Official Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Basal Insulin Alone or in Addition to Oral Antidiabetes Drugs (OADs)

NCT Number: NCT03285594

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AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: sotagliflozin/SAR439954

A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Basal Insulin Alone or in Addition to Oral Antidiabetes Drugs (OADs)

STUDY NUMBER: EFC14868

STUDY NAME: SOTA-INS

VERSION DATE / STATUS: Approval date (06-Mar-2018) / Approved

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NAMES AND ADDRESSES OF

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MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: sotagliflozin/SAR439954	**STUDY No.: EFC14868** **STUDY NAME: SOTA-INS**
TITLE	A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Basal Insulin Alone or in Addition to Oral Antidiabetes Drugs (OADs)
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objective:** To demonstrate the superiority of sotagliflozin 400 mg versus placebo with respect to hemoglobin A1c (HbA1c) reduction at Week 18 in patients with type 2 diabetes (T2D) who have inadequate glycemic control on basal insulin alone or with OADs. **Secondary objectives:** • To assess the effects of sotagliflozin 400 mg versus placebo on: - Change from Baseline to Week 18 in fasting plasma glucose (FPG) - Change from Baseline to Week 18 in body weight (BW) - Change from Baseline to Week 12 in systolic blood pressure (SBP) for patients with Baseline SBP ≥130 mmHg - Change from Baseline to Week 12 in SBP for all patients - Change form baseline to Week 52 in HbA1c - Change from baseline to Week 52 in BW • To assess the effects of sotagliflozin 200 mg versus placebo on: - Change from Baseline to Week 18 in HbA1c - Change from Baseline to Week 18 in BW - Change from Baseline to Week 18 in FPG - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg - Change form baseline to Week 52 in HbA1c - Change from baseline to Week 52 in BW • To evaluate the safety of sotagliflozin 400 mg and 200 mg versus placebo throughout the 52-week trial **Other objectives:** • To assess the effects of sotagliflozin 400 mg versus placebo on the proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Weeks 18, 26, and 52

	• To assess the effects of sotagliflozin 200 mg versus placebo on the proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Weeks 18, 26, and 52 • To assess the effects of sotagliflozin 200 mg versus placebo on the change from Baseline to Week 12 in SBP for all patients • To assess the effects of sotagliflozin 400 mg and 200 mg versus placebo on: - Change from baseline to Week 26 in HbA1c - Change from Baseline to Weeks 26 and 52 in SBP in all patients and the subset of patients with Baseline SBP ≥130 mmHg - Change from Baseline to Weeks 12, 26, and 52 in SBP in patients with Baseline SBP <130 mmHg - Change from Baseline to Weeks 12, 26, and 52 in diastolic blood pressure (DBP) for all patients and the subset of patients with Baseline DBP ≥80 mmHg - Change from Baseline to Week 52 in the total daily insulin dose - Proportion of patients requiring rescue therapy during the 52-week double-blind Treatment Period - Change from Baseline to Week 18 and Week 52 on 7-point Self-Monitored Blood Glucose (SMBG) profile (mean daily value at each time point) - Change from Baseline on estimated glomerular filtration rate (eGFR) - Change from Baseline in urinary albumin creatinine ratio (UACR) - Patient Qualitative Assessment of Treatment (PQAT) during the 52-week Treatment Period - Patient perception of treatment impact and satisfaction using the Treatment Related Impact Measure - Diabetes (TRIM-D) during the 52-week Treatment Period • To assess plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite. **Continuous Glucose Monitoring (CGM) substudy:** In the United States, a substudy employing Continuous Glucose Monitoring (CGM) technology will be performed to assess detailed glycemic profiles. The details of the CGM substudy procedures, endpoints and statistical analyses will be provided in a separate substudy protocol document.
STUDY DESIGN	This is a Phase 3, multicenter, randomized, double-blind (with single-blind Run-in Phase), placebo-controlled, parallel-group study. Patients with T2D will be included in this study if at Screening they have inadequate glycemic control (as demonstrated by a mean HbA1c $\geq$7.5% or HbA1c $\leq$10.5%), despite use of basal insulin (at a total daily dose that has been stable within $\pm$20% of the dose at Screening for 8 weeks, inclusive). Patients may also be using up to

