control awareness and correction per automated insulin delivery via algorithms (see more details about wearing 2 sensors in the Study Reference Manual).

During this mandatory 2-week Placebo Run-in Period (Week -2 to Day 1), CGM metrics and total daily insulin use data (uploaded from the eDiary) will be considered the participant's baseline values for these parameters. It is important that these 2-week baseline CGM data are fully captured. Equally important are the monitoring of the basal insulin/basal rate units administered per 24 hours as well as the premeal and correction boluses per 24 hours, administered either as MDI injections or by manual or AID pumps.

During the Placebo Run-in Period, participants are to acclimate to the study drug Pen, and prior to first dose will receive instruction on proper study drug administration procedures.

On Day 1, participants will enter a 16-week double-blind Treatment Period and will be randomized [redacted] to 1 of 4 treatment arms, as described in Section 6.1.

The pooled placebo Arm 1 will consist of 3 sets of ~[redacted] participants to receive the placebo dose volume-matched to a corresponding dose of CT-868. The total number (n~[redacted]) of placebo participants in Arm 1 will be similar to the number of participants in each of the CT-868 treatment arms (ie, n~[redacted] in each of Arms 2, 3, and 4).

Randomization will occur via interactive response technology (IRT). At the time of randomization, [redacted] By stratifying on these 2 factors, we can better understand the effects of CT-868 treatment on glycemic control in both insulin pump and MDI users across different HbA1c levels.

Participants, Investigators, all site personnel, and the Sponsor will be blinded to the treatment code for the duration of the study.

Before administering the first dose of study drug on Day 1, the following procedures must be completed to establish the baseline values for these assessments:

- Blood sample for safety laboratory testing (eg, HbA1c, glucose, and other biomarkers) as detailed in the Schedule of Assessments (Table 7).
- Body weight

- Dual energy X-ray absorptiometry (DEXA) (window up to +3 days after Day 1 allowed)
- [redacted]

Adjustments of insulin doses are based on experience with other adjunctive treatments for T1DM (ie, GLP-1RAs and SGLT2 inhibitors). For instance, when liraglutide or placebo was initiated, the pre-randomization total daily insulin dose was reduced by 25% for at least 1 day, and by a further 10% for at least 1 day when liraglutide/placebo doses were escalated to minimize [redacted] risk (Mathieu et al. 2016; Ahrén et al. 2016). With SGLT-2 inhibitor therapies, T1DM patients who were relatively well controlled (ie, HbA1c <7.5%) had 10%–20% reductions in insulin doses (Danne et al. 2019). A similar approach to insulin dose reduction is proposed in this trial to minimize risk of [redacted], which will be further guided by both the initial HbA1c value and subsequently, by the CGM data that is continuously obtained (see Table 3).

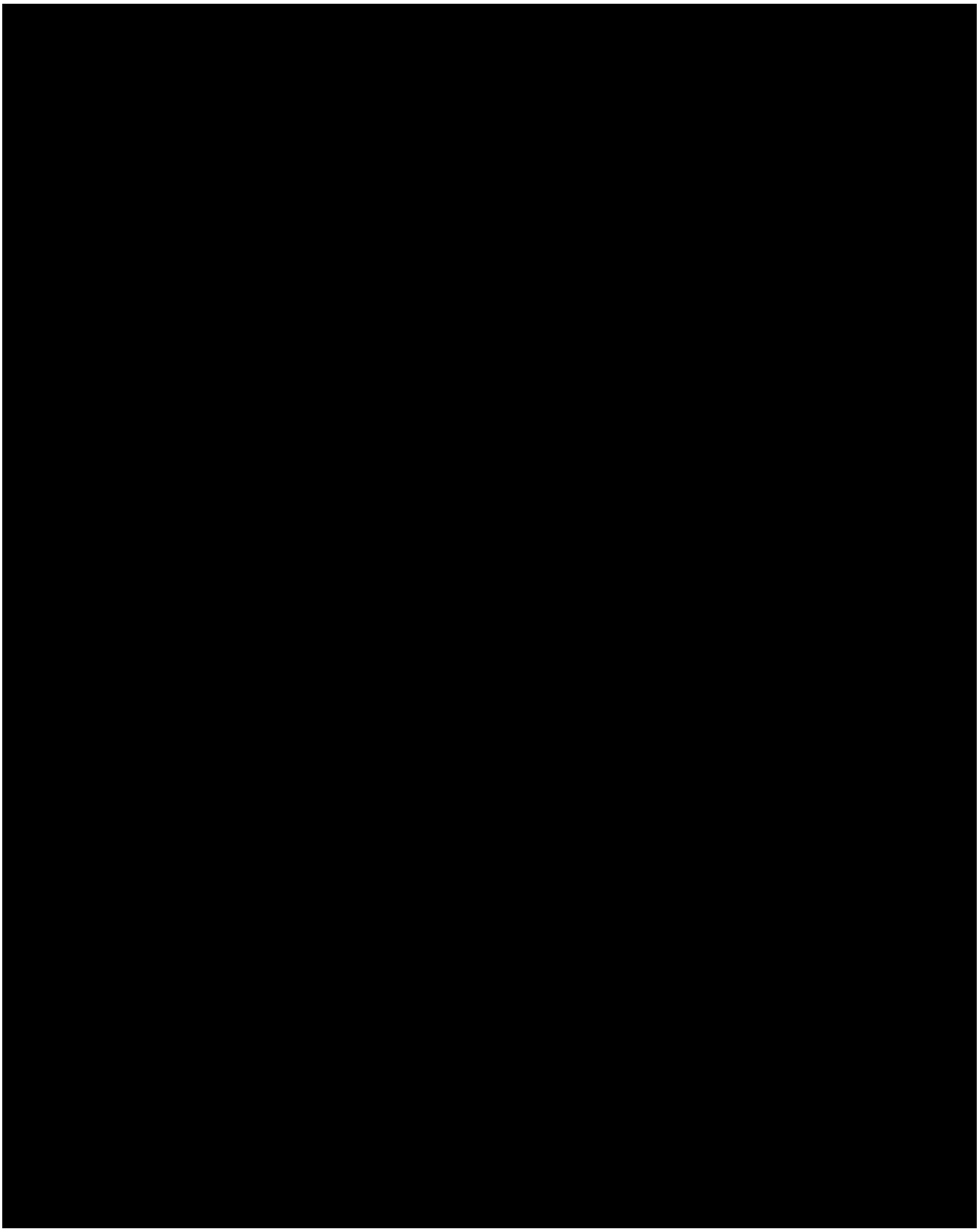
[redacted]

- [redacted]
- [redacted]

It is important to note that the recommendations in Table 3 are general guidelines based on precedented experience of other adjunctive therapies for T1DM. Ultimately, the study investigators have the final discretion to make appropriate insulin adjustments based on their clinical judgment given an individual's specific circumstance.

[redacted]

[redacted]



Prior studies of adjunctive treatments, especially SGLT-2 inhibitors in T1DM patients suggested an increased risk of [redacted] that may be precipitated due to insulin dose reduction. Thus, to mitigate risk for [redacted], especially at specified periods of insulin dose reduction, systematic and frequent ketone monitoring will be instituted with the following additional steps:

- During the mandatory Placebo Run-in Period, participants will be provisioned with ketone meter/test strips to measure capillary beta-hydroxybutyrate (BHB) and will receive instruction in ketone testing
- Any time a study participant is experiencing symptoms of severe nausea, vomiting, muscle aches, blurred vision, or any other concerning symptoms of hyperglycemia, they are required to obtain a finger-stick blood glucose via glucometer and test for ketones
- Any time CGM values goes above 250 mg/dL for ≥2 consecutive hours with or without symptoms (ie, extended Level 2 hyperglycemia), participants will be instructed to test for ketones and get finger-stick blood glucose via glucometer and to record those values in study diaries
- Participants will be educated regarding the avoidance, recognition, and interpretation/action of ketone test results in accordance with the International Consensus in managing [redacted] in T1DM (Danne et al. 2019) as specified in Table 4; they will also have ready access to a clinician throughout the study to assist and intervene as needed.
- All participants will be provisioned with adequate ketone testing supplies (ketone monitor and strips) for the duration of the study. In general, high ketones (capillary BHB or in urine) should be correlated with blood glucose (capillary or plasma) to adequately diagnose and monitor for [redacted] (for eg, if high ketones but low BG, it may not always signify true [redacted]). Participants should be encouraged to consume adequate fluids and maintain hydration during the study.

[redacted]

[redacted]

Just as undertreatment of insulin could lead to [redacted], overtreatment with insulin could lead to hypoglycemia. Following measures are undertaken to minimize risk of [redacted]

[redacted]

All study participants will be provisioned with glucagon (such as [redacted] or pre-mixed, shelf-stable pens per availability) for hypoglycemia rescue. In the event [redacted] re hypoglycemic episode, family and/or friends should be made aware of where the glucagon product is and how to administer it.

After randomization on Day 1, the first dose of study drug self-administration will be observed at the clinic and will occur after all the necessary baseline assessments are completed. Participants will once again be instructed to administer study drug by SC injection into the [redacted] at approximately the same time in the morning each day (to the greatest extent possible), for the next 16 weeks.

During the Treatment Period, in-person study visits will occur every 2 weeks starting at Week 2, with weekly phone calls (starting at Week 1) from qualified study site staff between the scheduled study visits.

All eligible participants will be provided with a study-specific CGM device that should be worn from Week -4 to Week 18.

At every in-person study visit from Week -4 through Week 18, CGM data will be uploaded from the [redacted] sensor into a [redacted] data capture system that is compliant with Title 21 of the Code of Federal Regulations Part 11, sensors checked, and adequate CGM-related supplies provisioned for each study participant. As each CGM sensor lasts only 10 days, prompt replacement every 10 days with a new sensor is required to ensure no interruption in glucose data collection; sensors will be replaced by the participant (adequate instruction on how to change sensors and proper care of the study-provided CGM device will be provided by qualified study staff).

