COVANCE

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Lexicon Pharmaceuticals, Inc.

Protocol No.: LX4211.1-312-T1DM

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Net Clinical Benefit of Sotagliflozin as Adjunct to Insulin Therapy in Type 1 Diabetes

Covance Study ID: 000000145143

STATISTICAL ANALYSIS PLAN

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APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

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[redacted] 25 MAR 2017
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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
A1C	hemoglobin A1C
ACR	albumin:creatinine ratio
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BHB	beta-hydroxy butyrate
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CCR	calcium:creatinine ratio
CEC	Clinical Endpoint Committee
CI	confidence interval
CL	confidence limit
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CSII	continuous subcutaneous insulin infusion
CV	Cardiovascular
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOSI	event(s) of special interest
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCR	glucose:creatinine ratio
GFR	glomerular filtration
GLM	generalized linear model
HDL-C	high-density lipoprotein cholesterol
IXRS	Interactive Voice/Web Response System
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LS means	least squares means
MACE	major adverse cardiovascular event

Abbreviation	Term
MAR	missing at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-treat
MMRM	mixed-effects model for repeated measurements
NRI	non-responder imputation
OC	observed cases
PP	Per-protocol
PT	preferred term
PSDD-NRS	Patient Satiety Daily Diary-Numeric Rating Scale
ROC	receiver operating characteristic
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SH	severe hypoglycemia
SMBG	self-monitoring of blood glucose
SOC	System Organ Class
T1D	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
ULN	upper limit of the normal reference range

1 SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	16 October 2015	Amendment 1
Electronic Case Report Form (eCRF)	18 September 2015	Version 1.0

2 PROTOCOL DETAILS

2.1 Study Objectives

2.1.1 Study Objectives

2.1.1.1 Primary Objective

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo in the proportion of patients with glycosylated hemoglobin A1C (A1C) <7.0% at Week 24 and no episode of severe hypoglycemia (SH) and no episode of diabetic ketoacidosis (DKA) after randomization.

2.1.1.2 Secondary Objectives

Secondary objectives of this study are to evaluate the change from Baseline of sotagliflozin versus placebo in a hierarchical order on the following:

- A1C
- Body weight
- Systolic blood pressure (SBP)
- Bolus insulin dose

2.1.1.3 Other Objectives

Other objectives of this study are:

To compare changes in several parameters in response to sotagliflozin versus placebo, as assessed by evaluations with specified cut points, and at specified time intervals during the 24-week Double-blind Treatment Period including:

- Parameters assessed as secondary objectives (A1C, body weight, SBP, bolus insulin dose)
- Proportion of patients with A1C reduction ≥0.4% and no increase in body weight
- Proportion of patients with A1C reduction ≥0.5% and no episode of SH
- Proportion of patients meeting success criteria for A1C and insulin
- Fasting plasma glucose (FPG)
- Total and basal (or non-bolus) insulin dose
- Diastolic blood pressure (DBP)
- Hypoglycemic events
- Measures of kidney function
- Patient-reported satiety (substudy)
- Safety of sotagliflozin 400 mg versus placebo

2.2 Overall Study Design

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Adult patients with type 1 diabetes mellitus (T1D) and body mass index (BMI) ≥18.5 kg/m^2 with inadequate glycemic control with insulin therapy (administered by subcutaneous injections or continuous subcutaneous insulin infusion [CSII]) are eligible for enrollment in this study if they meet all inclusion and no exclusion criteria.

A total of 1400 patients will be randomly assigned 1:1 between the following 2 treatment groups, stratified by BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), Week -2 A1C (≤9%, >9%) and use of CSII at Screening (Yes, No):

- Sotagliflozin 400 mg as two (2) 200-mg tablets, once daily, before the first meal of the day
- Placebo as two (2) placebo tablets (identical to sotagliflozin in appearance), once daily, before the first meal of the day

Patients will continue treatment with insulin(s) or insulin analog(s) during the study.

During the study, self-monitored blood glucose (SMBG) values will be reviewed by the Investigator and insulin doses will be adjusted if the SMBG trends do not meet standard of care T1D target goals. Suggested insulin titration algorithms are provided in the Site File Notebook. These algorithms may be modified based on the Investigator's clinical assessment.

Patients will participate in the study for approximately 32 weeks. The study includes a Screening Period of up to 2 weeks, followed by a 2-week single-blind placebo Run-in Period, a 24-week Double-blind Treatment Period, and a 30-day Follow-up Period.

Efficacy and safety assessments will be performed according to the study schedule.

This study will also include a substudy designed to evaluate satiety (appetite) in a subset of enrolled patients. Up to 280 patients (140 per treatment group) will be recruited for this substudy.

The study design is summarized in Figure 2.2-1.

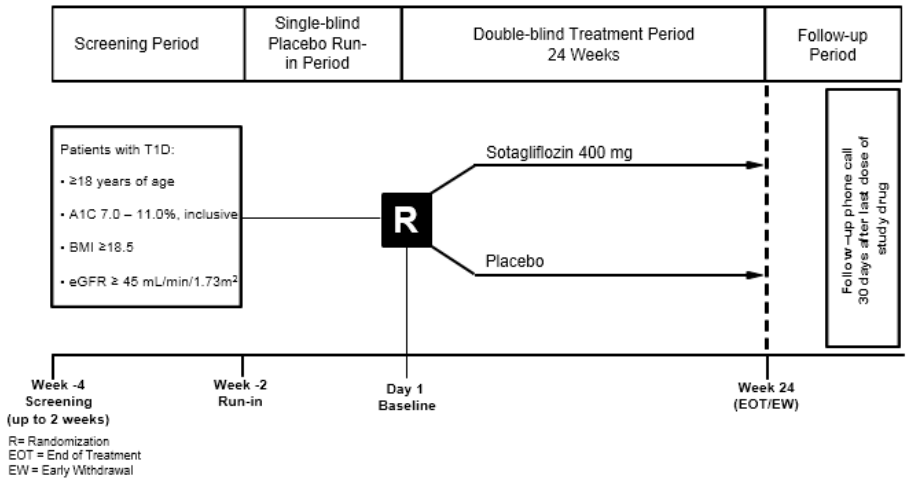

Figure 2.2-1 Study Schema

Adjudication of all deaths, event(s) of special interest (EOSIs), including major adverse cardiovascular events (MACE)/selected cardiovascular (CV) events, clinical or laboratory findings associated with drug-induced liver injury (DILI), DKA (including metabolic acidosis), and SH episodes (as well as hypoglycemia reported as a serious adverse event [SAE]) will be performed in a blinded manner by independent Clinical Endpoint Committee(s) (CEC[s]) composed of the appropriate experts. Details will be provided in the CEC(s) Charter(s).

An independent Data Monitoring Committee (DMC) will meet on a regular basis to review accumulating clinical safety data. Details will be provided in the DMC Charter.

2.3 Sample Size and Power

The sample size will be based on satisfying design assumptions made for the primary efficacy endpoint. The primary efficacy endpoint is a binomial proportion, a composite measure of glycemic control and safety. We have assumed that the majority of treatment effect will be observed in the glycemic control portion of the endpoint and for planning purposes, the rates of SH and DKA will be equal in both treatment groups. Little data are available to estimate the <7% A1C component of the endpoint in this patient population. Data reviewed from the LX4211.1-202 Phase 2 trial in type 2 diabetes mellitus (T2DM) and from other pertinent literature sources suggests that a difference between treatment groups of at least 0.15 may be expected for this variable. We will assume this effect size for the primary endpoint, but will perform an adjustment for the expected proportion of patients not having a DKA or SH event. A conservative assumption is made that the rates of DKA and SH are independent and their union is estimated to be ≤0.15. It is expected that 0.85 of the patients will not have a DKA or a severe hypoglycemic event over the course of the study. Adjusting the 0.15 effect size estimate by this value yields a target effect size for the primary endpoint ≈0.12. Since the underlying placebo rate is unknown for the composite outcome, we will assume a maximum variance construct under the alternative hypothesis for binomial proportions to estimate the sample size (ie, the mean of the pooled responses rates is 0.50). Assuming a 2-sided test with $\alpha = 0.05$ and 90% power, 380 patients are needed per treatment group to detect a difference in binomial proportions of at least 0.12 for the primary endpoint. The sample size estimate will be adjusted for dropouts in a manner to reflect that the primary analysis will be conducted in the modified Intent-to-Treat (mITT) patients. Dropouts are expected to be primarily a function of noncompliance: patients stopping early their randomized treatment, but followed to the 24-week visit. It is further assumed that the dropped (noncompliant) sotagliflozin patients will respond as the placebo patients and that there will be no drop-in patients in the placebo group. These assumptions net an adjusted effect size for detection of 0.12 x (1-0.20) ≈ 0.10, where the dropout rate over 24 weeks is assumed to be 20%. Based on this adjusted effect size, 544 patients are required per treatment group, for a total of 1088 patients across the 2 treatment groups.

The occurrence of SH is an important safety component of the primary endpoint. It is desirable that the study sample includes enough patients so that a reliable estimate of a treatment difference can be obtained for this outcome. Based on a literature review, it seems reasonable to assume that the rate of SH, defined as the number of patients experiencing at least 1 such episode divided by the number of mITT patients (ie, a binomial proportion), is ≤0.10 over a 24-week period. We will assume this rate is the same in both treatment groups, yielding an expected difference of 0.0. A 2-sided, 95% confidence interval (CI) based on normal approximation methods and corrected for continuity is associated with a distance value (ω) of 0.033 for a sample size of 700 patients per group; ω is the extended distance from the observed difference in one or both directions. The upper bound of this CI will exclude values greater than 0.05; ie, a 50% increase in the expected placebo rate.

Based on the considerations mentioned above, a sample size of 700 patients per treatment group (1400 total patients) seems to be an appropriate target for the study.

For the satiety substudy, assuming a dropout rate of 20% over the course of the study, a sample size of approximately 224 patients (112 per treatment group) demonstrating a change greater than 30% would be necessary to obtain statistical power at the recommended 80% level ($\alpha = 0.05$). To achieve this number of patients for evaluation, 280 patients will be recruited to participate in the substudy.