	2 OADs which may include metformin at a dose of at least 1500 mg/day or the maximum tolerated dose (documented). Patients who satisfy the entry criteria will be switched to Lantus® (1:1 dose conversion from basal insulin being used at Screening). The trial will consist of 3 periods: • An up to 6-week Screening Period comprised of: - An up to 2-week Screening phase - A 4-week Lantus titration/single-blind placebo Run-in Phase. • A 52-week double-blind Treatment Period comprised of: - An initial 18-week fixed-dose phase during which Lantus dose is held constant except for safety reasons - Subsequent 34 weeks during which Lantus can be titrated. • A 2-week, post-treatment Follow-up Period. **Screening Period** **Up to 2-week Screening phase (see Section 1.2)** **4-week Lantus titration/single-blind placebo Run-in Phase** If the patient satisfies the entry criteria, their basal insulin will be converted to Lantus supplied by the Sponsor (1:1 conversion based on units) and a 4-week Lantus optimization phase will commence at Week -4 (Visit 2). **Lantus titration:** The target range of fasting SMBG is 80-100 mg/dL (4.4-5.6 mmol/L). The titration will be based on SMBG readings performed before the first meal of the day for at least 5 days per week. The Lantus dose will be adjusted based on the mean of the 3 most recent fasting SMBG values according to the following titration rule: • ≥140 mg/dL (≥7.8 mmol/L): increase Lantus by 4 units, or split to 2 x 2 units • ≥120 mg/dL (≥6.7 mmol/L) but <140 mg/dL (<7.8 mmol/L): increase Lantus by 2 units • >100 mg/dL (>5.6 mmol/L) but <120 mg/dL (<6.7 mmol/L): increase Lantus by 1 unit • 80-100 mg/dL (4.4-5.6 mmol/L), inclusive: no change in dose • <80 mg/dL (<4.4 mmol/L): decrease Lantus by 2 units. Lantus dose adjustment will occur every 3 days (twice a week). The dose adjustments will be made in consultation with the study site either at site visits, phone visits, or unscheduled phone contacts. In case of hypoglycemia, insulin titration may be withheld according to the Investigator's medical judgment. During the 4-week Lantus titration/single-blind placebo Run-in Phase, patients will also take single-blind placebo, given as two (2) placebo tablets (identical to sotagliflozin 200 mg in appearance), once daily before the first meal of the day. In order to qualify for randomization, patients must demonstrate compliance at the end of

	the Run-in Phase, based upon tablet count (≥80%) and the Investigator's discretion. Patients will not initiate any new antidiabetic medication. The pre-existing OAD should remain stable without any changes. **Monitoring for serum ketones:** At Visit 2, patients will be provided meters and test strips for monitoring capillary blood beta-hydroxybutyrate (BHB). Patients will be instructed to measure their BHB levels by fingerstick if they experience any symptoms consistent with ketosis/ketoacidosis throughout the entire study period. Patients will be instructed on how to respond (seek help, hydrate, ingest carbohydrates, etc) if they present with possible ketoacidosis symptoms and the BHB value is abnormal (>0.6 mM/L). **Randomized Core Treatment Period: Weeks 0 to18** **Randomization:** To be randomized, patients must have HbA1c value ≥7% based on value obtained at Week -1 (Visit 5). Patients will be randomly assigned at a ratio of 2:1:1 respectively to one of 3 arms: • Sotagliflozin 400 mg, given as two (2) 200-mg tablets, once daily before the first meal of the day • Sotagliflozin 200 mg, given as one (1) 200-mg tablet and one (1) placebo tablet (identical to sotagliflozin 200 mg in appearance), once daily before the first meal of the day • Placebo, given as two (2) placebo tablets (identical to sotagliflozin 200 mg in appearance), once daily before the first meal of the day. Randomization will be stratified by the following 3 binary factors: HbA1c at Week -1 (≤8.5%, >8.5%) and SBP at Week -1 (<130 mmHg, ≥130 mmHg), sulfonylureas use at Week -1 (yes, no). Administration of blinded investigational medicinal product (IMP) begins at Randomization (Day 1). **Lantus dose:** The dose of Lantus should be held constant for the first 18 weeks unless glycemic rescue criteria are satisfied (see below). In addition, the doses of the two OADs (if applicable) should be held constant throughout the entire 52-week double-blind Treatment Period (ie, not changed except for safety reasons), and the dose of all antihypertensive medications should be held constant for the first 12 weeks (until Visit 11) except for safety reasons. **Hyperglycemic rescue:** For the first 18 weeks, the total daily insulin should remain stable (< ±10% from randomization dose, or <±4 units, whichever is less). Patients requiring glycemic rescue may initiate rescue therapy with prandial insulin, or glucagon-like peptide-1 (GLP-1) agonists, or another antidiabetic medication (except sodium-glucose cotransporter type 2 [SGLT2] inhibitors), according to the Investigator's clinical judgment and in accordance with the treatment guidelines. Criteria for hyperglycemic rescue have been set for different phases of the study (see STUDY TREATMENTS, Rescue Therapy) and are consistent with accepted treatment goals for diabetic therapy.

