NCT02531035

CLINICAL STUDY PROTOCOL

Protocol Number:	LX4211.1-312-T1DM LX4211.312 (Abbreviated number)
EudraCT Number:	2015-001709-15
Investigational Phase:	3
Protocol Title:	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
Amendment 1 Date:	16 October 2015
Original Version Date:	19 May 2015
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: (281) 863-3000
Medical Director:	[redacted] Lexicon Pharmaceuticals, Inc.

Investigator Signature Page

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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with all of the laws and regulations applicable to the jurisdiction in which the study is conducted.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB) or Ethics Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by Lexicon, the IRB/ERC, and, in certain cases, the Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator (Signature)	Date
Principal Investigator's Name (Print)	

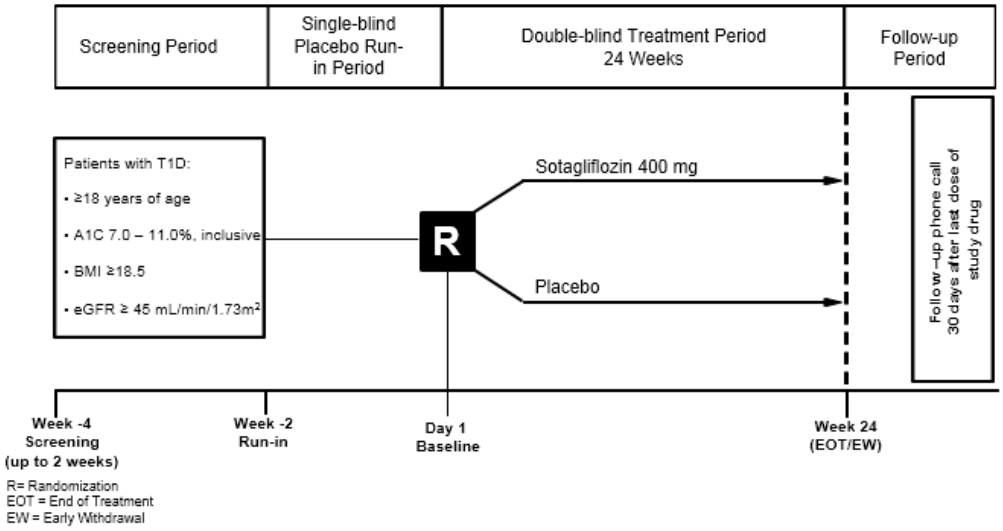
1. Synopsis

Name of Study Drug	Sotagliflozin (LX4211)
Protocol Number	LX4211.1-312-T1DM LX4211.312 (Abbreviated number)
Protocol Title	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
Phase of Development	Phase 3
Number of Study Sites	Approximately 134 sites with global distribution
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 and no episode of diabetic ketoacidosis (DKA) after randomization.
Secondary Objectives	Secondary objectives of this study are to evaluate the change from Baseline of sotagliflozin versus placebo in hierarchical order on the following: • A1C • Body weight • Systolic blood pressure (SBP) • Bolus insulin dose
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 severe hypoglycemia • 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
Methodology	This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adult patients diagnosed with type 1 diabetes mellitus (T1D), and body mass index (BMI) ≥18.5 kg/m2 who have inadequate glycemic control with insulin therapy (administered by subcutaneous injections or continuous subcutaneous insulin infusion [CSII]) are eligible for enrollment in this study as long as they meet all inclusion and no exclusion criteria. 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 adjusted if the SMBG trends do not meet standard of care (SOC) T1D target goals. **Note**: Subsequently, in this document, the term "insulin" includes insulin analog(s). The term "insulin analog" may also appear, as needed for clarity. Bolus insulin refers to regular insulin or fast-acting insulin analog administered via subcutaneous (SC) or inhaled route.

	All patients will have a Screening Period of up to 2 weeks. The single-blind placebo Run-in Period will begin at Week -2. In order to qualify for randomization, patients must demonstrate ≥80% compliance to taking the expected amount of placebo tablets during the Run-in Period. Following randomization, patients will have a 24-week double-blind Treatment Period and a 30-day Follow-up Period. Thirty days after the last dose of double-blind study drug a telephone call will be made to all patients to record information on serious adverse events (SAEs), events of special interest (EOSI), and any adverse event (AE) that was ongoing at the time of the End-of-Treatment (EOT) or Early Withdrawal (EW) visit. Approximately 1400 patients ≥18 years of age will be randomly assigned in a 1:1 ratio between the following 2 treatment groups, as an adjunct to their insulin therapy: • 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 The treatment randomization schedule will be centralized and 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). The desired balances will be accomplished by use of randomly permuted blocks of fixed size. The glycemic goals recommended for this study are to treat A1C and blood glucose to the following targets: A1C <7.0%, fasting/preprandial capillary plasma glucose 80-130 mg/dL (4.4-7.2 mmol/L), and 2-hour/peak postprandial capillary plasma glucose <180 mg/dL (<10.0 mmol/L). Goals may be adapted based on individual patient considerations consistent with American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) Guidelines. Insulin adjustment algorithms will be provided in the Site File Notebook to serve as reference, which may be modified based on the

	Investigator's clinical assessment. In order to avoid influencing the patients' and or Investigators' behavior, A1C and FPG results will be masked to study staff after randomization laboratories have been obtained. However, if the A1C is >11.0% at Week 16 or any determination thereafter, the value will be unmasked to the study sites to allow for appropriate diabetic management. In addition, the central laboratory urinalysis (UA) will not report urine glucose results to maintain the blind. Adjudication of all deaths, EOSI, including major adverse cardiovascular events (MACE)/other cardiovascular (CV) events, clinical or laboratory findings associated with potential drug-induced liver injury (DILI), severe hypoglycemia (or hypoglycemia reported as an SAE), and DKA events 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 Charter(s). An independent Data Monitoring Committee (DMC) will meet on a regular basis to review accumulating clinical study safety data. Following each meeting, the DMC will make a recommendation to the Sponsor regarding the study. Details describing the DMC processes and procedures are outlined in a separate DMC Charter. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data and integrity of the study's conduct. This study will also include a substudy in which patients will use a daily diary for the self-assessment of satiety (appetite). The substudy will include a subset of enrolled patients. The study design is presented graphically below:



Number of Patients	A total of approximately 1400 patients are expected to be randomly assigned to treatment. Assuming a 20% dropout rate, approximately 1120 patients are expected to complete the 24-week, double-blind Treatment Period while remaining on study treatment. A centralized randomization plan will be used to assign patients to study treatments. A subset of 280 patients will be recruited to participate in the satiety substudy. Assuming a 20% dropout rate, approximately 224 patients are expected to complete the 24-week double-blind Treatment Period while remaining on study treatment.
Patients	Eligible patients for this study will be ≥18 years of age, with a BMI ≥18.5 kg/m2, a confirmed diagnosis of T1D, and inadequate glycemic control on insulin therapy alone.
Treatments	The following study drug will be added as an adjunct to insulin therapy: • Sotagliflozin 400 mg as two (2) 200-mg tablets, once daily, before the first meal of the day OR • Placebo as two (2) placebo tablets (identical to sotagliflozin tablets in appearance), once daily, before the first meal of the day

Route of Administration	Oral
Duration of Participation	Approximately 32 weeks, as follows: • Screening Period (up to 2 weeks) • 2-week single-blind placebo Run-in Period • 24-week double-blind Treatment Period • Follow-up phone call 30 days after the last dose of double-blind study drug
Inclusion Criteria	Patients must meet **all** of the following criteria listed below to be considered eligible to participate in the study. For patients not meeting eligibility requirements, the reason for exclusion must be recorded. **Note**: Patients not eligible because of laboratory result(s) may have the laboratory test(s) repeated once during the Screening Period at the discretion of the Investigator to determine eligibility: 1) Patient has given written informed consent to participate in the study in accordance with local regulations 2) Adult patients 18 years and older with a diagnosis of T1D made at least 1 year prior to informed consent 3) Patients are being treated with insulin(s) or insulin analog(s) 4) Non-fast acting insulin dose is stable (±20%) for 2 weeks prior to the Screening Visit 5) At the Screening Visit, A1C must be between 7.0% and 11.0%, inclusive 6) BMI ≥18.5 kg/m^2 7) Must be willing and able to perform SMBG and complete the study diary as required per protocol 8) Females of childbearing potential must use an adequate method of contraception to avoid pregnancy throughout the duration of the study and for 30 days after the last dose of study drug. Females of childbearing potential include any female who has experienced menarche and who has not

	undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopause is defined as no menses for ≥12 months without another cause. For females with questionable menopausal history (eg, irregular menstrual periods and age >40 years) a documented serum follicle-stimulating hormone (FSH) level must be ≥30 mIU/mL. 9) Females of childbearing potential must have a negative serum or urine pregnancy test prior to the start of study drug. In the case of positive urine pregnancy testing, a negative serum sample for pregnancy testing, to confirm that the patient is not pregnant, must be obtained prior to start of study.
Exclusion Criteria	Patients who meet **any** of the following criteria will be excluded from participating in the study. For patients not meeting eligibility requirements, the reason for exclusion must be recorded. **Note:** Patients not eligible because of laboratory result(s) may have the laboratory test(s) repeated once during the Screening Period at the discretion of the Investigator to determine eligibility: 1) Therapies and/or medications a) Use of antidiabetic agent other than insulin(s) or insulin analog(s) at the time of screening (any medication other than insulin or insulin analog used for treatment of T1D must be washed out for at least 8 weeks prior to the Screening Visit) b) Any prior exposure to sotagliflozin c) Use of sodium-glucose cotransporter (SGLT) inhibitors within 8 weeks prior to Screening. **Note**: Patients taking an SGLT inhibitor may have that prohibited medication stopped, and may be considered for entry into the study if they have not been taking the prohibited medication for at least 8 weeks prior to Screening.

	d) Chronic systemic corticosteroid use, defined as any dose of systemic corticosteroid taken for more than 4 consecutive weeks within the 6 months prior to the Screening Visit. **Note**: Topical, inhaled, ocular, or nasal sprays containing corticosteroids are allowed. 2) Diabetes-related conditions: a) Type 2 diabetes mellitus or severely uncontrolled T1D as determined by the Investigator b) History of severe hypoglycemic event within 1 month prior to the Screening Visit c) History of DKA or nonketotic hyperosmolar state within 1 month of Screening OR ≥2 episodes of DKA or nonketotic hyperosmolar state within 6 months of Screening 3) Laboratory results a) Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 at Screening, as determined by the 4 variable Modification of Diet in Renal Disease (MDRD) equation b) Fasting triglycerides >600 mg/dL (>6.77 mmol/L). **Note**: Patients who fail Screening based on this criterion must have their fasting status verified, may have triglyceride-lowering medications adjusted, and be reevaluated during Screening. c) Abnormal liver function at Screening defined as any of the following: aspartate aminotransferase (AST) >2X upper limit of the normal reference range (ULN), alanine aminotransferase (ALT) >2X ULN, serum total bilirubin (TB) >1.5X ULN. **Note**: If it is the opinion of the Investigator and the Medical Monitor that an increase in bilirubin is due to Gilbert's syndrome, then

	the patient may participate. d) Screening beta-hydroxy butyrate (BHB) >0.6 mmol/L 4) Reproductive status: a) Females who are pregnant or breastfeeding or intend to be during the course of the study 5) Gastrointestinal/hepatic: a) By known history, serologic evidence of current infectious liver disease (hepatitis A, B, or C), including antihepatitis A virus (immunoglobulin M), hepatitis B surface antigen, or antihepatitis C virus. **Note**: Patients with isolated positive hepatitis B surface antibody may be included. b) Difficulty swallowing such that the patient cannot take the study drug c) History of pancreatitis within 12 months of screening, or any prior history of recurrent pancreatitis 6) Renal: a) Initiation of chronic dialysis within 30 days prior to the Screening Visit or expected to occur within 180 days after the Screening Visit b) Renal disease that required treatment with immunosuppressive therapy, or a history of dialysis or renal transplant c) History of hereditary glucose-galactose malabsorption or primary renal glucosuria 7) Cardiovascular: a) New York Heart Association Class III or IV heart failure within 3 months prior to Screening Visit

	b) Hypertensive urgency or emergency within 30 days prior to randomization. **Note**: Patients with uncontrolled hypertension at Screening will be allowed to enter the study provided that they are being aggressively treated for hypertension according to local guidelines. Examples of guidelines current at the time of protocol writing include those from the ADA and the European Society of Cardiology c) Patients with unstable/symptomatic or life-threatening arrhythmia or heart block. **Note**: Asymptomatic atrial fibrillation is not considered to be life-threatening and patients with asymptomatic atrial fibrillation will be permitted to enter the study. d) Patient has had any of the following within 3 months prior to the Screening Visit: i. Hospitalization due to unstable angina ii. Myocardial infarction (MI) iii. Coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty iv. Transient ischemic attack (TIA) or significant cerebrovascular disease 8) Hematologic: a) History of hemoglobinopathies (sickle cell anemia, thalassemia major, sideroblastic anemia) or other disorder that may interfere with A1C determination b) Donation or loss of >400 mL of blood or blood product(s) within 8 weeks prior to Screening 9) Immune system: Known severe immunocompromised status, including, but not limited to, patients who have undergone organ transplantation. **Note**: Patients with

	human immunodeficiency virus (HIV) may participate if the Investigator considers them otherwise suitable candidates for this study. 10) Malignancy or active treatment for malignancy (ie, radiation or chemotherapy, including monoclonal antibodies) within 5 years prior to the Screening Visit. **Note**: Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal breast cancer in situ, resected low-grade prostate cancer, or other malignancies that in the opinion of the Investigator and the Medical Monitor are considered cured, may participate. 11) Current eating disorder or increase or decrease of weight within the 12 weeks prior to Screening by more than 10% 12) Known allergies, hypersensitivity, or intolerance to sotagliflozin or any inactive component of sotagliflozin or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), unless the reaction is deemed irrelevant to the study by the Investigator 13) Administration of any other investigational drug or participation in an interventional clinical research study within 30 days or 5 half-lives (whichever is longer) of planned Screening Visit 14) History of alcohol or illicit drug abuse (using Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria) within 12 months prior to the Screening Visit 15) Patient is a study coordinator, employee of an Investigator or Investigator's site, or immediate family member of any of the aforementioned 16) Any condition that, in the opinion of the Investigator, may render the patient unable to complete the study 17) The presence of a clinically significant medical history, physical examination, or laboratory finding that, in the opinion of the Investigator or the Sponsor, may interfere

	with any aspect of study conduct or interpretation of results. The Investigator or the Sponsor will supply justification for exclusion, if applicable.
Sample Size Determination	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 severe hypoglycemia 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) patients 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 severe hypoglycemia event. A conservative assumption is made that the rates of DKA and severe hypoglycemia are independent and their union is estimated to be $\leq$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 $\approx$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 response 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 severe hypoglycemia 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 treatment difference can be obtained for this outcome. Based on a literature review, it seems reasonable to assume that the rate of severe hypoglycemia, 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 0.80 level (alpha = 0.05). To achieve this number of patients for evaluation, 280 patients will be recruited to participate in the substudy.
Statistical Methods	All primary efficacy analyses will be based on the mITT population. Supportive analysis of the efficacy data will be

	performed using the Per-protocol (PP) population. Primary analysis of the primary efficacy endpoint at Week 24 will use a Cochran-Mantel-Haenszel (CMH) test 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). Missing observations will be imputed as non-responders. A point estimate of treatment effect will be based on the sotagliflozin minus difference in binomial proportions. A 2-sided 95% CI will be estimated on the observed difference and will be based on normal approximation methods using a continuity correction factor. The individual components of the endpoint will be summarized separately using descriptive statistics. Sensitivity analysis of the primary endpoint will use a single imputation method to obtain a rectangular dataset. Imputations will be based on use of the last observation carried forward (LOCF) algorithm. The stratified CMH test will be applied to this imputed dataset. The stratified CMH test will also be applied to the PP dataset as an additional sensitivity analysis. Primary analysis of the continuous efficacy endpoints will use mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood (REML) method for estimation. The analysis model will include fixed, categorical effects of 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), time (study week), baseline-dependent variable-by-time interaction, and a treatment-by-time interaction. 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 sotagliflozin to placebo) and the 95% CIs 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. For binary endpoints estimated as binomial proportions, the frequency and proportion 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 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). These treatment group comparisons will be performed at Week 24 only. The earlier study weeks will use descriptive analyses to summarize the data. These descriptive statistics will include the patient counts and proportions, point estimates of treatment effect, and 95% CIs of the treatment effect. Missing observations at Week 24 will be imputed as non-responders; only the observed data will be summarized at the earlier study visits. Endpoints comprised of multiple outcomes will use descriptive methods to summarize each component by treatment group at each study week. The test for superiority of sotagliflozin 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 (α = 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 the 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 will be:

	1) A1C change from Baseline at Week 24 2) Body weight at Week 24 change from Baseline (absolute and percent change; the absolute change will be used in the sequence of analyses) 3) SBP change from Baseline at Week 16 in the subset of patients with Baseline SBP ≥130 mm Hg 4) Percent change from Baseline in bolus insulin dose at Week 24 In addition, raw P-values and 95% CIs will be computed for tests of all secondary endpoint hypotheses. These raw or unadjusted statistics will be used as descriptive summaries of the data and will not be used for formal testing of the hypotheses.
Safety Assessments	Safety and tolerability of sotagliflozin will be assessed by collection and analysis of AEs, EOSI, laboratory variables, vital signs, electrocardiograms (ECGs), and physical examinations.
Safety Data Analysis	Analysis of the safety data will be based on the Safety Population. Additional analyses may be performed on other populations or subpopulations. Safety analysis will be descriptive. Treatment-emergent adverse events (TEAEs) are defined as AEs reported after the first dose of double-blind study drug. Treatment-emergent adverse event summaries will include the overall incidence (number of patients with the event) and number of events by system organ class and preferred term, overall incidence sorted by descending frequency across treatment groups, events by maximum intensity, events by relationship to study treatment, and events leading to discontinuation of study drug; SAEs and EOSI will also be summarized. Listings will be provided for deaths, SAEs, and discontinuations due to AEs. Additional summaries or listings of AEs may also be provided. Vital signs, laboratory results, ECG results, and physical examination findings will be summarized descriptively at each time point. Actual and change from Baseline data will be calculated and

	summarized as appropriate. In addition, shift table analyses will be presented for the laboratory data. The efficacy analysis of hypoglycemic events will be conducted using MMRM and CMH tests. Since these data also serve as a measure of safety, additional analyses will be conducted. The first analysis will be performed 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 by SMBG, 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 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 study duration. The events will be modeled as a negative binomial process.
Meta-analysis	The occurrence of the following events will be statistically analyzed using data from this study combined with other Phase 2/3 trials conducted in T1D and T2DM patients: severe hypoglycemia, DKA, DILI, and MACE. Details of the analysis models and related assumptions will be documented in separate meta-analysis plans.

Table of Contents

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
A1C	hemoglobin A1C
ACE	angiotensin-converting enzyme
ACR	albumin:creatinine ratio
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blockers
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-HCG	β-human chorionic gonadotropin
BHB	beta-hydroxy butyrate
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CBC	complete blood count
CCR	calcium:creatinine ratio
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRA	clinical research associate
CRO	contract research organization
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
DBP	diastolic blood pressure
DDI	drug-drug interaction
DILI	drug-induced liver injury

Abbreviation	Definition
Table is continued on the next page	
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	daily dose causing 50% maximal glucose excretion in the first 24 hours following dosing
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOSI	event(s) of special interest
EOT	end-of-Treatment
ERC	Ethics Review Committee
EW	early Withdrawal
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCR	glucose:creatinine ratio
GD	gestational day
GI	gastrointestinal
GLM	generalized linear model
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide 1
GU	genitourinary
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPF	high-power field
I/C	insulin to carbohydrate ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
Continued on the next page	

Abbreviation	Definition
IDMS	isotope dilution mass spectrometry
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IOB	insulin on board
IRB	Institutional Review Board
IXRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
MACE	major adverse cardiovascular event(s)
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified Intent-to-Treat
MMRM	mixed-effects model for repeated measures
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
OGTT	oral glucose tolerance test
OTC	over-the-counter
PP	Per-protocol
PPG	postprandial glucose
PSDD	Patient Satiety Daily Diary
PSDD-NRS	Patient Satiety Daily Diary-Numeric Rating Scale
PV&DSS	Pharmacovigilance & Drug Safety Services
PYY	peptide YY
RBC	red blood cell
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SGLT	sodium-glucose cotransporter
SGLT1	sodium-glucose cotransporter type 1

Abbreviation	Definition
Continued on the next page	
SGLT2	sodium-glucose cotransporter type 2
SMBG	self-monitored blood glucose
SOC	standard(s) of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TB	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride(s)s
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
UA	urinalysis
UGE	urinary glucose excretion
ULN	upper limit of the normal reference range
US	United States

3. Introduction

3.1 Background Sotagliflozin (LX4211) and Disease

Incidence of Type 1 diabetes mellitus (T1D) varies widely globally, ranging from 0.1/100,000 per year in China and Venezuela to 36.5/100,000 per year in Finland.[1] Every year in the United States (US), on average more than 15,000 young people under the age of 20 years are diagnosed with T1D (Centers for Disease Control, 2011).[2] Maintaining glycemic control without hypoglycemia is a key therapeutic goal in T1D, to foster both near-term and long-term health. To date, this has only been achieved by maintaining strict dietary discipline with vigilant glucose monitoring linked to appropriate exogenous insulin use throughout the day. Chronic insulin use to maintain tight glycemic control presents significant challenges for patients, both logistically and medically, with constant approximations and adjustments made to accommodate various meals and activity levels. The challenges and inherent imperfections of such calculations contribute to the tendency of many T1D patients to maintain blood glucose levels at the high end or above recommended glycemic targets, in order to avoid the immediate dangers of hypoglycemia, ultimately at the expense of suffering long-term consequences of chronic high blood sugar.