3 EFFICACY AND SAFETY VARIABLES

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

The primary endpoint is to demonstrate the superiority of sotagliflozin 400 mg versus placebo in the proportion of patients with A1C <7.0% at Week 24 and no episode of SH and no episode of DKA after randomization when used as an adjunct in normal weight and overweight/obese adult patients with T1D who have inadequate glycemic control with insulin therapy.

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are to be measured as change from Baseline in sotagliflozin 400 mg compared to placebo for each of the following listed below:

- A1C at Week 24
- Body weight at Week 24 (absolute and percent changes)
- SBP at Week 16 in the subset of patients with Baseline SBP ≥130 mm Hg
- Bolus insulin dose at Week 24 (as an average over the 3-5 days prior to the visit)

3.1.3 Other Efficacy Endpoints

Other efficacy endpoints are:

- Secondary endpoints (A1C, body weight, SBP, bolus insulin dose) assessed at specified cut points and specified time intervals during the 24-week Double-blind Treatment Period
    - Changes from Baseline in the secondary endpoints by visit
    - Categories of A1C decrease from Baseline by study visit based on the following cut points:
        - ≥0.5% absolute in the subset of patients with Baseline A1C ≤9.0%
        - ≥1.0% absolute in the subset of patients with Baseline A1C ≤9.0%
        - ≥0.5% absolute in the subset of patients with Baseline A1C >9.0%
        - ≥1.0% absolute in the subset of patients with Baseline A1C >9.0%
        - ≥0.5% absolute or >10% in the subset of patients with Baseline A1C ≤9.0%
        - ≥1.0% absolute or >10% in the subset of patients with Baseline A1C ≤9.0%
        - ≥0.5% absolute or >10% in the subset of patients with Baseline A1C >9.0%
        - ≥1.0% absolute or >10% in the subset of patients with Baseline A1C >9.0%

  - Categories of Body weight percent decrease from Baseline by study visit based on the following cut points: ≥2%, ≥5%, and ≥10%
  - Categories of SBP, together with DBP, by study visit based on the following cut points:
    - SBP <140 and DBP <90 in the subset of patients with Baseline SBP ≥140 or DBP ≥90
    - SBP <130 and DBP <80 in the subset of patients with Baseline SBP ≥130 or DBP ≥80
  - Note: There are no cut points for bolus insulin dose other than the one already defined in the endpoint of "Proportion of patients meeting success criteria for A1C and insulin" below.
- Proportion of patients with A1C reduction ≥0.4% and no increase in body weight
- Proportion of patients with A1C reduction ≥0.5% and no episode of SH
- Proportion of patients meeting success criteria for A1C and insulin
  - Proportion of patients with decrease from Baseline in mean daily bolus insulin dose of >20% and a decrease from Baseline in A1C of >0.3%. Mean daily bolus insulin dose is defined as the mean bolus insulin dose as calculated based on results of at least 3 days of data during the preceding 3-5 days (consecutive or non-consecutive) prior to the clinic visit
- FPG
- Total and basal (or non-bolus) insulin dose
  - Mean total daily insulin dose by visit (as an average over the 3-5 days prior to the visit)
  - Mean daily basal (or non-bolus) insulin dose by visit (as an average over the 3-5 days prior to the visit)
- DBP
- Hypoglycemic events calculated as a daily average over the week prior to the visit for:
  - Hypoglycemic events/patient/day (≤70 mg/dL) by SMBG
  - Hypoglycemic events/patient/day (≤55 mg/dL) by SMBG
- Measures of kidney function:
  - Urine albumin: creatinine ratio (ACR), calcium: creatinine ratio (CCR), and glucose: creatinine ratio (GCR)
  - Serum creatinine
  - Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR)
- Proportion of patients with satiety increase ≥30% as measured by the Patient Satiety Daily Diary-Numeric Rating Scale (PSDD-NRS) (substudy)
- Change from Baseline in patient-reported satiety as measured by the PSDD-NRS (substudy)

3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of treatment-emergent adverse events (TEAEs), suspected adverse reactions, adverse events (AEs), AEs leading to discontinuation from the study drug or study, SAEs, and deaths
- Change from Baseline in clinical laboratory results, physical examination results, and vital signs
- EOSIs

4 ANALYSIS POPULATIONS

Unless otherwise specified, all efficacy analyses will be performed on the mITT population. Analysis of the primary endpoint will also be performed on the Per-protocol (PP) population. All safety analyses will be performed on the Safety population.

4.1 Randomized Population

All randomly assigned patients will be included in the Randomized population. Randomized patients are analyzed according to their randomized treatment.

4.2 Safety Population

All randomly assigned patients treated with at least 1 dose of study drug will be included in the Safety population. Safety patients are analyzed according to their actual treatment received on Day 1.

4.3 Modified Intent-to-treat Population

The mITT population will consist of all randomly assigned patients who have taken at least 1 dose of study drug. Patients in the mITT population will be analyzed according to their randomized treatment.

4.4 Per-protocol Population

The PP population will consist of all patients in the mITT population who completed treatment through the primary assessment of 24 weeks, and do not have any significant protocol deviations during Double-blind Treatment Period.

Significant protocol deviations are defined as those deviations considered having a major effect on the collection or interpretation of the primary efficacy endpoint. Section 4.4.1 details the classification of deviations.

4.4.1 Important Protocol Violations/Deviations Leading to Exclusion from the PP Population Analysis

Only those violations/deviations considered to have a major effect on efficacy will lead to complete exclusion of the patients from the PP population. For the purposes of this study, the following criteria have been identified as important protocol violations/deviations as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint.

Type	Deviation	Method of Identification
Prohibited Medications	Patients who took medications that were not permitted during the Double-blind Treatment Period	**Manual** review of blinded concomitant medications listing. Covance will provide the medical monitor with the list of concomitant medications taken by patients. The medical monitor will review this list and note any prohibited medications. Patients who took prohibited medications for a significant duration during the Double-blind Treatment Period may be excluded from the PP population.
Noncompliance During 24-week Double-blind Treatment Period	Patients who had low study drug compliance; (eg, repeated occurrence of compliance <80%)	**Programmatic** check and manual review based on the exposure and drug accountability data.
Errors in Treatment Allocation	Patients who received a wrong treatment at 1 or more study visits due to packaging or dispensing errors during the Double-blind Treatment Period	**Programmatic** check based on unblinded Interactive Voice/Web Response System (IXRS) database after the study is unblinded. The check will be done by comparing the bottle number that IXRS had assigned to the patient/visit against the bottle number actually used.
Clinical Trial Management System	Covance Clinical will provide the list of protocol deviations based on the clinical monitoring.	**Manual** review: This list will be reviewed and the important protocol deviations leading to exclusion from the PP population will be identified.

As defined in the table, the majority of the protocol deviations will be determined programmatically from the data. Those criteria that require clinical interpretation will be reviewed prior to database lock, following discussion with the medical monitor and Sponsor.

All important protocol deviations occurring during the study will be reviewed and approved by the Sponsor prior to database lock and unblinding. Should other categories of important protocol deviations be identified during the study (and prior to unblinding), but not anticipated at the time of preparing this SAP, they will be provided in a separate document and included in all relevant protocol deviation reviews and approvals.

4.5 Satiety Substudy Population

The Satiety substudy population will consist of all patients in the mITT population who have elected to participate in the satiety substudy and completed ≥8 satiety daily diaries during the single-blind placebo Run-in Period. Identification of all patients in the satiety substudy population will be determined before database lock and unblinding.

5 DATA HANDLING

5.1 Time Points and Visit Windows

Day 1, defined as the Baseline/Randomization visit, is also the first day that study treatment is planned to be started. Should study treatment start at a later date, Day 1 will be defined as the date that study treatment is initiated. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1; there is no Day 0.

The following visit windows defined in Table 5.1-1 will be used for the by-visit analyses of the primary endpoint, the secondary and other endpoints. All other analyses will use the nominal study visit as defined in the Study Schedule and eCRF.

In general, the Baseline value for a variable is defined as the last value collected or taken on or before Day 1, prior to the first dose of double-blind study drug. In cases where there are multiple such values, the non-missing value closest to the start of study treatment is selected. If time is available for an assessment on Day 1, it will be compared with dosing time on Day 1 to define the Baseline value.

If there are multiple visits (scheduled or unscheduled) within a visit window, the measurement closest to the target day of the visit will be used in the analysis. If the measurements are equally distant to the target day, then the later one will be used in the analysis. An exception to these rules applies to the variable hypoglycemic events per patient per day by SMBG, where a scheduled visit takes precedence over an unscheduled visit. Hypoglycemic events by SMBG are based on the data entered in a patient's study diary, and hence, it is more appropriate to choose the scheduled visit when a patient would typically return the diary to the site over an unscheduled visit.

Table 5.1-1 Definition of Visit Windows

Visit	Target Day of Visit[a]	A1C, Insulin, Hypoglycemic Events per Day by SMBG, Body Weight, Vital Signs, FPG, Serum Chemistry, Beta-hydroxy Butyrate (BHB)	Urinalysis, Urine Albumin, Urine Calcium, Urine Glucose, Urine Creatinine, PSDD-NRS[b]	Fasting Lipid Profile, Hematology
1 Baseline[c]	1	≤1	≤1	≤1
2 Week 4	29	2-43	--	--
3 Week 8	57	44-85	--	2-113
4 Week 16	113	86-141	--	--
5 Week 24	169	≥142	≥2	≥114

(a) Relative to the date of Baseline/Randomization visit (Day 1)
(b) For Satiety substudy population only.
(c) If time is available for an assessment on Day 1, it will be compared with dosing time on Day 1 to define Baseline value.

5.2 Handling of Dropouts or Missing Data

Missing data will not be imputed for safety analyses. The safety evaluations will be performed on observed data only.

For AEs with partial or missing onset or stop dates:

AE stop date will be imputed first as:

- If stop date is completely missing, assume it is ongoing (no imputation);
- For a partial AE stop date (day is missing, or both day and month are missing): December 31st, or last day of the month.

Then AE onset date will be imputed as:

- If onset date is completely missing: the first dose date;
- For a partial AE onset date (day is missing, or both day and month are missing):
    - Partial date < the first dose date: December 31st, or last day of the month
    - Partial date = the first dose date: the first dose date
    - Partial date > the first dose date: January 1st, or first day of the month

If the imputed AE onset date is after the AE stop date/imputed AE stop date, then the onset date will be set to the AE stop date/imputed AE stop date.