	The dose of double-blind study treatment (sotagliflozin or placebo) will not be adjusted throughout the study. **Weeks 19 to 52 Treatment Period** **Lantus Titration:** Lantus titration resumes after Visit 12 (Week 18). During Weeks 19 to 52, SMBG values will be reviewed with site staff at site visits as well as extemporaneously if the patient calls site due to low or high SMBG readings. The same titration rule as described above (for the 4 week pre-Randomization Lantus titration period) will be followed. The Lantus dose will be adjusted based on the mean of the 3 most recent fasting SMBG values according to the following titration rule: • ≥140 mg/dL (≥7.8 mmol/L): increase Lantus by 4 units, or split to 2 x 2 units • ≥120 mg/dL (≥6.7 mmol/L) but <140 mg/dL (<7.8 mmol/L): increase Lantus by 2 units, or split to 2 x 1 unit • >100 mg/dL (>5.6 mmol/L) but <120 mg/dL (<6.7 mmol/L): increase Lantus by 1 unit • 80-100 mg/dL (4.4-5.6 mmol/L), inclusive: no change in dose • <80 mg/dL (<4.4 mmol/L): decrease Lantus by 2 units. The doses of the two OADs (if applicable) should be held constant throughout the entire 52-week double-blind Treatment Period (ie, not changed except for safety reasons). In case of hypoglycemia, insulin titration may be withheld according to the Investigator's medical judgment. **Hyperglycemic rescue:** During Weeks 19 to 52, patients exceeding glucose rescue limits may have their Lantus dose up-titrated without a maximum limit as a first approach. If up-titration of the Lantus regimen, based on the previously described titration rules, has been unsuccessful (ie, increase in basal insulin is associated with low FPG values despite high HbA1c or elevated post-prandial values), it is appropriate to initiate rescue therapy with prandial insulin, or a GLP-1 agonist, or another antidiabetic medication (except SGLT2 inhibitors), according to the Investigator's clinical judgment and in accordance with the treatment guidelines. **Hyperglycemia rescue criteria:** Rescue is defined by the criteria described below (see STUDY TREATMENTS, Rescue Therapy). **2-Week, Post-treatment Follow-up Visit** Blood pressure (BP) and laboratory values will be assessed, and safety information including adverse events (AEs) will be collected. The HbA1c and centrally measured FPG will be masked to study sites and patients after Randomization and until study end. Additionally, urinalysis by dipstick will not include the measurement of urine glucose. **Early Termination** If a patient discontinues treatment with IMP any time during the Treatment Period, the patient will have a Premature End of Treatment (EOT) Visit, and a Follow-up Visit 2 weeks after the last

	dose of IMP. In addition, every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits, particularly the visits at Week 18 (Visit 12) and Week 52 (Visit 15). If the patient does not agree to site visits, the patient will be contacted by respective sites by telephone to inquire about safety status. If a patient discontinues (or completes) treatment and study at the same time, a single visit for both EOT and end of study (EOS) will be performed. The study design is presented graphically in Section 1.1. The CGM substudy will be detailed in a sub-protocol.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with T2D using any types of basal insulin alone or in combination with up to 2 OADs • Patient has given written informed consent to participate in the study in accordance with local regulations. **Major exclusion criteria:** • At the time of Screening age <18 years or <legal age of majority, whichever is greater • Type 1 diabetes mellitus • OAD dose not stable for 8 weeks before Screening • Use of basal insulin therapy (eg, insulin glargine, Neutral Protamine Hagedorn [NPH], detemir, or degludec) for less than 6 months before Screening • Dose of basal insulin (eg, insulin glargine, NPH, detemir, or degludec) not stable for 8 weeks before Screening (ie, total daily insulin dose increased or decreased by more than 20%) • Use of injectable diabetes drugs other than basal insulin (eg, insulin glargine, NPH, detemir, or degludec), ie, prandial or rapid-acting insulins, short-acting insulins, GLP-1 receptor agonists, or inhaled prandial insulin (Afrezza) within 8 weeks of Screening • Use of a selective SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) within 3 months prior to the trial • Use of systemic glucocorticoids (excluding topical, intra-articular, or ophthalmic application, nasal spray or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit • Patients with severe anemia, severe cardiovascular (including congestive heart failure New York Heart Association IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy that, according to the Investigator, will preclude their safe participation in this study, or will make implementation of the protocol or interpretation of the study results difficult • Known presence of factors that interfere with the Central Lab HbA1c measurement (eg, genetic Hb variants) compromising the reliability of HbA1c assessment or

	medical conditions that affect interpretation of HbA1c results (eg, blood transfusion or severe blood loss in the last 3 months prior to randomization, any condition that shortens erythrocyte survival) • Patient who has taken other investigational drugs or prohibited therapy for this study within 12 weeks or 5 half-lives from prior to Screening, whichever is longer • Patients unwilling or unable to perform SMBG (Section 8.2.1.4), complete the patient diary or comply with study visits and other study procedures as required per protocol • HbA1c <7.5% or HbA1c >10.5% measured by the central laboratory at Screening • HbA1c <7% measured by the central laboratory at Visit 5 (Week -1) • History of diabetic ketoacidosis or nonketotic hyperosmolar coma within 12 weeks prior to the Screening Visit • Pregnant (confirmed by serum pregnancy test at screening) or breastfeeding women • Women of childbearing potential not willing to use highly effective method(s) of birth control during the study treatment period and the follow-up period, or who are unwilling or unable to be tested for pregnancy (see Appendix A), during the study • Mean of 3 separate BP measurements >180 mmHg (SBP) or >100 mmHg (DBP) • History of gastric surgery including history of gastric banding or inflammatory bowel disease within 3 years prior to the Screening Visit. **Note:** Patients who have had bariatric surgery or gastric banding more than 3 years prior to the Screening Visit must have a stable weight (±10%) for 6 months prior to the Screening Visit. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) laboratory range • Total bilirubin >1.5 times the ULN (except in case of Gilbert's syndrome).
Total expected number of patients:	560 randomized patients in the main study.
STUDY TREATMENTS **Investigational medicinal products**	**Sotagliflozin 400 mg** • 200 mg tablets • Oral • 400 mg, given as two (2) 200-mg tablets, once daily before the first meal of the day.
	Sotagliflozin 200 mg • 200 mg tablets • Oral