Participants will manually enter their administered insulin doses into an eDiary and the data will also be reviewed at every visit. The insulin doses are entered as both the basal and bolus components, and the total daily doses.

Participants who are treated with an AID device will enter into their e-Diary their total daily basal insulin units administered during the 24-hour cycle and their total daily bolus insulin units administered during 24 hours. The 24-hour cycle is defined from midnight to midnight. On the day of in-person visits, participants will arrive at the study site undosed (ie, their last dose of study drug would have been ~24 hours prior to their visit) and following an overnight fast (~8 hours) for collection of blood samples for safety laboratories, biomarkers, CT-868 plasma concentrations, and other assessments, as applicable for each visit. After completion of all their in-person visit assessments, participants will dose themselves with their assigned study drug at the clinic, except at the Week 16 visit, which is their End of Treatment Visit.

Efficacy and safety of the study drug will be assessed by HbA1c, CGM data, body weight/body composition measurements, patient-reported outcomes (PROs), clinical AEs/ ADEs, vital signs, body weight, ECG, and safety laboratory assessments. Participants will also be instructed to report any symptoms of [redacted], and to provide narratives for each of the reported [redacted] events.

Safety will be monitored throughout the study by a blinded Safety Review Committee comprising the clinical research organization (CRO) Medical Monitor, a selected Principal Investigator, and the Sponsor’s medical officer.

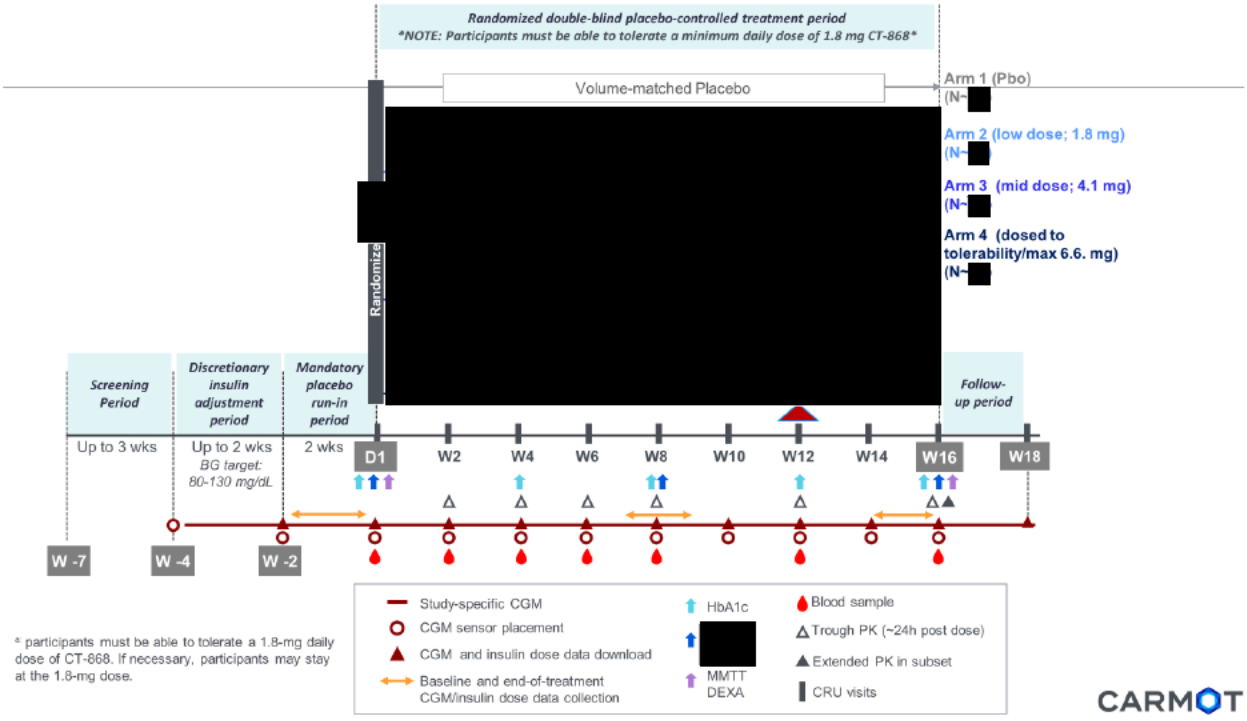
To characterize the PK profile of CT-868 in T1DM patients, a subgroup of participants will be asked to participate in an optional 24-hour PK sampling visit at Week 14. The PK sampling time points in each of the treatment arms will be collected as indicated in the Schedule of Assessments. Additional plasma samples may be collected for the analysis of CT-868 metabolites.

After the 16-week double-blind Treatment Period, participants will stop their assigned study drug and have a follow-up safety visit at Week 18/End of Study (2 weeks after the last dose of the study drug). During the safety follow-up period, all participants will continue their prescribed insulin treatments and follow usual standard of care for T1DM management.

The total duration of the study for each participant will be up to ~25 weeks (including the Screening Visit), and include the following as shown in Figure 1:

- 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 (ie, ≥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

Figure 1. Study Schematic



BG = blood glucose; CGM = continuous glucose monitoring; CRU = clinical research unit; D = day; DEXA = dual energy X-ray absorptiometry; [redacted] HbA1c = glycated hemoglobin; MMTT = mixed meal tolerance test; Pbo = placebo; PK = pharmacokinetic; [redacted] W = week; wks = weeks

3.2 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.

4.0 PARTICIPANT ELIGIBILITY CRITERIA

Participants who do not qualify for the study based on screening criteria deemed transitory, may be re-screened at the discretion of the Investigator. During re-screening, all assessments must be repeated.

4.1 Inclusion Criteria

Participants must meet all of the following criteria in order to be eligible to participate in the study:

1. Male or female participants, age ≥18 years to ≤65 years at the time of signing informed consent.
2. Have a documented clinical diagnosis of T1DM for ≥1 year before the Screening Visit. Clinical diagnosis requires the participant to have been insulin-deficient with the absolute requirement of insulin therapy starting at diagnosis or shortly after the end of the honeymoon period, either with MDIs, ie, basal insulin plus bolus insulin injections for meals or maintained on CSII with manual pumps or AID pump devices, except for the iLet Bionic Pancreas.

   NOTE: Participants with a diagnosis of T1DM and a fasting C-peptide of >0.6 ng/mL at the Screening Visit should be discussed with the study medical monitoring team prior to enrollment/randomization.
3. BMI ≥27.0 kg/m^2.
4. HbA1c value between 7.0% and 10.0%, inclusive, at the Screening Visit.
5. Treated with insulin either by means of an insulin pump for CSII, or by means of MDIs of insulin for ≥12 months prior to the Screening Visit. Participants with insulin pump treatment are eligible if the pumps are manually operated or are AID devices, except for the iLet Bionic Pancreas.
6. Must be on stable insulin formulation, dose (ie, within 10% of total daily basal dose), and devices (ie, not switching from MDI to manual or automated pump or vice versa) for ≥2 months prior to the Screening Visit and remain unchanged during the entire study, as judged and documented by the Investigator. Participant's insulin requirement must be >0.6 U/kg per day.
7. Must have some experience using a CGM device (with replacing sensors) within 3 months before the Screening Visit and be willing to wear a study-provided CGM device for the duration of the study.
8. Must be willing and able to be adherent to prescribed diabetes regimen and perform all prescribed diabetes self-management tasks (glucose and ketone monitoring/testing, change CGM sensors, adjust insulin doses if applicable, etc.).

9. Must be a non-smoker (ie, never smoked cigarettes or used any tobacco or nicotine containing products) or ex-smoker (ie, not smoked cigarettes or used any tobacco or nicotine-containing products during the last 6 months prior to the Screening Visit).

10. Female participants who engage in sex with men and female partners of male participants must use highly effective forms of contraception with either complete abstinence from sexual intercourse or double barrier contraception (including both male and female participants) during the entire duration of the study (ie, up to Week 18) or until at least 2 weeks after the last dose of CT-868. Male participants must refrain from sperm donation from start of study and for at least 2 weeks after the last dose of CT-868. Double barrier contraception is defined as a condom with spermicide and 1 other form of the following:

    a. Oral contraceptive pills

    b. Diaphragm with spermicide

    c. Intrauterine device

    d. Birth control patch (eg, Ortho Evra)

    e. NuvaRing®

    f. Documented evidence of surgical sterilization at least 6 months prior to screening, (ie, tubal ligation or hysterectomy for women or vasectomy for men)

    NOTE: Rhythm methods will not be considered highly effective methods of birth control and are not acceptable.

    NOTE: implanted/injectable contraceptives may be allowed provided participants have been on a stable dose and regimen of such contraceptives for ≥12 months prior to the Screening Visit.

    NOTE: Exception to double barrier contraceptive requirements may be considered if participants are with a same-sex partner and do not participate in bisexual activities where there is any risk of pregnancy.

11. Female participants of childbearing potential must have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test on Day 1 prior to randomization.

12. Female participants not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level >40 mIU/mL and estradiol ≤30 pg/mL at the Screening Visit or have documented evidence of having had a hysterectomy, bilateral oophorectomy, tubal ligation, or medically documented primary ovarian insufficiency.

    NOTE: In cases where female participants are peri-or post-menopausal and are undergoing hormone replacement therapy (HRT), either systemic or in the form of patches, the prescribed laboratory limits for FSH and estradiol levels may not accurately reflect their hormonal status. In such instances, the Investigator should consider the participant's clinical history and medical documentation, including the use of HRT, when assessing eligibility.