The imputed dates will not be listed. Study day relative to the first dose of double-blind study drug associated with missing or partial dates will not be displayed in AE listings.

In the event that a partial date (month/year or year) for concomitant medication is available, this information will be used as follows:

- When both month and year are available – first day of the month will be used for start date and the last day of the month will be used for the stop date.
- When only year is available – January 1st will be used for the start date and December 31th will be used for the stop date.

The imputed dates will only be used to determine whether a concomitant medication will be classified as prior medication or concomitant medication.

5.2.1 Non-responder Imputation

In the analysis of binary efficacy endpoints at Week 24, including the primary efficacy endpoint (ie, A1C <7.0% at Week 24 and no episode of SH and no episode of DKA after randomization), missing observations at Week 24 will be imputed as non-responders. This approach corresponds to non-responder imputation (NRI).

5.2.2 Observed Cases Datasets

Mixed-effects model for repeated measurements (MMRM) will be performed based on a missing at random (MAR) assumption using data actually observed - Observed Cases (OC) dataset. OC datasets will be used for analysis of all secondary efficacy endpoints and the other efficacy endpoints that are continuous. OC datasets will not impute any values for missing observations.

In the analysis of binary efficacy endpoints at study weeks other than Week 24, missing observations will not be imputed.

6 STATISTICAL METHODS

6.1 General Principles

All data processing, summarization, and analyses will be performed using the Hosted SAS Environment / Version 9.3 (or later) of the SAS® (SAS Institute, Cary, NC) statistical software package.

Unless specified otherwise, data will be displayed using the following treatment group labels, in the order presented:

- Placebo
- LX4211 400 mg
- Total (if applicable)

Sotagliflozin will be referred to as "LX4211" in all data displays. LX4211 is also the term used in the remaining sections of this SAP.

All data collected will be presented in listings by treatment group, center, patient, and visit (where applicable), unless otherwise specified.

Data will be presented in summary tables by treatment group, assessment, and visit (where applicable). The category "Missing" will be presented if the number missing is greater than zero for at least 1 treatment group.

Descriptive summary statistics for continuous variables will include the number of observations (N), mean, standard deviation (SD), median, minimum, and maximum.

Descriptive summary statistics for categorical variables will include frequency counts and percentages [n (%)]. Unless stated otherwise in the table shells, the denominator for percentage calculations will be the number of patients in the pertinent analysis population.

Dates will be displayed as DDMMMYYYY.

For continuous efficacy variables that are derived as percentage change from Baseline outcomes, the applied analyses and their results will be used for descriptive purposes. Exceptions to this statement are the secondary efficacy endpoints of percent change from Baseline at Week 24 in body weight and bolus insulin dose, and the other efficacy endpoints of percent change from Baseline by study visit in body weight, bolus insulin dose, total insulin dose, and basal (or non-bolus) insulin dose, where both descriptive and inferential summaries will be provided.

Analysis and summarization of treatment group comparisons for the primary and secondary efficacy endpoints will be reported in their original measurement units and converted values to accommodate regulatory review by Food and Drug Administration (FDA) and external authorities, where appropriate.

All significance tests will be 2-sided and use a 0.05 α-level unless specified otherwise.

6.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and total, and will include the number and percentage of patients:

- Screened
- Did Not Enter Single-blind Placebo Run-in Phase
- Entered Single-blind Placebo Run-in Phase
- Discontinued Single-blind Placebo Run-in Phase
- Randomized
- Treated
- Completed Study
- Discontinued Study
- Included in each study population (Randomized, mITT, Safety, PP, Satiety substudy)

The number and percentage of patients who complete the study and those who discontinue early (including a breakdown of the primary reasons for discontinuation) will be presented for the patients randomized in each treatment group.

A summary of patient enrollment by center will be provided by treatment group and overall. A summary of patient counts by randomization strata (BMI, A1C, CSII) will also be provided by treatment group.

6.3 Protocol Violations/Deviations

All important protocol deviations leading to exclusion from the PP population will be listed and summarized by treatment group for the mITT population.

The deviations will be identified before data are unblinded.

6.4 Demographics and Other Baseline Characteristics

Demographic and Baseline characteristics will be listed and summarized by treatment group and overall for the mITT population and the Satiety substudy population. Standard descriptive statistics will be presented for the continuous variables of:

- Age at study entry (years)
- Age at diagnosis (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Duration of diabetes (years)
- Daily insulin dose (units/day) as total, basal (or non-bolus), and bolus
- Total daily insulin (units/kg)
- Ratio of bolus to total insulin dose
- Sitting SBP (mm Hg)
- Sitting DBP (mm Hg)
- Pulse rate (bpm)

Counts and percentages of patients will be presented for the categorical variables of:

- Age at diagnosis (<18 years, ≥18 years)
- Age at study entry (<75 years, ≥75 years)
- Sex
- Circumcision status, if male

- Childbearing potential, if female
- Race
- Ethnicity
- Tobacco use history
- BMI categories (<25 kg/m^2, ≥25 kg/m^2) (randomization strata)
- Use of CSII (Yes, No) (randomization strata)
- A1C categories (≤9%, >9%) (randomization strata)

Baseline laboratory characteristics for a select number of tests will also be summarized by treatment group and overall for the mITT population. Standard descriptive statistics will be presented for the following laboratory tests:

- A1C (%) and A1C (mmol/mol)
- Estimated average glucose level (mg/dL)
- FPG (mg/dL)
- BHB (mmol/L)
- eGFR (MDRD) (mL/min/1.73 m^2) and categories (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2)
- Serum sodium (mEq/L)
- Serum potassium (mEq/L)
- Serum blood urea nitrogen (BUN) (mg/dL)
- Serum creatinine (mg/dL)
- Serum calcium (mg/dL)
- Serum phosphorous (mg/dL)
- Serum magnesium (mEq/L)
- Low-density lipoprotein cholesterol (LDL-C) (mg/dL)
- High-density lipoprotein cholesterol (HDL-C) (mg/dL)
- Non HDL-C (mg/dL)
- Triglycerides (mg/dL)
- Hematocrit (%)
- Hemoglobin (g/dL)
- Urine ACR
- Urine GCR
- Urine CCR

The estimated average glucose level will be calculated according to the method of Nathan et al[1] as (28.7 x Baseline value of A1C minus 46.7). Non-HDL-C will also be summarized and will be defined as the difference between the total cholesterol and HDL-C. Non-HDL-C includes all cholesterol present in lipoprotein particles that is considered atherogenic.

A summary of Baseline physical examination data will be presented by treatment group and overall for the mITT population.

No formal tests of statistical significance will be performed on the demographic and Baseline data.

6.5 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1 (or a later version if updated during the study). All medical history data will be listed, and the

number and percentage of patients with any medical history will be summarized for the mITT patients by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall.

6.6 Prior and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Covance using the WHO Drug Dictionary, version March 2015 (or a later version if updated during the study).

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to the first dose date of double-blind treatment.
- Concomitant medications are those with a start date on or after the first dose date of double-blind treatment, or those with a start date before the first dose date of double-blind treatment and a stop date on or after the first dose date of double-blind treatment.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications, prohibited concomitant medications taken during the Double-blind Treatment Period, concomitant medications taken during the Double-blind Treatment Period (excluding prohibited concomitant medications), and concomitant medications started during the Follow-up Period will be listed together and summarized separately for the mITT population. In addition, prohibited medications taken during Double-blind Treatment Period will be presented in a data listing.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least 1 medication within each therapeutic class (Anatomical Therapeutic Chemical [ATC]-Level 2), chemical subgroup (ATC-Level 4), and generic term.

6.7 Treatment Compliance and Exposure

Duration of exposure to double-blind medication will be defined as:

- (Date of last dose – Date of first dose) + 1

Treatment duration (days) will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment group for the Safety population.

Treatment duration will also be summarized by duration categories in days:

- <28 days
- ≥28 and <56 days
- ≥56 and <112 days
- ≥112 and <168 days
- ≥168 days

Percentage compliance is calculated as:

100 x (number of actual tablets taken/number of expected tablets taken),

where the number of actual tablets taken will be defined as the number of tablets dispensed minus the number of tablets returned. The number of tablets expected to be taken will be defined as 2 times the numbers of days in treatment period. When a bottle of study drug is not returned at a visit as expected, it

will be assumed that the number of tablets taken from that bottle is 0. Compliance will not be calculated for a patient if the patient does not return any bottles at all across all visits.

Percentage compliance will be summarized descriptively by treatment group for the Safety population.

The number and percentage of compliant patients will be presented for the Safety population, where compliant will be defined as percentage compliance between 80.0% and 120.0% inclusive. The following percentage compliance categories will also be presented:

- <80.0%
- ≥80.0% and ≤120.0%
- >120.0%

6.8 Efficacy

For binary efficacy endpoints estimated as binomial proportions, the frequency and percentage of patients achieving the outcome will be presented by treatment group at each assessed study week. The primary analysis of these endpoints will use a Cochran-Mantel-Haenszel (CMH) test stratified by the different levels of the randomization stratification factors of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), Week -2 A1C (≤9%, >9%), and use of CSII at Screening (Yes, No). The treatment group comparisons will be performed at Week 24 only. At other assessed study weeks, only descriptive statistics will be used to summarize the data. Point estimates of treatment effect and 2-sided 95% confidence limits (CLs) of the treatment effect (ie, LX4211 minus placebo) will be calculated at Week 24. The 95% CLs will be based on normal approximation methods using a continuity correction factor. Missing observations at Week 24 will be imputed as non-responders (ie, NRI); only the observed data will be summarized at the earlier study weeks. Endpoints comprised of multiple outcomes will use descriptive methods to summarize each component by treatment group at each study week.

Primary analysis of the continuous efficacy endpoints will use MMRM statistics based on the restricted maximum likelihood method for estimation. The analysis model will include treatment, randomization strata of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), randomization strata of Week -2 A1C (≤9%, >9%), randomization strata of use of CSII at Screening (Yes, No), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline dependent variable-by-time interaction as a covariate. For the endpoint of percent change from Baseline, the analysis model will not include the interaction covariate. An unstructured (co)variance structure will be used to model the within-patient errors. Other structures will be explored by use of Akaike's information criteria should the unstructured (co)variance structure not result in model convergence. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The adjusted mean change from Baseline by each study week for each treatment group will be estimated in the framework of this model, as well as the between-group differences (comparing LX4211 to placebo) and the 95% CLs for the adjusted mean. All post-Baseline observations collected at scheduled visits will be used in the MMRM, including data collected after the discontinuation of study drug. An analysis of covariance (ANCOVA) will be applied where only 1 post-Baseline scheduled visit occurs; ie, the MMRM analysis omitting the time-related effects.