	• 200 mg, given as one (1) 200-mg tablet and one (1) placebo tablet (identical to sotagliflozin 200 mg in appearance), once daily before the first meal of the day.
Noninvestigational medicinal product(s)	**Placebo** • Tablets identical in appearance to sotagliflozin 200 mg • Oral • Two (2) placebo tablets, once daily before the first meal of the day. **Lantus (insulin glargine, 100 U/mL)** • Prefilled pen (3.0 mL solution) • Subcutaneous injection • Lantus to be provided by the Sponsor at the beginning of the Lantus titration phase. Patients who are receiving any basal insulin other than Lantus before screening will switch to Lantus. For patients who are using long-acting insulin analogs other than Lantus (eg, Levemir, Tresiba, Basaglar), the existing basal insulin will be converted to an equivalent dose of Lantus on a 1:1 unit basis (ie, the same dose on the day before Visit 2). If the patient is using Toujeo® (glargine U-300/mL), the initial Lantus dose is 80% of the existing Toujeo dose as recommended in the Lantus label. If the patient is using NPH twice daily, it's recommended that the converted Lantus dose should be reduced by 20% and given once daily. If using NPH once a day, it can be converted to Lantus unit-to-unit. • Metformin (optional) tablets to be administered as per Principal Investigator and in accordance with local labeling • Other OADs (up to 2 in total, including metformin) to be administered as per Principal Investigator and in accordance with local labeling, with the exception of SGLT2 inhibitors.
	Rescue Therapy The threshold values for rescue are defined as follows, depending on study period: • From Baseline Visit (Visit 6, Day 1) to Visit 10 (Week 8) (including value at Visit 10): FPG >270 mg/dL (15.0 mmol/L) • From Visit 10 (Week 8) to Visit 11 (Week 12) (including value at Visit 11): FPG >240 mg/dL (13.3 mmol/L) • From Visit 11 (Week 12) up to Visit 12 (Week 18): FPG >200 mg/dL (11.1 mmol/L) or HbA1c ≥8.5% (the 8.5% criteria does not apply if the HbA1c decrease from Baseline was ≥1.5%) • From Visit 12 (Week 18) up to the EOT, Visit 15 (Week 52): FPG >170 mg/dL (9.4 mmol/L) or HbA1c ≥8.0% (the 8.0% criteria does not apply if the HbA1c decrease from Baseline was ≥1.5%). Routine fasting SMBG and central laboratory alerts on FPG (and HbA1c at Week 12 and onwards) are set up to ensure that glycemic parameter results remain within predefined thresholds.

	If a central laboratory FPG and/or HbA1c is above the threshold, the Investigator will receive an alert from the central laboratory. Upon receipt of a central laboratory rescue alert, a central laboratory re-test must be completed and confirmed. Likewise, patients are instructed to contact the sites for a confirmatory FPG test via central lab in case of consecutive 3 days high readings in fasting SMBG. Hyperglycemia must be confirmed as exceeding the criterion for rescue before rescue therapy is initiated. The central Lab FPG confirmation should be performed as soon as possible preferably within 7 days by unscheduled visit. The recommended approach to rescue if rescue thresholds have been reached despite up-titration of the Lantus dose includes initiating a prandial dose of short-acting insulin, or GLP-1 agonist, or another antidiabetic medication (except SGLT2 inhibitors) according to the Investigator's clinical judgment and in accordance with the treatment guidelines. If a patient requires rescue, the IMP received at Randomization should continue and must remain blinded until EOS.
ENDPOINTS	**Primary endpoint (Sotagliflozin 400 mg dose):** Change from Baseline to Week 18 in HbA1c. **Secondary endpoints (Sotagliflozin 400 mg dose):** • Change from Baseline to Week 18 in FPG • Change from Baseline to Week 18 in BW. • Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg • Change from Baseline to Week 12 in SBP for all patients • Change from Baseline to Week 52 in HbA1c • Change from Baseline to Week 52 in BW **Secondary endpoints (Sotagliflozin 200 mg dose):** • Change from Baseline to Week 18 in HbA1c • Change from Baseline to Week 18 in BW. • Change from Baseline to Week 18 in FPG • Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg • Change from Baseline to Week 52 in HbA1c • Change from Baseline to Week 52 in BW **Other efficacy endpoints (Sotagliflozin 400 mg and 200 mg):** • Proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Weeks 18, 26, and 52 • Change from Baseline to Week 26 in HbA1c • Change from Baseline to Week 12 in SBP for all patients in the sotagliflozin 200 mg arm, and from Baseline to Weeks 26 and 52 in SBP for all patients and the subset of patients with Baseline SBP ≥130 mmHg in the sotagliflozin 400 mg and 200 mg arms