13. Testosterone use (prior and current) will be allowed if testosterone has been used for hormonal replacement (similar concept to that of thyroid hormone replacement) as long as the participant's dose has been stable within the last 6 months and no significant changes in testosterone dose (>25%) are anticipated during the course of the study, along with corresponding stable weight (ie, no increase or decrease >5%).
14. Must have unimpaired cognition (ie, without history of any cognitive deficits) and able to communicate well with the Investigator to understand and comply with all the requirements of the study (including maintaining their usual lifestyle patterns throughout the study).
15. Willing and able to understand, provide, and sign the written informed consent.

NOTE: Use of lipid lowering and/or antihypertensive medications are allowed, provided dosage/regimen of these medications have remained stable within the last 2 months prior to the Screening Visit.

4.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from participation in the study:

1. Diagnosis of Type 2 diabetes mellitus (T2DM) or any other types of diabetes (for example, latent autoimmune diabetes in adults or maturity-onset diabetes of the young forms), except T1DM.
2. Experienced DKA within 3 months prior to the Screening Visit.
3. Experienced severe hypoglycemia (Level 3 as defined in the ADA Standards of Medical Care in Diabetes (ADA 2024) within 3 months prior to the Screening Visit.
4. [redacted]
5. Use of any insulin preparation that is not delivered through CSII or MDI (eg, inhaled insulin).
6. Significant changes in diet or exercise regimen within 3 months prior to the Screening Visit or plans to undertake any of these during the study duration (eg, very low calorie, low carbohydrate, very high protein, ketogenic diets, time restricted eating/intermittent fasting, or other nutritional intervention, or initiating a new exercise program).
7. Prior use (ie, within 6 months prior to the Screening Visit) or current use of any of the following:
    a. Any medication (except insulin) that could interfere with glycemic control (eg, monoamine oxidase inhibitors, growth hormone, bromocriptine)

b. Any adjunctive treatments for diabetes (eg, pramlintide, metformin, glucagon-like peptide-1 [GLP-1] analogs [eg, exenatide], GLP-1 receptor agonists (GLP-1RAs) [eg, semaglutide, liraglutide, or dulaglutide], GLP-1/GIP RA (Mounjaro™), SGLT-2 inhibitors, sulfonylureas, or dipeptidyl peptidase 4 inhibitors)

c. Any prescription medication(s), and/or any over-the-counter product(s) including herbal and/or dietary supplements for weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone-bupropion, semaglutide, liraglutide, garcinia cambogia extract, Hydroxycut®, or glucomannan), or for weight gain (eg, growth hormone, anabolic steroids, or amino acid supplements)

d. Are receiving or have received within 3 months prior to the Screening Visit chronic (>14 consecutive days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (eg, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the Investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) during the study participation

e. Any prescribed or non-prescribed drugs that are known to interfere with gut motility, including but not limited to chronic opioids, anticholinergics, antispasmodics, linaclotide, or dopamine antagonists

8. History of treatment intolerance, allergic reactions, or lack of efficacy (ie, non-responders) with prior use of any GLP-1 analogs, GLP-1RAs, or GLP-1/GIP RAs.

9. Any self-reported body weight gain or loss of ≥5% within 3 months prior to the Screening Visit.

10. Have had or is planning to have during the study duration any surgical treatment for obesity (of any type) or with a weight loss device or any other weight loss procedure (eg, Lap-Band®, intragastric balloon, duodenal sleeve, resurfacing).

    NOTE: Liposuction and/or abdominoplasty may be allowed based on the Investigator's discretion, if performed >1 year before the Screening Visit, provided all other eligibility criteria are met.

11. Have obesity induced by other endocrinologic disorders (eg, Cushing syndrome, acromegaly, or inadequately treated hypothyroidism) or diagnosis of monogenetic or syndromic forms of obesity (eg, melanocortin 4 receptor deficiency or Prader-Willi syndrome).

12. A diagnosis and/or history of clinically significant gastroparesis, gastric motility, gastric emptying abnormalities, malabsorption disorders (eg, celiac disease), chronic constipation, chronic diarrhea, inflammatory bowel disease, bowel resection, irritable bowel syndrome, or severe gastroesophageal reflux disease.

13. Any of the following within 6 months prior to the Screening Visit: myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (including participants who may have percutaneous transluminal coronary angioplasty [PTCA] planned and/or anticipated during the study period, such as participants with prior angiographic evidence that may require PTCA); transient ischemic attack, cerebrovascular accident, hospitalization for congestive heart failure, or presenting at Screening with high-risk factors (eg, high blood lipid values) predisposing to cardiovascular events.

14. Current New York Heart Association Class III or IV heart failure.

15. Presence of clinically significant ECG findings at the Screening Visit (eg, corrected QT interval using Fridericia's formula [QTcF] >450 msec for male participants, QTcF >470 msec for female participants, left bundle branch block), or any other ECG findings considered to be indicative of active cardiac disease or with abnormalities, in the opinion of the Investigator, that are expected to interfere with the interpretation of ECG changes over the study duration or may present a safety issue to the participant.

16. Uncontrolled hypertension (ie, mean seated systolic blood pressure ≥160 mm Hg and/or mean seated diastolic blood pressure ≥100 mm Hg) at the Screening Visit (Investigator has the discretion to repeat at least once based on their clinical judgment).

17. Any clinically significant change in ophthalmologic examination within 12 months prior to the Screening Visit, including history and/or presence of clinically significant proliferative retinopathy, macular edema, or other diabetes-related eye disease. The ophthalmological examination must be documented in the medical record, not just patient reported. This examination is expected to be part of usual standard of care for their T1DM management and is not a protocol-defined assessment. If an appointment is available, this examination can be performed during the Screening Period.

18. History of any hematologic conditions that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle cell disease, other hemoglobinopathies).

19. Uncontrolled thyroid disease, defined as having active symptoms (eg, palpitations, lethargy, weight gain, or weight loss) and/or having a thyroid-stimulating hormone (TSH) value <0.4 or ≥4.5 mIU/L ± 10% as the upper normal range at the Screening Visit. If TSH is below or above normal, free T3 and T4 are automatically measured (ie, by reflex testing from the same blood sample).

    NOTE: Participants receiving adequate treatment for hypothyroidism may be included, provided they are clinically asymptomatic, TSH is within normal reference ranges, and their thyroid hormone replacement dose has remained stable for ≥2 months prior to the Screening Visit.

20. Have had an organ transplantation or are awaiting an organ transplantation.
21. Have had any major surgery/medical procedure within 12 months of the Screening Visit, or plan to undergo any major surgeries or major procedures during the study.
22. History or diagnosis of major depressive disorder within 2 years of the Screening Visit, or any history or diagnosis of other severe psychiatric conditions (eg, schizophrenia; bipolar disorder, eating disorder, or other serious mood, anxiety, or hyperactivity disorder).

    - NOTE: Participants with depression or anxiety whose disease state, in the opinion of the Investigator, is considered stable and expected to remain stable throughout the study, may be considered for inclusion only if their conditions are adequately controlled by stable doses of selective serotonin reuptake inhibitors (other than paroxetine) for ≥6 months prior to the Screening Visit, and are expected to continue the same doses for the entire study duration. Participants whose conditions are controlled by other types of anti-depressants or mood stabilizers (see Table 6) are excluded from this study, since many anti-depressants and mood stabilizers are associated with body weight/composition and glucose changes.

      NOTE: If a participant has a history of non-serious or non-severe anxiety or mood disorder, in other words, mild forms of these disorders, AND the participant has not been taking or is not planning to take any medications with a potential impact on weight, appetite, or gut motility (even if names of such medications are not explicitly stated in the protocol), then the subject may participate in the study, provided other eligibility criteria are fulfilled.

23. History or current diagnosis of acute or chronic pancreatitis, or risk factors for pancreatitis, such as history of alcoholism, cholelithiasis (without cholecystectomy), hypercalcemia, or severe hypertriglyceridemia.
24. Presence of any other clinically relevant medical and/or psychiatric conditions that would constitute a risk to the participant when taking the study drug or confound study endpoints and/or interfere with study assessments, as determined by the Investigator at the Screening Visit.
25. Presence of any of the following findings during the Screening Period, as determined by the central laboratory:

    a. Alanine aminotransferase (ALT), or aspartate aminotransferase (AST), or gamma glutamyl transpeptidase (GGT) >3.0× the upper limit of normal (ULN) of the reference range

       Note: Participants with prior history of nonalcoholic fatty liver disease are eligible to participate in this study if their ALT level is ≤3.0×ULN of the reference range.

    b. Alkaline phosphatase (ALP) >1.5×ULN of the reference range
    c. Total bilirubin >1×ULN of the reference range
    d. Amylase or lipase level of >2×ULN of the reference range

e. Fasting triglycerides level of >500 mg/dL

f. Estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease equation of <45 mL/min/1.73 m^2

g. Calcitonin ≥20 ng/L, if eGFR is ≥60 mL/min/1.73 m^2; or calcitonin ≥35 mg/L, if eGFR is <60 mL/min/1.73 m^2

h. History of, or positive hepatitis screen (including hepatitis B surface antigen [HBsAg] and anti-hepatitis C virus)

i. Positive HIV antibody screen

j. Hemoglobin level of <11 g/dL (male participants) or <10 g/dL (female participants)

NOTE: The Investigator has discretion to repeat laboratory assessments once if they believe there is a high likelihood that the results were spurious and do not accurately represent the participant's true values. Repeat assessments (no more than one per laboratory parameter) must be within the Screening Period. The reason for repeat assessments should be documented.

26. Unable to abstain from using >1000 mg acetaminophen/paracetamol every 6 hours, per the safety information associated with the study-provided CGM device (eg, [redacted]).