Despite the broad availability of insulin therapy for T1D, there remain large segments of the patient population for whom adequate glycemic control is not consistently achieved. For example, according to the T1D registry,[3] (~30% <15 years old, ~70% <30 years old), of the 26,127 total registrants, 23% have poor glycemic control with inability to achieve a hemoglobin A1C (A1C) <9.0%, while ~17% of registrants with the same standards of care (SOC) and medical providers are able to attain an A1C <7.0%. It is likely that a spectrum of pathophysiological and socioeconomic drivers contribute to the wide disparity in glycemic control that is observed, and that certain groups within the T1D population find it particularly difficult to maintain glycemic control with currently available therapies.

Given the challenges associated with improving treatment outcomes for groups that have a history of especially poor control, there is a need to identify a safe and simple pharmacological treatment that can consistently improve glycemic control when added to insulin regimens. Importantly, attention must also be given to the goal of improving the quality of life in T1D patients by reducing insulin injection burden and the need for strict glucose monitoring.

3.1.1 The Potential Role of Dual SGLT1 and SGLT2 Inhibition

Sotagliflozin (LX4211) is a novel, orally delivered, small molecule dual inhibitor of sodium-glucose cotransporter type 1 (SGLT1) and sodium-glucose cotransporter type 2 (SGLT2) that

was designed to reduce glucose absorption in the gastrointestinal (GI) tract via SGLT1 inhibition and renal glucose reabsorption via SGLT2 inhibition. Lexicon's studies of knockout mice lacking either SGLT1 or SGLT2, or both, led to the discovery that inhibiting both targets pharmacologically could achieve metabolic and glycemic control without causing hypoglycemia.

Note: Sotagliflozin and investigational drug LX4211 are used interchangeably in this protocol.

Because sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 and is unlike the selective SGLT2 modulators currently in development, sotagliflozin provides a potentially unique mechanism of action.

The sodium-glucose cotransporter (SGLT) inhibitors currently approved for treatment of type 2 diabetes mellitus (T2DM) (canagliflozin, dapagliflozin[4] or empagliflozin[5]) or with clinical data in T1D, (dapagliflozin and empagliflozin) are selective SGLT2 inhibitors and therefore primarily target the kidney, where SGLT2 reabsorbs ~90% of filtered glucose. SGLT1 is the primary transporter for absorption of glucose and galactose in the intestine. SGLT1 inhibition by sotagliflozin delays and reduces glucose absorption in the proximal intestine thereby improving postprandial glycemic control with lower peak glucose levels and decreased glycemic variability. In addition, more glucose delivery distally triggers increased L-cell release of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), a natural peptide hormone response associated with enhanced glycemic and appetite control, findings that have been substantiated with numerous animal and human mechanistic studies.[6,7] The overall sotagliflozin treatment effect is a reduction in glucose load through a balanced inhibition of SGLT1 and SGLT2, offering the potential for T1D patients to achieve better glycemic control in combination with insulin therapies.

With sotagliflozin, the desirable effects of SGLT2 inhibition are maintained and complemented with SGLT1 inhibition in the GI tract to produce clinically meaningful reductions in postprandial glucose (PPG). The net result is improved glycemic control with lower urinary glucose excretion (UGE) than seen with selective SGLT2 inhibitors. The latter is an important finding which is predicted to allow sotagliflozin to maintain efficacy in patients with renal impairment as well as reduce the side effects associated with high UGE such as genitourinary (GU) tract infections. Notably, a recently completed proof-of-concept study in 30 T2DM patients with moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] 15-59 mL/min/1.73 m^2) randomly assigned 1:1 to placebo or 400 mg sotagliflozin showed a significant decrease in PPG excursion and an increase in GLP-1 secretion in these patients with high unmet medical need, in which SGLT2 inhibitors have little efficacy, while maintaining a favorable safety and pharmacokinetic profile. After 1

week, patients on sotagliflozin had a 50-60 mg/dL reduction in PPG compared to Baseline. Notably, this difference was preserved in the patient subgroup with severe renal impairment; efficacy is usually reduced in patients with severe renal impairment with selective SGLT2 inhibitors.

3.1.1.1 Potential Effects on Mealtime Glycemic Control

Mealtime insulin without sotagliflozin: Under the current mealtime treatment paradigm for T1D, exogenous insulin administration determines both glycemic control (PPG excursion triggered by ingested carbohydrate) and energy flux (facilitated glucose transport into cells) – therefore coupling 2 treatment objectives with a single insulin dose. As a result, to maintain normoglycemia after carbohydrate ingestion, which is usually excessive for most patients, the amount of insulin required is usually greater than the amount required for optimal energy flux over a very narrow range – resulting in a narrow therapeutic index.

Mealtime insulin with sotagliflozin: Based on results from oral glucose tolerance tests (OGTT) in controlled settings in multiple studies, sotagliflozin's unique dual mechanism of action is expected to act as a buffer against postprandial hyperglycemia with a daily capacity of approximately 60-100 g glucose. In some individuals, this capacity could buffer the entire carbohydrate content of more than 1 meal a day. This is explained below.

> Assuming a 2000 calorie diet, and a diet consisting of 40% carbohydrates, 800 calories (200 g) is derived from carbohydrates (for simplification, 100% of carbohydrates are assumed to be glucose). For a diet consisting of 60% carbohydrates, 1200 calories (300 g) is derived from carbohydrates. On average, each meal may contain 65 g of glucose in the 40% carbohydrate, 2000 calorie diet, and 100 g of glucose in the 60% carbohydrate diet.

With the glucose-buffering capacity afforded by sotagliflozin, mealtime glycemic control is expected to be influenced by both mealtime insulin and sotagliflozin, thereby decoupling glycemic control from energy flux. As a result, it is expected that:

- Energy flux will continue to be primarily determined by insulin dose.
- Glycemic control will be determined by both insulin dose and sotagliflozin, thereby requiring lower insulin doses to maintain glycemic goals, and also less precision of insulin dosing due to reduced variability in blood glucose.
- Less insulin will be required at mealtime to meet the goal of avoiding postprandial hyperglycemia.
- This will, in effect, lower the insulin to carbohydrate (I/C) ratio.

- This will result in a requirement for less mealtime insulin on board (IOB), for a given amount of carbohydrate.
- Less mealtime IOB will lower the risk of hypoglycemia.

Current experience in humans is described in Section 3.5.

3.2 Sotagliflozin Pharmacology

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2, designed to reduce glucose absorption in the GI tract via SGLT1 inhibition and renal glucose reabsorption via SGLT2 inhibition. Unlike selective SGLT2 modulators currently in development, sotagliflozin provides dual inhibition, representing a potentially unique mechanism of action.

3.2.1 Studies in Mice

3.2.1.1 Nondiabetic, Diet-induced, Obese Mice

Administration of single doses of sotagliflozin to nondiabetic mice improved glucose tolerance. Repeat-dose administration to diabetic mice not only improved glucose tolerance, but also lowered A1C.

The acute effect of sotagliflozin on facilitating glucose excretion in the nondiabetic, diet-induced, obese mouse was evaluated in 5 studies, each of which examined a control and 1 or more of the following doses of sotagliflozin: 0.003, 0.03, 0.1, 0.3, 3, 10, 30, and 60 mg/kg.

Sotagliflozin caused a dose-dependent increase in glucose excretion over the 24-hour period immediately following dosing. The minimally effective dose was 0.1 mg/kg. The daily dose causing 50% maximal glucose excretion in the first 24 hours following dosing (ED_{50}) was calculated to be approximately 1.8 mg/kg. Single doses of 10 mg/kg and 60 mg/kg sotagliflozin caused a pharmacologic effect for at least 72 hours after dosing.

The acute effect of sotagliflozin on oral glucose tolerance in the nondiabetic, diet-induced, obese mouse was evaluated at the following doses: 0.03, 0.3, 3, and 30 mg/kg. Sotagliflozin produced a dose-dependent improvement in glucose tolerance. Based upon the area under the plasma concentration-time curve (AUC) from Time 0 to Hour 4 values and, under these experimental conditions where sotagliflozin was concomitantly administered with dextrose at the start of the OGTT, the minimally effective dose of sotagliflozin for improving glucose tolerance in the normal mouse was found to be 3 mg/kg.

3.2.1.2 Diabetic Mice

The effect of repeated daily treatment with sotagliflozin on lowering blood glucose in the diabetic mouse was evaluated in 2 studies. The first study examined the effect of vehicle

versus sotagliflozin oral suspension (5 mL/kg dose volume) for 25 days at 1 and 10 mg/kg in mice with established hyperglycemia.

Sotagliflozin, at both 1 mg/kg and 10 mg/kg, produced a decrease in A1C concentrations. The reduction following treatment with sotagliflozin failed to reach statistical significance due to an unexpected decrease in A1C concentrations in the vehicle treated mice. Sotagliflozin did produce the expected significant increase in UGE. Fed blood glucose concentrations were also reduced by sotagliflozin.

The second repeat-dose study in diabetic mice examined the effect of sotagliflozin at 1 mg/kg on slowing the progression to severe hyperglycemia in young mice. Mice in the control group exhibited an increase in A1C, whereas mice treated with sotagliflozin did not exhibit such increases. UGE was increased with sotagliflozin, both at the start of dosing and at the end of the 5-week dosing period. In addition, diabetic mice treated with sotagliflozin daily for 5 weeks exhibited improved glucose tolerance.

3.2.2 Studies in Rats

The acute effect of sotagliflozin on facilitating glucose excretion in the nondiabetic rat was evaluated in 4 studies, each of which examined a vehicle control and one or more of the following doses of sotagliflozin: 0.3, 1, 3, 10, and 50 mg/kg. Sotagliflozin resulted in a dose-dependent increase in glucose excretion during the first 24 hours following dosing. All doses evaluated produced a significant increase in glucose excretion. The ED_{50} was calculated as 0.75 mg/kg; the effect increased with increasing dose up to the highest dose tested (50 mg/kg). At doses of 1 mg/kg and above, the pharmacologic effect of sotagliflozin was maintained for at least 2 days following a single oral dose.

3.2.3 Studies in Dogs

The acute effect of sotagliflozin on facilitating glucose excretion in the nondiabetic dog was evaluated in 2 studies, each of which included a predose (Baseline) control value and 1 of the following doses of sotagliflozin: 0.003, 0.01, 0.03, 0.1, 0.3, and 3 mg/kg. Sotagliflozin resulted in a dose-dependent increase in glucose excretion during the first 24 hours following dosing. The minimally effective dose for facilitating glucose excretion was 0.1 mg/kg. The ED_{50} was calculated to be 0.2 mg/kg. At doses of 0.1 mg/kg and above, the pharmacologic effect of sotagliflozin was maintained for at least 2 days following a single oral dose.

3.2.4 Summary of Pharmacology

The preclinical pharmacology studies of sotagliflozin were designed to evaluate the compound's mechanism of action and effects in vivo. Sotagliflozin consistently facilitated significant glucose excretion in nondiabetic, diet-induced obese mice, and normal rats and

dogs in a dose-dependent fashion during the first 24 hours following oral administration. Depending on the species and the dose of sotagliflozin, the pharmacologic effect of the compound could be maintained for 48 hours or longer. The ED_{50} for sotagliflozin was 1.8 mg/kg/day in the mouse. The ED_{50} was approximately 0.75 mg/kg/day for rats and approximately 0.2 mg/kg/day for dogs. Importantly, sotagliflozin reduced hyperglycemia in a diabetic mouse model and improved glucose tolerance in both diabetic and nondiabetic mice.

Detailed pharmacology information may be found in the Investigator's Brochure.

3.3 Sotagliflozin Toxicology

Toxicology studies including Good Laboratory Practice (GLP)-compliant mammalian toxicology, genetic toxicology, and safety pharmacology have been completed with sotagliflozin. Chronic toxicology studies with sotagliflozin have been completed in the rat and the dog. Results from these studies are summarized in Sections 3.3.1, 3.3.2, and 3.4.

Additional details can be found in the Investigator's Brochure.

3.3.1 Toxicology Studies in Rats

A 26-week chronic toxicology study with sotagliflozin has been completed in the rat. Doses administered were 30, 75, or 300 mg/kg/day. Results showed that sotagliflozin produced nonadverse clinical effects and pathology changes, most of which reversed (or exhibited reversibility) during the recovery phase. Clinical effects included relative decreases in body weight gain and body weight change for males given 75 mg/kg/day and animals given 300 mg/kg/day, and increased food consumption for all groups given sotagliflozin. Clinical pathology changes included minor hematology findings, higher urine volume, increased urine calcium and inorganic phosphorus excretion, increased serum urea nitrogen concentration, and minimally higher serum alanine aminotransferase (ALT) activity at all dose levels; and higher serum alkaline phosphatase (ALP) activity and serum gamma glutamyltransferase activity for animals given 300 mg/kg/day. Administration of sotagliflozin at all dose levels resulted in declines in bone turnover and calciotropic hormone levels. The trends for decreases in bone turnover markers at the low dose were generally marginal and not considered biologically significant.

Postmortem observations included increased kidney weights at all dose levels (reversed in males and was reversing in females with recovery) and reversible increased adrenal weights without microscopic correlates in males given ≥75 mg/kg/day and females given 300 mg/kg/day. Microscopic findings included reversible minimal to slight dilatation of renal cortical tubules in males given ≥30 mg/kg/day and females given ≥75 mg/kg/day; reversible transitional cell hyperplasia/hyperkeratosis within the renal pelvis and

hyperplasia/hypertrophy in the urinary bladder for females given 300 mg/kg/day; an increased severity of prostatic inflammation at the terminal and recovery sacrifices in males given ≥75 mg/kg/day; minimal to moderate increased trabecular bone adjacent to the growth plate of the sternum in males given ≥30 mg/kg/day and females given ≥75 mg/kg/day; and hyperplasia/hyperkeratosis of the nonglandular stomach at the junction of glandular stomach for males given ≥30 mg/kg/day that was still present at the recovery sacrifice in animals given 75 or 300 mg/kg/day. Based on the results of this study, the no observed adverse effect level (NOAEL) for sotagliflozin administered by oral gavage for at least 26 weeks to male and female rats is 30 and 75 mg/kg/day, respectively. These dose levels correspond with a Week 26 maximum observed plasma concentration (C_{max}) of 2360 ng/mL and $AUC_{0\text{-}24\ hours}$ values of 15,077 ng•hr/mL for males, with respective values of 13,333 ng/mL and 84,145 ng•hr/mL for females.

3.3.2 Toxicology Studies in Dogs

A 39-week chronic toxicology study with sotagliflozin has been completed in the dog. Doses administered were 20, 60, or 200 mg/kg/day. Results showed that sotagliflozin produced nonadverse clinical effects and pathology changes, most of which reversed or exhibited reversibility during the recovery phase. Clinical effects included clinical observations typical for animals given 200 mg/kg/day and increased food consumption for all groups given sotagliflozin. Clinical pathology changes were reversible and included effects on urinalysis (UA) and urine excretion tests at all dose levels and minimal to mild effects on serum glucose during Week 13 at all dose levels and during Week 40 of the dosing phase at >60 mg/kg/day. Anatomic pathology findings were noted at all dose levels and were limited to reversible increased kidney weights without microscopic correlates and reversible decreased hepatocellular glycogen. Based on the results of this study, the NOAEL for sotagliflozin administered by oral gavage for at least 39 weeks to male and female beagle dogs is 200 mg/kg/day, the highest dose level evaluated. This dose level corresponds with C_{max} and $AUC_{0\text{-}24\ hours}$ values of 21,867 ng/mL and 158,334 ng•hr/mL, respectively, for males and of 20,867 ng/mL and 143,795 ng•hr/mL, respectively, for females at Week 39 of the dosing phase.

3.4 Reproductive Toxicity

Initial reproductive toxicity studies assessing maternal, embryo/fetal toxicity and teratogenic potential have been conducted in both pregnant rats and rabbits. The NOAEL for maternal toxicity and developmental toxicity for sotagliflozin in Sprague-Dawley rats is 100 mg/kg/day. This dose corresponds to a gestational day (GD) 17 C_{max} of 7183 ng/mL and $AUC_{0\text{-}24\ hours}$ of 78,012 ng•hr/mL. The NOAEL for maternal reproductive function and

embryo-fetal developmental toxicity for sotagliflozin in New Zealand White rabbits was 200 mg/kg/day, the highest dose tested in this study. This dose corresponds to a GD20 C_{max} of 5623 ng/mL and $AUC_{0\text{-}24\ hours}$ of 18,145 ng•hr/mL.

3.5 Clinical Trials of Sotagliflozin in Humans

More than 600 subjects have participated in clinical studies of sotagliflozin. No significant safety concerns have been identified in the sotagliflozin drug program, and sotagliflozin has been well-tolerated in all studies to date. Serious adverse events (SAEs) and discontinuations due to adverse events (AEs) have been infrequent and have been balanced between treatment and comparator groups. Reports of treatment-emergent adverse events (TEAEs) across all sotagliflozin studies for which data are available were generally balanced between treatment and comparator groups. Headache was reported as a possible adverse reaction that occurred in ≥5% of subjects in sotagliflozin clinical studies, and was reported at a greater rate in sotagliflozin-treated subjects than placebo; however, most were assessed as mild to moderate, and most resolved spontaneously.

There was no common theme or imbalances in SAEs, nor were there significant imbalances between sotagliflozin and comparators in AEs. Cumulatively, during the clinical trial program 8 SAEs were reported by 6 patients (4 T2DM and 2 T1D), all of which were assessed as unrelated to study drug; those reported by 4 T2DM patients in the Phase 2 study LX4211.1-202-T2DM who received sotagliflozin included pulmonary embolism, deep vein thrombosis (DVT), bile duct stone, cholangitis and lower limb fracture, while a myocardial infarction (MI) was experienced by a patient receiving placebo. Two SAEs of diabetic ketoacidosis (DKA) were reported by 2 subjects treated with sotagliflozin in the Phase 2 T1D study LX4211.1-203-T1DM; both SAEs were assessed by the Investigator as due to failure of insulin delivery via insulin pump. In both cases, the patients had full recovery and resumed study drug within 48-72 hours of onset of DKA.

More information on the safety of sotagliflozin and on the clinical program can be found in the Investigator's Brochure.

3.5.1 Digoxin Drug-Drug Interaction (DDI) Study

Study LX4211.1-114-NRM was a drug-drug interaction study in healthy subjects, where LX4211 was shown to increase systemic exposure of digoxin, a sensitive P-gp substrate. Least squares mean digoxin Cmax, AUC0-last, and AUC0-inf increased by 51.9%, 31.1%, and 26.9%, respectively, following administration of digoxin in the presence of steady-state LX4211 compared to administration of digoxin alone. It can be concluded from these results that LX4211 acts as a mild P-gp inhibitor and may therefore result in elevation of digoxin levels. Given these data, it may be necessary to decrease digoxin dose by approximately

30-50% or to modify the digoxin dosing frequency when sotagliflozin is administered. All patients should be evaluated about concurrent medication at each visit and those taking concomitant digoxin should have digoxin concentrations monitored. If the digoxin is being managed by another physician, that physician should also be informed about this potential interaction. Additionally, we recommend that the patient's concomitant medications be evaluated as to whether they are P-gp substrates and the drug labels of these drugs be reviewed to determine if dosage reductions are recommended.

3.5.2 Clinical Trials in T1D

Sotagliflozin has been evaluated in a 4-week, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept trial in the US (LX4211.1-203-T1DM). A total of 36 patients, 18-55 years of age, with inadequately controlled T1D with an A1C range at Baseline of 7.0-9.0% have completed the study. Prior to the double-blind portion, the trial was initiated with an open-label "pioneer" group of 3 patients, in order to determine the appropriate recommended reduction in mealtime bolus insulin.