	• Change from Baseline to Weeks 12, 26, and 52 in SBP in patients with Baseline SBP <130 mmHg • Change from Baseline to Weeks 12, 26, and 52 in DBP for all patients and for the subset of patients with Baseline DBP ≥80 mmHg • Change from Baseline to Week 52 in total daily insulin dose • Proportion of patients requiring rescue therapy during the 52-week double-blind Treatment Period • Change from Baseline to Weeks 18 and 52 in 7-point SMBG profile (mean daily value and at each time point) • Change from Baseline in eGFR • Change from Baseline in UACR during the 52-week Treatment Period • PQAT at Weeks 18 and 52 • Change in TRIM-D from Baseline to Week 52 for total score and 5 domain scores. **Safety endpoints:** • AEs, hypoglycemia (all, severe and/or documented symptomatic hypoglycemia), events of special interest (EOSI), adverse events of special interest (AESI), AEs leading to discontinuation from the IMP, serious adverse events (SAEs), and deaths • Markers of calcium metabolism • Safety laboratory results, vital signs results, and 12-lead electrocardiogram (ECG) results. **Pharmacokinetic endpoints:** Plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite. **CGM substudy endpoints:** The list of endpoints will be outlined in a separate substudy protocol.
ASSESSMENT SCHEDULE	See Section 1.2
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size/power calculations were performed based on the primary endpoint. Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 280 patients in the sotagliflozin 400 mg arm and 140 patients in the placebo arm will provide at least 95% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 18 between sotagliflozin 400 mg and placebo. A sample size of 140 patients in the sotagliflozin 200 mg arm and 140 patients in the placebo arm will provide 80% power to detect a treatment difference of 0.4% in mean HbA1c change from Baseline to Week 18 between sotagliflozin 200 mg and placebo (SD 1.2%; 5% significance level 2-sided).

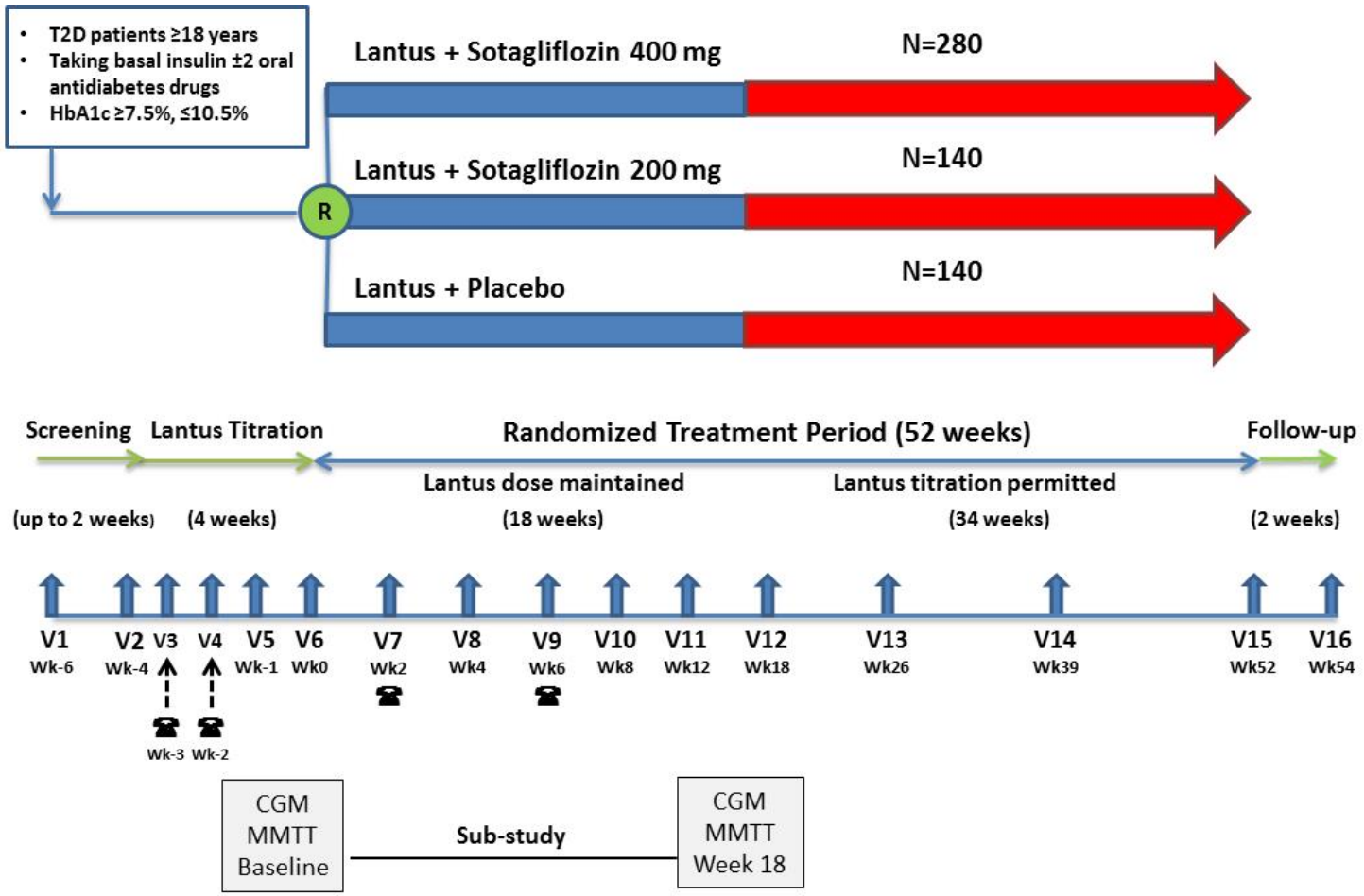
	The total sample size will be 560 patients to be randomized (280 patients in the sotagliflozin 400 mg arm; 140 patients in the sotagliflozin 200 mg arm; 140 patients in the placebo arm). **Analysis population:** Efficacy analyses will be based on the intention to treat (ITT) population, defined as all randomized patients irrespective of compliance with the study protocol and procedures. Patients will be analyzed according to the treatment group to which they are randomized. **Analysis of the primary efficacy endpoint:** Analysis of the primary efficacy endpoint (change from Baseline to Week 18 in HbA1c) will be performed using the ITT population, using HbA1c measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. The primary efficacy endpoint of change in HbA1c from Baseline to Week 18 will be analyzed with missing values imputed by control-based multiple imputation method under the missing not at random framework. • For placebo patients, missing data will be imputed based on the placebo group data • For patients in the sotagliflozin groups, missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model. Each of the complete datasets will be analyzed by the analysis of covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and Baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from Baseline to Week 18 for the sotagliflozin 400 mg arm and placebo arm, as well as the between-group difference (comparing sotagliflozin 400 mg arm versus placebo) and the 95% confidence interval (CI) using contrast statements. Summary statistics (for Screening value, Baseline value, observed values, and observed changes from Baseline) at scheduled visits will be provided for each treatment group. The summary will include the number of observations, mean, SD, standard error (SE), minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from Baseline (±SE) at each of the scheduled visits (using observed cases [OC]). **Baseline definition:** The Baseline value is defined generally as the last available value before the first dose of double-blind IMP or the last available value