27. Unable to tolerate adhesive tape or has any unresolved adverse skin condition/reaction (eg, psoriasis, rash, *Staphylococcus* infection) in areas of CGM sensor placement.

28. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin carcinoma, in situ carcinoma of the cervix, or in situ prostate cancer) <5 years prior to the Screening Visit.

29. Have any active or clinically significant infection, including COVID-19 within 14 days prior to screening, or has a history of long-COVID-19 syndrome.

    NOTE: Usual symptoms experienced secondary to post-COVID-19 vaccinations are not exclusionary. All participants are required to follow site-specific COVID-19 protocols, if applicable, during the entire study.

30. Have personal or family history (first-degree relative) of medullary thyroid carcinoma or a genetic condition that predisposes to medullary thyroid carcinoma (ie, thyroid C-cell hyperplasia or multiple endocrine neoplasia Type 2A or Type 2B).

31. History of atopy (severe or multiple allergic manifestations), clinically significant multiple or severe allergies to prescription or nonprescription drugs, intolerance to topical corticosteroids, or history of severe hypersensitivity reactions.

32. A known allergy to any component of the study drug formulation or any other condition not listed in this section (eg, hypersensitivity or intolerance) that is a contraindication to GLP-1RAs or GLP-1/GIP RAs.

33. Planning to or anticipating initiation of any medications that may affect body weight or glucose metabolism during study participation, including current use of any prescribed or non-prescribed agents in the prohibited medication list (see Table 6).
34. Women who are pregnant, breastfeeding, intends to become pregnant, or is of childbearing potential and not using a highly effective contraceptive method if engaged in a heterosexual relationship.
35. History of alcohol addiction, and/or routinely consumes alcohol in the amount that exceeds 21 units per week (men) and 14 units per week (women) (1 unit of alcohol is defined as 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, or 1.5 oz or 45 mL of distilled spirits), as assessed during the Screening Visit.
36. History of use of known drugs of abuse within 12 months of the Screening Visit.
37. Has a positive alcohol test and/or positive drug test at Screening Visit
38. Prior or current participation in any other study that is evaluating CT-868.
39. Participation in any other investigational drug study for any indication in which receipt of an investigational drug product occurred within 5 half-lives or 60 days, whichever is longer, prior to the Screening Visit.
40. Participation in any other clinical study within 3 months prior to the Screening Visit, including current enrollment in any other type of clinical research judged not to be scientifically or medically compatible with this study, with the exception of investigational vaccines, in which case, participants may be enrolled 3 months after the last dose, regardless of follow-up in another clinical study.
41. Inability to comply with a daily SC injection regimen of study drug or is unwilling to wear and appropriately maintain the study-provided CGM device for the study duration (including the Follow-up Period), or unwilling to maintain their usual lifestyle patterns/regimen throughout the entire study.
42. Have donated ≥500 mL of blood, or have received a blood transfusion, or experienced severe blood loss within 3 months of the Screening Visit, or have donated blood of any volume within 1 month of the Screening Visit, or plan to donate blood during study participation.
43. Unwilling to adhere to the protocol requirements during the study or unwilling to cooperate or comply with the requirements of this study, or whose T1DM is managed by someone other than the participant (eg, by a caregiver), or is considered by the Investigator or Sponsor to be an unsuitable candidate for the study.

5.0 DISCONTINUATION AND WITHDRAWAL CRITERIA

Discontinuation of treatment can be decided by either the Investigator (for safety, behavioral, compliance, or administrative reasons) or the participant (see Section 5.4). A participant who discontinues study drug on their own initiative should be encouraged to resume study drug as soon as possible.

Participants who discontinue study drug should continue with the scheduled visits, undergo all protocol-specified procedures and assessments to ensure continued data collection, especially on safety-related endpoints. At a minimum, the procedures for the primary and key secondary endpoints (such as HbA1c and body weight) should be performed. Participants are encouraged to continue their eDiary through the rest of the study to capture the insulin doses.

In addition, all efforts should be made to have the participant attend at least the Week 16 Visit containing the final data collection of primary and secondary endpoints. If the participant refuses to attend the Week 16 Visit, information about the attempts to follow up with the participant must be documented in the participant's medical record.

The following describes when discontinuation should be considered at either the study level or participant level, which would be determined by the SRC in cooperation with study Investigator(s) who will all work closely together on a frequent basis when events that could potentially trigger these criteria arise.

5.1 Overall Study Level Discontinuation Criteria

Enrollment and further dosing in the entire study may be paused after consultation with the SRC to enable the Sponsor’s review of any of the following occurrences:

≥1 participant experiences a Grade 5 TEAE

≥3 participants experience the same Grade 4 TEAE

≥6 participants experience the same Grade 3 non-GI-related TEAE

If the Investigator and Sponsor determine any of these occurrences are unrelated to study drug, enrollment/dosing may resume.

5.2 Individual Participant Study Drug Discontinuation Criteria

The Investigator may temporarily discontinue study drug, for example, due to an AE/ADE (eg, severe nausea or constipation, or unable to deliver a dose with the Pen), a clinically significant laboratory value, or a natural disaster. If study drug discontinuation is due to an AE/ADE, the event is to be followed and documented. Every effort should be made by the Investigator to maintain participants in the study and to restart study drug promptly after any temporary discontinuation, as soon as it is safe to do so. The dates of study drug discontinuation and restart will be documented.

Discontinuation of the study drug for an individual participant should be considered by the Investigator in consultation with the SRC when a study participant meets any of the following criteria:

- Any event or abnormality that is considered to put the participant at unacceptable risk to continue dosing.
- Any infection that is considered to be serious.
- Any Grade 4 Common Terminology Criteria for AEs (CTCAE) TEAE/treatment-emergent adverse device effect (TEADE) attributable to study drug or device.

  NOTE: If the event is determined by the SRC to be unrelated to study drug and has resolved (if laboratory abnormalities, values must return to baseline), a participant may be rechallenged with study drug with close follow-up (ie, 1 to 2 clinical assessments per week for the first 2 weeks after rechallenging). If a second Grade 4 TEAE/TEADE occurs after rechallenging, study drug must be permanently discontinued for that individual participant.
- Any event that is considered by the Investigator and/or Sponsor to be attributable to study drug and highly suggestive of severe drug-induced liver injury, as defined by the Drug Induced Liver Injury Network (Rockey et al. 2010). Examples may include injury with any of the following findings:

Clinical manifestations (eg, liver-related hospitalization, diagnosis of acute liver failure)

Concerning symptoms consistent with the diagnosis of acute drug-induced liver injury (eg, abdominal pain, vomiting, jaundice)

Biochemical manifestations such as those described below based on the FDA guidance regarding individual participant stopping criteria for drug-induced liver injury (CDER 2009):

  - ALT or AST >8× ULN
  - ALT or AST >5×ULN for >2 weeks
  - ALT or AST >3×ULN and total bilirubin >2×ULN or international normalized ratio >1.5×ULN
  - ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3×ULN
  - ALP >2.5×ULN and total bilirubin >×ULN or
  - ALP >2.5×ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

  NOTE: These discontinuation rules should only be applied if an alternative reason is not identified and thus, the event is presumed to be study drug related. In the event a clear alternative cause to drug-induced liver injury is identified (eg, passage of a gallstone) these stopping rules may not apply. All cases that potentially trigger these rules will be reviewed by the SRC, who will determine whether study drug may be

continued for that participant. If study drug is permanently discontinued, the participant should be encouraged to remain in the study, if possible.

- Unable to tolerate a minimum of 1.8 mg/day of CT-868 in any of the 4 arms.
- Any serious study drug related hypersensitivity reaction.
- Experiences ADA Level 3 hypoglycemia, defined as a severe event characterized by impaired mental (cognitive) and/or physical functioning that requires external assistance from another person for recovery in the absence of any confounding conditions that lower blood glucose.
- 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.

- Calcitonin ≥100 ng/L.
- eGFR <15 mL/min.
- Development of any exclusion criteria during the study, including pregnancy.
- Intention of becoming pregnant during the study.
- Simultaneous participation in another clinical trial involving approved or non-approved investigational medicinal products.
- Violates the eligibility criteria and was inadvertently randomized. If a participant is randomized in violation of inclusion, exclusion, or randomization criteria, this will be handled as a major protocol deviation (see Section 11.1), and the Ethics Committee (EC) or Institutional Review Board (IRB) and regulatory authorities must be notified according to local requirements.

- Any other TEAE (including and not limited to [redacted] AEs), TEADE, SAE, serious adverse device effect (SADE), or clinically significant laboratory value for which the Investigator believes that permanent study drug discontinuation for that individual participant is the appropriate measure to be taken.
- Any TEAE that results in a treatment discontinuation should be reported within 24 hours.

5.3 Individual Participant's Study Drug Discontinuation May Be Considered

The following may be situations where study drug discontinuation for an individual participant may be considered (with consultation of the Sponsor medical monitor):

- Any prescription or over-the-counter medication for weight loss is given for more than 1 week.
- Any prohibited anti-hyperglycemic agent(s) for more than 1 week.
- Any nonfatal major cardiovascular events.
- 3 or more moderate study related ISRs occurring a week or more apart.
- [redacted]
- At any time during the study, CGM values are <54 mg/dL (3.0 mmol/L) with or without symptoms related to hypoglycemia for a consecutive ≥120 minutes (ie, extended Level 2 hypoglycemia)

  NOTE: It is important to recognize a compression low (false low) blood glucose reading from a true low blood glucose. If CGM low alarms are going off (especially during the night), a finger-stick blood glucose via glucometer must be performed and recorded in study diaries to verify that these are true low blood glucose values meeting the criteria above versus due to sensor compression (eg, from pressing an arm by sleeping on one side). Investigators have the discretion to determine whether any low blood glucose is an artifact (eg, related to compression), and to document the reasons that the low blood glucose values do not meet the criteria for considering the hypoglycemic event as discontinuation criteria. Participants are also instructed to get a finger-stick blood glucose via glucometer if they are

experiencing symptoms related to hypoglycemia (such as diaphoresis, weakness, dizziness, tachycardia).