Summarization of the inferential statistics will include the Least Squares means (LS means), standard error (SE) of the estimates, p-values, and 2-sided CLs. These statistics will be provided for the within treatment group changes from Baseline and for the comparison of LX4211 versus placebo for the change from Baseline scores.

The test for superiority of LX4211 versus placebo based on the primary efficacy endpoint will be performed at the 2-sided 0.05 α-level. If this null hypothesis is rejected, a sequential procedure will be used to maintain the overall Type I error rate at a 2-sided, 0.05 α-level across analyses of the secondary endpoints at Week 24. The secondary endpoints will be specified in a hierarchy and the first listed will be tested at the same Type I error used for the primary endpoint comparison ($\alpha = 0.05$). If this test rejects the null hypothesis, then the next listed secondary endpoint will be tested at the same Type I error rate. This testing sequence will continue as long as a null hypothesis is rejected at the 0.05 α-level. The testing sequence will be broken at the first instance that a null hypothesis is not rejected. Once the sequence is broken, no later hypothesis in the hierarchy will be tested. The order of testing for the secondary endpoints will be:

- A1C change from Baseline at Week 24
- Body weight at Week 24 change from Baseline (absolute and percent change; the absolute change will be used in the sequence of analyses)
- SBP change from Baseline at Week 16 in the subset of patients with Baseline SBP ≥130 mm Hg
- Percent change from Baseline in bolus insulin dose at Week 24

6.8.1 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of patients with A1C <7.0% at Week 24 and no episode of SH and no episode of DKA from randomization to Week 24. The analysis of this endpoint will be based upon the mITT population. The frequency and percentage of patients with A1C <7.0% at Week 24 and no episode of SH or episode of DKA from randomization to Week 24 will be presented by treatment group. For this endpoint, only positively adjudicated SH and DKA events will be assessed over the cumulative randomized 24-week Double-blind Treatment Period. The cut-off dates for the inclusion of SH and DKA events, along with other EOSIs, are described in detail in Section 6.9.2. In brief, the cut-off date is the date of the last dose of double-blind study drug for SH events and 30 days after the date of the last dose of study drug for DKA.

Analysis of the primary efficacy endpoint at Week 24 will be performed using the CMH test and 95% CLs based on normal approximation methods with a continuity correction factor, as described in Section 6.8 for binary efficacy endpoints. The individual components of the endpoint will be summarized separately using descriptive methods. Each of these components will be expressed as a binomial proportion: proportion of patients with A1C <7.0% at Week 24, proportion of patients with no episodes of DKA from randomization to Week 24, and proportion of patients with no episodes of SH from randomization to Week 24.

Bar charts displaying proportions of patients with A1C <7.0% at Week 24 and no episode of SH or episode of DKA will be presented from randomization to Week 24 by treatment groups.

6.8.2 Sensitivity Analysis

Analysis of the primary efficacy endpoint, as described in Section 6.8.1, will also be performed on the PP population as a sensitivity analysis.

Sensitivity analysis of the primary efficacy endpoint will be performed by applying the patient's date of the last dose of double-blind study drug as the cut-off for inclusion of SH and DKA events in the analysis.

Another analysis will be performed by applying 30 days after the patient's date of the last dose of double-blind study drug as the cut-off for inclusion of SH and DKA events in the analysis.

6.8.3 Secondary Efficacy Analysis

Analysis of the secondary efficacy endpoints will be based on the mITT population. Descriptive statistics for secondary efficacy endpoints will be presented by treatment group and by study visit where appropriate. All post-Baseline data will be used in the analyses where inferential statistics are presented, including observations occurring after discontinuation of study drug. The secondary efficacy endpoints are to be measured as change from Baseline in LX4211 400 mg compared to placebo for each of the following sections and will be analyzed using MMRM model as specified for continuous efficacy endpoints in Section 6.8.

Figures displaying mean change from Baseline by visit and LS mean change at Week 24 will be presented by treatment groups.

6.8.3.1 Change from Baseline in A1C at Week 24

Descriptive statistics of A1C at each visit, the change from Screening to Baseline in A1C, and the change from Baseline in A1C at post-Baseline visits will be presented by treatment group and visit. The treatment effects at Week 24 will be evaluated using MMRM statistics with the change from Baseline as the endpoint and Baseline A1C -by-time interaction as a covariate.

6.8.3.2 Body Weight at Week 24 (Absolute and Percent Change)

Body weight and change from Baseline in body weight at each visit will be summarized by treatment group using standard descriptive statistics. The treatment effects at Week 24 will be evaluated using MMRM statistics with absolute change from Baseline as the endpoint and Baseline body weight-by-time interaction as a covariate. Inferential statistics will be based on the absolute change from Baseline in body weight.

Similarly, percent change from Baseline in body weight will be analyzed using MMRM statistics with percent change from Baseline as the endpoint and with no covariate.

6.8.3.3 Change from Baseline in SBP at Week 16 in the Subset of Patients with Baseline SBP ≥130 mm Hg

SBP and change from Baseline in SBP at each visit will be summarized by treatment group using standard descriptive statistics. Change from Baseline in SBP at Week 16 in the subset of patients with Baseline SBP ⩾130 mm Hg will be analyzed using MMRM statistics with change from Baseline as the endpoint and Baseline SBP -by-time interaction as a covariate. Descriptive statistics and tests for group differences will be provided for Week 16 and other visits as well.

6.8.3.4 Change from Baseline in Bolus Insulin Dose at Week 24 (as An Average Over The 3-5 Days Prior to The Visit)

For each day with complete insulin data, the daily bolus (for all patients, for patients on pre-mixed insulin, the bolus is defined as the rapid acting component; eg, a patient receiving a daily total of 50 IU of Novolin® 70/30 insulin, 15 units (0.3 x 50) is assessed as the "daily bolus" insulin), daily basal (for

patients using insulin pumps and patients using subcutaneous injections), daily non-bolus (for patients receiving intermediate insulin; eg, a patient taking a daily total of 50 IU of Novolin® 70/30 insulin, 35 units (0.7 x 50) is assessed as the "daily non-bolus" insulin) and total daily insulin (for all patients) will be calculated. These calculated values will be entered in the eCRF.

Mean daily bolus insulin dose will be defined as the average of daily bolus insulin doses as calculated above based on results of at least 3 days of data during the preceding 3-5 days (consecutive or nonconsecutive) prior to the clinic visit. Dose on Day 1 will be excluded from Baseline calculation. Mean daily bolus insulin dose and percent change from Baseline in mean daily bolus insulin dose at Week 24 will be summarized by treatment group using standard descriptive statistics. The treatment effects at Week 24 will be evaluated using MMRM statistics with percent change from Baseline as the endpoint and with no interaction covariate. Inferential statistics will be based on the percent change from Baseline in mean daily bolus insulin dose.

In addition, absolute change from Baseline in mean daily bolus insulin dose will be summarized using standard descriptive statistics and the treatment effect will be evaluated using MMRM statistics with change from Baseline as the endpoint and Baseline mean daily bolus insulin dose-by-time interaction as a covariate.

6.8.4 Other Efficacy Analysis

Analysis of other efficacy endpoints will be based on the mITT population, with the exception of the 2 endpoints based on the PSDD-NRS, which will be based on the Satiety substudy population. Descriptive statistics for these efficacy endpoints will be presented by treatment group and by study visit where appropriate. All post-Baseline data will be used in the analyses, including observations occurring after discontinuation of study drug.

For continuous efficacy endpoints, MMRM or ANCOVA model will be used as specified in Section 6.8. The choice in statistical models depends on whether the measurement process is over multiple timepoints (MMRM) or at a single timepoint (ANCOVA).

For binary efficacy endpoints, CMH test and 95% CLs based on normal approximation methods with a continuity correction factor will be used, as described in Section 6.8.

Figures displaying mean change from Baseline by visit, LS mean change, and bar charts displaying proportions, will be presented by treatment groups for selected parameters, as appropriate.

6.8.4.1 Change from Baseline in A1C, Body Weight, SBP, and Bolus Insulin Dose

Change from Baseline in A1C, body weight (absolute and percent change), SBP and mean daily bolus insulin dose (percent and absolute change) are analyzed as secondary endpoints at Week 24. The same MMRM analysis performed for the Week 24 endpoint will be used to extract the results for each visit. Descriptive statistics and tests for group differences will be presented for all visits.

In addition, the frequency and percent of patients achieving an A1C <7.0 will be presented by treatment group and visit.

Summary statistics of mean daily bolus insulin dose as percent of the Baseline measure will also be provided.

6.8.4.2 Proportion of Patients by Visit Achieving an A1C Decrease from Baseline by Various Criteria

The following A1C decrease categories will be assessed by visit:

- ≥0.5% absolute in the subset of patients with Baseline A1C ≤9.0%
- ≥1% absolute in the subset of patients with Baseline A1C ≤9.0%
- ≥0.5% absolute in the subset of patients with Baseline A1C >9.0%
- ≥1% absolute in the subset of patients with Baseline A1C >9.0%
- ≥0.5% absolute or >10% in the subset of patients with Baseline A1C ≤9.0%
- ≥1% absolute or >10% in the subset of patients with Baseline A1C ≤9.0%
- ≥0.5% absolute or >10% in the subset of patients with Baseline A1C >9.0%
- ≥1% absolute or >10% in the subset of patients with Baseline A1C >9.0%

The frequency and percent of patients belonging to each A1C decrease category above will be presented by Baseline A1C categories, treatment group and visit and analyzed using the methods described for binary efficacy endpoints in Section 6.8.

6.8.4.3 Proportion of Patients by Visit with Reduction in Body Weight by Prespecified Amounts of ≥2%, ≥5%, and ≥10%

The frequency and percent of patients with reductions in body weight will be presented for the prespecified amounts of: ≥2%, ≥5%, and ≥10%, by treatment group and visit and analyzed using the methods described for binary efficacy endpoints in Section 6.8.