	prior to Randomization for patients who were randomized but never exposed to IMP. **Analysis of secondary efficacy endpoints:** The secondary endpoints will be analyzed using a similar approach to the primary efficacy endpoint, with missing values imputed by the control-based multiple imputation method under the missing not at random framework. For each of the continuous secondary endpoints, each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and Baseline secondary endpoint value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 18 (Week 12 for SBP endpoints) for each treatment group, as well as the between-group difference (comparing each sotagliflozin group versus placebo) and the 95% CI using contrast statements. For HbA1c endpoint, results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 18 for sotagliflozin 200 mg arm and placebo arm, as well as the between-group difference (comparing the sotagliflozin 200 mg arm versus placebo arm) and the 95% CI using contrast statements. The categorical secondary efficacy variables of HbA1c <6.5% or <7% at Week 18 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), and randomization strata of sulfonylureas use at Week -1 (yes, no). For the HbA1c <7% or <6.5% analysis, patients with missing HbA1c data at Week 18 will be considered non-responders in the ITT population. Summary statistics for the secondary endpoints at scheduled visits will be provided for each treatment group. **Analysis of other efficacy endpoints:** Except for patient reported outcome (PRO) endpoints, the analysis of other endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using OC will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time. For TRIM-D scores (total and domain scores), descriptive statistics will be presented by treatment group per visit. The change from Baseline to endpoint will be analyzed using a similar approach as the primary efficacy endpoint with missing values imputed by control-based multiple imputation method under the missing not at random framework. **Analysis of Safety Data:** All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. These analyses will be based on the safety population, which is defined as all randomized patients who receive at least 1 dose of double-blind IMP, regardless of the

	amount of treatment administered. Patients will be analyzed for safety analyses according to the treatment actually received. The safety analyses will be provided for the 18-week randomized Treatment Period and for the entire 52-week double-blind Treatment Period.
DURATION OF STUDY PERIOD (per patient)	Up to 60 weeks, including an up to 6-week Screening Period (comprised of an up to 2-week Screening phase and a 4-week, Lantus titration/single-blind placebo Run-in Phase), a 52-week double-blind Treatment Period, and a 2-week post-treatment Follow-up Visit.
STUDY COMMITTEES	**Steering committee:** ☒ Yes ☐ No **Data monitoring committee:** ☒ Yes ☐ No **Adjudication committee:** ☒ Yes ☐ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Abbreviations: CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c; MMTT = mixed-meal tolerance test; R = Randomization; T2D = type 2 diabetes.