All participants will be provided with glucometers with necessary supplies. Participants will be educated on glucose monitoring, managing their hypoglycemic symptoms and instructed to seek medical care.

5.4 Participant Withdrawal or Discontinuation

A participant may prematurely discontinue study drug and/or withdraw from the study at any time.

A participant who prematurely discontinues study drug should be encouraged to continue their participation in the study and complete all visits and procedures as per protocol, especially the visit at Week 16. The reasons for premature discontinuation of study drug must be documented in the eCRF. Reasons include, but are not limited to, the following:

- Withdrawal of consent.
- Any event, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the participant.
- Pregnancy.
- Participant failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the Sponsor or regulatory authority.
- Initiation of any of the following medications:
    - Any GLP-1 analog, GLP-1RA or GLP-1/GIP RA
    - Pramlintide, metformin, sodium-glucose cotransporter-2 inhibitors, sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, or any glucose-lowering agent other than insulin
    - Any anti-obesity medication, including (but not limited to) liraglutide, semaglutide, tirzepatide, orlistat, phentermine-topiramate, phentermine, bupropion, naltrexone, and over-the-counter weight loss supplements
    - Any herbal remedies with either glucose-lowering or weight loss effects
- Severe allergic reactions to the study drug.
- Any stopping rule as described in Section 5.0.

See Section 5.2 for the individual participant level discontinuation criteria.

If a participant withdraws consent prematurely from the study for any reason despite efforts from the site, the participant should complete the Early Termination (ET) Visit (see Table 7). In this case, if the withdrawal of consent happens before Week 16, the ET visit should be within 7 days

of the last dose of the study drug. The reason for participant withdrawal must be documented in the eCRF.

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.

5.5 Participants Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly does not return for scheduled visits and is unable to be contacted by the study site. The site must attempt to contact the participant and reschedule the missed visit as soon as possible to counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study. Before a participant is deemed lost to follow-up, the Investigator must make every effort to regain contact with the participant (contact attempts should be documented in the participant’s source document). If the participant continues to be unreachable at the End of Treatment Visit, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

5.6 Replacement of Study Participants

Replacement of participants post-randomization is not allowed.

6.0 STUDY TREATMENTS

6.1 Treatment Groups, Study Drug Administration, and Titration Scheme

Participants will be randomized at a ratio of [redacted] to 1 of 4 treatment arms. CT-868 and placebo are to be titrated per protocol and in Arms 3 and 4, according to the individual participant's tolerability up to a maximum dose of 4.1 mg CT-868 or 6.6 mg CT-868 (administered as 2 injections of [redacted] mg CT-868 each) or volume-matched placebo, respectively.

Starting from the Placebo Run-in to Week 16, participants will be instructed to self-administer the dose in accordance with the Instructions for Use (IFU) as an SC injection in the [redacted] at the same time each morning (to the greatest extent possible), irrespective of meals (except on Day 1 and Weeks 4, 8, 12, and 16 when participants should arrive at the study site/clinic having fasted overnight at least 8 hours). Injection sites on the [redacted] will be rotated by quadrant to reduce potential for ISRs. The participant will have the opportunity to ask questions if clarification from the study staff is needed. On subsequent clinic visit days, self-administration will occur in the clinic and will be observed by clinic staff, and further clarification will be provided as required.

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

Participants will be administered study drug according to the titration schedule specified in Table 5.

Table 5. 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]	[redacted]

[a:] Administered as [redacted] doses of [redacted] mg each.

[b:] Administered as [redacted] doses of [redacted] mg each.

[c:] No up-titrations in dose will be allowed after Week 12 (ie, 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 with particular tolerability problems, randomized to Arm 2, Arm 3, or Arm 4 must tolerate a minimum of 1.8 mg/day of the study drug to continue participation in the study. If the Investigator believes that the participant will not tolerate 1.8 mg/day despite undertaking all the symptomatic relief measures to mitigate tolerability issues, the participant will be discontinued from 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.

6.2 Missed Doses

If a participant inadvertently misses 1 or more doses, they should resume dosing as soon as possible. If the time since the last scheduled dose was missed is <8 hours, the participant may administer the missed dose immediately. If the time since the last scheduled dose was missed is ≥8 hours, the participant should wait until the next scheduled dose to resume dosing. A missed dose should not affect the scheduled dosing time of the day. Any missed dose should be recorded in the medication diary provided to participants.

If 2 or more consecutive doses, but less than a week, of study drug are missed, the participant should be encouraged to re-commence the treatment if considered safe per the Investigator's discretion and if the participant does not meet any of the discontinuation criteria (Section 5.2). The study drug should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing time of the day.

If a whole week of consecutive doses is missed for any reason, the participant must re-titrate up from their most recent prior dose level for at least 1 week, if considered safe per the Investigator's discretion and if the participant does not meet any of the discontinuation criteria. For example, if a participant who is maintained at the 4.1 mg dose level misses a full week of dosing, they must start at [redacted] mg for 1 week and resume their 4.1 mg dose the following week; they cannot immediately restart at 4.1 mg.

It is recommended that the Investigator consult the Sponsor Medical Monitor in case of persistent deviations from the planned escalation regimen, including any questions related to re-initiation of study drug.

Each missed dose should be recorded in the eCRF, as per participant's recollection. If a "treatment status" session previously has been made in IWRS to indicate discontinuation of study drug, a new "treatment status" session must be made to resume study drug.

6.3 Dose Interruptions

At Investigator's discretion, dose interruptions may be permitted to facilitate tolerability. If a participant interrupts study drug, they should resume study drug as soon as feasible after the Investigator deems it acceptable to do so.

6.4 Randomization and Blinding

A randomized, double-blinded, placebo controlled, multi-center trial design is chosen to minimize bias in the assessment of the efficacy and safety of once daily SC administration of CT-868 versus placebo as an adjunct to insulin in overweight and obese participants with T1DM. Randomization of participants will be managed by an IRT system. Participants meeting eligibility criteria will be randomized at Visit 4 (Day 1) in a [redacted] ratio to 1 of 4 treatment arms. The randomization will be stratified based on the HbA1c level measured at Screening (<8.5% or ≥8.5%) and their method of insulin administration (pump or MDI). This stratification

will help to give a better understanding of the effects of CT-868 treatment on glycemic control in both insulin pump and MDI users across different HbA1c levels.

Participants will be assigned a randomization number which is associated with the treatment assignment as determined by the IRT system. The IRT system will manage all aspects of treatment and titration and logistical aspects of study product supply.

The master randomization lists will be kept by Medpace IRT and confidentially supplied to the PK laboratory, the independent unblinded statistician, or any other unblinded staff as needed.

Due to the titration scheme, participants and study staff will be aware of the volume of study drug the participants are receiving; however, they will not be aware of whether they are receiving CT-868 or the placebo.

Randomized participants who terminate study participation for any reason before the first administration of study drug will retain their randomization and treatment number. Randomization numbers will not be reused.

Randomized participants who prematurely discontinue the study will not be replaced. See Section 5.0 for details.

6.5 Breaking the Blind

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.

6.6 Drug Supplies

6.6.1 Formulation and Packaging

The CT-868 Injection, [redacted] mg/mL (active) is formulated as a clear, colorless, sterile aqueous solution at a concentration of [redacted] mg/mL in [redacted]

The CT-868 Placebo Injection contains the same ingredients as the active without CT-868. The CT-868 Injection, [redacted] mg/mL and Placebo Injection, manufactured in compliance with Good Manufacturing Practice standards by the contract manufacturer, is filled into sterile [redacted]-mL Type 1 glass cartridges. Each active cartridge contains approximately [redacted] mg/[redacted] mL of CT-868.

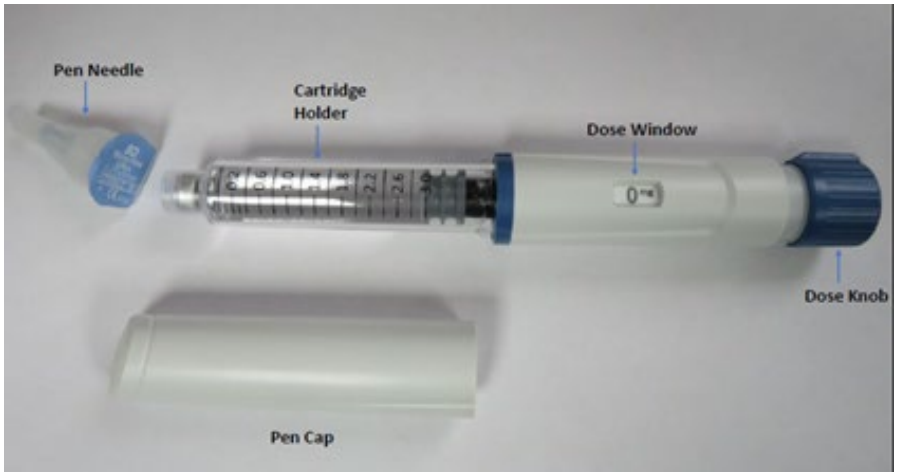
The filled cartridge is assembled with the pen injector components as an integrated drug product (CT-868 Pen) for single-patient, multi-dose once-daily SC administration to deliver [redacted] fixed doses of [redacted] mg ([redacted] mL), 1.8 mg ([redacted] mL), [redacted] mg ([redacted] mL), [redacted] mg ([redacted] mL), and 4.1 mg ([redacted] mL). Additional details on formulation and composition are provided in the Investigator's Brochure.