6.8.4.4 Proportion of Patients by Visit Achieving an A1C Reduction ≥0.4% and No Increase in Body Weight

The frequency and percentage of patients achieving an A1C reduction ≥0.4% and no increase in body weight will be presented by treatment group and visit and analyzed using the methods described for binary efficacy endpoints in Section 6.8.

6.8.4.5 Proportion of Patients Achieving an A1C Reduction ≥0.5% at Week 24 and No Episode of SH

The frequency and percentage of patients achieving an A1C reduction ≥0.5% at Week 24 without SH events from randomization to Week 24 will be presented by treatment group and analyzed using the methods described for binary efficacy endpoints in Section 6.8.

6.8.4.6 Proportion of Patients by Visit Meeting Success Criteria for A1C and Insulin

The frequency and percentage of patients with decrease from Baseline in mean daily bolus insulin dose of >20% and a decrease from Baseline in A1C of >0.3% will be presented by treatment group and visit and analyzed using the methods described for binary efficacy endpoints in Section 6.8.

6.8.4.7 Change from Baseline in FPG

Descriptive statistics of FPG (mg/dL) will be presented by treatment group and visit. Change from Baseline in FPG at Week 24 and other visits will be analyzed using MMRM statistics with change from Baseline as the endpoint and Baseline FPG-by-time interaction as a covariate. Treatment effects at Week 24 and other visits will be presented.

6.8.4.8 Change from Baseline in Total and Basal (or Non-bolus) Insulin Dose

Change from Baseline in the following endpoints will be analyzed by visit:

- Mean total daily insulin dose by visit (as an average over the 3-5 days prior to the visit)
- Mean daily basal (or non-bolus) insulin dose by visit (as an average over the 3-5 days prior to the visit)

Change from Baseline in the above endpoints will be analyzed using MMRM statistics with change from Baseline as the endpoint and Baseline dependent variable-by-time interaction as a covariate. Descriptive statistics and tests for group differences will be summarized for all visits.

In addition, percent change from Baseline in mean total daily insulin dose and mean daily basal (or non-bolus) insulin dose will be summarized using standard descriptive statistics and the treatment effect will be evaluated using MMRM statistics with percent change from Baseline as the endpoint and with no covariate.

Summary statistics of mean total daily insulin dose and mean daily basal (or non-bolus) insulin dose as percent of the Baseline measure will also be provided.

6.8.4.9 Change from Baseline in DBP

Change from Baseline in DBP will be analyzed using MMRM statistics with change from Baseline as the endpoint and Baseline DBP -by-time interaction as a covariate. Descriptive statistics and tests for group differences will be summarized by visit.

6.8.4.10 Proportion of Patients by Visit with SBP <140 mm Hg and DBP <90 mm Hg in the Subset of Patients with Baseline SBP ≥140 mm Hg or DBP ≥90 mm Hg

The frequency and percent of patients with SBP <140 mm Hg and DBP <90 mm Hg will be presented in the subset of patients with Baseline SBP ≥140 mm Hg or DBP ≥90 mm Hg, by treatment group and visit and analyzed using the methods described for binary efficacy endpoints in Section 6.8, except the CMH and NRI will be applied to Week 16 instead of Week 24.

6.8.4.11 Proportion of Patients by Visit with SBP <130 mm Hg and DBP <80 mm Hg in the Subset of Patients with Baseline SBP ≥130 mm Hg or DBP ≥80 mm Hg

The frequency and percent of patients with SBP <130 mm Hg and DBP <80 mm Hg will be presented in the subset of patients with Baseline SBP ≥130 mm Hg or DBP ≥80 mm Hg, by treatment group and visit and analyzed using the methods described for binary efficacy endpoints in Section 6.8, except the CMH and NRI will be applied to Week 16 instead of Week 24.

6.8.4.12 Change from Baseline by Visit in Hypoglycemic Events Calculated as a Daily Average over the Week Prior to the Visit

Change from Baseline in the following endpoints will be analyzed by visit:

- Hypoglycemic events/patient/day (≤70 mg/dL) by SMBG
- Hypoglycemic events/patient/day (≤55 mg/dL) by SMBG

Change from Baseline in hypoglycemic events, calculated as a daily average over the week prior to the visit, will be analyzed using MMRM statistics with change from Baseline as the endpoint and Baseline-

dependent variable-by-time interaction as a covariate for each of the 2 hypoglycemic event definitions: ≤70 mg/dL by SMBG, and ≤55 mg/dL by SMBG. Descriptive statistics and tests for group differences will be summarized for all visits.

6.8.4.13 Measures of Kidney Function

Change from Baseline in the following measures of kidney function will be analyzed by visit:

- Urine ACR, CCR, and GCR
- Serum creatinine
- MDRD eGFR

The following equation will be used to derive the MDRD eGFR:

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

where Scr is serum creatinine reported in mg/dL.

Change from Baseline in serum creatinine and eGFR will be analyzed using MMRM statistics with change from Baseline as the endpoint and Baseline dependent variable-by-time interaction as a covariate. Descriptive statistics and tests for group differences will be summarized for all visits.

Change from Baseline in urine ACR, CCR, and GCR will be analyzed using an ANCOVA model with Baseline dependent variable as a covariate. Descriptive statistics and tests for group differences will be summarized.

6.8.4.14 Proportion of Patients with Satiety Increase ≥30% as Measured by The PSDD-NRS (Substudy)

In the Satiety substudy, patients are instructed to complete the satiety daily diary each day before the first meal of the day during the 2-week single-blind placebo Run-in Period (14 days, ±3 days) and for the last 14 days, ±3 days of the Double-blind Treatment Period (ie, each day during Weeks 23 and 24). Patient satiety (ie, average level of hunger) is evaluated using an 11-point PSDD-NRS, from 0=’very full’ to 10=’very hungry’.

The 14 days closest to, but not greater than Day 1 (and before start of study drug) will be selected for the Baseline assessment for a patient. The 14 days closest to, but not greater than the Week 24 visit (or the day of the last dose of study drug, if earlier than the Week 24 visit) will be selected for the Week 24 assessment for a patient. For each assessment period, the average of the non-missing PSDD-NRS scores during that period and which were entered in the daily diary before the first meal of the day will be calculated and used in the analysis, provided that the patient has at least 8 such non-missing scores in that period. If the patient has less than 8 non-missing scores for a period which were entered in the daily diary before the first meal of the day, then the patient’s PSDD-NRS score is set to missing for that period.

The frequency and percentage of patients with satiety increase ≥30% from Baseline at Week 24 will be presented by treatment group for the Satiety substudy population visit and analyzed using the methods described for binary efficacy endpoints at Week 24 in Section 6.8.

6.8.4.15 Change from Baseline in Patient-reported Satiety as Measured by The PSDD-NRS (Substudy)

Change from Baseline to Week 24 in PSDD-NRS will be analyzed using an ANCOVA model fitted for treatment, BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), Week -2 A1C (≤9%, >9%), and use of CSII at Screening (Yes, No), as fixed categorical effects, and Baseline PSDD-NRS as a covariate. Descriptive statistics and tests for group differences will be summarized.

6.8.5 Subgroup Analyses

Subgroup analyses of the efficacy variables will be performed for the different levels of Baseline characteristics and the randomization stratification factors. Of particular interest are the subgroup analyses of the primary efficacy endpoint and the first secondary efficacy endpoint (ie, change from Baseline to Week 24 in A1C) by:

- Age at diagnosis (<18 years, ≥18 years)
- Age at study entry (<75 years, ≥75years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, other)
- Stratification for BMI categories (<25 kg/m^2, ≥25 kg/m^2)
- Stratification for use of CSII (Yes, No)
- Stratification categories of Week -2 A1C (≤9%, >9%)
- Week -2 A1C (<7.7%, ≥7.7%)
- Week -2 A1C (≤8.5%, >8.5%)
- Baseline eGFR status (≥45 to <60 mL/min/1.73 m^2 , ≥60 mL/min/1.73 m^2)

For the primary efficacy endpoint, the CMH test will be stratified by BMI at Screening (<25 kg/m^2, ≥25 kg/m^2; excluded if it is a subgroup variable), Week -2 A1C (≤9%, >9%; excluded if it is a subgroup variable), and use of CSII at Screening (Yes, No; excluded if it is a subgroup variable).

For the change from Baseline to Week 24 in A1C, the MMRM model will have treatment, BMI at Screening (<25 kg/m^2, ≥25 kg/m^2; excluded if it is a subgroup variable), Week -2 A1C (≤9%, >9%; excluded if it is a subgroup variable), use of CSII at Screening (Yes, No; excluded if it is a subgroup variable), time (study week), and a treatment-by-time interaction as fixed categorical effects, and Baseline A1C-by-time interaction as a covariate.

In addition, change from Baseline in SBP (mm Hg) at Week 16 will be summarized and analyzed using using MMRM statistics with the change from Baseline at Week 16 as the endpoint and Baseline SBP -by-time interaction as a covariate, for the following subgroups:

- Baseline SBP <130 mm Hg
- Baseline SBP <140 mm Hg
- Baseline SBP ≥140 mm Hg

All subgroup analyses will be exploratory.

6.8.6 Net Clinical Benefit

Summaries for the following net clinical benefit endpoints assessed at the end of Double-blind Treatment Period will be provided for each treatment group in the mITT population:

- A1C at Week 24 <7.0% and SH
- A1C at Week 24 <7.0% and no SH
- A1C at Week 24 <7.0% and DKA
- A1C at Week 24 <7.0% and no DKA
- A1C at Week 24 <7.0% and no weight gain
- A1C at Week 24 <7.0% and weight gain >5%
- A1C at Week 24 <7.0% and weight loss >5%
- A1C at Week 24 <7.0% and bolus insulin reduction ≥20%
- A1C at Week 24 <7.0% and bolus insulin reduction ≥30%
- A1C at Week 24 <7.0% and basal (or non-bolus) insulin reduction ≥20%
- A1C at Week 24 <7.0% and basal (or non-bolus) insulin reduction ≥30%
- A1C at Week 24 <7.0% and total insulin reduction ≥20%
- A1C at Week 24 <7.0% and total insulin reduction ≥30%
- A1C at Week 24 <7.0% and no SH and no weight gain
- A1C at Week 24 <7.0% and no SH and no DKA and no weight gain

Only positively adjudicated SH and DKA will be included in these summaries, and the cut-off dates for their inclusion are defined in Section 6.9.2. Similar summaries will be presented for other net clinical benefit measures at Week 24: A1C reduction of at least 0.3%, 0.4%, and 0.5%, with the associated SH, DKA, weight gain, and insulin reduction benefit categories. Exceptions are the summaries for A1C reduction of at least 0.4% and no weight again; A1C reduction of at least 0.5% and no SH; and A1C reduction of at least 3% and bolus insulin reduction ≥20%, as these are either identical or very similar to 3 other efficacy endpoints (see Section 6.8.4.4 to Section 6.8.4.6).