1.2 STUDY FLOW CHART

	Screening Period					Double-Blind Treatment Period[a]										FU Period
	Screen-ing	Run-in (Lantus titration, single-blind placebo Run-in)				No titration of Lantus (except for safety)							Lantus titration permitted			
VISIT	1	2	3☎[b]	4☎[b]	5	6	7☎	8	9☎	10	11	12	13	14	15	16[c]
Week	-6	-4	-3	-2	-1	0	2	4	6	8	12	18	26	39	52	54
Day (window [days])	-42	-28 (±3)	-21 (±2)	-14 (±2)	-7 (±2)	1 (-)	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	378 (±3)
Informed consent	X															
Inclusion criteria	X															
Exclusion criteria	X	X	X	X	X	X										
Demographics	X															
Medical/Surgical History	X															
Medication History	X															
Body weight, height[d]	X	X			X	X		X		X	X	X	X	X	X	X
Vital signs[e]	X	X			X	X		X		X	X	X	X	X	X	X
Physical Examination:																
Complete	X												X			
Abbreviated[f]		X			X	X		X		X	X	X		X	X	X
Concomitant Medication	X	X			X	X		X		X	X	X	X	X	X	X
Diet & exercise instruction		X			X	X							X		X	
Instruction on basic GU hygiene & hydration					X	X		X		X	X	X	X	X	X	
Interactive response technology (IRT) contact	X	X				X		X		X	X	X	X	X	X	X

	Screening Period					Double-Blind Treatment Period[a]										FU Period
	Screen-ing	Run-in (Lantus titration, single-blind placebo Run-in)				No titration of Lantus (except for safety)							Lantus titration permitted			
VISIT	**1**	**2**	**3☎[b]**	**4☎[b]**	**5**	**6**	**7☎**	**8**	**9☎**	**10**	**11**	**12**	**13**	**14**	**15**	**16[c]**
Week	**-6**	**-4**	**-3**	**-2**	**-1**	**0**	**2**	**4**	**6**	**8**	**12**	**18**	**26**	**39**	**52**	**54**
Day (window [days])	**-42**	**-28 (±3)**	**-21 (±2)**	**-14 (±2)**	**-7 (±2)**	**1 (-)**	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**378 (±3)**
Randomization						X										
Dispense glucose meter, Beta-hydroxybutyrate (BHB) meter		X														
Dispense glucose test strips and BHB strips		X				X		X		X	X	X	X	X	X	
Measurement of capillary BHB at the site						X		X		X		X	X	X	X	
Dispense diary	X	X				X		X		X	X	X	X	X	X	
Collect/review diary		X			X	X		X		X	X	X	X	X	X	X
Instruction on diabetic ketoacidosis symptoms, glucose testing		X			X	X		X		X	X	X	X	X	X	
Dispense IMP and Lantus		X				X		X		X	X	X	X	X		
IMP and Lantus accounting & compliance					X	X		X		X	X	X	X	X	X	
Review results of SMBG and recommend Lantus dose adjustments as necessary[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record results of a 7-point SMBG[h]						X						X			X	
12-lead ECG[i]	X					X							X			

	Screening Period					Double-Blind Treatment Period[a]										FU Period
	Screen-ing	Run-in (Lantus titration, single-blind placebo Run-in)				No titration of Lantus (except for safety)							Lantus titration permitted			
VISIT	1	2	3☎[b]	4☎[b]	5	6	7☎	8	9☎	10	11	12	13	14	15	16[c]
Week	-6	-4	-3	-2	-1	0	2	4	6	8	12	18	26	39	52	54
Day (window [days])	-42	-28 (±3)	-21 (±2)	-14 (±2)	-7 (±2)	1 (-)	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	378 (±3)
Laboratory Assessments[j]																
FPG[k]	X					X		X		X	X	X	X	X	X	
BHB						X		X		X		X	X	X	X	
HbA1c	X				X	X		X		X	X	X	X	X	X	
Clinical Chemistry [l]	X				X	X		X		X	X	X	X	X	X	X
Hematology	X					X					X		X	X	X	
Fasting lipids						X						X			X	
Pregnancy test (WOCBP)[m]	X					X		X		X	X	X	X	X	X	
FSH and/or estradiol as needed[m]	X															
Plasma concentration[n]								X				X	X		X	
Markers of calcium metabolism[o]						X							X			
Urinalysis w/microscopy[p]	X					X							X			
Collection of home overnight urine for albumin, protein, creatinine, calcium, phosphorus, magnesium, glucose, and albumin-creatinine ratio[q]						X					X		X		X	

	Screening Period					Double-Blind Treatment Period[a]										FU Period
	Screen-ing	Run-in (Lantus titration, single-blind placebo Run-in)				No titration of Lantus (except for safety)							Lantus titration permitted			
VISIT	1	2	3☎[b]	4☎[b]	5	6	7☎	8	9☎	10	11	12	13	14	15	16[c]
Week	-6	-4	-3	-2	-1	0	2	4	6	8	12	18	26	39	52	54
Day (window [days])	-42	-28 (±3)	-21 (±2)	-14 (±2)	-7 (±2)	1 (-)	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	378 (±3)
[redacted]																
PRO: PQAT[t]												X			X	
PRO: TRIM-D[t]	X					X						X	X	X	X	
Evaluate for glycemic rescue						To be assessed and reported throughout the Treatment Period										
Hypoglycemia	To be assessed and reported throughout the study															
AEs/SAEs/AESI/EOSI[u]	To be assessed and reported throughout the study															

a If a patient discontinues treatment with IMP early during the Treatment Period, the patient will have a Premature EOT Visit, and a Follow-up Visit 2 weeks after the last dose of IMP. However, every effort will be made to have the patients return to the site for all scheduled visits, in particular the visits at Week 18 (Visit 12) and Week 52 (Visit 15). If the patient does not agree to a site visits, the patient will be contacted by telephone to inquire about safety status. If a patient discontinues (or completes) treatment and study at the same time, a single visit for both EOT and EOS will be performed.