During the double-blind expansion phase, the threshold for correction insulin to treat hyperglycemia was lowered, with patient-specific threshold and algorithm determined by the Investigators based on individual goals. The study met the primary endpoint of reduction in total daily bolus insulin, as well as exploratory endpoint of 0.55% reduction in A1C after 29 days of treatment, both of which were highly statistically and clinically significant. Two reports of DKA were reported by 2 separate patients treated with sotagliflozin. Both events were reported by the Investigators as related to pump failure and unrelated to study drug. No events of severe hypoglycemia or SAE related to hypoglycemia have been reported.

3.6 Rationale for Current Study

3.6.1 Rationale for Selection of Dose

The proposed 400 mg once-daily dose is based on the results of the Phase 2b study LX4211.1-202-DM. In that study, doses of 75 mg once daily, 200 mg once daily, 200 mg twice daily, and 400 mg once daily sotagliflozin were tested over a 12-week, double-blind period. The 400 mg once daily dose was chosen for further evaluation based on its A1C lowering effect and the overall safety and tolerability observed at this dose. At 12 weeks, the 400 mg dose lowered A1C by a mean of 0.92%, while placebo lowered A1C by a mean of 0.09%. Lower doses were less effective than the 400 mg dose and did not have any advantages in safety or tolerability. The overall incidence of AEs on 400 mg once daily was similar to placebo. A maximum dose of sotagliflozin has not been established in terms of either safety or A1C reduction.

From a safety perspective, sotagliflozin was well-tolerated across studies. In healthy subjects, sotagliflozin was well-tolerated following single doses up to 2000 mg, and in multiple doses up to 800 mg over 10 days. Furthermore, in a thorough QT study, single doses of sotagliflozin (800 mg and 2000 mg) were well-tolerated and did not prolong the QT interval. Additionally, evaluation of metabolites in urine and plasma of healthy subjects resulted in no safety concerns following single doses of 400 mg sotagliflozin. In patients with T2DM, single doses of 400 mg in combination with sitagliptin, and multiple doses up to 400 mg in combination with metformin over 12 weeks, were also well-tolerated.

3.6.2 Rationale for Study Design and Control Groups

This study is designed to demonstrate the efficacy and safety of sotagliflozin when used as adjunct therapy in normal weight and overweight/obese patients with T1D treated with insulin. Sotagliflozin will be compared to placebo, consistent with regulatory guidance. The 24-week duration for assessment of A1C, which is a component of the primary efficacy endpoint, is assessed to be sufficient for achieving steady state conditions for sotagliflozin. Moreover, the "net benefit" primary endpoint chosen for this study (proportion of patients with A1C <7.0% at Week 24 and no episode of severe hypoglycemia and no episode of DKA) is clinically relevant. In this study, self-monitored blood glucose (SMBG) values will be reviewed by the Investigator and insulin doses adjusted if the SMBG trends are not meeting SOC T1D target goals.

Bias will be minimized by stratified allocation to treatment groups made based on body mass index (BMI) at Screening (<25 kg/m^2, ≥25 kg/m^2), Week -2 A1C (≤9%, >9%) and use of continuous subcutaneous insulin infusion (CSII) at Screening (Yes, No).

A placebo control will be used to allow for an unbiased assessment of treatment effects and safety data. The comparison with placebo is justified since patients will continue use of prescribed insulin therapy, and the patients' glycemic status will be monitored and adjustments made to insulin dose based on prespecified glycemic targets.

Bias will be minimized by randomly assigning the patients to treatment groups; blinding the patients, the Investigators, and the Sponsor to the treatment allocations; and by adjudication of death and event(s) of special interest (EOSI) in a blinded fashion.

A parallel-group design was selected because it is free of the assumptions underlying competing designs (eg, crossover). Inclusion of patients with eGFR ≥45 mL/min/1.73 m^2 is justified based on study LX4211.107, which demonstrated glycemic efficacy in diabetic patients with moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m^2).

3.6.3 Rationale for Patient-reported Outcomes: Satiety Substudy

This substudy is designed to demonstrate the effects of sotagliflozin on patient self-reported satiety. Based on the dual mechanism of action of sotaglifozin, it is anticipated that sotagliflozin will increase satiety. As result of dual inhibition, more glucose delivered distally will trigger increased L-cell release of GLP-1 and PYY, a natural peptide hormone response associated with enhanced glycemic and appetite control; these findings have been substantiated with numerous animal and human mechanistic studies.[8,9]

The instrument selected for the study, the Patient Satiety Daily Diary (PSDD) utilizes the Patient Satiety Daily Diary Numeric Rating Scale (PSDD-NRS).[8,9,10]

Patient-reported satiety is measured on an 11-point numeric rating scale as a daily diary measured prior to first meal. This single item measure has been utilized in diabetes studies to assess increased fullness as well as decreased hunger ratings relative to change in glucose and insulin responses. Numeric rating scales of satiety are well-accepted by Regulatory Agencies and are both sensitive to change and able to discriminate along the clinical severity continuum.

The PSDD is described in Section 8.1.6 and included in Appendix H.

3.7 Benefit/Risk of Sotagliflozin

In this study, sotagliflozin is being investigated as an adjunct to insulin treatment in patients with T1D with poor glycemic control. The attributes of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, and its insulin-independent mechanism of action are well-suited to address the needs of this population with high unmet medical need. While insulin has been available as a life-saving therapeutic option for patients with T1D, the risk of hypoglycemia inherent with insulin use significantly limits the ability to achieve target glycemic goals for many patients with T1D. As a result, many patients with T1D purposely maintain hyperglycemia.[11] As noted earlier, based on the T1D registry[3], only approximately 17% of registered T1D patients are able to achieve a target A1C <7.0%. Six to 10% of deaths in young patients with T1D are directly attributable to hypoglycemia, likely from cardiac arrhythmias.[12] A recent publication evaluating national trends for US Hospital admissions related to hyperglycemia and hypoglycemia reported an increase in rates of admission for severe hypoglycemia among diabetic patients 65 years and older during the period between 1999 to 2011.[13] Patients with T1D who are able to achieve target goals are only able to do so with rigorous monitoring of glucose, insulin dosing, dietary intake and lifestyle management, factors which increase burden and negatively impact quality of life. Therefore, ability of an oral agent like sotagliflozin to potentially achieve glycemic control safely when

added to insulin, without increasing the risk of hypoglycemia offers an attractive potential for patients with T1D.

Improvements in A1C, fasting plasma glucose (FPG), and PPG were observed with sotagliflozin in multiple studies in patients with T2DM. Glycemic efficacy with A1C and PPG reduction, reduction in total bolus and total daily insulin, and a trend towards reducing hypoglycemic events were also observed in the Phase 2 T1D study. As anticipated from the mechanism of action, treatment with sotagliflozin resulted in increased UGE (from inhibition of SGLT2) as well as increased incretin levels (from inhibition of SGLT1). In addition, the reductions in body weight, blood pressure (BP), and triglycerides observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

In patients with T1D, the glucose-buffering capacity afforded by sotagliflozin and mealtime glycemic control is expected to be influenced by both mealtime insulin and sotagliflozin, thereby decoupling glycemic control from energy flux. As a result, it is anticipated that patients will need lower and less precise doses of insulin to reduce variability in blood glucose. The lower amount of IOB at mealtime should reduce the risk of hypoglycemia. The ability to maintain better glycemic control with a simplified insulin regimen provided by sotagliflozin offers the possibility of long-term health benefits. The anticipated lower insulin requirement may also lead to lower risk of hypoglycemic events and improved quality of life.

Few safety issues have been identified in the sotagliflozin drug program. To date, sotagliflozin has been well-tolerated in all studies, with the majority of AEs assessed as mild to moderate in severity, and with most resolved spontaneously. Two patients in the sotagliflozin group in the T1D proof of concept study reported an event of DKA; in each case basal insulin was within 7% of baseline, and the event was attributed by the Investigator to insulin pump-related etiologies. Both cases were associated with high blood glucose readings >300 mg/dL, a finding expected in DKA and notable in that this value did not appear to be masked by sotagliflozin treatment. Based on the SGLT2 inhibitor mechanism of action, GU infections are recognized as a potential risk that will be monitored as an EOSI in all Phase 3 clinical trials. In completed trials to date, the rate of GU infections has been low and well balanced across sotagliflozin and placebo treatment groups. With the exception of DKA noted above, SAEs and discontinuations due to AEs have been uncommon and have been balanced between sotagliflozin and placebo or comparator groups. These have been uncommon and have responded to standard treatment.

Therefore, we believe sotagliflozin presents a favorable benefit-risk assessment based on its tolerability and safety profile known to date.

4. Study Objectives

4.1 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 A1C <7.0% at Week 24 **and** no episode of severe hypoglycemia and no episode of DKA after randomization.

4.2 Secondary Objectives

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

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

4.3 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 severe hypoglycemia
- Proportion of patients meeting success criteria for A1C and insulin
- 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

5. Investigational Plan

5.1 Overall Study Design

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

Adult patients with T1D and BMI ≥18.5 kg/m2 with inadequate glycemic control with insulin therapy (administered by subcutaneous injections] or CSII are eligible for enrollment in this study if they meet all inclusion and no exclusion criteria. Inclusion and exclusion criteria are listed in Section 6.1 and Section 6.2.

A total of 1400 patients will be randomly assigned 1:1 between the following 2 treatment groups:

- 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

It should be noted that all tablets (placebo and 200-mg) are identical in appearance.

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

Note: Subsequently, in this document, the term "insulin" includes insulin analogs. The term "insulin analog" may also appear, as needed for clarity. Bolus insulin refers to regular insulin or fast-acting insulin analog which may be administered via subcutaneous (SC) or inhaled route.

During the study, SMBG values will be reviewed by the Investigator and insulin doses adjusted if the SMBG trends do not meet SOC 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. Further details are presented in Section 7.6.1.

Patients will participate in the study for up to 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. The study periods are described in detail in Section 5.1.1 to Section 5.1.5.

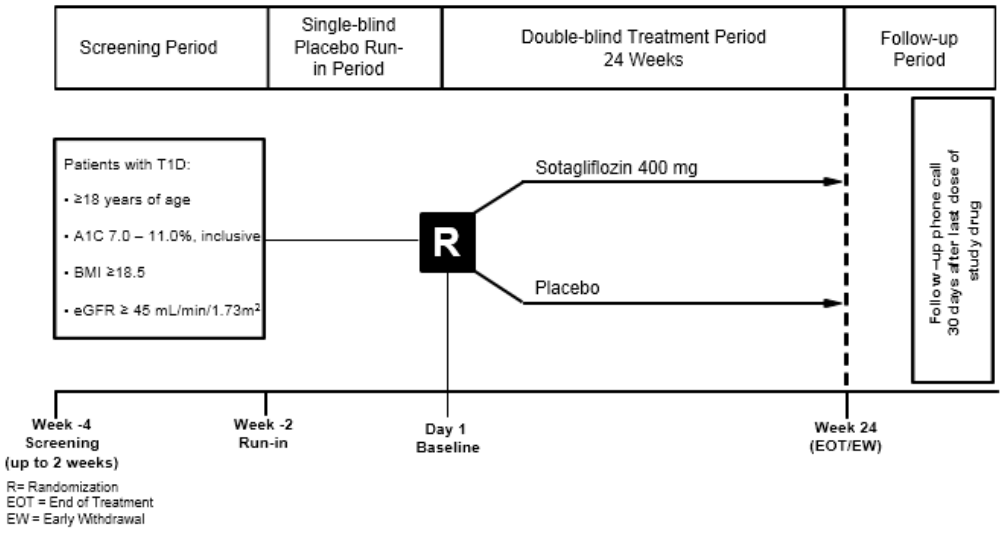
Efficacy measures are described in Section 8.1. The definition of efficacy endpoints and the methods used to analyze efficacy are described in Section 10.3.1 and Section 10.4.1, respectively.

Safety assessments are presented in detail in Section 8.2 and Section 9. Safety endpoints are defined in Section 10.3.2 and the methods used to summarize safety measures are described in Section 10.4.3.

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. Additional details are presented in Section 8.1.6.

The study design is summarized in Figure 5.1-1.

Figure 5.1-1: Study Schema



Adjudication of all deaths, EOSI, including major adverse cardiovascular events (MACE)/selected cardiovascular (CV) events, clinical or laboratory findings associated with drug-induced liver injury (DILI), DKA, and severe hypoglycemia episodes (as well as hypoglycemia reported as an 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 study safety data, as described in Section 9.6.1.

5.1.1 Screening Period

Written informed consent will be obtained from all patients before beginning any study related screening procedures. The collection of SAEs will begin after the patient has signed informed consent. Participation in the satiety substudy will be discussed at this time.

5.1.2 Single-blind Placebo Run-in Period

Patients will begin the single-blind placebo Run-in Period at Week -2.

At the beginning of the single-blind placebo Run-in Period, patients electing to participate in the satiety substudy will receive packets of satiety daily diaries. The patients will be instructed to complete the paper diary each day before the first meal of the day for the duration of the single-blind placebo Run-in Period (14 days, ±3 days). Patients will be reminded to bring the diaries with them on Day 1 (Baseline).

Patients will receive diet and exercise counseling according to nutritional recommendations for a healthy lifestyle consistent with American Diabetes Association (ADA)[14], the European Association for the Study of Diabetes (EASD)[15], or similar local guidelines, with a goal of weight maintenance to be followed for the study duration.

Glucose meter, BHB meter and supplies will be dispensed at the Run-in visit. Patients will also be educated on the use of the glucose meter and BHB meter provided for use during this study and use of the study diary to record insulin doses, SMBG, and hypoglycemic events (please see Section 7.6.1.3 for SMBG and insulin data required for CRF entry).

Compliance with the administration of single-blind placebo tablets and compliance with recording data in the study diary will be assessed during the single-blind placebo Run-in Period. Patients must demonstrate good compliance with placebo tablets (≥80%) during the single-blind placebo Run-in Period to be eligible for randomization. Compliance will be calculated as specified in Section 7.5.1.

5.1.3 Unscheduled Visits

During the course of the study, additional contact by telephone call, or unscheduled site visit, (or both) may be considered, based on Investigator's discretion. Assessments completed during these visits (on-site or by telephone call), may include evaluation of SMBG data, insulin doses, AEs (eg, volume depletion, elevated creatinine), hypoglycemic events, etc. The Unscheduled Visit electronic case report form (eCRF) will be completed for each unscheduled telephone contact or site visit.

5.1.4 24-Week Double-blind Treatment Period

Following completion of the single-blind placebo Run-in Period, eligible patients will enter the 24-week, double-blind Treatment Period. Patients will be randomly assigned 1:1 in parallel between the 2 treatment groups: sotagliflozin 400 mg or placebo.

The double-blind Treatment Period includes 5 clinic visits (Baseline, and Weeks 4, 8, 16, and 24).

For all patients, clinic visits should be scheduled in the morning at approximately the same time of day.

In regard to patients taking antihypertensive medications, the Investigator will be asked to maintain dosages unchanged between Baseline and Week 16, if this is consistent with proper medical management of the patient.

For patients in the satiety substudy, the satiety daily diaries completed during the single-blind placebo Run-in Period will be collected at Day 1 (Baseline). At the visit scheduled for Week 16, these patients will receive packets of satiety daily diaries. At the beginning of Week 23, patients will receive a telephone call to remind them to start recording information onto the satiety daily diaries. The patients will be instructed to complete the paper diary each day, before the first meal of the day for the last 2 weeks of the double-blind Treatment Period (ie, during Week 23 and during Week 24, a total of 14 days, ±3 days). The diaries will be returned to the site at the visit scheduled for the end of Week 24.

5.1.5 Follow-up Period

All patients will have a contact 30 days after the last dose of study drug to obtain information on SAEs, EOSI, and any AEs that were ongoing at the time of the EOT/EW Visit.

6. Study Population

Patients included in this study will be ≥18 years of age with a confirmed diagnosis of T1D and inadequate glycemic control on insulin therapy alone.

6.1 Inclusion Criteria

Patients must meet **all** of the following criteria listed below to be considered eligible to participate in the study. For patients not meeting eligibility requirements, the reason for exclusion must be recorded. **Note**: Patients not eligible because of laboratory result(s) may have the laboratory test(s) repeated once during the Screening Period at the discretion of the Investigator to determine eligibility:

1) Patient has given written informed consent to participate in the study in accordance with local regulations
2) Adult patients 18 years and older with a diagnosis of T1D made at least 1 year prior to informed consent
3) Patients are being treated with insulin(s) or insulin analog(s)
4) Non-fast acting insulin dose is stable (±20%) for 2 weeks prior to the Screening Visit
5) At the Screening Visit, A1C must be between 7.0% and 11.0%, inclusive
6) BMI ≥18.5 kg/m2
7) Must be willing and able to perform SMBG and complete the study diary as required per protocol
8) Females of childbearing potential must use an adequate method of contraception to avoid pregnancy throughout the duration of the study and for 30 days after the last dose of study drug. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopause is defined as no menses for ≥12 months without another cause. For females with questionable menopausal history (eg, irregular menstrual periods and age >40 years) a documented serum follicle-stimulating hormone (FSH) level must be ≥30 mIU/mL.
9) Females of childbearing potential must have a negative serum or urine pregnancy test prior to the start of study drug. In the case of positive urine pregnancy testing, a negative serum sample for pregnancy testing, to confirm that the patient is not pregnant, must be obtained prior to start of study.

6.2 Exclusion Criteria

Patients who meet **any** of the following criteria will be excluded from participating in the study. For patients not meeting eligibility requirements, the reason for exclusion must be recorded. **Note:** Patients not eligible because of laboratory result(s) may have the laboratory test(s) repeated once during the Screening Period at the discretion of the Investigator to determine eligibility:

1) Therapies and/or medications:
    a) Use of antidiabetic agent other than insulin(s) or insulin analog(s) at the time of screening (any medication other than insulin or insulin analog used for treatment of T1D must be washed out for at least 8 weeks prior to the Screening Visit)

b) Any prior exposure to sotagliflozin

c) Use of SGLT inhibitors within 8 weeks prior to Screening. **Note**: Patients taking an SGLT inhibitor may have that prohibited medication stopped, and may be considered for entry into the study if they have not been taking the prohibited medication for at least 8 weeks prior to Screening.

d) Chronic systemic corticosteroid use, defined as any dose of systemic corticosteroid taken for more than 4 consecutive weeks within the 6 months prior to the Screening Visit. **Note**: Topical, inhaled, ocular, or nasal sprays containing corticosteroids are allowed.

2) Diabetes-related conditions:

a) Type 2 diabetes mellitus, or severely uncontrolled T1D as determined by the Investigator

b) History of severe hypoglycemic event within 1 month prior to the Screening Visit

c) History of DKA or nonketotic hyperosmolar state within 1 month of Screening OR ≥2 episodes of DKA or nonketotic hyperosmolar state within 6 months of Screening

3) Laboratory Results:

a) Estimated glomerular filtration rate <45 mL/min/1.73 m^2 at Screening, as determined by the 4 variable Modification of Diet in Renal Disease (MDRD) equation

b) Fasting triglycerides >600 mg/dL(>6.77 mmol/L). **Note**: Patients who fail Screening based on this criterion must have their fasting status verified, may have triglyceride-lowering medications adjusted, and be reevaluated during Screening.

c) Abnormal liver function at Screening defined as any of the following: aspartate aminotransferase (AST) >2X upper limit of the normal reference range (ULN), ALT >2X ULN, serum total bilirubin (TB) >1.5X ULN. **Note**: If it is the opinion of the Investigator and the Medical Monitor that an increase in bilirubin is due to Gilbert's syndrome, then the patient may participate.

d) Screening beta-hydroxy butyrate (BHB) >0.6 mmol/L

4) Reproductive status:

a) Females who are pregnant or breastfeeding or intend to be during the course of the study

5) Gastrointestinal/hepatic:
   a) By known history, serologic evidence of current infectious liver disease (hepatitis A, B, or C), including antihepatitis A virus (immunoglobulin M), hepatitis B surface antigen, or antihepatitis C virus. **Note**: Patients with isolated positive hepatitis B surface antibody may be included.
   b) Difficulty swallowing such that the patient cannot take the study drug
   c) History of pancreatitis within 12 months of screening, or any prior history of recurrent pancreatitis
6) Renal:
   a) Initiation of chronic dialysis within 30 days prior to the Screening Visit or expected to occur within 180 days after the Screening Visit
   b) Renal disease that required treatment with immunosuppressive therapy, or a history of dialysis or renal transplant
   c) History of hereditary glucose-galactose malabsorption or primary renal glucosuria
7) Cardiovascular:
   a) New York Heart Association Class III or IV heart failure within 3 months prior to Screening Visit[16]
   b) Hypertensive urgency or emergency within 30 days prior to randomization. **Note**: Patients with uncontrolled hypertension at Screening will be allowed to enter the study provided that they are being aggressively treated for hypertension according to local guidelines. Examples of guidelines current at the time of protocol writing include those from the ADA[14] and the European Society of Cardiology.[15]
   c) Patients with unstable/symptomatic or life-threatening arrhythmia or heart block. **Note**: Asymptomatic atrial fibrillation is not considered to be life-threatening and patients with asymptomatic atrial fibrillation will be permitted to enter the study.
   d) Patient has had any of the following within 3 months prior to the Screening Visit:
      i. Hospitalization due to unstable angina
      ii. MI
      iii. Coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty
      iv. Transient ischemic attack (TIA) or significant cerebrovascular disease

8) Hematologic:
   a) History of hemoglobinopathies (sickle cell anemia, thalassemia major, sideroblastic anemia) or other disorder that may interfere with A1C determination
   b) Donation or loss of >400 mL of blood or blood product(s) within 8 weeks prior to Screening
9) Immune system: Known severe immunocompromised status, including, but not limited to, patients who have undergone organ transplantation. **Note**: Patients with human immunodeficiency virus (HIV) may participate if the Investigator considers them otherwise suitable candidates for this study.
10) Malignancy or active treatment for malignancy (ie, radiation or chemotherapy, including monoclonal antibodies) within 5 years prior to the Screening Visit. **Note**: Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal breast cancer in situ, resected low-grade prostate cancer, or other malignancies that in the opinion of the Investigator and the Medical Monitor are considered cured, may participate.
11) Current eating disorder or increase or decrease of weight within the 12 weeks prior to Screening by more than 10%
12) Known allergies, hypersensitivity, or intolerance to sotagliflozin or any inactive component of sotagliflozin or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), unless the reaction is deemed irrelevant to the study by the Investigator
13) Administration of any other investigational drug or participation in an interventional clinical research study within 30 days or 5 half-lives (whichever is longer) of planned Screening Visit
14) History of alcohol or illicit drug abuse (using Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria [17]) within 12 months prior to the Screening Visit
15) Patient is a study coordinator, employee of an Investigator or Investigator's site, or immediate family member of any of the aforementioned
16) Any condition that, in the opinion of the Investigator, may render the patient unable to complete the study
17) The presence of a clinically significant medical history, physical examination, or laboratory finding that, in the opinion of the Investigator or the Sponsor, may interfere

with any aspect of study conduct or interpretation of results. The Investigator or the Sponsor will supply justification for exclusion, if applicable.