CT-868 active and placebo pens will be supplied individually labeled and packaged with the IFU in a carton. Within each dose group, the CT-868 active and placebo pens will be identical in appearance.

The CT-868 Pen is designed for use with the commercially available sterile [redacted] second Gen 4 mm (5/32")×32 G pen needle from [redacted] supplied separately. No other pen needles have been evaluated with the pen. A new needle is used for each daily dose.

Key features of the CT-868 Pen are shown in Figure 2.

Figure 2. CT-868 Pen Injector, [redacted] mg/mL



The materials used in the CT-868 Pen are standard materials for medical devices. Materials that may come in contact with the participants have been assessed for biocompatibility in accordance with ISO 10993-1. The CT-868 Pen is biocompatible when used as intended.

6.6.2 Study Drug Preparation and Dispensing

The CT-868 and placebo Pens must be stored refrigerated and brought to room temperature prior to dosing. Written dose preparation instructions are included in the IFU.

Prior to the first dose (Placebo Run-in), participants will be instructed to self-administer the dose in accordance with the IFU as an SC injection in the [redacted]. Self-administration should occur, to the greatest extent possible, at the same time each morning), irrespective of meals. Injection sites on the [redacted] will be rotated by quadrant to reduce potential for ISRs.

On Day 1 and Weeks 4, 8, 12, and 16, participants should arrive at the study site/clinic having fasted overnight at least 8 hours. The participant will have the opportunity to ask questions regarding clarification from the study staff. On clinic visit days, self-administration will occur in the clinic and will be observed by clinic staff, and additional clarification will be provided as required.

At the clinical site, the CT-868 Pens will be dispensed and stored according to the Pharmacy Manual.

At the participants' home, study participants must store the Pen in the carton in the refrigerator and allow the Pen to come to room temperature prior to SC administration according to the IFU. After administration of the study drug with the CT-868 Pen, the needle must be removed from the Pen and discarded in an FDA-approved sharps container. The Pen cap must be replaced, and the Pen must be stored in the carton, without the needle, in the refrigerator until the next dose. Participants will be instructed to keep the study drug out of the reach of children and other family members who may have access to the storage location.

6.6.3 Treatment Compliance

Treatment compliance is defined as the number of doses administered per protocol/number of doses prescribed per protocol. Treatment compliance will be assessed using the participant's diary.

6.6.4 Storage and Accountability

At the clinical site, the study drug is to be stored refrigerated at 2°C to 8°C (36°C to 46°F) in a secure, controlled-access location.

At the participant's home, the study drug is to be stored in the refrigerator. Participants will be instructed to take care in keeping study drug out of the reach of children and other family members who may have access to the storage location.

The Investigator is responsible for ensuring that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and to inspection by regulatory authorities at any time. Each shipment of drug supplied for the study will contain a shipping manifest to assist the Investigator in maintaining current and accurate inventory records.

Upon receipt of the study drug, the designated site personnel will visually inspect the shipment, verify the number and condition of study drug received, and confirm receipt of study drug.

At the completion of the study, all used and unused study drug will be returned to the Sponsor or Sponsor's representative or disposed of by the clinic, per the Sponsor's or Sponsor's representative written instructions.

6.7 Prior and Concomitant Medications and/or Procedures

Use of the agents (prescription or nonprescription) listed in Table 6 is prohibited from the time points specified until completion of all study activities for the entire study duration.

Table 6. Prohibited Medications

Medication or Class	Indication/ Confounders	From Time Point Specified
Any adjunctive antidiabetic treatment (other than insulin or insulin analogs), including and not limited to GLP-1 analogs, GLP-1 RAs, GLP-1/GIP RA, SGLT-2i, DPP-4i, sulfonylureas, pramlintide, bromocriptine **Note**: any insulin preparation that is not delivered through CSII or MDI (eg, inhaled insulin) is also prohibited.	Glycemic control	Within 6 months of the Screening Visit
Oral or systemic corticosteroids (known to interfere with glucose or insulin metabolism)	For example, chronic or acute non-infectious inflammatory conditions, auto-immune diseases for any duration longer than 14 consecutive days	Within 3 months of the screening visit (topical, intraocular, intranasal, intra-articular or inhaled preparations of steroid may be allowed at the discretion of the Investigator)
Serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, mood stabilizers, methylphenidate, lithium, paroxetine, monoamine oxidase inhibitors **Note**: If adequately controlled by stable doses of SSRIs (other than paroxetine) for ≥6 months prior to Screening, and, provided that their doses/regimen are anticipated to remain stable for the entire study duration, SSRIs may be allowed based on the judgement of the Investigator. In addition to SSRIs, the use of bupropion (Wellbutrin) may also be considered for participants who have been on a consistent dose for at least 6 months prior to Screening. Participants are anticipated to remain on stable doses for the duration of the study. The inclusion of participants taking bupropion or SSRIs (other than paroxetine) should be based on the judgment of the Investigator, who will evaluate the risk-benefit profile for each individual participant.	Neuropsychiatric diseases	At Screening
Weight lowering pharmacotherapy and/or dietary supplements These include but not limited to: Saxenda® (liraglutide), Wegovy® (semaglutide), Munjaro® (tirzepatide), Xenical® or Allī® (orlistat), Meridia® (sibutramine), Acutrim® (phenylpropanolamine), Sanorex® (mazindol), Apidex® (phentermine), BELVIQ® (lorcaserin), Qsymia® (phentermine/topiramate combination), Contrave® (naltrexone/bupropion), Asenlix® (Clobenzorex), Solucaps® (Mazindol), Redotex® (aloine, atropine, diazepam, norpseudoephedrine, triyodotironine), berberine, resveratrol, other sympathomimetic agents, thyroid hormones (for non-thyroid indications), growth hormone,	Weight loss	Within 6 months of the Screening Visit

Medication or Class	Indication/ Confounders	From Time Point Specified
or any non-herbal supplements/alternative remedies with unknown/unspecified content		
Weight gain inducing pharmacotherapy and/or dietary supplements These include but not limited to growth hormone, anabolic steroids, protein/amino acid supplements. These agents may also interfere with glucose or insulin metabolism	Weight gain	Within 6 months of the Screening Visit **Note:** use of marijuana/ cannabis during study participation is prohibited, except in cases where participants who have medical marijuana cards and need to take marijuana to treat their existing medical condition(s).
Testosterone use (prior and current) will be allowed if testosterone is used for hormonal replacement (similar concept to that of thyroid hormone replacement) as long as the participant's dose has been stable within last 6 months and no significant changes in testosterone dose (>/= 25%) are anticipated during the course of the study along with corresponding stable weight (ie no increase or decrease ≥/=5%)	Weight gain	Stable dose of testosterone within the last 6 months
Prescribed or non-prescribed drugs, including but not limited to chronic opioids, anticholinergics, linaclotide, antispasmodics, or dopamine antagonists	Interference with gut motility	Within 6 months of the Screening Visit
Acetaminophen exceeding 1,000 mg every 6 hours	Pain medication and CGM interference	During [redacted] CGM wear period
Use of injectable or implanted contraceptives	Contraception (can interfere with body weight/composition)	Within 12 months of the Screening Visit
Any drug, other than those provided in this study, that has not received regulatory approval	Any	At Screening

CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DPP-4 = dipeptidyl peptidase-4; GIP-RA = glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1 = glucagon-like peptide -1, GLP-1RA – glucagon-like peptide-1 receptor agonist; MDI = multiple daily dose; SGLT-2 = sodium-glucose transport protein-2; SSRI = selective serotonin reuptake inhibitor

Any procedures for weight loss (bariatric surgery of any type, devices such as Lap-Band®, intragastric balloon, etc.), or blood donation of ≥500 mL, or organ donation/transplantation are also prohibited during study participation.

Lipid lowering and/or anti-hypertensive medications are allowed provided dosage/regimen of these medications have remained stable within the last 2 months prior to Screening Visit and should be continued at stable doses during the Run-in Period and throughout the study duration. Such medications have also been safety co-administered in other CT-868 trials (especially in CT-868-002 where a significant proportion of patients with T2DM were maintained on concomitant statins, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers,

all substrates of OATP1B1/1B3 hepatic transporters, without experiencing any clinically significant issues or concerns).

All participants in this study are closely monitored with frequent safety assessments (eg, clinical assessments, measurement of liver enzymes/bilirubin levels, and other parameters).

6.7.1 Lifestyle Restrictions

Participants should maintain their usual level/regimens of physical activity, diet, and lifestyle patterns throughout the entire study (ie, will not begin a new diet, eating pattern, or exercise program or participate in any unusually strenuous physical exertion).

6.7.2 Documentation of Prior and Concomitant Medication Use

Any medication (prescription and over-the-counter) taken at least once from Screening through the end of study (EOS) as well as the reason for use will be recorded in the source documents and the eCRFs.

7.0 STUDY PROCEDURES

Study procedures will follow the Schedule of Assessments (Appendix A).

7.1 DEXA Scan

A DEXA scan will be performed at baseline and Week 16 or early termination (ET). The baseline DEXA scan may be performed up to +3 days after Day 1 randomization, but every effort should be made to perform the DEXA scan prior to the first dose of the study drug.. No contrast (oral or intravenous) scans are permitted for a week prior to the DEXA scan (nuclear medicine isotopes may involve longer delays) and no calcium supplements are to be taken by the participants on the morning prior to the DEXA scan. DEXA scans will assess body composition (fat and lean mass) and bone mineral density.