6.9 Safety

6.9.1 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary Version 17.1 (or a later version if updated during the study) and classified as TEAEs as follows:

- TEAEs are events with start date on or after the date of first dose of double-blind study treatment and up to 30 days after date of last dose of double-blind study treatment. Some AEs may be attributed to the long-term effects of study drug and will be included in the analysis of TEAEs even if the onset is more than 30 days after the last dose of study drug.

All AE data will be listed by treatment group. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of SAEs, AEs leading to discontinuation of double-blind study treatment and AEs resulting in death will be produced.

Summary of TEAEs will be presented by treatment group for the Safety population.

The relationship between an AE and study treatment is assessed as definitely, probably, possibly, unlikely, or not related. A treatment-related AE is an AE considered by the Investigator as definitely, possibly, or probably related to treatment or with unknown/missing relationship to treatment.

An overview table will summarize the number and percentage of patients with at least 1 of the following TEAEs, where patients with more than 1 TEAE in a particular category are counted only once in that category:

- Any TEAE
- Drug-related TEAE
- Severe drug-related TEAE
- Treatment-emergent SAE
- Treatment-emergent, Drug-related SAE
- TEAE leading to study drug discontinuation
- Drug-related TEAE leading to study drug discontinuation
- TEAE leading to death

The number and percentage of patients reporting each AE will be summarized by SOC and PT for the Safety population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs reported by at least 5% of patients in any treatment group, by SOC and PT
- TEAEs related to treatment, by SOC and PT
- TEAEs related to treatment, by PT
- TEAEs by relationship to treatment, by SOC and PT
- TEAEs by severity, by SOC and PT
- TEAEs related to treatment by severity, by SOC and PT
- TEAEs causing discontinuation from treatment, by SOC and PT
- TEAEs related to treatment causing discontinuation from treatment, by SOC and PT
- Treatment-emergent SAEs, by SOC and PT
- Treatment-emergent SAEs related to treatment, by SOC and PT
- TEAEs leading to death, by SOC and PT
- SAEs during Screening or Run-in Period leading to death, by SOC and PT

In the above summaries, patients with more than 1 AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than 1 AE within a particular PT are counted only once for that PT. For summaries by maximum severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. In a similar manner, summaries prepared by drug relationship will select the event with the greatest degree of relationship when a patient reports multiple occurrences of the same event.

No statistical comparisons of AEs between treatment groups will be performed.

6.9.2 Events of Special Interest

Events of special interest will be captured from first dose of double-blind study drug until 30 days after last dose of study drug.

EOSIs are:

- Hypoglycemia

- DKA (including all events of metabolic acidosis)
- Volume depletion
- Myocardial infraction/hospitalization for unstable angina
- Stroke
- Hospitalization for heart failure
- Coronary revascularization
- Genital mycotic infections
- Urinary tract infections
- Diarrhea
- Pancreatitis
- Bone fractures
- Venous thrombotic events
- DILIs
- Renal events
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, thyroid, pancreatic, and prostate)
- Amputations

Based on an Information Request sent by FDA, amputations are to be added as an EOSI. This request came during the ongoing conduct of the study and methods for identifying this event will differ from those planned at the start of the study for the other listed EOSIs. Amputations will be identified as follows: The sponsor will collect all necessary data for patients who might experience amputation while participating in the study. A list of PTs will be created to identify events which may lead to amputation or which may be associated with amputations, to include amputation and conditions such as extremity ulcers, necrosis, extremity infections, etc. This predefined list of PTs will be utilized to search the database to identify the reported events of amputation and relevant events that could result in a treatment requiring amputation. Once those events are identified, sites will be queried for additional details if necessary. This information will be processed in a manner to categorize amputations as an EOSI and analyzed as the other EOSIs listed in this section.

Other AEs may be determined to be of special interest. EOSIs will be captured from first dose of double-blind study drug until 30 days after last dose of study drug. The following EOSIs may be attributed to the long-term effects of study drug: CV events (including death), bone fractures, venous thrombotic events, DILIs, and malignancies. In case any of these events is spontaneously reported by a patient, the event may be included in the analysis even if the onset is 30 days after last dose of study drug. Other EOSIs, excluding hypoglycemic events, will be included in the analysis if the onset is within 30 days of last dose of study drug. For a hypoglycemic event, the date of the last dose of double-blind study drug will be the cut-off date, regardless of the time of the hypoglycemic event; that is, a hypoglycemic event that occurs on the same day as the day of the last dose of double-blind study drug will be included in the analysis, even if it occurs at a time later than the last dose.

Events of special interest that will require adjudication by CEC are: MACE and specific CV events, DILIs, DKA (including all events of metabolic acidosis), and SH; EOSIs of SH, DKA, and CV events, if reported prior to randomization as SAEs, will be adjudicated as well.

An overall summary of number and percentage of patients with any Investigator-determined EOSIs will be presented by treatment group and overall for the Safety population. An overall summary of positively

adjudicated EOSIs will also be presented by treatment group. The summaries of Investigator-determined and positively adjudicated EOSIs will also be presented by use of CSII at Screening (Yes, NO).

Additional overall summaries will be presented for Investigator-determined EOSIs and positively adjudicated EOSIs, separately, for each of 3 time periods described as follows:

- EOSIs which start on or after the date and time of first dose of double-blind study drug and up to 30 days after the date of last dose
- EOSIs which start on or after the date and time of first dose of double-blind study drug and up to and including the date of last dose
- EOSIs which start after the date of last dose and up to 30 days after the date of last dose.

If the start time of an EOSI and/or the time of first dose of double-blind study drug is missing, then only the dates will be compared in determining the inclusion of the EOSI in the analysis for the time period of interest.

For the first and third time periods above, hypoglycemic events with onset after the date of last dose and up to 30 days after the date of last dose will be included.

Incidence rates by SOC and PT will be presented for all Investigator-determined EOSIs, those classified as serious, and those leading to study drug discontinuation.

Incidence rates by SOC and PT will be presented for all positively adjudicated EOSIs, those classified as serious, and those leading to study drug discontinuation.

Bar charts will be presented to show the incidence rates of positively adjudicated DKA and SH events, respectively, by time intervals for each treatment group.

Figures displaying recurrent events of positively adjudicated DKA or SH events by time of onset during treatment and by patient will be presented for each treatment group.

A by-patient listing of all EOSIs will be provided.

6.9.3 Death

The number and percentage of deaths, and associated primary cause of death (investigator-reported and positively adjudicated), will be summarized by treatment group and overall for the Safety population.

6.9.4 Hypoglycemic Events

Hypoglycemic events will be categorized as either (1) SH or (2) documented hypoglycemia. An episode may meet criteria for both categories. Hypoglycemic events will be classified as SH, documented symptomatic hypoglycemia, or documented asymptomatic hypoglycemia per the following definitions:

1. SH has occurred if the answer is yes to any of the following 3 questions:
    a) Did the patient have an episode of suspected hypoglycemia treated with any form of carbohydrate or with glucagon that required the assistance of others to treat?
    b) Did the patient lose consciousness during the episode?
    c) Did the patient have a seizure during the episode?

2. Documented hypoglycemia: documented hypoglycemia will be defined as symptomatic or asymptomatic based on the following 2 definitions:
    a) Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by a concurrent fingerstick (SMBG) or venous glucose result of ≤70 mg/dL [3.9 mmol/L].
    b) Documented asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured fingerstick (SMBG) or venous glucose result of ≤70 mg/dL [3.9 mmol/L].

Severe and documented hypoglycemia will be further characterized as follows:

- Nocturnal hypoglycemia defined by the time of day: any hypoglycemia that occurs between 00:00 and 05:59, regardless of whether the patient was awake or woke up because of the event;
- Diurnal hypoglycemia defined by the time of day: any hypoglycemia that occurs between 06:00 to 23:59.

SH will be further characterized as:

- Nocturnal hypoglycemia by sleep status: hypoglycemia that wakes the patient from sleep after having gone to bed in the evening and before getting up in the morning before administration of any insulin.

Hypoglycemia will be summarized as the incidence of patients (%) with at least 1 hypoglycemic event, number of hypoglycemic events per patient per year of exposure, and the number of hypoglycemic events per patient per day, by treatment group, separately for the Baseline Period (ie., 2-week placebo Run-in Period), Double-blind Treatment Period (including only those events that occur between date and time of first dose and date of last dose of double-blind study drug) and Follow-up Period (including only those events that occur after the date of last dose of double-blind study drug and on or before the 30-Day Follow-up). The incidence rate of nocturnal hypoglycemic events by time, nocturnal hypoglycemic events by sleep status, and diurnal hypoglycemic events will be presented. Similarly, total documented hypoglycemia (symptomatic and asymptomatic), documented symptomatic hypoglycemia, documented asymptomatic hypoglycemia, total hypoglycemic events (ie, SH or documented hypoglycemia), SH events, and positively adjudicated SH events will be summarized.

Incidence rates of positively adjudicated SH events by treatment group and use of CSII at Screening (Yes, No) will be presented for the Double-blind Treatment Period.