6.3 Cessation of Study Drug and Termination of Study Participation

It is important to distinguish among 3 terms:

- Temporary cessation of study drug administration – refers to temporarily halting study drug administration, which may be resumed at a later date.
- Permanent cessation of study drug administration - refers to permanent cessation of study drug administration.
- Termination of study participation – refers to withdrawal of consent, or refusal to participate in any further clinic visits or procedures.

6.3.1 Temporary Cessation of Study Drug

If a patient misses more than 3 consecutive doses, the patient should contact the site for instructions. Upon visiting the site for a scheduled visit, if a patient is documented to have interrupted study drug for >5 consecutive days, the site must notify the Sponsor and/or the Sponsor's designee to obtain appropriate instructions. The Medical Monitor will assess the clinical scenario (with escalation to the Sponsor for input, if needed) and respond to the site.

Some patients with liver function abnormalities may be required to temporarily cease taking study drug. There has been no liver signal identified in preclinical and clinical studies to date. The proactive algorithm is designed to establish uniform and complete follow-up of patients with liver chemistry abnormalities and prevent unintentional re-challenge.

Temporary cessation of study drug that is resumed at a later date does not constitute permanent cessation or "discontinuation." Only patients who are permanently ceasing study drug administration should be deemed as permanently stopping study drug.

6.3.2 Permanent Cessation of Study Drug

Study drug administration may be halted for any of the following reasons:

- A life-threatening or serious adverse effect
- Noncompliance, including refusal of the study drug and/or failure to adhere to the study requirements as specified in the study protocol
- The Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study

- The Sponsor decides to terminate the study
- The patient meets specific criteria for liver function abnormalities
    - **Note**: There has been no liver signal identified in preclinical and clinical studies to date. The proactive algorithm is designed to establish uniform and complete follow-up of patients with liver chemistry abnormalities and prevent unintentional re-challenge.

Temporary or permanent cessation of study drug administration is NOT considered to be withdrawal of consent from study participation unless the patient explicitly withdraws informed consent.

6.3.3 Termination of Study Participation and/or Withdrawal of Consent

A patient has the right to discontinue study participation at any time, for any reason, and may leave the study without specifying a reason. The Investigator should make all efforts to obtain information about possible underlying AEs leading to the decision to withdraw from study participation. Any AE, EOSI, and SAE information elicited must be documented in the patient's source documents and the eCRF.

Unless a patient who prematurely discontinues trial participation specifically withdraws consent for any follow-up contact, all patients will continue to be contacted as specified in the protocol through the end of the study. There are a number of options for continuing follow-up once a patient decides to cease taking study drug. Investigators and site staff should encourage patients to allow as much follow-up as possible, and will need to clearly identify which aspects of the clinical trial the participants are discontinuing. Whenever possible, documentation should be collected in writing as to which of the following options the patient has chosen.

- The patient opts to permanently cease taking study drug only. In this case, the patient continues to complete all study activities per protocol.
- The patient is not willing to continue planned clinic visits/assessments, but will agree to phone call assessments in accord with the clinic visit schedule.
- The patient is not willing to continue planned clinic visits/assessments or phone call assessments, but will allow the Investigator access to their medical records and end-of-study telephone contact.
- The patient is not willing to be contacted but does allow the Investigator access to their medical records/contact with their care provider. In this case, the patient agrees

to continue as a study participant by allowing information collected from his/her medical records to be used for research purposes. The patient does not agree to be contacted via phone, email, and/or postal mail for follow-up visits and/or study updates.

- The patient is not willing to allow any direct contact, access to medical records, or contact with care provider. In this case, public records may be used to confirm vital status at end of study.
- The patient formally withdraws consent (ideally in writing, as detailed below) to participate further in any component of the study. In this case, the patient does not want any further medical information to be used for this research. Information that has already been obtained will remain as part of the research record, but no additional information will be added to the research record.

For the purposes of this protocol, only patients who are not willing to allow any direct contact, access to medical records, or contact with care provider will be deemed as patients who have withdrawn consent.

If a patient decides to withdraw consent from the study participation, it is necessary to ensure that relevant safeguards are put in place to maintain the individual's safety in the case of any future safety issues that are discovered. In this case, the decision to withdraw informed consent should be put in writing and, if possible, signed by the patient or patient's representative. A copy of this document should be maintained at the study site (with key data items recorded in the eCRF). This written information should specify which aspect(s) of the study consent is being withdrawn as described below. In accordance with International Conference on Harmonisation (ICH) guidelines, Food and Drug Administration (FDA) guidance, and other international ethical directives, data that have already been collected and incorporated into the study database, including the results of laboratory assays, will continue to be processed. In addition, every effort should be made to have the patient return to the clinic for a final EOT visit as described in Appendix A.

If the patient or the patient's representative refuses to withdraw consent in writing, the site must document and the Investigator must attest by signature, the reason for the patient's failure to withdraw the consent in writing. The Sponsor or designee should be immediately notified.

6.3.4 Lost-to-Follow-Up

If a patient repeatedly fails to return for any scheduled visit(s) and cannot be contacted or located by the site staff, Investigators will be expected to continue to try to contact those

patients until the end of the trial. This level of diligence is necessary in order to obtain (at a minimum) vital status (whether the patient is alive), and thus avoid being lost to follow-up for efficacy and safety assessment. All sites will receive training on how vital status may be monitored in accordance with local practices/regulations for patients who are unable to be contacted.

6.4 Criteria for Termination of the Study or Study Site

6.4.1 Early Termination of the Study

If the Steering Committee, Sponsor, DMC, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or terminated, this action may be taken after appropriate consultation between the Steering Committee, Sponsor, and the DMC. Full details on the roles of the Steering Committee and DMC will be provided in each committee's respective charter. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug

6.4.2 Early Termination of a Study Center

Conduct of the study at a particular center may be terminated for the following reasons:

- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent FDA, European Medicines Agency (EMA), and/or other applicable Regulatory Authorities regulations
- Submission of knowingly false information from the research facility to the Sponsor, Sponsor-designated contract research organization (CRO) or vendors, study monitor, or the FDA, EMA, and/or other applicable Regulatory Authorities
- Insufficient adherence to protocol requirements

The Investigator also has the right to withdraw from participating in the study at any time.

If a study center or Investigator is terminated, the Sponsor will make all efforts possible to have another investigative site assume responsibility for continuing trial activities.

Study termination and follow-up will be performed in compliance with the conditions set forth in the following sections of the Code of Federal Regulations (CFR): 21 CFR 312.50 and 21 CFR 312.56, and other local Regulatory Authorities.

6.5 Method of Assigning Patients to Treatment

Patients will be randomly assigned between 2 parallel treatment groups in a 1:1 manner. The treatment randomization schedule will be centralized and 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). The schedule will also account for the substudy in satiety. The desired balances will be accomplished by use of randomly permuted blocks of fixed size. An Interactive Voice/Web Response System (IXRS) will be used as a central mechanism to assign patients to study treatment. The study is double-blind so the study treatment assigned to each patient will not be revealed to the Investigator, patient, Sponsor, or designee until the decision is made to unblind the study. Data from individual patients may be unblinded if deemed medically necessary by the Investigator, or as required by local regulation in the case of an unexpected SAE.

6.6 Replacement of Patients

Patients will not be replaced in this study.

7. Treatment

Patients will take single-blind placebo tablets once daily, orally, before the first meal of the day during the single-blind placebo Run-in Visit (see Section 7.2)

Patients will take sotagliflozin 400 mg or placebo (in identical tablet form), once daily, orally, before the first meal of the day, during the double-blind Treatment Period (see Section 7.3).

The study drug eCRF will be completed each time study drug is dispensed (see Section 7.5.1).

7.1 Study Drug Identification

The identity, potency, strength, and appearance of the study drugs used are presented in Table 7.1-1. It should be noted that the placebo and 200-mg tablets will be identical in appearance.

Table 7.1-1: Study Drug Identification

Product	Potency/Strength	Appearance
Sotagliflozin (LX4211) Film-Coated Tablet	200 mg	White, oval shaped coated tablets
Placebo for Sotagliflozin (LX4211) Film-Coated Tablet	N/A	White, oval shaped coated tablets

7.2 Single-blind Placebo Run-in Period

Upon determination of eligibility, each patient will be assigned placebo tablets to complete the 2-week single-blind Run-in Period. Each bottle will be labeled with a 1-panel, blinded label. Prior to dispensation, the Investigator/qualified designee will complete spaces on the bottle label to specify the Patient Number and Date Dispensed. In addition, the protocol number, batch number, the number of tablets, route of administration, directions for use, bottle number, storage conditions, and use by date will be indicated on the label.

During the 2-week single-blind placebo Run-in Period, patients will take placebo tablets once daily, before the first meal of the day. The tablets should be taken with water and should be taken whole.

On days of clinic visits, patients should be instructed not to take their dose of single-blind placebo tablets in the morning. . On days of clinic visits, site personnel will provide instructions to the patients for dosing with single-blind placebo tablets based on scheduled procedures. The date and time of the last dose of placebo tablets prior to the clinic visit will be recorded in the eCRF.

In order to qualify for randomization, patients must have ≥80% compliance to taking the expected amount of placebo tablets during the 2-week single-blind placebo Run-in Period. In addition, patients should also demonstrate compliance with entering required data in the study diary.

Details concerning the methods used for the titration of insulin to maintain glycemic targets in this time period are presented in Section 7.6.1.2.

7.3 24-Week Double-blind Treatment Period

On Day 1 of the double-blind Treatment Period, patients will be randomly assigned in a 1:1 ratio between the following 2 treatment groups, as an adjunct to their insulin therapy:

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

Upon randomization, and at each dispensing visit thereafter, patients will be provided individual bottles of study drug. Sufficient quantity of study drug will be provided to allow prescribed daily dosing until the next scheduled dispensing visit. Each dispensing unit (bottle) will be labeled with a 1-panel, double-blind label printed in black. Prior to dispensation, the Investigator/qualified designee will complete spaces on the study drug label to specify the Patient Number, and Date Dispensed. In addition, the protocol number, batch number, quantity of tablets, route of administration, directions for use, bottle number, storage conditions, and use-by date will be indicated.

Except on days of clinic visits, patients should be instructed to dose with double-blind study drug before the first meal of the day. Two tablets of double-blind study drug should be taken with water and should be taken whole. If a patient misses a dose by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken, and dose reductions are not permitted.

On days of clinic visits, double-blind study drug will not be taken the morning of a scheduled clinic visit. Patients will take the assigned dose of double-blind study drug for that day per site personnel instructions based on scheduled procedures. The date and time of administration of the last dose of study drug prior to the clinic visit will be recorded in the eCRF. Details concerning the methods used for the titration of insulin to maintain glycemic targets in this time period are presented in Section 7.6.1.2.

7.4 Study Drug Adjustment/Interruption

The dosage of double-blind study drug may not be adjusted throughout the study. For safety reasons, should a patient experience an adverse event, the study drug may be temporarily interrupted.

Upon visiting the site for a scheduled visit, if a patient is documented to have interrupted study drug for >5 consecutive days, the site must notify the Medical Monitor and/or designee and be in receipt of a response prior to continuing the patient in the study on study drug. The Medical Monitor will assess the clinical scenario (if needed with escalation to the Sponsor for input) and respond to the site on a case-by-case basis as to the appropriateness of continuing the patient in study on study drug.

In cases of clinically significant volume depletion, study drug may be temporarily discontinued until the event has resolved. The Medical Monitor must be informed of these cases.

Note: If serum creatinine increases by ≥30% above the baseline value during the study, then the Investigator should consider assessment of: volume status, diuretic dosage, discontinuing nonsteroidal anti-inflammatory drugs (NSAIDs), and other relevant testing including renal imaging techniques, as appropriate.

Sodium-glucose cotransporter type 2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. All patients will be advised to maintain proper fluid intake and to consider increasing it if they sense greater thirst, increased urination, or if they feel dizzy or faint.

7.5 Handling and Dispensing of Study Drug

The Sponsor will be responsible for ensuring that the quality of the study drug is adequate for the duration of the trial. Study drugs, both active and placebo, should be stored at 15-30°C (59-86°F) in induction-sealed bottles as determined by the Sponsor and defined in the Investigator's Brochure.

Study drug should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients. The study drug must be dispensed only from official study sites by authorized personnel according to local regulations.

All study drug supplies that will be used in the study must be maintained securely under the direct responsibility of the Investigator or delegated by the Investigator to the hospital pharmacist, or other personnel licensed to store and dispense drugs. All drugs shall be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of drugs issued and returned is maintained.

7.5.1 Dispense Study Drug and Record Compliance

The Investigator must maintain accurate records of study drug receipt, dispensing information, and disposition. Sponsor will provide forms to facilitate inventory control, if the staff at the investigational site does not have an established system that meets these requirements.

Patients will be instructed to bring their empty bottles and any unused study drug to each clinic visit. Pill counts will be performed at each clinic visit by a member of the site staff to determine compliance. Pill count will be recorded on the study drug eCRF.

Treatment compliance will be calculated as:

$$\frac{\text{(Number of tablets dispensed – Number of tablets returned) X 100}}{\text{Number of tablets expected to be taken}}$$

The number of tablets expected to be taken should be 2 times the number of days since the last visit. The Investigator/qualified designee will remind patients at each visit regarding the importance of following the protocol defined schedule for taking study drug. Reasons for not following study drug administration as described in the protocol should be clearly recorded in the source documents.

Patients will be deemed "compliant" if their calculated compliance is between 80% and 120%, inclusive. If a patient's compliance is noted to be less than 80% or greater than 120% on 2 consecutive visits, the patient should be counseled by study personnel, and the Sponsor/designee should be contacted to recommend appropriate study continuation.

7.5.2 Return of Study Drug

Bottles of used, partially used, and unused study drug products should be retained until the clinical research associate (CRA) has been able to complete drug accountability and reconciliation.

Upon completion or termination of the study, all unused and/or partially used study drug must be returned to the Sponsor or designee, if not authorized by the Sponsor to be destroyed at the site.

All study drug returned to the Sponsor or designee or other authorized party must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original bottles (eg, bottles that have clinical labels attached). Empty bottles should not be returned to the Sponsor or designee. It is the Investigator's responsibility to arrange for disposal of all empty bottles, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused study drug should be arranged by the assigned site Monitor.

7.5.3 Destruction of Study Drug

If study drug is to be destroyed at the site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by the Sponsor, procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, and appropriate records of the

disposal have been documented and provided to the Sponsor or designee. Unused study drug can only be destroyed after being inspected and reconciled by the responsible CRA.

7.6 Concomitant Medications

Concomitant medications, supplements, or products used to maintain health taken from 2 weeks prior to the Screening Visit through the End of Study, including those specified in the inclusion/exclusion criteria, **must** be recorded in the source documents. Dose modifications of any other long-term (stable dose) medications that the patients are on at study entry are discouraged during the study period; **any modification** of concomitant medications from Screening and throughout the study period **must be recorded in the source documents with justification for the change.**

The following medications are not permitted during the Treatment Period:

- Any marketed or investigational antidiabetic agent, other than insulin(s) or insulin analog(s) (any medication other than insulin or insulin analog used for treatment of T1D must be washed out for at least 8 weeks prior to the Screening Visit)
- Chronic systemic corticosteroid use, defined as any dose of systemic corticosteroid taken for more than 2 consecutive weeks. **Note**: Topical, inhaled, ocular, or nasal spray corticosteroids are allowed.
- The use of SGLT inhibitors (other than double-blind study drug) is not permitted during the Treatment Period

7.6.1 Glycemic Goals and Adjustment of Insulin Dose

7.6.1.1 Glycemic Goals

The glycemic goals recommended for this study are to treat A1C and blood glucose to the following targets: A1C <7.0%, fasting/preprandial capillary plasma glucose 80-130 mg/dL (4.4-7.2 mmol/L), and 2-hour/peak postprandial capillary plasma glucose <180 mg/dL (<10.0 mmol/L). Goals may be adapted based on individual patient considerations consistent with ADA/EASD Guidelines.[14,15]

Suggested insulin adjustment algorithms are provided in the Site File Notebook to serve as reference, which may be modified based on the Investigator's clinical assessment.

7.6.1.2 Assessment of Glycemia and Adjustment of Insulin

For all patients, a study diary will be provided to record insulin doses, and episodes of hypoglycemia, as well as presence or absence of symptoms associated with these hypoglycemic episodes. The primary SMBG data sources will be glucose meter data from the

web-based portal and/or point-of-care glucose meter download/meter memory review. These primary data sources are supplemented by other available data, study diary, and laboratory blood glucose values. Additionally, for patients using CSII as the method of insulin delivery, the pump memory or downloaded pump data will provide daily basal, daily bolus, and total daily insulin data. Data to be recorded in the eCRF is outlined below. SMBG values obtained using the glucose meter provided for this study will be reviewed and guidance for the adjustment of insulin doses will be provided as per Section 7.6.1.4 and Section 7.6.1.5.

Upon review of SMBG data, if results do not meet the glycemic goals recommended for this study, then Investigators will assess the need for a change in insulin dosing. Following any change in insulin dosing, a follow-up call should be arranged within 1 week, to assess response to the therapy change, and any need for additional change(s). The recommended target for fasting/preprandial glucose is 80-130 mg/dL (4.4-7.2 mmol/L). Good clinical judgment is to be exercised while titrating the basal insulin dose, which should not be titrated any more frequently than every 3-4 days. Recommended target for 1-2-hour PPG by SMBG is <180 mg/dL, while avoiding hypoglycemia. Goals may be adapted for individual patients, if deemed necessary.

Patients who experience hypoglycemia as a result of a missed meal, unusual exercise, or alcohol use should receive counseling on the correction of these behaviors.

If needed, additional contact should be made available for patients to discuss dose adjustments in between scheduled site visits. During these visits (on-site or phone), patients will report their SMBG data, insulin doses and hypoglycemic events to the study site.

The dose of double-blind study treatment will not be adjusted at any time during the study.

7.6.1.3 Entering SMBG and Insulin Data into the eCRF

Patients will perform SMBG as instructed during the 3-5 days (consecutive or non-consecutive) prior to each clinic visit (see Section 8.2.2).

Calculation of SMBG Data for eCRF:

Self-monitored blood glucose values from the preceding 3-5 days (consecutive or non-consecutive) prior to each clinic visit will be assessed. Self-monitored blood glucose data will be obtained from as many available sources as possible, which include but are not limited to: (1) the memory of the glucose meter; (2) meter download, (3) SMBG from web-portal,; and (4) paper diary. The SMBG will be reviewed to obtain the glucose values for the preceding 3 to 5 days and the glucose values will be reviewed by the site to identify any unusual high or low values or any trends which may require a change in insulin dose(s). The patient should be questioned to obtain a possible explanation for unusual high or low values, and to confirm

that the values (from the glucose meter's memory and/or from other data sources) were obtained from the patient. A "clinical average" will be calculated from the acceptable available glucose values that have been collected and entered into the eCRF. (The "clinical average" does not imply arithmetic mean)

Calculation of Insulin Data for eCRF:

Insulin doses during the preceding 3-5 days (consecutive or non-consecutive) prior to each clinic visit will be assessed. Insulin dosing data will be obtained from as many available sources as possible which include but are not limited to: (1) the memory of the glucose meter if insulin data is entered into the meter; (2) meter download if insulin data is entered into the meter; (3) insulin pump memory; (4) insulin pump download; (5) insulin pump data from web portal; and (6) study diary. 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. Based on results of at least 3 days of data, the mean daily bolus, mean daily basal and mean total daily insulin (bolus + basal) will be calculated. These calculated values will be entered into the eCRF.