Not all sites will have the ability to perform DEXA scans, and not all sites that can perform the DEXA scans will have the ability to provide all the protocol-requested data points.

[redacted]

7.3 Study Diary

Within the eDiary, participants will keep diaries to document hypoglycemic, hyperglycemic, and hyperglycemia plus ketoacidosis events, insulin dose, and study drug administration. Study staff will review the diary at each study visit and discuss it with the participant.

Participants will enter insulin dose information into the designated log within the eDiary application, and will also be prompted to document in their diary any hypoglycemic, hyperglycemic, and hyperglycemia plus ketoacidosis events as they occur from the start of the insulin adjustment period to the end of study (Week 18) as outlined in the Schedule of Assessments (Appendix A). They will also enter the time of study drug administration each morning from the start of the randomization visit to the end of the 16-week treatment visit.

Maintaining accurate and up-to-date records in the diary is crucial for the study team to monitor the participant's diabetes management and ensure the safety and efficacy of the study treatment. The study team will closely monitor the diary entries to identify any issues or non-compliance in a timely manner. Please refer to the Study Reference Manual regarding these requests.

8.0 EFFICACY ASSESSMENTS

Efficacy will be assessed by HbA1c, various CGM metrics, body weight/body composition measurements, and PROs. The study endpoints are displayed in Table 2.

9.0 SAFETY ASSESSMENTS

Safety assessments will include the following:

- AEs/ADEs, including injection site reactions
  NOTE: Only TEAEs/TEADEs will be summarized.
- AEs/ADEs of special interest [redacted]
- [redacted]
- Vital signs
- Physical examinations
- ECGs
- Clinical laboratory tests (hematology, chemistry, including beta-hydroxybutyrate, amylase, lipase, calcitonin, and urinalysis)

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.

9.1 Adverse Events/Adverse Device Effects

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 AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An ADE is defined as an AE related to the medical device; in this study, the medical device is the pen device with which the study drug is administered. This includes any event that is the result of incomplete user manual information or of incorrect use of the medical device.

All AEs/ADEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. The Investigator should update the appropriate eCRF if additional follow-up information becomes available (eg, the AE/ADE has subsided, stabilizes, or the condition becomes chronic in nature).

AEs, which include clinical laboratory test results, will be monitored and documented from the time of informed consent until the EOS. Participants should be instructed to report any event that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at Screening, Investigators should make an assessment for AEs/ADEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the Screening Visit should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at the Screening Visit and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Thus, abnormal test results that are determined to be an error should not be reported as an AE, while laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should usually be reported as an AE if any of the following are applicable:

- An intervention is required as a result of the abnormality
- Action taken with the study drug is required as a result of the abnormality or
- Based on the clinical judgment of the Investigator

Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

9.1.1 Adverse Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse reaction. “Responses” to a medicinal product mean that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

9.1.2 Unexpected Adverse Reaction/Unexpected Adverse Device Effect

An unexpected adverse reaction is defined as an adverse reaction/ADE, the nature or severity of which is not consistent with the applicable product information.

9.1.3 Assessment of AEs/ADEs by the Investigator

The Investigator will assess the severity (intensity) of each AE/ADE and will also categorize each AE/ADE as to its potential relationship to study drug.

9.1.3.1 Assessment of Severity

The severity of all AEs/ADEs should be graded according to the CTCAE version 5.0. For those AE/ADE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; or
- CTCAE Grade 5: Death related to the AE/ADE

9.1.3.2 Causality Assessment

The relationship of an AE/ADE to the administration of study drug is to be assessed according to the following definitions:

- **No (not related or unlikely related):** The time course between the administration of study drug and the occurrence or worsening of the AE/ADE rules out a causal relationship and/or another cause (concomitant drugs, therapies, complications, etc.) is suspected; or
- **Yes (possibly, probably, or definitely related):** The time course between the administration of study drug and the occurrence or worsening of the AE/ADE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

NOTE: The definition implies a reasonable possibility of a causal relationship between the event and the study drug or device. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- **The temporal sequence from study drug administration:** The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- **Underlying, concomitant, intercurrent diseases:** Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- **Concomitant drug:** The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them might be recognized to cause the event in question.
- **Known response pattern for this class of study drug:** Clinical and/or nonclinical data may indicate whether a particular response is likely to be a class effect.

- **Exposure to physical and/or mental stresses:** The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- **The pharmacology and PK of the study drug:** The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.1.4 Adverse Events of Special Interest

The Investigator will monitor each participant for clinical and laboratory evidence of pre-defined AESIs throughout their participation in this study. AESIs are selected non-serious or serious adverse events and must be recorded in the eCRF.

For the AESIs listed below, the AE must be reported as “possibly”, “probably” or “definitely” related to study drug. Any of these AESIs have to be reported to the Sponsor within 24 hours. The following would be considered as AESIs for this study (many of these are generally associated with GLP-1, GLP-1/GIP receptor agonists, and the broader incretin drug class):

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

9.2 Serious Adverse Events/Serious Adverse Device Effects

An AE/ADE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE/ADE
- NOTE: An AE/ADE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalization
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE/SADE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect; or
- An important medical event

  NOTE: Important medical events that do not meet any of the above criteria may be considered SAEs/SADEs when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

  An SADE includes device deficiencies that might have led to the SADE, in a participant, user, or other person, if: a) suitable action had not been taken; or b) intervention had not been made; or c) if circumstances had been less fortunate. They are handled under the SAE reporting system.

9.3 Serious Adverse Event/Serious Adverse Device Event Reporting − Procedures for Investigators

9.3.1 Initial Reports

All SAEs/SADEs occurring from the time of informed consent until the EOS must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the EOS, any SAE/SADE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE/SADE, complete the AE form with the SAE/SADE information electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Clinical Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Clinical Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line, and fax/email the completed paper SAE form to Medpace (contact information listed in Section 9.6) within 24 hours of awareness. When the EDC system becomes available, the SAE/SADE information must be entered within the subsequent 24 hours.

9.3.2 Follow-Up Reports

The Investigator must continue to follow the participant until the SAE/SADE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the participant dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE/SADE form electronically in the EDC system for the study and submit any supporting documentation (eg, participant discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs/SADEs.

9.4 Pregnancy Reporting

If a participant becomes pregnant during the study, the Investigator is to stop dosing with study drug immediately and the participant should be withdrawn from the study.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring during the study must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero form for completion. The Investigator/site must complete the Exposure In Utero form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male participant becomes pregnant while the participant is receiving study drug, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the Exposure In Utero form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.5 Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the FDA and to applicable EC/IRBs, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case, or 5 days if caused by the Pen. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported, as applicable, to the FDA and to applicable EC/IRBs as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also submit any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

9.6 Special Situation Reports

Special Situation Reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the participant has taken additional dose(s) or the Investigator has reason to suspect that the participant has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, participant, or consumer. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of participants missing doses of investigational product are not considered reportable as medication errors.

- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situation Report form will only be completed if a complaint is associated with an adverse reaction.

9.6.1 Safety Contact Information

All special situation events as described in Sections 9.3 to 9.6 must be reported on the Special Situation Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs/ADEs associated with these Special Situation Reports should be reported as AEs/ADEs or SAEs/SADEs as well as recorded on the AE/ADE eCRF and/or the SAE/SADE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.



9.7 Clinical Laboratory Evaluations

Clinical laboratory tests (serum chemistry, hematology, HbA1c, amylase and lipase, urinalysis, calcitonin, lipid profile, and blood biomarkers) will be performed at visits specified in the Schedule of Assessments (Appendix A). 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.

9.8 Vital Signs

Vital signs (temperature, heart rate, and blood pressure) will be performed at visits specified in the Schedule of Assessments (Appendix A). Participants should not drink coffee for 1 hour prior to collection and should be seated for ≥10 minutes prior to collection.

9.9 Electrocardiograms

ECGs (12-lead) will be performed at visits specified in the Schedule of Assessments (Appendix A).

In addition, ECGs will also be performed in the subgroup of participants who participate in the optional 24-hour PK assessment at Week 14. The ECG will be performed at the study drug's approximate T_{max} time (~10 hours postdose).

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.

9.10 Physical Examinations

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

A comprehensive full physical examination should minimally include clinical evaluations of the head, neck, thyroid, eyes, ears, nose, throat, chest, heart, lungs, lymph nodes, [redacted], skin, extremities, musculoskeletal and neurological.

A brief physical examination should minimally include clinical evaluations of the heart, lungs, and skin (especially around injection sites and pump/CGM placement areas). Additional systems may be examined based on any symptoms exhibited by the participant.

Both the full and brief physical examinations will be performed by a qualified healthcare professional and any significant findings will be documented in the participant's medical record.

9.11 Anti-Drug Antibody Assessments

The antidrug antibody assessments will be performed at visits specified in the Schedule of Assessments (Appendix A) and in case of severe ISRs and hypersensitivity reactions. Blood samples for antidrug antibody and PK predose trough concentration analysis will be collected ~24 hours after the preceding dose.

10.0 STATISTICS

Details of statistical parameters and methods to be applied will be provided in a Statistical Analysis Plan (SAP) prior to database lock and unblinding.

10.1 Analysis Populations

The Intent-to-Treat (ITT) population includes 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 and key secondary endpoints.

The modified Intent-to-Treat (mITT) population includes all randomized participants who receive at least 1 dose of study drug and have at least 1 postdose measurement of HbA1c. This population will be used as the supplementary analysis on the primary and key secondary endpoints, as well as the main analysis population for other secondary and exploratory endpoints.

The Safety population includes all randomized participants who receive at least 1 dose of study drug. All safety endpoints will be summarized using the Safety population according to the actual treatment assigned.