Change from Baseline in hypoglycemic events calculated as a daily average over the week prior to the visit will be analyzed as a continuous variable as described in Section 6.8.4.12. Since these data also serve as a measure of safety, additional analyses will be conducted. The first analysis of hypoglycemic events will be conducted using CMH tests stratified by the randomization factors at each clinic visit. These tests will provide inferential and descriptive summaries of the relative risk estimate for each of the 2 hypoglycemic event definitions: ≤70 mg/dL and ≤55 mg/dL by SMBG. The patient incidence of these hypoglycemic events will be counted over the week prior to the scheduled clinic visit used in the analysis. The second analysis of these data will examine the relative risk for each of the hypoglycemic event definitions over the entire Double-blind Treatment Period by use of a generalized linear model (GLM). The GLM will include fixed, categorical effects of treatment; BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), Week -2 A1C (≤9%, >9%), use of CSII at Screening (Yes, No), and an offset term for ~~treatment duration~~

(natural logarithm of the treatment duration). The event rates will be modeled as a negative binomial process.

Kaplan-Meier plots of cumulative percentage of patients with the following categories of hypoglycemic events will be presented by treatment group:

- SH
- Documented hypoglycemia
- Nocturnal SH by time of day
- Diurnal SH by time of day
- Nocturnal SH by sleep status
- Nocturnal documented hypoglycemia by time of day
- Diurnal documented hypoglycemia by time of day

Patient listings for SH events (including hypoglycemic events reported as SAEs) reported by the Investigator and adjudicated by the CEC will be provided.

6.9.5 Diabetic Ketoacidosis

An assessment for DKA will be performed if a patient has any symptoms or signs that the Investigator believes may be consistent with DKA or if urine ketones are positive or blood BHB is >0.6 mmol/L. In these cases the Investigator will determine if an assessment for metabolic acidosis is appropriate and if yes, then the Possible DKA CRF will be completed.

Summary statistics by treatment group and overall for the actual values and change from Baseline in BHB based on central laboratory results will be provided by visit. Point-of-care BHB results will be listed. Similar summaries will be presented for urine ketones.

Cross-tabulation of A1C (using the following categories: <7%, ≥7% to <8%, ≥8% to <9%, ≥9% to <10%, ≥10 %, and overall) vs. BHB (using the following categories: 0, <0.2, ≥0.2, ≥0.3, ≥0.5, ≥0.6, ≥1.0, ≥2.0, and ≥3.0 mmol/L) during Double-blind Treatment Period will be provided for each treatment group. In addition, cross-tabulation of A1C vs. urine ketones results will be presented.

Urine ketones cross-tabulated with BHB results will be presented for the Double-blind Treatment Period.

Total daily insulin, daily bolus insulin, and daily basal (or non-bolus) insulin, as percentage of the corresponding Baseline dose, will be cross-tabulated with BHB for the Double-blind Treatment Period. The insulin doses, in unit/kg, will also be cross-tabulated with BHB.

Incidence of BHB >0.6 mmol/L during the Double-blind Treatment Period will be analyzed by a logistic regression model adjusting for treatment, Baseline A1C, Baseline BHB, and age at T1D diagnosis (<18 years of age, ≥18 years of age). In addition, incidence of BHB >0.6 mmol/L during the Double-blind Treatment Period will be analyzed by a logistic regression model adjusting for treatment, Baseline A1C, change from Baseline to Week 24 in A1C, Baseline BHB, change from Baseline to Week 24 in mean daily basal (or non-bolus) insulin dose, and age at T1D diagnosis (<18 years of age, ≥18 years of age). Receiver operating characteristic (ROC) curves for assessing the accuracy of predictions will be presented for both logistic regression models. ROC curves will plot sensitivity vs. (1-specificity) for the prediction of BHB >0.6 mmol/L. The area under ROC curves as quantitative summary measures will be provided.

Box plots of BHB will be presented for Baseline and Week 24 visit by treatment group.

Scatter plots of A1C vs. BHB and urine ketones, and urine ketones vs. BHB will be presented for Baseline and Double-blind Treatment Period separately for each treatment group.

Scatter plots of BHB vs. total daily insulin dose, daily bolus insulin dose, and daily basal (or non-bolus) insulin dose as percentage of the corresponding Baseline dose and as units/kg will be presented for Double-blind Treatment Period by treatment group.

6.9.6 Acidosis-related Adverse Events

Incidence of treatment-emergent acidosis-related AEs will be summarized to include patient counts and percentages by treatment group, and by use of CSII at Screening (Yes, No) as well, for the following: (serious and non-serious) acidosis-related AEs, serious acidosis-related AEs, non-serious acidosis-related AEs, positively adjudicated metabolic acidosis, and positively adjudicated metabolic acidosis that were also DKA.

Acidosis-related AEs are those that satisfy the trigger terms for metabolic acidosis defined in the table below. All acidosis-related AEs were adjudicated for metabolic acidosis. All cases of positively adjudicated metabolic acidosis were then adjudicated for the presence or absence of DKA.

Trigger Terms for Metabolic Acidosis	
Trigger Terms Typically Associated With Elevated BHB	**Trigger Terms That <u>May Not</u> Be Associated with Elevated BHB**
Acetonaemia	Acidosis Hyperchloraemic
Blood Ketone Body	Metabolic Acidosis
Blood Ketone Body Increased	Lactic Acidosis
Blood Ketone Body Present	Renal Tubular Acidosis
Diabetic Ketoacidosis	Acidosis
Diabetic Ketoacidotic Hyperglycemic Coma	Uraemic Acidosis
Ketoacidosis	Diabetic Coma
Urine Ketone Body	Diabetic Hyperglycemia Coma
Urine Ketone Body Present	Diabetic Metabolic Decompensation
	Hyperglycemic Coma
	Hyperglycemic Seizure
	Hyperglycemic Unconsciousness

The trigger terms correspond to MedDRA PTs. All trigger terms in both columns of the table will be included in the search for acidosis-related AEs, without regard to the presence or absence of an associated elevated BHB value.

6.9.7 Drug-induced Liver Injury Events

Summaries by treatment group for liver safety laboratory abnormalities will be provided based on the Investigator-reported and positively adjudicated data, and laboratory data.

The incidence of liver enzyme or bilirubin abnormalities will be summarized by treatment group based on laboratory data regardless of the Investigator reports. The number and percentage of patients with post-

Baseline elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin according to various multiples of the upper limit of normal (ULN) will be presented:

- ALT >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- ALT >3xULN and total bilirubin >2xULN
- AST >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST >3xULN and total bilirubin >2xULN
- ALT or AST >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- ALT >3xULN and total bilirubin >2xULN or AST >3xULN and total bilirubin >2xULN
- ALT and AST >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- ALT >3xULN and total bilirubin >2xULN and AST >3xULN and total bilirubin >2xULN

All analyses described above will be performed for the Safety population.

Scatter plots of maximum ALT vs. maximum total bilirubin and maximum AST vs. maximum total bilirubin per patient will be presented. Maximum values are presented by number of multiples of ULN.

A patient listing will be presented for those patients with Investigator-reported abnormalities and corresponding adjudication results. A patient listing of laboratory results of liver enzyme and bilirubin abnormalities will be presented for DILI events.

6.9.8 Laboratory Evaluations

Data for the following hematology, serum chemistry, lipid profile, and urinalysis analytes received from the central laboratory will be listed and summarized by treatment group and visit (Table 6.9-1). If data for any additional analytes are also received then these will be listed only.

Table 6.9-1 Central Laboratory Assessments

Hematology	Serum Chemistry	Lipid Profile	Urinalysis
Complete blood count (CBC) Differential Platelet count Hemoglobin Hematocrit	Sodium Potassium Chloride Carbon dioxide (bicarbonate) BUN Creatinine Glucose (serum) ALT AST Total bilirubin Alkaline phosphatase (ALP) Uric acid Calcium Phosphorus Total protein Albumin Magnesium Creatine phosphokinase (CPK) Lactate dehydrogenase (LDH)	Total cholesterol Triglycerides HDL-C LDL-C Non-HDL-C	Urine albumin Urine calcium Urine glucose Urine creatinine Urine pregnancy test **Urine dipstick with microscopy:** Specific gravity pH Protein Blood Ketones Bilirubin Urobilinogen Nitrate Leukocyte esterase

Other Blood Samples
A1C FPG Serum pregnancy test - females only Follicle-stimulating hormone (FSH) - if necessary to confirm postmenopausal status BHB Anion gap Thyroid stimulating hormone (TSH)

All summaries of laboratory test results will be presented in International System of Units (SI) and conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">"sign (ie those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory evaluations measured on a continuous scale will be summarized by visit using standard descriptive statistics for the Safety population. Changes from Baseline will also be summarized. For analysis by visit, analysis windowing as described in Section 5.1 will be utilized for each scheduled visit such that unscheduled visit will also be considered. For each laboratory analyte, the Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

The incidence rate of patients with diabetic specific laboratory results during the Double-blind Treatment Period will be presented for the following abnormality values:

- BHB >0.6, >1.0, >2.0, and >3.0 mmol/L
- Serum sodium >150 mEq/L
- Blood hematocrit >55%

- Decrease from Baseline in eGFR ≥25%

For hematology and serum chemistry, shift tables presenting movement in and out of reference range from Baseline to each scheduled post-Baseline visit will be provided for each treatment group.

Mean change from Baseline with standard error bars will be plotted by visit for select laboratory parameters for the Safety population.

6.9.9 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit.

- sitting SBP and DBP (mm Hg)
- pulse rate (bpm)
- respiration rate (breaths/min)
- body temperature (°C)

Vital signs data and changes from Baseline in vital signs will be summarized by visit using standard descriptive statistics for the Safety population. The Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment. For analysis by visit, analysis windowing as described in Section 5.1 will be utilized for each scheduled visit such that unscheduled visit will also be considered.

6.9.10 Electrocardiograms

The ECG Core Laboratory will review protocol-scheduled ECGs to assess the presence of Q-waves (ie, potential "silent" MI) and/or left bundle branch block (LBBB). Any new incidence of Q-wave or LBBB identified by the ECG Core Laboratory will be considered a possible unreported MI. The assessments recorded on the final "outcome" ECG Core Laboratory Assessment Forms will be used for the analysis.

The following qualitative ECG measurements will be listed and summarized by treatment group and visit for the Safety population:

- Presence of Q-waves
- New Q-waves
- Presence of LBBB
- New LBBB

6.9.11 Physical Examination

Physical examination results (normal or abnormal) and details of abnormalities will be listed for each patient.

For each physical examination body system, the number and percentage of patients with abnormalities at Baseline and post-Baseline will be summarized by treatment group for the Safety Population.