7.6.1.4 Insulin Adjustment on Day 1

All patients will take the first dose of double-blind study drug at the site. The study drug is to be administered prior to the first meal of the day (which is typically breakfast for most patients). For the first meal on Day 1, patients will be instructed to decrease their calculated (or usual) mealtime carbohydrate bolus insulin by 30%.

Subsequent adjustments in insulin dosing will be made based on SMBG trends, as assessed by the Investigator.

The mealtime insulin adjustment recommendations for Day 1 are based on results from the T1D study (LX4211.1-203-T1DM). It is expected that the I/C ratio will be decreased by approximately 30% with sotagliflozin treatment. It is also predicted that such an adjustment will convey appropriate margins of safety for both the treated and placebo groups. The I/C ratio will be subsequently adjusted as frequently as required by the Investigator to meet glycemic goals recommended for this study. It is expected that the Investigator will evaluate the postprandial blood glucose after the first dose of study drug and continue the 30% reduction in the mealtime I/C ratio if these values are in an acceptable range, and make

changes to the I/C ratio as clinically indicated for subsequent meals. The Investigator is encouraged to access the SMBG glucose uploaded from the patient's meter, and/or other appropriate sources of blood glucose data at least daily for the first few days after initiation of study drug and assess if further changes in insulin reduction are required. No change in high blood glucose correction factor (sliding scale), basal (or non-bolus) insulin, or basal rate is recommended at initiation of study drug, although the Investigator is not prohibited from making any changes in any insulin dose consistent with meeting glycemic goals recommended for this study.

7.6.1.5 Insulin Adjustment Strategy

- The need for insulin adjustments will be evaluated by the Investigator with the goal of maintaining or improving glycemic control consistent with the glycemic target ranges, local SOC, and the individual needs of the patient (see Section 7.6.1.2).
- Suggested insulin adjustment algorithms are provided in the Site File Notebook to serve as reference, which may be modified based on the Investigator's clinical assessment.
- When insulin is adjusted, it is recommended that any changes be made in increments of 10% or less, as assessed appropriate by the Investigator.
- During the course of the study, increases in insulin that affect the appropriate insulin action time period should be considered if the SMBG pattern or trajectory over 3-5 days is assessed as above the patient's individualized target range, and there is no evidence of hypoglycemia in the insulin-action time period (see Section 7.6.1.2).
- During the course of the study, decreases in insulin, which affect the appropriate insulin-action time period, should be considered if the SMBG pattern or trajectory is assessed as below the patient's individualized target range.

7.6.1.6 Unmasking of Patients Not Meeting Glycemic Targets

In order to avoid influencing patient and/or Investigator behavior, A1C and FPG results will be masked to study staff after randomization laboratories have been obtained. However, if the A1C is >11.0% at Week 16 or any determination thereafter, the A1C result will be unmasked to allow for appropriate diabetic management.

If an Investigator is unmasked to an A1C value >11.0%, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and evaluate possible causes, such as:

- Appropriate basal and mealtime insulin titration

- Compliance with treatment
- Compliance with diet and exercise
- Intercurrent disease

Note: The central laboratory UA will not include the measurement of urine glucose.

7.6.2 Concomitant Antihypertensive Medication and Treatment of Hypertension

Patients with elevated SBP and/or DBP, either naïve to medication or on therapy may enter the study. However, it is mandatory that their BP be treated aggressively and according to current local guidelines. Examples of guidelines current at the time of protocol writing include those from the ADA[14] and the European Society of Cardiology.[15]

The current ADA recommendations for the treatment goals for hypertension are:

- Patients with diabetes and hypertension should be treated to an SBP goal of <140 mm Hg.
- A lower systolic target, such as <130 mm Hg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.
- Patients with diabetes should be treated to a DBP <90 mm Hg. A lower diastolic target, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden.
- Patients with a BP >120/80 mm Hg should be advised on lifestyle changes to reduce BP.

Patients admitted to the study with BP exceeding that mandated by Good Clinical Practice (GCP) or regional SOC guidelines must be appropriately treated by either the Investigator or the referring physician.

The Investigator is asked to keep antihypertensive medication dosages unchanged between Baseline and Week 16, if this is consistent with proper medical management of the patient, since BP will be evaluated as an endpoint at Week 16. Since sotagliflozin may cause intravascular volume contraction, symptomatic hypotension may occur after initiating sotagliflozin particularly in patients with impaired renal function, elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB], or patients with low SBP. Before initiating sotagliflozin in patients

with 1 or more of these characteristics, volume status should be assessed and corrected and patients monitored for signs and symptoms after initiating therapy.

7.6.3 Concomitant Lipid Medication and Dyslipidemia/Lipid Management

Patients with hyperlipidemia/dyslipidemia should be treated in accordance with local and regional SOC.

7.6.4 Other Concomitant Medications

Initiation or adjustments of therapies for BP, lipids, and renal function will be left to the Investigator's discretion. All concomitant therapy should be driven towards achievement of levels recommended by local or regional SOC. The Screening and Run-in Periods will provide an opportunity to adjust concomitant medications as needed towards achievement of metabolic targets, but these medications may be adjusted at any time during the study. The Investigator should instruct the patient to notify the site about any new medications he or she takes after the start of the study. All medications and significant non-study drug therapy that the patient takes after the start of study treatment should be listed on the Concomitant Medication eCRF.

Starting any over-the-counter (OTC) medications or use of herbal supplements during the study should be strongly discouraged unless medically necessary. If use of a supplement is reported, it must be documented in the source documents.

Concomitant medications taken from 2 weeks prior to the Screening Visit through the End of Study, including those specified in the inclusion/exclusion criteria, must be recorded in the source documents and eCRF. Any modification of concomitant medications from Screening and throughout the study period must be recorded in the source documents and eCRF pages.

7.7 Blinding and Unblinding of Study Drug

In this treatment-blinded study, the designated group and treatment assigned to each patient will not be revealed to the Investigator, the patient, or the Sponsor or designee, until the decision is made to unblind the study. Data from individual patients may be unblinded if deemed medically necessary by the Investigator or as required by local regulation in the case of an unexpected SAE. The IXRS will be used to perform emergency unblinding by authorized individuals.

Because of the glycosuric effect of sotagliflozin, urine glucose values will be masked to all study staff.

The randomization schedule will be maintained by the designee performing IXRS for this study. Investigators, study site personnel associated with this trial, patients, and the Sponsor and its designee involved in the conduct of the study will remain blinded to individual patients' treatment assignments until database lock.

During the study, the blind is to be broken only when the safety of a patient is at risk and the treatment plan is dependent on the study treatment received. If the unblinding occurs without the knowledge of the Sponsor and/or designee, the Investigator must notify the Sponsor and/or designee as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

The Sponsor or designee will not release the randomization schedule to any party except upon formal written request by the Sponsor. The request must be approved by the appropriate Sponsor personnel, according to the Sponsor's standard operating procedures (SOPs). Details of any disclosure of the randomization schedule will be recorded in the site's study files and the Trial Master File. A copy will also be sent to the Sponsor and/or designee. The blinding of the study will be broken after the database has been locked. To maintain continuous blinding and study integrity, analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data. Details describing the DMC processes and procedures will be outlined in a separate DMC Charter.

8. Efficacy, Pharmacokinetic, Safety, and Other Assessments/Procedures

A Schedule of Assessments, with detailed time points, is provided in Appendix A. Study procedures and assessments are presented by visit in Appendix I. The efficacy endpoints derived from these assessments/procedures and the methods used to analyze these data are described in Section 10.3.1 and Section 10.4.1.

8.1 Assessment of Efficacy

It should be noted that the primary efficacy endpoint includes assessments of the incidence of severe hypoglycemia and DKA. These are discussed in Section 9.5.1 and Section 9.5.2, respectively.

8.1.1 A1C

Fasting blood samples will be used for the assessment of A1C.

8.1.2 Fasting Plasma Glucose and SMBG

Blood glucose values determined by SMBG will be obtained from data downloaded from the SMBG meter, the study diary and values obtained during clinic visits. The SMBG procedure is described in Section 8.2.2.

In the evaluation of safety, hypoglycemia (based on SMBG) and symptoms suggestive of hypoglycemia will be assessed as described in Section 9.5.1.

8.1.3 Insulin

The usage of insulin (or insulin analog) will be assessed from diary data for all patients. In addition, for patients using CSII, insulin data will be accessed from the pump download.

8.1.4 Kidney Function

Urinary albumin, calcium, glucose, and creatinine will be obtained from urine samples and used to derive albumin:creatinine ratio (ACR), calcium:creatinine ratio (CCR), and glucose:creatinine ratio (GCR).

Serum creatinine will be obtained from clinical chemistry samples and used in the calculation of MDRD eGFR (Appendix D).

8.1.5 Body Weight and Blood Pressure

The methods used to evaluate BP (SBP and DBP) and body weight are presented in Section 8.2.4 (Vital Signs) and Section 8.2.5 (Physical Examinations, Height, and Weight), respectively. The information will be evaluated for efficacy at the time points described in Section 10.3.1.2 and Section 10.3.1.3.

8.1.6 Patient-reported Outcome: Satiety (Substudy)

In the satiety substudy, the patients will be 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 (each day during Weeks 23 and 24). The instrument used will be the PSDD. The diary is presented in Appendix H.

Patient satiety will be evaluated using a 11-point PSDD-NRS. Patients will be asked to indicate their average level of hunger (satiety) over the past 24-hour period from 0 ‘very full’ to 10 ‘very hungry’.

8.2 Assessment of Safety

Assessments for safety include AEs, SMBG, clinical laboratory assessments, electrocardiograms (ECGs), physical examination, weight, and vital signs.

Adjudication of all deaths, MACE/other selected CV events, DILI, severe hypoglycemia (and SAEs of hypoglycemia), and DKA will be performed in a blinded manner by a committee(s) composed of experts. Details will be provided in the charter of the adjudication committee(s). Please refer to Section 9.6 for details.

8.2.1 Adverse Events

Monitoring and reporting of AEs (including SAEs, EOSI, and AEs leading to discontinuation) are described in detail in Section 9.

8.2.2 SMBG Procedures

Glucose meters will be supplied to all patients at the start of the Run-in Period at Week -2 in order to perform SMBG.

Fingerstick fasting blood glucose by SMBG will be measured in the clinic with the study-provided meter at each visit per the schedule in Appendix A. These results should be recorded in the eCRF. (If the study-provided meter is not available at a particular visit, then another glucose meter may be utilized).

Patients should be instructed to self-assess blood glucose levels regularly to allow appropriate glycemic control and insulin titration.

Fasting pre-breakfast SMBG:

- Patients should be encouraged to check fasting pre-breakfast SMBG daily for the entire duration of the study.

5-point SMBG profile:

- 5-point SMBG profile (fasting pre-breakfast, before and 2 hours after lunch, before dinner and bedtime) will be performed on at least 3 days per week before each visit for the duration of the treatment period.

8-point SMBG profile:

- It is recommended that at least one (1) 8-point SMBG profile be performed during the week prior to the clinic visit (fasting [before] and 2 hours after breakfast, before and 2 hours after lunch, before and 2 hours after dinner, bedtime, and once during the nocturnal period [typically 02:00 or 03:00]).

In addition, it is recommended that:

- The Investigator considers SMBG in the nocturnal period if fasting or bedtime SMBG readings are lower than goal, or there are unexplained high fasting SMBG results, which could be consistent with recovery from nocturnal hypoglycemia.
- Patients should perform SMBG prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving.
- SMBG frequency and timing should be dictated by the patient's specific needs and goals.
- Patients will be requested to monitor blood glucose levels with increased frequency whenever they experience any illnesses (eg, cold, flu), or symptoms of hyperglycemia or hypoglycemia.

Symptoms of hypoglycemia may include shakiness, dizziness, sweating, hunger, headache, pale skin color, sudden moodiness or behavior changes (such as crying for no apparent reason), clumsy or jerky movements, seizure, difficulty paying attention or confusion, or tingling sensations around the mouth. Patients will be instructed to record any hypoglycemic episodes or presence of hypoglycemic symptoms (Yes or No) in the study diary provided.

Patients will also be instructed to record SMBG values that are ≤70 mg/dL (≤3.9 mmol/L) in the study diary.

8.2.3 Selected Laboratory Tests

All laboratory tests will be sent to the central lab for analysis, with the exception of urine pregnancy test, point of care BHB and fingerstick glucose, which will be assessed at the site per Appendix A.

Blood and urine derived central laboratory tests for hematology, serum chemistry (including lipid profile), hormones, and other assessments are presented in Table 8.2.3-1. This table also includes laboratory tests such as FSH (females, if necessary to confirm postmenopausal status), thyroid stimulating hormone (TSH) (at Screening only; if abnormal, free thyroxine will be measured), and serum pregnancy tests (for females of childbearing potential). Details describing the UA (dipstick and microscopic examination) are presented in Section 8.2.3.1. Details concerning pregnancy testing are presented in Section 8.2.3.2.

The Schedule of Assessment is presented in Appendix A.

Table 8.2.3-1: Central Laboratory Assessments

Serum Chemistry

-Sodium	-Total bilirubin (TB)
-Potassium	-Alkaline phosphatase (ALP)
-Chloride	-Uric acid
-Carbon dioxide (bicarbonate)	-Calcium
-Blood urea nitrogen (BUN)	-Phosphorus
-Creatinine	-Total protein
-Glucose (serum)	-Albumin
-Alanine aminotransferase (ALT)	-Magnesium
-Aspartate aminotransferase (AST)	-Creatine phosphokinase (CPK)
	-Lactate dehydrogenase (LDH)

Hematology	**Lipid Profile**
-Complete blood count (CBC) -Differential -Platelet count -Hemoglobin -Hematocrit	-Total cholesterol (TC) -Triglycerides (TGs) -High-density lipoprotein cholesterol (HDL-C) -Low-density lipoprotein cholesterol (LDL-C) will be calculated by Friedwald equation -Non-HDL-C will be calculated as the difference between TC and HDL-C
Other Blood Samples	Urine
-A1C -Fasting plasma glucose (FPG) -Serum pregnancy test - females only -Follicle-stimulating hormone (FSH) (if necessary to confirm postmenopausal status) -Beta-hydroxy butyrate (BHB) (point-of-care and central lab) -Anion gap -Thyroid stimulating hormone (TSH) (at Screening only, if abnormal, free thyroxine will be measured)	Dipstick (including ketones) -Calcium -Albumin -Glucose (blinded to all study staff) -Creatinine -Urine pregnancy test (β human chorionic gonadotropin [β-HCG]) - females only

8.2.3.1 Urinalysis

Urinalysis (urine dipstick with microscopy) by a central laboratory will be performed at the time points shown in Appendix A.

Urine dipstick includes:

- Specific gravity
- pH
- Protein
- Blood

- Ketones
- Bilirubin
- Urobilinogen
- Nitrate
- Leukocyte esterase

Urine microscopy includes, but is not limited to, the detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment.

In an effort to minimize bias in the study, Investigators, staff, and the Sponsor or designee will be blinded to urine glucose results until after database lock. Investigators and the study staff will be instructed that they are not to perform local UA with reagent strips (dipstick) for the same reason. In order to evaluate a urinary tract infection, the Investigator should request microscopic and culture as clinically indicated, but should not use a dipstick.

If a dipstick analysis for the presence of ketones is deemed clinically necessary, the dipstick should not provide glucose data. The Ketostix® (ketones only) reagent strip or similar is appropriate for this purpose; use of the Keto-Diastix® (ketones and glucose) reagent strip is not appropriate. Sites and study personnel will remain blinded to the urine glucose and GCR data. The urinary glucose data will be analyzed after unblinding of the database.

Referral to urology is recommended for all patients with gross hematuria or high-grade hematuria (>50 red blood cells [RBCs]/high-power field [HPF]) on a single UA.

Referral to urology and urologic evaluation is recommended for males or females with asymptomatic microscopic hematuria or symptomatic hematuria (unilateral flank pain, lower irritative voiding symptoms, recurrent urinary tract infections despite appropriate use of antibiotics, etc) that produces >3 RBC/HPF on 2 of 3 properly performed and collected UAs. (**Note:** Urine specimens should be collected >48 hours after exercise. The UA should also be done when the urine is fresh, if possible, by a standardized methodology to avoid the lysis of formed elements from heat or chemical breakdown.) If there is an identifiable benign etiology for an isolated episode of hematuria, such as vigorous exercise, sexual activity, trauma, viral illness, or infection, it will be noted as part of the medical record. However, multiple episodes that meet the above criteria should be referred.

8.2.3.2 Contraception and Pregnancy Testing

Females of childbearing potential who participate in this study must use reliable contraceptive methods. For this study, females are considered to be of childbearing potential,

i.e. fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

For this study the following methods of contraception are considered to be acceptable effective contraceptive measures (based on annual failure rate of <1% when used consistently and correctly):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner

Serum pregnancy testing is performed at Screening. Urine pregnancy testing for females of childbearing potential based on urine samples will be performed as specified in Appendix A. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

8.2.3.3 Collecting Fasting Blood Sample and Urine for Storage

Fasting blood sample and spot urine sample will be collected in all patients on Day 1 and Week 24 (or at EOT/EW for patients who discontinue the study), frozen, and archived for potential evaluation of safety biomarkers as needed for additional study analyses. These

samples will be collected and stored in accordance with all national and local regulations, and after the patient has completed the informed consent process. If no analysis of the sample is performed, it will be destroyed when safety assessments required for regulatory submission of this study are complete. No genetic testing will be performed on these samples.

8.2.4 Vital Signs

Vital signs (pulse rate, respiration rate, temperature, and BP) will be measured as per the schedule in Appendix A.

An automatic sphygmomanometer will be dispensed to sites. For BP, the patient will have 3 measurements taken on the nondominant arm while seated (see Appendix G). Prior to the first measurement, the patient should remain seated at rest for at least 5 minutes. Following the 5-minute rest period, 3 separate seated BPs should be measured with at least 1 minute between BP measurements and with the cuff fully deflated between measurements. The value for analysis and entry criteria (Screening) will be the mean of these 3 measurements. It is recommended that BPs be assessed by the same person, if feasible, using the same calibrated equipment, on the same arm. Additional measurements may be obtained if clinically indicated.

Three seated pulse rate measurements will be obtained. The mean of the 3 seated pulse rate measurements will constitute the pulse rate value for that visit.

Note: Vital sign measurements should be measured after the patient has been seated for at least 5 minutes and prior to phlebotomy.

8.2.5 Physical Examinations, Height, and Weight

Complete physical examinations will be performed at Screening, and Week 24 (or EOT). 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.

Height (without shoes) will be measured once, during Screening.

Weight will be measured at Screening and at all other clinic visits. The patient should be weighed at approximately the same time of day, wearing minimal clothing (ie, no coat/shoes), and using the same calibrated scale at each visit, where possible. BMI will be calculated.

8.2.6 Electrocardiograms

The 12-lead ECG will be performed as per the schedule in Appendix A. The 12-lead ECG recordings should be conducted prior to the morning study drug administration. ECGs should be recorded either prior to phlebotomy or at least 30 minutes after phlebotomy.

All ECGs will be sent to a central ECG vendor for evaluation. Details on processing will be provided to the sites in a separate ECG manual.

8.2.7 Demographics

The following variables will be recorded on the appropriate eCRF: age, sex, and race/ethnicity (as permitted by local regulations).

8.2.8 Medical History

A general medical history will be collected at the Screening Visit and Week -2. The eCRF will include specific questions about relevant exclusion criteria, for example, a history of DKA.

8.2.9 Other Assessments

Other assessments will be completed as per the schedule Appendix A and include: informed consent, medication history, FSH for females who are postmenopausal, and TSH (at Screening only; if abnormal, free thyroxine will be measured).

8.3 Study Procedures and Assessments by Visit

Study procedures and assessments are presented by visit in Appendix A and Appendix I.

8.3.1 General Guidelines

The timing of the visits and follow-up telephone contacts for this trial are given relative to the day of randomization. The patients should be encouraged to return for their visits as close to the scheduled visit date as possible. Patients should be encouraged to fast (with the exception of water or noncaffeinated, zero-calorie beverages) for at least 8 hours before collection of any fasting laboratory samples. 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 and on the laboratory requisition form. ALL data collected will be used in the evaluations, including data that may originate outside the investigative site, such as non-visit (unscheduled) clinical laboratory evaluations.