The Per Protocol (PP) population includes all participants in the mITT population who do not have a major protocol deviation that would potentially impact the primary efficacy endpoint. This analysis population will be used for the supplementary analysis for the primary and key secondary endpoints only.

The PK population includes 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.

10.2 Statistical Methods

10.2.1 Efficacy Analyses

Efficacy results will be summarized and listed by randomized treatment group. For all analyses, unless specified otherwise as with CGM metrics, baseline is defined as the last available non-missing value prior to the start of treatment on Day 1. The 3 placebo groups will be pooled prior to analysis for comparison to each dose level of CT-868.

The ITT population will be the primary population for the analysis of primary and key secondary efficacy endpoints. There is 1 estimand of interest in comparing efficacy of CT-868 doses with placebo relative to the primary endpoint of change in HbA1c from baseline to Week 16 – the “treatment regimen” estimand. It represents the efficacy irrespective of adherence to study drug. This will be used to guide the analyses for the primary and key secondary endpoints.

The primary and key secondary efficacy endpoints, change in HbA1c (%) and percent change in body weight from baseline to Week 16, will be analyzed using analysis of covariance

(ANCOVA) models with treatment as the factor and the baseline, HbA1c strata (<8.5% or ≥8.5%) for percent change in body weight only, and methods of insulin administration (pump or MDI) as the covariates. The primary efficacy summary measure will be evaluated using the differences in the least squares (LS) means, with 95% confidence intervals and associated 1-sided p-value from this ANCOVA model. Missing data will be imputed using the retrieved dropout (RD) approach (Wang et al 2022, Wang et al 2023). Specifically, for participants who discontinue 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 treatment group, (ie, those who discontinued treatment early but have HbA1c measurements at Week 16) using a multiple imputation approach.

All statistical tests will be 1-sided and will be performed using a 5% significance level (alpha). Each CT-868 arm will first be compared with the pooled placebo group and then the 3 CT-868 arms with each other. To protect the overall alpha level on the primary endpoint, the hypothesis testing will be performed sequentially. When testing for efficacy, overall treatment effect will be evaluated first. When the overall treatment effect is statistically significant at 5%, Arm 4 will be compared with placebo (Arm 1), then if significant at 5%, Arm 3 will be compared with placebo (Arm 1), and finally, if significant, Arm 2 will be compared with placebo (Arm 1).

The primary and key secondary efficacy endpoints will also be analyzed using the PP population (ANCOVA models with RD) and mITT with mixed model for repeated measures (MMRM) models as supplemental analyses. For MMRM, participants with at least 1 non-missing primary and key secondary endpoints will be included. The treatment effect on the change from baseline in HbA1c to Weeks 4, 8, and 12 will be evaluated in this model. Details will be described in the SAP. The impact of actual final doses will be investigated in separate analyses.

MMRM models will also be used to analyze other continuous endpoints of repeat structure.

Binary HbA1c endpoints will be compared between treatments using logistic regression adjusting for treatment, baseline HbA1c, and methods of insulin administration (pump or MDI) as covariates. Similar analyses will be performed for other binary endpoints. Treatment differences will then be expressed as an odds ratio.

Number of events will be compared between treatments using a negative binomial regression model, adjusting for baseline, HbA1c strata and methods of insulin administration (pump or MDI), and using time in study as an offset. The assessment will be expressed as a risk ratio.

10.2.2 Pharmacokinetic Analysis

PK data will be analyzed to determine the steady-state trough CT-868 exposure in all enrolled overweight and obese T1DM participants. These data will also be used in a population PK model together with PK data from other CT-868 studies to evaluate the PK of CT-868 in different populations, such as overweight and obese otherwise healthy participants and overweight and

obese participants with T2DM. The latter will be covered in a population PK analysis plan for the CT-868 program.

To characterize the PK profile of CT-868 in T1DM patients, a subgroup of [redacted] participants per treatment arm will be asked to participate in an optional 24-hour PK sampling visit at Week 14.

10.2.3 Safety Analyses

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 assignment. TEAEs/TEADEs will be coded and summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. TEAEs/TEADEs will be summarized by the number of participants with at least 1 TEAE for overall TEAEs and for each subtype such as related TEAEs/TEADEs, serious TEAEs/TEADEs, discontinuations of treatment due to TEAEs/TEADEs, and TEAEs/TEADEs of different intensity.

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

Details will be described in the SAP.

10.2.4 Interim Analysis

An interim analysis might be conducted after at least 50% subjects have completed 16 weeks of treatment. Details will be provided in the SAP.

10.2.5 Sample Size Determination

Approximately 96 participants will 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 1-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.

11.0 DATA MANAGEMENT AND RECORD KEEPING

11.1 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the procedures and processes as specified in the protocol. A major or significant protocol deviation occurs when there is non-adherence to the protocol that might significantly (a) impact the completeness, reliability, and/or accuracy of the study data or (b) affect a participant's rights, safety, or well-being. The Investigator or designee must document and explain any protocol deviation in the participant's source documentation. Any significant protocol deviation will be investigated and reported by the Sponsor and may lead to the participant being withdrawn from the study, termination of the Investigator's participation in the study, and/or other actions.

The Sponsor or designee will be notified of known significant protocol deviations by the Investigator. Protocol deviations found throughout the course of monitoring visits are to be documented by the clinical monitor. The ethics committee should be notified of all applicable protocol deviations, in accordance with reporting requirements of the ethics committee, in a timely manner by the Investigator.

11.2 Data Management

11.2.1 Data Handling

Data will be entered into eCRFs in the EDC system by personnel allocated to this task, as documented on the site delegation log, and will be reviewed by the (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

11.2.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.2.3 Data Entry

Data will be recorded using the EDC system as the study is in progress. All delegated site personnel will log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

11.2.4 Medical Information Coding

The following dictionaries will be used for coding medical information:

- Medical Dictionary for Regulatory Activities (latest) for AEs/ADEs and medical history

- WHO Drug Dictionary for prior and concomitant medications

11.2.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to ensure accurate, consistent, and reliable data. Data identified as erroneous or missing will be referred to the investigative site for resolution through data queries.

The eCRFs will be reviewed and electronically signed by the Investigator.

11.3 Record Keeping

Records of participants, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.4 End of Study

The end of the study (study completion) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last participant in the study.

12.0 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible. This study will be conducted in compliance with the protocol and with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) guidelines for GCP, and applicable regional regulations.

12.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (ie, Medpace) to ensure the IRB/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of participants. The study will only be conducted at sites where written IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, Informed Consent Form (ICF), advertisements (if applicable), written information given to the participants, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of participants in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for participant recruitment, and any other written information regarding this study to be provided to a participant or participant's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

12.3 Informed Consent Procedures

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor/designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation, and that participants have sufficient opportunity to have all questions answered in a suitable facility. The Investigator must ensure that the participant has been informed of his/her rights to privacy and his/her rights and guarantees regarding his/her protection, in particular the right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification. The Investigator will obtain written informed consent from

each participant before any study-specific activity is performed, unless the activity is part of standard of care for the participant and/or indication, and should document in the source that consent was obtained prior to enrollment in the study.

Participants must be able to understand, provide, and sign the written informed consent. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies.

A copy of the signed ICF will be given to the participant.

12.4 Future Use of Biological Samples

In order to be able to address future scientific questions, participants will be asked to voluntarily donate optional biospecimens for banking. If the participant agrees, banked samples may be used for future non-pharmacogenetic research and drug development projects, eg, to identify participants who are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects.

Participation in biobanking is voluntary and not a prerequisite for participation in the study. Biobanking will only occur after informed consent has been given in accordance with local ethical and regulatory requirements.

Serum and plasma samples for future research studies may be stored for participants who have consented. It is the responsibility of the Investigator or designee (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to have his/her samples stored for future research in a contract laboratory facility under the responsibility of the Sponsor and its potential partners after adequate explanation of the aims, methods, objectives, and potential hazards. Participants must receive an explanation that they are completely free to refuse long-term storage of their samples for future research and may withdraw consent at any time and for any reason during the storage period of the specimen(s), and that refusal of long-term storage does not preclude participation in the study.

Participant samples and information will be stored in a secure storage area and will be identified only by a coded participant identification number. Participant samples will be kept for a maximum of 5 years, after which the samples will be destroyed according to the standard procedures of the laboratory.

At any time, if informed consent is withdrawn, no new data will be added to the study database. Data already obtained from the samples will continue to be kept and used. Participants have the right to request their identifiable samples be destroyed at any time and to be informed of any plans for new analyses on the retained samples.

Measures are in place to comply with the applicable rules for the collection, biobanking, and future use of biological samples and clinical data, including the following:

- Sample and data usage must be in accordance with the ICF.
- The facilities storing biological samples from clinical study participants are qualified for the storage of biological samples collected in clinical studies.
- An appropriate sample and data management system is in place, including audit trails for clinical data and/or samples, and the ability to identify and destroy such samples according to ICF.
- Data and/or samples may be transferred to third parties and other countries as specified in the ICF.

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the enrollment of any participant in this study, the Sponsor/designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor/designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. Study monitoring may include onsite, remote, or a combination of both onsite and remote monitoring. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site designee, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor/designee, applicable foreign health authorities, and the IRB/IEC, as appropriate. Participants or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Participant medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating participants (sufficient information to link records, such as eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator or institution, or to the Sponsor.

12.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for 1 year after the completion of the study.

13.0 STUDY ADMINISTRATIVE INFORMATION

Any Amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC and applicable competent authorities, unless immediate implementation of the change is necessary for participant safety. In this case, the situation must be documented and reported to the IRB/IEC and applicable competent authorities within 5 working days.

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Appendix A. Schedule of Assessments

Table 7. Schedule of Assessments

	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	

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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											

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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; [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 B. Clinical Laboratory Analytes

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.