7 CHANGES IN THE PLANNED ANALYSES OF THE PROTOCOL

- The protocol (Section 10.3.1.3) stated that the secondary endpoints (A1C, body weight, SBP, and bolus insulin dose) will be assessed at specified cut points. The specific cut points to use are provided in this SAP (see Section 3.1.3).

- Sensitivity analysis of the primary efficacy endpoint using the Last Observation Carried Forward (LOCF) algorithm to impute missing data will not be performed. The analysis of the primary efficacy endpoint will use NRI to impute missing data at Week 24 (see Section 5.2.1).
- Two sensitivity analyses of the primary efficacy endpoint using the same cut-off dates for SH and DKA events have been added (see Section 6.8.2).
- Summary statistics of mean bolus insulin dose, total daily insulin dose, and mean daily basal (or non-bolus) insulin dose as percent of the Baseline measure will be provided, as stated in Sections 6.8.3.4 and 6.8.4.8.
- Analysis of the primary efficacy endpoint and the change from Baseline to Week 24 in A1C will be performed for the subgroups defined by age at study entry (<75 years, ≥75 years), sex, race, and Week -2 A1C (≤8.5%, >8.5%).
- Analysis of SBP change from Baseline to Week 16 will be performed for the subgroups defined by Baseline SBP <130 mm Hg, <140 mm Hg, and ≥ 140 mm Hg.
- EOSI events will be summarized by treatment groups across all patients (planned) and for the subgroups determined by use of CSII at Screening (Yes, No).
- For EOSIs of Malignancies of special interest, "thyroid" has been added to the list of malignancies in Section 6.9.2.
- Amputations have been added to the EOSIs specifically listed in Section 6.9.2 (note: per Section 9.5 of the protocol, AEs other than the EOSIs listed in the protocol may be determined to be of special interest).
- Additional overall summaries will be presented for EOSI for 3 time periods described in Section 6.9.2.
- Incidence of BHB >0.6 mmol/L during Double-blind Treatment Period will be analyzed by logistic regression models.
- Incidence of treatment-emergent acidosis-related AEs will be analyzed.

8 REFERENCES

1. Nathan DM, Kuenen J, Borg R, Zheng H, Shoenfeld D, Heine RJ. Translating the A1C Assay Into Estimated Average Glucose Values. Diabetes Care 2008;31:1473-1478. [Erratum, Diabetes Care 2009;32:207.]

9 APPENDICES

Appendix 1 - Schedule of Events

Main Study Schedule of Assessments

Week/Visit	Screening	Single-blind Placebo Run-in	Double-blind Treatment Period					Follow-up Period
	Wk -4	Wk -2 [a]	Day 1 Baseline [b]	Wk 4	Wk 8	Wk 16	Wk 24 or EOT/EW	30 Days Post EOT/EW [c]
Window (days)	-	±3	-	±3	±3	±3	±3	+7
Initiation Activities								
Informed consent/assent	X							
Assess inclusion/exclusion criteria	X	X	X					
Demography	X							
Complete medical history	X	X						
Register patient for Screening in IXRS	X							
Register patient for Run-in in IXRS		X						
Randomization			X					
Procedures/Events								
Complete physical examination [d]	X						X	
Symptom-related brief physical examination [d]		X	X	X	X	X		
Weight [e]	X	X	X	X	X	X	X	
Height	X							
Vital signs [f]	X	X	X	X	X	X	X	
12-lead ECG [g]	X		X				X	
Patient–centered Site Activities								
Review SMBG and make adjustment to insulin dose as needed to meet ADA/EASD Guidelines			X	X	X	X	X	
Record insulin dose and SMBG data on the eCRF			X	X	X	X	X	
Dispense patient study diary and glucose testing strips (meter at first visit) [h]		X	X	X	X	X		
Dispense Ketostix® or similar to measure urine ketones for DKA assessment per Section 9.5.2 [i]	X							
Dispense BHB meter and testing strips		X						
Review study diary and record hypoglycemic symptoms or events			X	X	X	X	X	
Diet and exercise instruction [j]	X	X						

	Screening	Single-blind Placebo Run-in	Double-blind Treatment Period					Follow-up Period
Week/Visit	**Wk -4**	**Wk -2 [a]**	**Day 1 Baseline [b]**	**Wk 4**	**Wk 8**	**Wk 16**	**Wk 24 or EOT/EW**	**30 Days Post EOT/EW [c]**
Window (days)	**-**	**±3**	**-**	**±3**	**±3**	**±3**	**±3**	**+7**
Recommendations on basic genitourinary hygiene, maintaining hydration and recognition of DKA and its management			X	X	X	X		
Assess compliance			X	X	X	X	X	
Record concomitant medications [k]	X	X	X	X	X	X	X	
Record SAEs [l]	X	X	X	X	X	X	X	X
Record AEs [m]			X	X	X	X	X	X
Record EOSIs			X	X	X	X	X	X
Dispense single-blind placebo tablets		X						
Dispense Double-blind study drug			X		X	X		
Patient Reported Outcome (Patients in substudy only)								
Dispense satiety daily diaries and review instruction for use [n]		X				X		
Collect satiety daily diaries [o]			X				X	
Laboratory/glycemic Assessments								
A1C [p]	X	X	X	X	X	X	X	
Fingerstick glucose on site	X	X	X	X	X	X	X	
Fasting plasma glucose [p]	X		X	X	X	X	X	
Fasting serum chemistry [p]	X		X	X	X	X	X	
Fasting lipid profile [p]	X		X		X		X	
BHB (central lab)	X	X	X	X	X	X	X	
BHB (point-of-care)	X	X	X	X	X	X	X	
Hematology	X		X		X		X	
Urine albumin, calcium, glucose, creatinine			X				X	
Urinalysis with microscopy	X		X				X	
Pregnancy test (serum) [q]	X							
Pregnancy test (urine) [q]			X				X	
Follicle stimulating hormone (females only) [r]	X							
Thyroid stimulating hormone [s]	X							

	Screening	Single-blind Placebo Run-in	Double-blind Treatment Period					Follow-up Period
Week/Visit	**Wk -4**	**Wk -2 [a]**	**Day 1 Baseline [b]**	**Wk 4**	**Wk 8**	**Wk 16**	**Wk 24 or EOT/EW**	**30 Days Post EOT/EW [c]**
Window (days)	**-**	**±3**	**-**	**±3**	**±3**	**±3**	**±3**	**+7**
Fasting blood sample and random urine for storage			X				X	

A1C = hemoglobin A1C; ADA = American Diabetes Association; AE = adverse event; BHB = beta-hydroxy butyrate; BP = blood pressure; EASD = European Association for the Study of Diabetes; eCRF = electronic case report form; DKA = diabetic ketoacidosis; ECG = electrocardiogram; EOSI = Events of Special Interest; EOT = End of Treatment; EW = early withdrawal; IXRS = Interactive Voice/Web Response System; SAE = serious adverse event; SMBG = self-monitored blood glucose; Wk = Week

a. The duration of the single-blind placebo Run-in Period is 14 days, ±3 days.
b. All laboratory assessments occur prior to first dose of Double-blind study drug. All visit dates will be scheduled based on the date of randomization with a ±3 days visit window allowed.
c. All patients will have a follow-up telephone contact 30 days after the last dose of study drug to collect information on any SAEs, any EOSI, or AEs that were ongoing at the time of the EOT/EW Visit.
d. A complete physical examination will include, at minimum, a review of the patient's general appearance, head, eyes, ears, nose and throat, neck, heart, lungs, abdomen, back and extremities, skin, and general neurological system. A symptom related brief physical exam will only occur if the patient is experiencing symptoms or AEs. If a symptom related brief physical exam is required, it should include a review of all body systems that relate to the symptoms and/or AE the patient is experiencing.
e. Patients should be weighed at approximately the same time of day, wearing minimal clothing, ie, no coat/shoes, using the same calibrated scale where possible.
f. Vital sign measurements should be measured after the patient has been seated for at least 5 minutes and prior to phlebotomy.
g. The 12- lead ECG recordings should be obtained prior to the morning study drug administration. ECG recording should be recorded either prior to phlebotomy or at least 30 minutes after phlebotomy.
h. The patient will be provided with a study diary and glucose monitoring supplies for use at home. These supplies will be provided to all sites by the Sponsor.
i. After the initial dispensation at the Screening Visit, additional Ketostix® (or similar) will be dispensed on an as needed basis.
j. Counseling frequency may be increased at the discretion of the Investigator.
k. Concomitant medications taken from 2 weeks prior to the Screening Visit through the EOT, including those specified in the inclusion/exclusion criteria, must be recorded in the source documents.
l. All SAEs will be collected starting with signing informed consent/assent and continue until 30 days after the last dose of study drug.
m. The collection of AEs will start after the first dose of Double-blind study drug. All AEs ongoing at the EOT/EW visit should be followed for at least 30 days following the last dose of study drug or until the event has resolved, the condition has stabilized, the etiology of the event is determined to be not related to study drug, or the patient is lost to follow-up.
n. Patients participating in the satiety substudy will be instructed to complete their satiety daily diaries before the first meal of the day. The patients will be instructed to complete the diaries each day during the 14day, ±3 days single-blind placebo Run-in Period and each day for the last 14 days, ±3 days of the Double-blind Treatment Period (during Week 23 and Week 24).
o. Entries on the satiety daily diaries should be reviewed and recorded on the eCRF.

p. Fasting blood samples should be taken after the patient has fasted for at least 8 hours; patients should only drink water or noncaffeinated, zero-calorie beverages. If the patient is unable to fast as above, the scheduled "fasting" laboratory samples will still be collected, and the non-fasting status will be noted in the eCRF.
q. Serum pregnancy test must be performed at Screening, and the result reviewed prior to beginning the single-blind Run-in Period for all females with childbearing potential unless there is documented history of menopause or they are surgically sterile. All other required pregnancy tests can be performed via a urine test. Baseline urine test result must be reviewed prior to Randomization. The Investigator may perform additional tests at their discretion or as required by local regulations.
r. If necessary, follicle-stimulating hormone will be measured at Screening to confirm postmenopausal status.
s. If abnormal, free thyroxine will be measured.

Appendix 2 - Table, Figure and Listing Shells

The table, figure, and listing shells and corresponding Table of Contents will be created in a separate file. These files are provided for review purposes only and are not considered part of the final SAP document.