Any events that occur between scheduled visits should be recorded by the Investigator as soon as they come to his or her attention.

Note: If serum creatinine increases by ≥30% above the Baseline value during the study, then the Investigator should consider assessment of: volume status, diuretic dosage, discontinuing NSAIDs, and other relevant testing including renal imaging techniques, as appropriate.

Sodium-glucose cotransporter type 2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. All patients will be advised to maintain proper fluid intake and to consider increasing it if they sense greater thirst, more urine production, or if they feel dizzy or faint. Investigators should consider closer monitoring of renal function in patients assessed to be at risk for deterioration of renal function. This may include evaluation of relevant laboratory tests at an unscheduled visit a week after initiating double-blind study drug.

Visits should be scheduled in the morning, at approximately the same time of day.

Prior to each visit, patients should be contacted and reminded of the date and time of their appointment.

In addition, the patient should be instructed to:

1. Bring the study drug bottles (used and unused) to the clinic. **Note**: Patients should not take study drug on the day of the visit until instructed by site staff. Patients should be instructed to take their basal insulin on the day of the visit, but not to take bolus insulin on the day of the visit until instructed by site staff.
2. Bring glucose meter and study diary to the clinic visit

Study assessments will be done according to the following detailed visit schedule presented in the subsequent sections.

At each visit, patients will be asked if to their knowledge any EOSI has occurred since the last visit.

8.3.2 Guidelines for Diet and Exercise during Study

Instructions for diet and exercise will be provided to patients. All patients will be provided with guidance on diet and exercise consistent with ADA guidelines for individuals with T1D, including training in carbohydrate counting during the Screening and single-blind Run-in Periods. Compliance with diet and lifestyle recommendations will be discussed with the patient throughout the study and specifically in case of insufficient glycemic control. In addition, guidance will be provided to all patients regarding GU hygiene and on maintaining general hydration (Appendix F).

8.3.3 Restrictions during Study

Restrictions during the study are described below:

1. Patients must maintain compliance with the dietary and physical activity changes and goals communicated at Screening and during the single-blind placebo Run-in Period.
2. Patients should be encouraged to maintain stable diet and exercise activities consistent with their normal practices at study entry and for the duration of the study.
3. Strenuous exercise should be avoided for 24 hours before planned clinic visits due to possible effect on safety laboratory assessments.
4. Addition of new concomitant medications will be restricted as per Section 7.6.
5. Females of childbearing potential must practice an acceptable method of birth control, as detailed in Section 8.2.3.2.

9. Safety Reporting

9.1 Adverse Events

Non-serious AE collection (including EOSI) will be initiated after the first dose of double-blind study drug.

Any sign, symptom, or illness occurring prior to the first dose of double-blind study drug will be captured in the medical history. Treatment-emergent adverse events are defined as any AEs reported after the first dose of double-blind study drug.

An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring in any phase of the clinical study whether or not associated with the study drug and whether or not considered related to the study drug. This definition includes an exacerbation of preexisting medical conditions or events, historical conditions not present prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug interaction, or the significant worsening of the disease under investigation that is not recorded elsewhere in the eCRF. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Any treatment-emergent abnormal laboratory result which is assessed as clinically significant by the Investigator should be recorded as an AE. In the event of clinically significant abnormal laboratory test values, the tests should be repeated and followed up until they have

returned to the normal range and/or an adequate explanation of the abnormality is determined.

Adverse events should not be solicited with leading questions that suggest specific signs or symptoms. Rather, AEs should be solicited by asking the patient a non-leading question such as: "Do you feel different in any way since receiving the dose or since the last assessment?"

The Investigator will evaluate all AEs with regard to the maximum intensity and relationship to study drugs, as follows:

Maximum intensity should be assigned using 1 of the following 3 severity grades

Mild:	aware of event but easily tolerated
Moderate:	discomfort, enough to cause interference with usual activity
Severe:	incapacitating: patient unable to work or perform usual activity

Relationship to study drug

Not related:	• Does not follow a reasonable temporal sequence from administration of the drug • Event is reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment; there is no reasonable causal link between the study drug and the AE
Unlikely related:	• Temporal sequence from administration of the study drug to event onset suggests a doubtful or improbable causal relationship • Alternative explanation (including underlying disease, complications, concomitant drugs, or concurrent treatment) is plausible and more likely
Possibly related:	• That follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), or • For which the possibility of the study drug being the causative factor (eg, existence of similar reports attributed to the suspected drug and its analogs; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable
Probably related:	• That follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and • For which the possibility of factors other than the drug, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause
Definitely related:	• Follows a clear temporal sequence from administration of the

study drug
- Could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Disappears or decreases on cessation or reduction in dose of the study drug
- Reappears or worsens when the study drug is re-administered
- Follows a response pattern known to be associated with administration of the study drug

The degree of certainty with which an AE is attributed to treatment with study drug (or alternative causes, eg, natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of known pharmacology of the study drug and/or reaction of a similar nature being previously observed with the study drug or the class of study drug.

All AEs that occurred during treatment 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. For each patient for whom an AE was reported that did not resolve before the end of the reporting period, follow-up information on the subsequent course of events must be submitted to the Sponsor. This requirement indicates that follow-up may be required for some AEs after the patient has completed his/her participation in the study.

9.2 Serious Adverse Events

All SAEs will be collected starting with signing informed consent and continue until 30 days after the last dose of study drug. Specific information regarding collection of CV events is described in Section 9.5 (Events of Special Interest).

An SAE is defined as any event that results in any of the following outcomes:

1. Death;
2. Life-threatening situation, defined as one in which a patient is at immediate risk, in the Investigator's opinion, of death from the reaction as it occurs. This does not include an event that might have caused death if it had occurred in a more severe form;
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
4. Inpatient hospitalization or prolonging of an inpatient hospitalization;

5. Congenital anomaly/birth defect in the offspring of a patient who received study drug; or
6. Medical or surgical intervention that is necessary to prevent 1 of the outcomes listed in this definition

The term "hospitalization" refers to any surgery or treatment that requires a formal admission into the hospital regardless of length of stay. This term does not include an emergency room visit or admission to an outpatient facility.

Hospitalization for preplanned elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'non-serious' attributed according to the standard criteria. Additionally, if the elective procedure had to be performed sooner than planned due to a worsening of the underlying medical condition, then the worsening medical condition would need to be reported as an AE.

All SAEs, regardless of assessment of causal relationship to study drug, must be reported as follows:

- Complete the SAE form utilizing the AE eCRF in the electronic data capture (EDC) system and submit within 24 hours of learning of the event.

The CRO will provide the Investigators with blank SAE forms, which are to be completed in the event that access to the EDC system is not available. If the EDC system cannot be accessed, the completed SAE forms will be faxed to the Covance Pharmacovigilance & Drug Safety Services (PV&DSS) number below. Once the EDC system is available, the SAE information must be entered within 24 hours of the system availability.

Information not available at the time of the initial report must be documented in the EDC within 24 hours of receipt of the new information. Substantiating data such as relevant hospital or medical records and diagnostic test reports should be also submitted via fax to:

Covance Pharmacovigilance & Drug Safety Services (PV&DSS) at:

Region	Telephone Number	Fax Number
United States	+1 (888) 724-4908	+1 (888) 887-8097
Outside United States	+44 1628 548171	+44 1628 540028

An SAE that occurs after completion of the study but, in the opinion of the Investigator, is related to the study drug, should be reported as described for an SAE. If an AE does not meet the FDA's definition of "serious" but is considered by the Investigator to be related to the

study drug and of such clinical concern as to influence the overall assessment of safety, it must be reported as defined for an SAE.

All patients (including discontinued patients) with an SAE must be followed until the event resolves or reaches a new Baseline, but for a minimum of 30 days after the last dose of study drug. Additionally, if the patient has died, the Investigator will obtain appropriate records to determine the cause of death, which include but are not limited to death certificate, hospital records, or autopsy results.

9.3 Suspected Unexpected Serious Adverse Reactions

The applicable Regulatory Authorities and all participating Investigators shall be notified by a written expedited safety report of any suspected adverse reaction that is both serious and unexpected (eg, suspected unexpected serious adverse reaction [SUSAR]), no later than 15 calendar days from the "date learned" of the event. An AE is considered to be an adverse reaction if the relationship between the AE and the study drug is classified by the Investigator and/or Sponsor as "possibly related," "probably related," or "definitely related." In addition, the applicable Regulatory Authorities will be notified within 7 calendar days of any unexpected fatal or life-threatening suspected adverse reaction. An unexpected AE is any adverse drug event which is not listed in the current Investigator's Brochure or is not listed at the specificity or severity that has been observed. Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. The following examples provide types of evidence that would suggest a causal relationship between the drug and the AE: (A) a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome); (B) one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture); (C) an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

An untoward and unintended response to a non-study drug is, by definition, not a SUSAR.

9.4 Precautions

9.4.1 Pregnancy

Any patient who becomes pregnant during the study must be discontinued from treatment immediately and should be followed through delivery or termination of the pregnancy. In pregnancies that progress to term, any congenital abnormalities/birth defects in the offspring of a patient who received study drug should be reported as an SAE. The outcome of the pregnancy and the presence or absence of a congenital abnormality will be documented by completion of a Pregnancy Questionnaire and a Pregnancy Outcome Form in accordance with GCP and ICH guidelines and the Sponsor's SOPs. Female patients should also notify the Investigator if they become pregnant within 30 days after last dose of study drug. The Sponsor must be notified of all pregnancies reported to the Investigator (see Section 9.2 for contact information).

9.5 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.

Events of Special Interest are characterized as:

A) Specific events that may be related to the mechanism of action of the drug, or which may be of special concern because of toxicity issues associated with the study drug or study drug class. For example, by increasing the urinary excretion of glucose, SGLT inhibitors also increase urinary output. This may lead to volume depletion in some patients. In order to provide better information about the incidence and extent of this AE, additional information will be collected about any reports of volume depletion or AEs associated with volume depletion.

B) Rare events not known to be related to the mechanism of action of the drug or class, which are of interest to the Sponsor.

All hypoglycemic events are considered EOSI. With the exception of hypoglycemia, all EOSI are considered to be AEs and should be reported on the AE eCRF as described in Section 9.1. For each EOSI reported, sites will be prompted to complete an EOSI Targeted Questionnaire. (In case an EOSI meets criteria to be reported as an SAE, please follow procedures as described in Section 9.2).

- Events of Special Interest are:
    - Hypoglycemia (see Section 9.5.1)
    - DKA, including all cases of metabolic acidosis (see Section 9.5.2)

- Volume depletion
- MACE and specific CV Events
- 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, pancreatic, and prostate)

Note: Other AEs may be determined to be of special interest. As applicable, relevant Medical Dictionary for Regulatory Activities (MedDRA) terms will be described in the Statistical Analysis Plan (SAP).

The following EOSI will be adjudicated in a treatment blinded fashion: severe hypoglycemia (or hypoglycemia reported as an SAE), DKA (including all cases of metabolic acidosis), MACE/other specified CV events, and DILI.

For the EOSI that require adjudication, the site will need to collect and submit copies of supporting source documents to the Sponsor's designee. Specific instructions regarding this process will be provided in the Site File Notebook. Algorithms defining the evaluation of liver laboratory abnormalities (possible DILI) are located in Appendix E.

Details regarding the membership, remit, and operations of the adjudication committee will be contained in the respective charter.

9.5.1 Hypoglycemia or Symptoms Suggestive of Hypoglycemia

Hypoglycemia is a common complication of insulin therapy. According to recent data, severe hypoglycemia is common in T1D with at least one SH event in the prior 3 months reported by 6% of the 2,561 participants in a survey of those with T1D. The highest occurrence being in those age 50 years and older [18]. Whenever the patient has symptoms suggestive of hypoglycemia, SMBG should be performed prior to treatment of the event with carbohydrate administration unless safety considerations necessitate immediate treatment prior to

confirmation with SMBG. For every episode of hypoglycemia, regardless of severity, the patients should complete the appropriate hypoglycemia data in the study diary provided by the study site. In addition, especially in case of recurrent episodes of hypoglycemia, the patients should be encouraged to contact their study site for instructions on appropriate management of their diabetes.

Patients are instructed to contact the Investigator as soon as possible following any severe hypoglycemic episode for review of data and to assess if a change in insulin therapy is required.

The patient will record whether symptoms of hypoglycemia were present or absent for each episode of documented hypoglycemia on the provided study diary as soon as possible after the episode, so that this information can be reviewed by the site during the next visit. Documentation for duration of a hypoglycemic episode is only required for cases of severe hypoglycemia.

Treatment of documented hypoglycemia requires the ingestion of carbohydrates (glucose). In most cases, 15 to 20 grams of glucose is the preferred treatment. A rise in blood sugar and change in symptoms should occur within 15 to 20 minutes. Re-treatment may be required in certain instances. The patient should be instructed to retest blood glucose 15 to 20 minutes after treatment, and re-treat every 15 to 20 minutes if hypoglycemia has not resolved.

Standardized definitions of hypoglycemia are being utilized across the sotagliflozin development program. The definitions and procedures described below will be implemented across the sotagliflozin program.

In the sotagliflozin program, hypoglycemic events will be categorized as either (1) Severe Hypoglycemia or (2) Documented Hypoglycemia. An episode may meet criteria for both categories. In accordance with the February 2008 FDA draft Diabetes Guidance[19], and the 2012 EMA Diabetes Guideline[20], hypoglycemic events reported in this trial will be classified as severe hypoglycemia, documented symptomatic hypoglycemia, or documented asymptomatic hypoglycemia per the following definitions:

1. Severe hypoglycemia: Severe hypoglycemia 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?

-OR-

c. Did the patient have a seizure during the episode? Note: "patient requires the assistance of others to treat" means that the neurologic impairment was severe enough to prevent self-treatment in the opinion of those providing assistance to treat. **Note**: Assisting a patient out of kindness, when assistance is not required, should not be considered as "requiring the assistance of others to treat."

2. Documented symptomatic and asymptomatic hypoglycemia:

   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].

   -OR-

   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]

Hypoglycemia is considered an EOSI for the sotagliflozin program. The Investigator will record all occurrences of documented hypoglycemia or severe hypoglycemia in the Hypoglycemia Reporting eCRF. In case an event meets criteria for both documented and severe hypoglycemia, both sections of the Hypoglycemia Reporting eCRF will be completed. Hypoglycemia data will be assessed at each visit by evaluating all available glycemic data. The primary data sources will be glucose meter data from the web-based portal and/or point-of-care glucose meter download/meter memory review. These primary data sources are supplemented by other available data, study diary, and laboratory blood glucose values.

Because the analysis for hypoglycemia will be based on data recorded on the Hypoglycemia Reporting eCRF and not the AE eCRF, it is requested that the Investigator not submit hypoglycemic events on the AE eCRF unless the episode meets criteria for an SAE (as described in Section 9.2). However, the Investigator is not prohibited from characterizing hypoglycemia as an AE. Any event of hypoglycemia reported as an AE will be cross-checked to ensure that the event is also reported on the Hypoglycemia Reporting eCRF.

All hypoglycemia events reported by the Investigator as severe and/or reported as SAEs will be adjudicated by experts blinded to the treatment assignment. Details regarding processes to be followed will be described in the CEC Charter.

Hypoglycemia will be analyzed as incidence of patients (%) with at least 1 hypoglycemic event and the number of severe hypoglycemic events per patient per year of exposure, and the number of documented hypoglycemic events per patient per day. Subanalysis of total

documented hypoglycemia (symptomatic plus asymptomatic), documented symptomatic hypoglycemia, documented asymptomatic hypoglycemia and severe hypoglycemic events will be performed.

Severe and documented hypoglycemia will be further characterized as follows:

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

Severe hypoglycemia will be further characterized as:

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

9.5.2 Diabetic Ketoacidosis

Diabetic ketoacidosis is the most serious hyperglycemic emergency in patients with T1D and T2DM. According to recent data, DKA is common in T1D with at least one DKA event in the prior 3 months reported by 3% of the 2,561 participants in a survey of those with T1D.The highest occurrence being in young adults (5%), and those with high A1C (up to 12% in those with A1C ≥ 9%) [18]. In adult patients mortality of less than 2% has been reported in controlled clinical studies; mortality is increased in the elderly and patients with life-threatening concomitant illnesses. Common precipitating factors include infections, intercurrent illnesses, psychological stress, and noncompliance with insulin therapy. Clinical features of DKA at presentation can be nonspecific; however, most patients complain of polydipsia and polyuria for several days before onset of DKA. Other common symptoms include generalized weakness, weight loss, nausea, vomiting, and abdominal pain. The laboratory triad of hyperglycemia, ketonemia, and metabolic acidosis defines DKA. A commonly used classification of mild, moderate, and severe DKA is described below in Table 9.5.2-1. In regard to the 2 cases of DKA that occurred with empagliflozin,[5] it was noted that 1 patient presented with plasma glucose of 17.0 mmol/L (306 mg/dL) and another presented with plasma glucose of 11.8 mmol/L (212 mg/dL). The authors noted, “Specifically, both patients presented with plasma glucose concentrations that could be interpreted as lower than typically associated with diabetic ketoacidosis.” In the sotagliflozin T1D phase 2 study, (LX4211.203), the 2 cases with DKA that occurred on sotagliflozin had blood glucose values of 30.7 mmol/L (553 mg/dL) and 20.9 mmol/L (376 mg/dL). However,

it is possible that DKA could present with glucose values ≤250 mg/dL in patients treated with sotagliflozin.

Table 9.5.2-1 Diagnostic Criteria for DKA for Patients Not Treated with Investigational Agents

	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25 - 7.30	7.00 - 7.24	<7.0
Serum bicarbonate (mEq/L)	15 - 18	10 - <15	<10
Urine ketones[a]	Positive	Positive	Positive
Serum ketones[a]	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)[b]	Variable	Variable	Variable
Anion gap[c]	>10	>12	>12
Alteration in sensorial or mental obtundation	Alert	Alert/drowsy	Stupor/coma

[a]Nitroprusside reaction method
[b]Effective serum osmolality = 2[Na^+ (mEq/L)] + [glucose (mg/dL)/18]
In the table, anion gap = [Na^+] – [Cl^- + HCO_3^-] with the normal anion gap referenced as "between 7 and 9 mEq/L, and an anion gap > 10-12 mEq/L indicates the presence of increased anion gap metabolic acidosis". However, the normal range for each of the individual measurements varies depending upon the specific methodology used. In addition, the serum potassium can be included in the anion gap measurement, resulting in a normal range that is approximately 4 mEq/L higher than the number calculated using the preceding equation. As a result, interpretation of the anion gap should be based on the laboratory reference range for the anion gap, and considering baseline values for the individual patient.
Source: Adapted from Kitabchi, 2009 [21]

The therapeutic goals in DKA management include restoration of circulatory volume and tissue perfusion, decreasing serum glucose, clearance of serum ketoacids, and correction of electrolyte abnormalities.

Instructions for the patient and site staff:

At every clinic visit blood BHB (central laboratory and point-of-care) testing will be conducted. At visits where UA is performed, the evaluation will include urine ketone determination by dipstick.

It is possible that GI or other AEs occurring with LX4211 may mask presenting symptoms of DKA (Appendix F). These symptoms include but are not limited to: inability to maintain oral intake, generalized weakness, excessive thirst, abdominal pain, nausea, vomiting, rapid weight loss, fever, frequent urination, fruity-scented breath, confusion, acute illness and/or consistently elevated blood glucose. Therefore, it is important that patients with GI complaints or intercurrent illness be instructed by the site to measure their blood or urine ketone or blood BHB levels.

(Note: In some patients alcohol may be a possible trigger for ketosis).

If ketosis is present (moderate or higher for urine ketones or blood BHB level is >0.6 mmol/L), then the patient will be asked to contact the Investigative site immediately. In this situation, the investigator should consider instructing the patient to take rapid acting insulin by syringe (not insulin pump) as well as eat carbohydrates in order to reverse the ketosis. After rechecking the ketones, the investigator should consider instructing the patient to take additional doses of rapid acting insulin every 2 hours until elevated ketones are normalized. Because the amount of insulin needed to lower ketones will also lower blood glucose, it is necessary for the patient to increase carbohydrate intake. Typically this would be 15-30 grams of carbohydrate each hour provided by a glucose containing sports drink or oral rehydration fluid. The site will evaluate if an assessment for metabolic acidosis is appropriate. If laboratory testing confirms presence of metabolic acidosis, then the "Possible DKA" eCRF will be completed. If nausea and vomiting are present and the patient is unable to keep liquids down the patient should be evaluated in an Emergency Room.

If a patient is scheduled for a procedure or surgery that requires withholding oral intake (NPO), it is recommended that study drug is held from the day prior to procedure or surgery and resumed the day after procedure or surgery is complete and patient is tolerating adequate oral intake.

An independent adjudication committee composed of experts in T1D will adjudicate cases of DKA (including all cases of metabolic acidosis) in a blinded fashion (see Section 9.6). Details regarding processes to be followed will be described in the charter.

9.6 Safety Monitoring and Oversight Committees

9.6.1 Data Monitoring Committee

The DMC is an expert advisory group, made up of members independent of the Sponsor and/or designee that is responsible for evaluating cumulative safety data at regular intervals. The primary objective of the DMC is to monitor patient safety by reviewing the available clinical data at scheduled time points. The DMC may also conduct ad hoc meetings, as necessary. Following each meeting, the DMC will make a recommendation to the Sponsor regarding the study. The details regarding the DMC processes and procedures will be outlined in the DMC Charter, which will be finalized prior to the review of any data.

9.6.2 Clinical Endpoint Committee

The CEC(s) is/(are) composed of experts in cardiology and neurology (and other appropriate medical specialties such as hepatology and endocrinology) who are independent of the Sponsor and the CRO. The CECs will review and adjudicate all deaths, EOSI, including

MACE/selected CV events (MI, stroke, hospitalization due to unstable angina, urgent coronary revascularizations and hospitalization due to heart failure), clinical or laboratory findings associated with DILI, DKA, and severe hypoglycemia episodes (as well as hypoglycemia reported as an SAE) in a treatment-blinded fashion. DILI events will also be assessed for causality.

The details regarding the CEC processes and procedures will be outlined in the CEC Charter(s), which will be finalized prior to the review of any data.

9.6.3 Steering Committee

The Steering Committee will serve in an advisory capacity to the Sponsor on multiple clinical trials in the sotagliflozin development program. This committee will meet at regular intervals throughout the program to receive status updates on each of the individual trials and to provide recommendations regarding trial status and conduct of the studies in the sotagliflozin program included in their remit. The Steering Committee will operate under the principles, and have the roles and responsibilities, outlined in the Steering Committee Charter.

10. Statistical Methodology

10.1 Determination of Sample Size

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 severe hypoglycemia 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 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 severe hypoglycemia event. A conservative assumption is made that the rates of DKA and severe hypoglycemia 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 severe hypoglycemia 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 treatment difference can be obtained for this outcome. Based on a literature review, it seems reasonable to assume that the rate of severe hypoglycemia, 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 0.80 level (alpha = 0.05). To achieve this number of patients for evaluation, 280 patients will be recruited to participate in the substudy.

10.2 Analysis Populations

10.2.1 Randomized Population

Randomized patients are those who provide informed consent, and have a randomized kit allocated and assigned to study treatment by IXRS. Data summaries using this population will include all Baseline data as appropriate (eg, patient demographics).

10.2.2 Modified Intent-to-Treat and Per-Protocol Populations

The mITT population includes all randomly assigned patients who have taken at least 1 dose of study drug during the Treatment Period. Treatment group assignment will be based on the randomized treatment, which may not match the actual treatment received.

The Per-protocol (PP) population includes all patients in the mITT population who complete treatment through the primary assessment of 24 weeks, and have no significant protocol violations that will impact the collection or interpretation of efficacy data. Identification of all patients in the PP population will be determined before the database lock and unblinding. The PP patients will be assigned to treatment groups based on the treatment they received.

The Satiety population includes all patients in the mITT population who elect to participate in the satiety substudy and completed ≥8 satiety daily diaries (ie, the PSDDs) during the placebo Run-in Period. Identification of all patients in the satiety population meeting these criteria will be determined before database lock and unblinding.

10.2.3 Safety Population

Safety analyses will be based on the Safety population, defined as all randomly assigned patients who have taken at least 1 dose of study drug and are classified according to their actual treatment received.

10.3 Study Endpoints

10.3.1 Efficacy Endpoints

10.3.1.1 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 severe hypoglycemia 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.

10.3.1.2 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 change)
- 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)

10.3.1.3 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
- 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 severe hypoglycemia
- 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 ACR, CCR, and GCR
  - Serum creatinine
  - MDRD eGFR
- Proportion of patients with satiety increase ≥30% as measured by the PSDD-NRS (substudy)
- Change from Baseline in patient-reported satiety as measured by the PSDD-NRS (substudy)

10.3.2 Safety Endpoints

Safety endpoints are as follows:

- Incidence of TEAEs, suspected adverse reactions, 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
- EOSI (see Section 9.5)

10.4 Statistical Methods

A more detailed description of the analysis and reporting of data will be provided in an SAP. An overview of the main analysis strategy is provided in the following sections.

10.4.1 Efficacy Analyses

All primary efficacy analyses will be based on the mITT population. Supportive analysis of the efficacy data will be performed using the PP population.

Primary analysis of the primary efficacy endpoint at Week 24 will use a Cochran-Mantel-Haenszel (CMH) test 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). Missing observations will be imputed as non-responders. A point estimate of treatment effect will be based on the sotagliflozin minus difference in binomial proportions. A 2-sided 95% CI will be estimated on the observed difference and will be based on normal approximation methods using a continuity correction factor. The individual components of the endpoint will be summarized separately

using descriptive statistics. 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 ≥1 episodes of DKA after randomization, and proportion of patients with ≥1 episodes of severe hypoglycemia after randomization.

Sensitivity analysis of the primary endpoint will use a single imputation method to obtain a rectangular dataset. Imputations will be based on use of the last observation carried forward (LOCF) algorithm. The stratified CMH test will be applied to this imputed dataset. The stratified CMH test will also be applied to the PP dataset as an additional sensitivity analysis.

Primary analysis of the continuous efficacy endpoints will use mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood (REML) method for estimation. The analysis model 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), time (study week), Baseline-dependent variable-by-time interaction, and a treatment-by-time interaction. 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 sotagliflozin to placebo) and the 95% CIs 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.

For binary endpoints estimated as binomial proportions, the frequency and proportion 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 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). These treatment group comparisons will be performed at Week 24 only. The earlier study weeks will use descriptive analyses to summarize the data. These descriptive statistics will include the patient counts and proportions, point estimates of treatment effect, and 95% CIs of the treatment effect. Missing observations at Week 24 will be imputed as non-responders; only the observed data will be summarized at the earlier study visits. Endpoints comprised of multiple outcomes will use descriptive methods to summarize each component by treatment group at each study week.

The test for superiority of sotagliflozin 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 (α = 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 the 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 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

In addition, raw P-values and 95% CIs will be computed for tests of all secondary endpoint hypotheses. These raw or unadjusted statistics will be used as descriptive summaries of the data and will not be used for formal testing of the hypotheses.

10.4.2 Subgroup Analyses

Subgroup analyses of the efficacy variables will be performed, as needed, for the different levels of the randomization stratification factors and the subgroups derived by other efficacy endpoint definitions (eg, SBP). Of particular interest are subgroup analyses of the efficacy variables by Baseline eGFR status (≥45 to <60 mL/min/1.73 m^2 versus ≥60 mL/min/1.73 m^2), Week -2 A1C (≤9.0%, >9.0%), Week -2 A1C (≤7.7% versus ≥7.7%), BMI (<25 kg/m^2, ≥25 kg/m^2), use of CSII at Screening (Yes, No), and age at time of T1D diagnosis (≤18 years of age, >18 years of age). Additional subgroup analyses may be conducted and will be described in the SAP. All subgroup analyses will be exploratory.

10.4.3 Safety Analyses

Safety analysis will primarily involve examination of descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Summaries will be prepared by treatment group and, as needed, by clinic visit. These

summaries will be based on the Safety population and other subpopulations as needed. All safety data (AEs, EOSI, laboratory test results, vital signs, ECG results, and physical examinations) will be provided in listings.

The evaluation of AEs is described in Section 10.4.3.1.

Vital signs, physical examination findings, laboratory results, and ECGs will be summarized descriptively at each time point. Actual and change from Baseline data will be calculated and summarized. In addition, shift table analyses will be presented for the laboratory data.

The analysis of hypoglycemic events will be conducted per the definitions provided in Section 9.5.1 and methods described for binary, continuous, and other variables in Section 10.4.1. Since these data also serve as a measure of safety, additional analyses will be conducted. The first analysis will be performed 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 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 study duration. The events will be modeled as a negative binomial process.

10.4.3.1 Adverse Events

All AEs will be coded and listed by body system and preferred term based on MedDRA. Summaries using descriptive statistics will be provided for TEAEs, drug-related AEs, and AEs by intensity. Treatment-emergent adverse events are those events not present at Baseline, but occurring after the start of study treatment, or if existing at Baseline, increasing in intensity after the initiation of study drug. When multiple occurrences of the same event are reported for the same patient, summaries made by intensity will select the event with the highest intensity. 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. On-study deaths will be reported for deaths occurring during the active phase of the Treatment Period and 30 days after stopping study drug. Also, deaths occurring outside the 30-day window, but secondary to an AE reported within the 30-day post-Treatment Period, will be reported.

Treatment-emergent adverse event summaries will include the overall incidence (number of patients with the event) and number of events by system organ class and preferred term,

overall incidence sorted by descending frequency across treatment groups, events by maximum intensity, events by relationship to study treatment, and events leading to discontinuation of study drug; SAEs and EOSI will also be summarized. Listings will be provided for deaths, SAEs and discontinuations due to AEs. Additional summaries or listings of AEs may also be provided.

10.4.4 Meta-analyses

The occurrence of the following events will be statistically analyzed using data from this study combined with other Phase 2/3 trials conducted in T1D and T2DM patients: severe hypoglycemia, DKA, DILI, and MACE. Details of the analysis models and related assumptions will be documented in separate meta-analysis plans.

11. Study Management

Ethical and Regulatory Standards are presented in Appendix B; Investigator Obligations are presented in Appendix C.

The Investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, etc.

All data on the eCRF must be recorded in accordance with the eCRF completion guidelines. If a correction is necessary, it should be made by the Investigator or a designated qualified individual as specified within the guidelines. All eCRFs should be completed in their entirety and stored in a confidential and secure location. The Investigator must sign the Investigator's statement in each patient's eCRF indicating that the data reported are accurate.

At the study site, CRAs will verify eCRFs against source documentation using a targeted approach consistent with Risk-Based Monitoring guidance. Computer programmed edit checks will be run against the database to check for discrepancies and ensure that the data are reasonable. The safety database will be reconciled with the clinical database. All issues resulting from the computer generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor and/or designee, clinical study personnel, and the study Investigators.

11.1 Data Handling and Quality Assurance

11.1.1 Data Recording

Entries made in the eCRF must be verifiable against source documents (the patient's medical records) with the exception of race and ethnicity. For all other data, source documentation must be available.

In this protocol, all information captured ("entered," "documented," "recorded") becomes part of the Sponsor's database.

11.1.2 Description of General Procedure

The designated CRO will supply each investigational site with access to a web-based EDC computer system. Edit checks and data logic checks are at the point of entry and are validated according to the CRO's SOPs. All data entered into the system is transferred to a secure database maintained by the CRO.

Access to the EDC system at the site, for vendors, for the Sponsor and Sponsor's designee, is password protected. Study access is granted to site personnel only after they have been trained in the use of the EDC system.

The EDC system contains a system-generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available at the Investigator's site and at the Sponsor and/or designee.

Data entries should be made into the EDC system in a timely manner after a clinic visit, but not to exceed 10 days after the clinic visit has occurred. All data entered must be supported by source documents maintained for all patients enrolled in this study.

11.2 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's and Sponsor's designee's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, eCRF completion, and address any concerns or questions regarding the study conduct. A risk-based monitoring approach is planned for this study, where elements of targeted source data verification focusing on critical data and risk-targeted monitoring interventions will be employed. The risk-based monitoring approach will be documented in the monitoring plan. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study

procedures, source data verification, drug accountability, use of concomitant therapy by patients, general safety documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to the Sponsor and/or Sponsor's designee, and to regulatory inspectors.

11.3 Audits and Inspections

The Sponsor and/or Sponsor's designee, Regulatory Authority, or Institutional Review Board (IRB) or Ethics Review Committee (ERC) may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor and/or Sponsor's designee immediately if contacted by a regulatory agency about an inspection at their site.

11.4 Amendments

Any amendments to the protocol will be written by the Sponsor or designee and approved by the Sponsor. All amendments must be submitted to the appropriate IRB or ERC for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form (ICF), which also must be submitted for IRB or ERC approval prior to administration to patients. If any changes to the eCRF are required, the Sponsor or Sponsor's designee will issue supplemental or revised eCRF pages.

11.5 Record Keeping

11.5.1 Drug Accountability

The Investigator must maintain accurate records of study drug receipt, dispensing information, and disposition. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.5.2 Health Insurance Portability and Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 HIPAA Privacy Regulation and any applicable updates). The Investigator shall ensure that

study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and other local applicable regulations, and in a form satisfactory to the Sponsor.

11.5.3 Financial Disclosure

The Investigator and any sub-Investigator shall provide to the Sponsor and/or Sponsor's designee sufficient accurate financial information to allow the Sponsor and/or Sponsor's designee to submit complete and accurate financial certification or disclosure statements to the FDA and/or other applicable Regulatory Authorities. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.5.4 Access to Original Records

It is an expectation of Regulatory Authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.5.5 Retention of Study Documents

According to 21 CFR Part 312.62, ICH E6, and the guidance documents applying to clinical trials in Volume 10 of the publication "The rules governing medicinal products in the European Union," study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor and/or Sponsor's designee. The Investigator must notify the Sponsor and/or Sponsor's designee in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor and/or Sponsor's designee must be contacted to arrange alternative record storage options.

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. Where the archiving procedures do not meet the minimum timelines required by the Sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The Investigator/institution must notify the Sponsor and/or Sponsor's designee if the archival arrangements change (eg, relocation or transfer of ownership).

The Investigator site file is not to be destroyed without the Sponsor's and/or Sponsor's designee's approval.

The Investigator's contract will contain all regulations relevant for the investigational site.

12. Administrative Structure of the Study

The study will be monitored by the Sponsor and/or designee. The following functions for this study will be performed by organizations designated by the Sponsor: medical monitoring, data management and statistical analysis, study drug randomization and distribution, routine site monitoring, medical writing, SAE reporting, and project management. Additionally, an independent DMC, CEC, and T1D Steering committee will provide oversight.

13. Appendix A – Schedule of Assessments (Study LX4211.312)

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						

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
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 EOSI			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							
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.

14. Appendix B – Ethical and Regulatory Standards

This study is to be conducted according to international standards of Good Clinical Practice (GCP), applicable regional regulations, and applicable institutional research policies and procedures.

Specific regulations should be followed as applicable including:

- Volume 10 of the publications "The rules governing medicinal products in the European Union"
- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, August 2011
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Additionally, this protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor and/or Sponsor's designee before commencement of this study. The Investigator should provide a list of IEC/IRB members and their affiliate to the Sponsor and/or Sponsor's designee.

All patients for this study will be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IEC/IRB for the study. The formal consent of a patient, using the IEC/IRB-approved consent form, must be obtained before that patient undergoes any study procedure. The consent form must be signed by the patient or legally acceptable surrogate, and the Investigator-designated research professional obtaining the consent.

Copies of GCP guidances and regulations are available from the Sponsor and/or Sponsor's designee upon request (eg, ICH GCP, relevant local regulations such as sections of the US Code of Federal Regulations, the Declaration of Helsinki). The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities.

The ethical standards defined within GCP are intended to ensure that:

- Human patients are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings;
- The potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc., is the Sponsor of the Investigational New Drug (IND) Application. The Sponsor and/or designee is responsible for the following:

- Selecting qualified Investigators,
- Providing Investigators with the information they need to properly conduct an investigation,
- Ensuring proper monitoring of the investigation,
- Ensuring that the study is conducted according to the general investigational plan and the clinical protocol contained in the IND,
- Maintaining the IND and the Clinical Trial Application,
- Ensuring that applicable Regulatory Authorities and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied,
- Ensuring the study is conducted in accordance to FDA and ICH guidelines and regulations.

15. Appendix C – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the patient Informed Consent Form (ICF) will be approved by the Institutional Review Board (IRB) or Ethics Review Committee (ERC) before enrollment of any patients. The opinion of the IRB or ERC will be dated and given in writing. A copy of the letter of approval from the IRB or ERC and a copy of the approved ICF will be received by the Sponsor prior to shipment of study drug supplies to the Investigator.

The Investigator will ensure that the IRB or ERC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to patients. The Investigator will also ensure that no changes will be made to the protocol without IRB or ERC approval.

As a part of the IRB's or ERC's requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB or ERC at intervals appropriate to the degree of patient risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every patient prior to clinical trial participation. The rights, safety, and wellbeing of the trial patients are the most important considerations and should prevail over interests of science and society.

As described in Good Clinical Practice (GCP) guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators must provide the Sponsor with a fully executed Form FDA 1572 (Statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide the Sponsor with his/her own curriculum vitae and current curriculum vitae for each sub-Investigator listed on Form FDA 1572.

Protection of Human Subjects (21 CFR Part 50)

Informed consent must be obtained from every patient before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB- or ERC-approved consent form and signed by the patient or the patient's legally authorized representative. Non-English-speaking patients must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the

patient signing it. Another copy must be kept in the Investigator's files and made available to the FDA and/or other applicable Regulatory Authorities representatives upon request. If, for any reason, patient risk is increased as the study progresses, a revised, IRB- or ERC-approved consent form must be signed by the patient. Before the study begins, a sample of the consent form must be provided to the Sponsor and/or Sponsor's designee for review. The FDA and/or other applicable Regulatory Authorities may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all patients.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB or ERC within 5 working days. In this situation, the Investigator may not administer any subsequent product to that patient until informed consent and IRB or ERC approval are obtained.

Informed Consent

Written informed consent must be obtained from each patient prior to entry in the study. One copy of the signed informed consent document will be given to the patient, and another will be retained by the Investigator. Additionally, the participant must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

In situations where the participant is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor or the designated CRO and by the Investigator's IRB or ERC prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA and/or other applicable Regulatory Authorities and representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and the patient's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

When appropriate, one or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus, if the patient is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs the patient may incur from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective.

Study Documentation

IRB or ERC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB or ERC prior to enrollment of participants in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, International Conference on Harmonisation (ICH), GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB's or ERC's approval, which specifically identifies the study/protocol and a list of the committee members, must be received by the Sponsor and/or Sponsor's designee prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for reevaluation and reapproval will be submitted by the Investigator to the IRB or ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor and/or Sponsor's designee provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB or ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB or ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant adverse events (AEs), including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability records, Sponsor/Investigator correspondence, IRB or ERC correspondence, protocol and amendments, information regarding monitoring activities, patient exclusion records, electronic case report forms (eCRFs), and data queries.

Confidentiality

The anonymity of participating patients must be maintained. Patients will be identified by their initials and an assigned patient number on eCRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the patient (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by Regulatory Authorities, the clinical monitor, or Sponsor and/or Sponsor's designee's personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor and/or Sponsor's designee to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB or ERC, the patient, or the applicable Regulatory Authorities) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each patient, and return to the Sponsor or designee, or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol.

16. Appendix D – Calculations

Calculation of estimated glomerular filtration rate (eGFR):

Use these eGFR calculators to estimate kidney function for adults and children.

At this time, all laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry (IDMS) traceable. In the US and other countries, nearly all methods from the major global manufacturers now have calibration traceable to an IDMS reference measurement procedure. Consequently, the calculators for older nonstandardized creatinine methods are no longer available on this web site.

In adults (patients 18 years and older), the recommended equation for estimating eGFR from serum creatinine is the Modification of Diet in Renal Disease (MDRD) Study equation. The IDMS-traceable version of the MDRD Study equation is used. Either equation below may be used based on whether the laboratory reports conventional units or SI units:

Conventional Units (for use predominantly in the US):

http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-conventional-unit.asp

SI Units (for use predominately outside the US):

http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units.asp

17. Appendix E – Algorithm for Liver Safety Laboratory Abnormality Signals

Reference:

2009 FDA Guidance for Industry "Drug-Induced Liver Injury – Premarketing Clinical Evaluation"

Step 1: Confirmation of Elevated ALT and/or AST:

Contact the Medical Monitor to discuss the case and procedures to follow.

In general, an increase of serum ALT and/or AST to >3X ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and TB) to confirm the abnormalities and to determine if they are increasing or decreasing.

If symptoms persist or repeat testing shows serum ALT and/or AST >3X ULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening (see below). If close monitoring is not possible, the drug should be discontinued.

Step 2: If Possible Liver Signal identified, Close Observation Required:

Contact the Medical Monitor to discuss the case and procedures to follow.

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels ≥3X ULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets

- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function, as appropriate (eg, International Normalized Ratio [INR], direct bilirubin)
- Considering gastroenterology or hepatology consultations

Step 3: Decision to Stop Study Drug Administration:

Contact the Medical Monitor to discuss the case and procedures to follow.

Discontinuation of treatment should be considered if:

- ALT or AST >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and (TB >2X ULN or INR >1.5)
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Step 4: Evaluate Data for Alternate Causes of Liver Signal:

Contact the Medical Monitor to discuss the case and procedures to follow.

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- Acute viral hepatitis. The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for

Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

- Alcoholic and autoimmune hepatitis. Acute alcoholic hepatitis usually is recurrent, with a history of bingeing exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (eg, antinuclear or other antibodies).
- Hepatobiliary disorders. Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.
- NASH. NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.
- Cardiovascular causes. Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum aminotransaminase (eg, aminotransaminase >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.
- Concomitant treatments. It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

Step 5: Follow-Up to Resolution:

Contact the Medical Monitor to discuss the case and procedures to follow.

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

Step 6: Rechallenge:

Contact the Medical Monitor to discuss the case and procedures to follow.

Whether or not to rechallenge a subject who showed mild DILI is a difficult decision. Reexposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with reexposure. Rechallenge may not be considered negative unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A negative rechallenge does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of rechallenge to verify drug causation would give a false negative result.

Generally, rechallenge of subjects with significant aminotransferase elevations (>5X ULN) should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge, and the Institutional Review Board consulted.

18. Appendix F – Recommendations on Basic Genitourinary Hygiene, Maintaining Hydration and Recognition of DKA and its Management

Basic Genitourinary Hygiene:

Patients with diabetes are at risk for developing genitourinary (GU) infections. The following guidelines should be communicated to females and uncircumcised males regarding GU infections.

Patient communication cards will be printed with the following for patients with T1D:

For females:

"The following advice may be useful in helping you to keep your bladder and urethra free from infection:

- Go to the toilet as soon as you feel the need to urinate, rather than holding it in.
- Wipe from front to back after going to the toilet.
- Practice good hygiene by washing your genitals every day, and before having sex.
- Empty your bladder after having sex."

For uncircumcised males:

"The following advice may be useful in helping you to keep the foreskin free from infection:

- Wash the end of your penis and foreskin with soap and water (do not let soap get in the opening).
- After your shower or bath, dry the end of your penis and foreskin properly and replace the foreskin.
- Also, when you urinate, slide the foreskin back enough so that urine does not get on the foreskin-this helps to keep it clean."

Maintaining Hydration:

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. All patients will be advised to maintain proper fluid intake and to consider increasing it if they sense greater thirst, more urine production, or if they feel dizzy or faint.

Patient communication cards will be printed with the following for patients with T1D:

"The following advice may be useful in helping you to maintain proper hydration and prevent dehydration:

- Dehydration is when your body loses too much fluid, frequently due to diarrhea or increased urination. The study drug may cause increased urination.
- If you are thirsty, we recommend drinking water or non-caloric liquids.
- Consider increasing the amount of fluids you drink if:
  - You sense greater thirst than usual
  - You have a dry mouth or cracked lips
  - You have a fever
  - You have diarrhea or vomiting
  - You urinate more frequently or in larger amounts than usual
  - You get up in the middle of the night to urinate (more than usual)
  - You feel dizzy or light-headed
  - You exercise, or when it is hot outside"

Recognition of Diabetic Ketoacidosis (DKA) and its Management:

Patients with T1D are at risk for developing DKA. DKA is always preceded by ketosis. In many cases, ketosis can be treated and resolved with administration of additional rapid acting insulin and will therefore not progress to DKA. The following is applicable for all patients with T1D. Investigators and subjects should be aware of the fact that GI adverse events occurring with sotagliflozin may mask presenting symptoms of DKA, and that in some patients, alcohol could be a trigger for ketosis. Therefore, whenever Adverse Event data is collected or the patient reports an intercurrent illness (including infections), generalized weakness, increased weight loss, gastrointestinal symptoms including nausea, vomiting, or abdominal pain or other symptoms or signs that the Investigator believes may be consistent with DKA, then the Investigator will instruct the patient to measure ketones (urine ketones or or blood BHB) .

If ketosis is present (moderate or higher for urine ketones or blood BHB level is >0.6 mmol/L), then the patient will be asked to contact the Investigative site immediately. In this situation, the investigator should consider instructing the patient to take rapid acting insulin by syringe (not insulin pump) as well as eat carbohydrates in order to reverse the ketosis. After rechecking the ketones, the investigator should consider instructing the patient to take

additional doses of rapid acting insulin every 2 hours until elevated ketones are normalized. Because the amount of insulin needed to lower ketones will also lower blood glucose, it is necessary for the patient to increase carbohydrate intake. Typically this would be 15-30 grams of carbohydrate each hour provided by a glucose containing sports drink or oral rehydration fluid.

The site will evaluate if an assessment for metabolic acidosis is appropriate. If laboratory testing confirms presence of metabolic acidosis, then the "Possible DKA" eCRF will be completed. If nausea and vomiting are present and the patient is unable to keep liquids down, the patient should be evaluated in an Emergency Room.

If a patient is scheduled for a procedure or surgery that requires withholding oral intake (NPO), it is recommended that study drug is held from the day prior to procedure or surgery and resumed the day after procedure or surgery is complete and patient is tolerating adequate oral intake.

In some patients alcohol may trigger onset of ketosis.

Patient communication cards will be printed with the following:

"The following list may help you to recognize Diabetic Ketoacidosis (DKA).

- Inability to maintain oral intake
- Generalized weakness
- Abdominal (belly) pain
- Increased weight loss
- Fever
- Frequent urination, including at night
- Fruity-scented breath
- Confusion
- Acute illness
- Consistently elevated blood glucose
- Feeling very thirsty or drinking a lot
- Nausea or vomiting
- Having trouble thinking clearly or feeling tired

It is possible to have DKA even if your blood glucose is not elevated. Regardless of your blood glucose level, if you have any of these symptoms on the list, then measure your blood or urine ketone or blood BHB level. If the urine ketones are high (your study doctor may instruct you that this is a level of "moderate" or more than "moderate") or blood BHB level is above 0.6 mmol/L, then contact your study site immediately for assistance with managing your diabetes."

In some patients alcohol use may lead to production of ketones by your body.

If you are scheduled for a procedure or surgery that requires you to not take any food or liquids, please contact your study doctor for instructions on continuing study drug. In such cases your study doctor may advise you NOT to take your study drug from the day prior to the procedure or surgery until after the procedure or surgery is complete, and you are taking food and liquids as you normally do.

19. Appendix G – Measurement of Blood Pressure and Pulse Rate

Equipment

1. Blood pressure measurements will be taken by an automated blood pressure monitor or a manual sphygmomanometer.
2. Bladder Length – Should nearly or completely encircle the patient's arm. For many adults, the standard "adult" size bladder is not long enough and the "large" size bladder is recommended.
3. Bladder Width – Should be at least 40% of the bladder length

Patient Factors

Extraneous variables associated with the measurement of blood pressure (BP) should be minimized. These include:

1. Food intake, caffeine-containing beverages, cigarette smoking, or strenuous exercise within 2 hours prior to measurement
2. Full urinary bladder
3. The patient should not be allowed to talk while BP is being measured.
4. The patient should be placed in the examination room and the cuff should be placed on the patient's nondominant arm. The proper sized cuff should fit snugly with the lower edge 2 to 3 cm above the antecubital fossa.
5. The patient should be allowed to sit quietly in a comfortably warm place (temperature around 25°C or 77°F) for 5 minutes with the arm supported at heart level, preferably with the cuff in place and with no restrictive clothing on the arm. The patient should be encouraged not to tense his or her muscles.

Nondominant Arm

The patient's nondominant arm should be the arm declared by the patient as being nondominant. The nondominant arm should then be used for all seated BP measurements throughout the study.

Measurement Technique

Following the 5-minute rest period, 3 separate seated BPs should be measured with at least 1 minute between BP measurements and with the cuff fully deflated between measurements. All BPs will be recorded in the patient's electronic case report form (eCRF). The mean of the 3 seated BPs will constitute the BP value for that visit.

Three seated pulse rate measurements will be obtained. The mean of the 3 seated pulse rate measurements will constitute the pulse rate value for that visit.

20. Appendix H – Satiety Visual Analog Scale

Patient Satiety Daily Diary (PSDD)

INSTRUCTIONS

Please complete this worksheet before your first meal of the day on each of the 14 diary days, ±3 days.

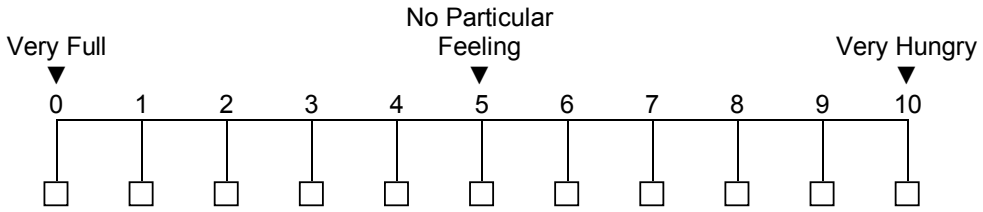
Please enter the date and time in the box below.

Please enter today's date below: Please enter the time:

_____/_____/_____ _____:_____ _____ _____

Day Month Year Hour Minute AM PM

Please clearly mark an 'x' in the box (☒) that best describes your average level of hunger over the preceding 24 hours.



21. Appendix I – Study Procedure by Visit

Screening Clinic Visit (Week -4 to -2)

Patients will be screened for up to 2 weeks.

When scheduling the visit, remind patients that they should fast and only drink water or noncaffeinated, zero-calorie beverages for at least 8 hours prior to the visit. 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 and the laboratory requisition form.

Perform the following examinations and assessments and complete the appropriate eCRFs:

1. Informed consent should be obtained prior to the start of any screening procedures
2. Review and verify eligibility based on inclusion/exclusion criteria
3. Obtain demographics
4. Obtain complete medical history
5. Register patient for Screening in IXRS
6. Perform complete physical examination
7. Measure weight and height
8. Measure vital signs (pulse rate, BP, respiratory rate, and temperature)
9. Obtain fingerstick glucose by meter.
10. Perform 12-lead ECG
11. Dispense Ketostix®. **Note**: After the initial dispensation of Ketostix at this visit, additional Ketostix (or similar) will be dispensed on an as needed basis.
12. Provide patients with diet and exercise instructions
13. Record concomitant medications
14. Record SAEs
15. Obtain fasting venous blood samples for:
    a. A1C
    b. FPG
    c. Serum chemistry
    d. Blood BHB: point-of-care and central lab
    e. Hematology
    f. Lipid profile
    g. Serum pregnancy test (females with childbearing potential only)
    h. Follicle-stimulating hormone (females only)

i. Thyroid stimulating hormone (If abnormal, free thyroxine will be measured)

16. Obtain urine sample for:
    a. Urinalysis with microscopy

Run-in Period Clinic Visit (Week -2)

All patients will have a 2-week single-blind, placebo Run-in Period prior to Randomization. Compliance will be assessed during the single-blind, placebo Run-in Period. Patients must have good compliance (≥80%) during the single-blind, placebo Run-in Period to be eligible for randomization.

When scheduling the visit, remind patients that they should fast and only drink water or noncaffeinated, zero-calorie beverages for at least 8 hours prior to the visit. 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.

Perform the following examinations and assessments and complete the appropriate eCRFs:

1. Assess inclusion/exclusion criteria
2. Obtain complete medical history
3. Register patient for Run-in in IXRS
4. Perform symptom-related brief physical examination
5. Measure weight
6. Measure vital signs (pulse rate, BP, respiratory rate, and temperature)
7. Obtain fingerstick glucose by meter
8. Dispense study diary, glucose testing strips, glucose meter, and remind the patient to bring the study diary to each visit.
9. Dispense BHB meter and testing strips
10. Provide patients with diet and exercise instructions
11. Record concomitant medications
12. Record SAEs
13. Obtain fasting venous blood samples for:
    a. A1C
    b. Blood BHB: point-of-care and central lab
14. Dispense single-blind placebo tablets
15. Provide patients with first dose of placebo tablets for Run-in Period
16. Remind patients to bring study diary to each visit
17. Remind patients to bring used bottles of placebo tablets to the next visit

18. Patients participating in the satiety substudy:
    a. Dispense package of satiety daily diaries
    b. Remind patients to complete the satiety daily diaries each day before the first meal of the day, for the duration of the single-blind placebo Run-in Period (14 days, ±3 days)
    c. Remind patients to bring the satiety daily diaries to the next visit (Day1, Baseline)

24-Week Double-blind Treatment Period (Day 1 to Week 24)

Following completion of the single-blind, placebo Run-in Period, eligible patients will enter the 24-week, double-blind Treatment Period.

Note: If serum creatinine increases by ≥30% above the baseline value during the study, then the Investigator should consider assessment of: volume status, diuretic dose, discontinuing NSAIDs, and other relevant testing including renal imaging techniques, as appropriate.

Sodium-glucose cotransporter type 2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. All patients will be advised to maintain proper fluid intake and to consider increasing it if they sense greater thirst, more urine production, or if they feel dizzy or faint.

Note: The collection of AEs begins after the first dose of double-blind study drug.

24-Week Double-blind Treatment Clinic Visit (Day 1)

When scheduling the visit, remind patients that they should fast and drink only water or noncaffeinated, zero-calorie beverages for at least 8 hours prior to the visit. 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.

Patients should also be reminded that they are NOT to take study drug on the day of clinic visits until instructed by site staff.

Perform the following examinations and assessments and complete the appropriate eCRFs:

1. Access inclusion/exclusion criteria
2. Randomization
3. Perform symptom-related brief physical examination
4. Measure weight
5. Measure vital signs (pulse rate, BP, respiratory rate, and temperature)
6. Perform 12-lead ECG
7. Obtain fingerstick glucose by meter to supplement review of SMBG and insulin data

8. Review SMBG and make adjustment to insulin dose as needed to meet ADA/EASD guidelines
9. Record insulin dose and SMBG on eCRF
10. Review study diary and record hypoglycemic symptoms or events
11. Dispense patient's study diary, glucose testing strips, and BHB testing strips as needed
12. Patients participating in the satiety substudy:
    a. Collect satiety daily diaries
    b. Review and record entries into the eCRF
13. Provide basic instruction on genitourinary hygiene, maintaining hydration, and recognition and management of DKA
14. Assess compliance/collect study drug
15. Record concomitant medications
16. Record SAEs
17. Record AEs (after first dose of double-blind study drug)
18. Record EOSI
19. Obtain fasting venous blood samples for:
    a. A1C
    b. FPG
    c. Serum chemistry
    d. Blood BHB: point-of-care and central lab
    e. Hematology
    f. Lipid profile
    g. Fasting blood for storage for future safety analysis
20. Obtain urine sample for:
    a. Urine pregnancy test (females with childbearing potential only)
    b. Urine albumin, calcium, glucose, and creatinine
    c. Urinalysis with microscopy
    d. Random urine for storage for future safety analysis
21. Dispense double-blind study drug
22. Provide patient with first dose of double-blind study drug and record dose time on eCRF
23. Remind patients to bring used bottles of double-blind study drug to the next visit

24-Week Double-blind Treatment Clinic Visits (Weeks 4, 8, and 16)

When scheduling each visit, remind patients that they should fast and drink only water or noncaffeinated, zero-calorie beverages for at least 8 hours prior to the visit. 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.

Patients should also be reminded that they are NOT to take study drug on the day of clinic visits until instructed by site staff.

Perform the following examinations and assessments and complete the appropriate eCRFs:

1. Symptom-related brief physical examination
2. Measure weight
3. Measure vital signs (pulse rate, BP, respiratory rate, and temperature)
4. Obtain fingerstick glucose by meter to supplement review of SMBG and insulin data
5. Review SMBG and make adjustment to insulin dose as needed to meet ADA/EASD guidelines
6. Record insulin dose and SMBG on eCRF
7. Review study diary and record hypoglycemic symptoms or events
8. Dispense patient's study diary, glucose testing strips, and BHB testing strips as needed
9. Provide basic instruction on genitourinary hygiene, maintaining hydration, and recognition and management of DKA
10. Assess compliance/collect study drug
11. Record concomitant medications
12. Record SAE
13. Record AEs
14. Record EOSI
15. Obtain fasting venous blood samples for:
    a. A1C
    b. FPG
    c. Serum chemistry
    d. Hematology (Week 8 only)
    e. Lipid profile (Week 8 only)
    f. Blood BHB: point-of-care and central lab
16. Dispense double-blind study drug (Weeks 8 and 16 only)
17. Remind patients to bring used bottles of double-blind study drug to the next visit
18. Patients participating in the satiety substudy:

a. At the Week 16 visit, patients will be provided a packet including the satiety daily diaries
b. Remind patients to complete the satiety daily diaries each day before the first meal of the day, for the duration of Week 23 and Week 24 (14 days, ±3 days).
c. At the beginning of Week 23, patients will receive a telephone call to reminded them to start using the satiety daily diaries
d. Remind patients to bring the satiety daily diaries to the next visit (visit at Week 24)

End of the 24-Week Double-blind Treatment Clinic Visit (Week 24)

When scheduling the visit, remind patients that they should fast and drink only water or noncaffeinated, zero-calorie beverages for at least 8 hours prior to the visit. 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.

Perform the following examinations and assessments and complete the appropriate eCRFs:

1. Perform complete physical examination
2. Measure weight
3. Measure vital signs (pulse rate, BP, respiratory rate, and temperature)
4. Perform 12-lead ECG
5. Obtain fingerstick glucose by meter to supplement review of SMBG and insulin data
6. Review SMBG and make adjustment to insulin dose as needed to meet ADA/EASD guidelines
7. Record insulin does and SMBG data on eCRF
8. Review study diary and record hypoglycemic symptoms or events
9. Assess compliance/collect study drug
10. Record concomitant medications
11. Record SAEs
12. Record AEs
13. Record EOSI
14. Obtain fasting venous blood samples for:
    a. A1C
    b. FPG
    c. Serum chemistry
    d. Hematology

e. Lipid profile
f. Blood BHB: point-of-care and central lab
g. Fasting blood for storage for future safety analysis

15. Obtain urine sample for:
    a. Urine pregnancy test (females with childbearing potential only)
    b. Urinalysis with microscopy
    c. Urine albumin, calcium, glucose, and creatinine
    d. Random urine for storage for future safety analysis
16. Patients participating on the satiety substudy:
    a. Collect all satiety daily diaries
    b. Review and record entries on the eCRF

Follow-up Telephone Contact: 30 Days after End-of-Treatment

At 30 days post-treatment, or 30 days following EW, perform the following assessments and complete the appropriate eCRFs:

1. Telephone the patient to:
    a. Record SAEs
    b. Follow-up any ongoing AEs
    c. Record EOSI

22. References

1. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuimilenhto J. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care. 2000;23(10):1516-1526.
2. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed January 18, 2015.
3. T1D Registry. https://t1dexchange.org/pages/clinic-registry/. Accessed January 13, 2015.
4. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study [published online ahead of print]. Diabetes Care. 2014. http://www.ncbi.nlm.nih.gov/pubmed?term=(Henry%20R%20Chalamandaris%5BTitle%5D)%20AND%20Dapagliflozin. Accessed January 18, 2015.
5. Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes Care. 2014;37(5):1480-1483.
6. Arakawa K, Ishihara T, Oku A, et al. Improved diabetic syndrome in C57BL/KsJ-db/db mice by oral administration of the Na(+)-glucose co-transporter inhibitor T-1095. Br J Pharmacol. 2001;132(2):578-586.
7. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-2157.
8. Gutzwiller JP, Drewe J, Göke B, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol. 1999;276(5):R1541-R1544.
9. Chapman I, Parker B, Doran S, et al. Effect of pramlintide on satiety and food intake in obese subjects and subjects with type 2 diabetes. Diabetologia. 2005;48(5):838-848.
10. Talley NJ, Verlinden M, Geenen DJ, et al. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: a randomised, double blind, placebo controlled trial. Gut. 2001;49(3):395-401.
11. Willis WD, Diago-Cabezudo JI, Madec-Hily A, et al. Medical resource use, disturbance of daily life and burden of hypoglycemia in insulin-treated patients with diabetes: results from a European online survey. Expert Rev Pharmacoecon Outcomes Res. 2013;13(1):123-130.
12. Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med. 2007;356(18):1842-1852.
13. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med. 2014;174(7):1116-1124.
14. American Diabetes Association. Standards of Medical Care in Diabetes – 2014. Diabetes Care. 2014;37(Suppl 1):S14-S80. http://care.diabetesjournals.org/content/37/Supplement_1/S14.extract. Accessed January 18, 2014.
15. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular disease. European Heart Journal. http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-diabetes-ft.pdf. Accessed January 18, 2015.

16. Martin D. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.
17. DSM-V Criteria for Substance-Related Disorders. Criteria for Substance Use (LEVEL 2 – Substance Abuse – Adult). http://www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures. Accessed January 18, 2015.
18. Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, Maahs DM and Tamborane WV. Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry. Diabetes Care 2015;38:971–978.
19. FDA Guidance for Industry: Diabetes mellitus - developing drugs and therapeutic biologics for treatment and prevention. Lines 1144 – 1215. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071624.pdf. Accessed January 18, 2015.
20. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Accessed January 13, 2015.
21. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-1343.