b To ensure effective Lantus dose titration during the Run-in Phase, patients will be instructed to call the Investigator to discuss the necessary adjustments in Lantus dose if they have 2 or more SMBG measurements above 100 mg/dL or below 80 mg/dL.

c Two weeks after the last dose of IMP.

d Height to be measured only at Screening.

e Vital sign measurements (sitting blood pressure [BP], heart rate): 3 separate seated BP and heart rate measurements should be taken with at least 1 minute between readings, following a 5-minute rest period and prior to phlebotomy (if applicable).

f The abbreviated physical exam should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs if necessary.

g Fasting (pre-breakfast/pre-injection if available) SMBG: during the 4-week Run-in Lantus titration period, fasting SMBG should be performed daily. Thereafter, the number of fasting SMBG checks can be reduced according to the Investigator's judgment, however at least 3 fasting (pre-breakfast) SMBG measurements per week should be done from Weeks 0 to 18 and 3 measurements during the week prior to study visits from Weeks 19 to 52 (Section 8.2.1.4). Patients will review SMBG values with site staff either at site visits, phone visits or extemporaneously if patient feels high or low SMBG values may necessitate a dose adjustment. See Table 2 for permitted adjustments. Patients should be advised to check SMBG whenever they experience any symptoms of hypoglycemia, if possible, before taking the treatment. **Note:** Units in table represent plasma glucose values as glucometers used for SMBG display results already adjusted to plasma concentration and no conversion is required.

h 7-point SMBG profile (before [pre-injection after randomization] and 2 hours after breakfast, lunch and dinner, and bedtime): at least ONE day during the weeks prior to Weeks 0 (Visit 6), 18 (Visit 12), and 52 (Visit 15).

i The 12-lead ECG recordings should be obtained after at least 10 minutes in a supine position and prior to IMP administration. The ECG will be evaluated as "normal" or "abnormal".

j All laboratory assessments occur prior to dose of double-blind IMP (when applicable).
k FPG is performed in fasting state, ie, without any food intake (except for water) for at least 8 hours.
l Clinical chemistry includes amylase and lipase: please see the list in Table 4.
m Serum pregnancy testing only at Screening; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to beginning the Run-in Phase for all women of childbearing potential (WOCBP, 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. For women of non-reproductive potentials (Appendix A), follicle-stimulating hormone [FSH] and/or estradiol levels should be tested in case the definition of postmenopausal or premenopausal can't be satisfied, eg, no medical documents of hysterectomy or cessation of menses without an alternative medical cause is < 12 months.
n Plasma concentration samples for sotagliflozin and sotagliflozin-3-O-glucuronide collected on Weeks 4, 18, 26, and 52 may be drawn with the other laboratory assessments but MUST be collected before administration of IMP.
o All patients will have lab assessments for markers of calcium metabolism. The markers of calcium metabolism include: serum calcium, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum phosphorus, and serum parathyroid hormone.
p Urinalysis includes urine dipstick and microscopy. Dipstick includes assessment of specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrate, and leukocyte esterase. Microscopy includes, but is not limited to, detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment. In the event of abnormal urinalysis findings suspicious of urinary tract infection (UTI), urine culture should be performed. Positive urine culture determination will be based upon the criteria of the reporting laboratory. Additionally, urine culture should be performed if at any point the Principal Investigator suspects the presence of a UTI.
q Patients will collect overnight urine on Weeks 0, 12, 26 and 52 (Visits 6, 11, 13 and 15). In the night prior to the visits: the urine before sleep will be discarded and the urine during sleep and the first morning urine (after getting up) will be collected. The visits should be re-scheduled to allow for the urine collection in case a patient missed it. Urinary albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine) and glucose will be assessed.

[redacted]

t Patient Reported Outcomes (PROs): Patient Qualitative Assessment of Treatment (PQAT) to be administered to approximately 70 English-speaking patients at Week 18 and 52; Treatment Related Impact Measure - Diabetes (TRIM-D) to be administered to all patients included in the study at Screening, Baseline, and Weeks 18, 26, 39, and 52.
u All serious adverse events (SAEs), adverse events (AEs), AEs of special interest (AESI), and events of special interest (EOSI) will be collected starting from signing informed consent and continue until the end of the study. All AEs that occur during treatment should be followed until study completion (or until patients leave the study) or until the event has resolved, the condition has stabilized or the patient is lost to follow-up. All patients will have a Follow-up visit 2 weeks after the last dose of IMP to collect safety information.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

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3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BHB:	beta-hydroxybutyrate
BMI:	body mass index
BP:	blood pressure
BW:	body weight
CEC:	Clinical Endpoint Commitee
CGM:	continuous glucose monitoring
CI:	confidence interval
CRF:	case report form
CRO:	contract research organization
CSR:	clinical study report
CV:	cardiovascular
DBP:	diastolic blood pressure
DILI:	drug-induced liver injury
DKA:	diabetic ketoacidosis
DMC:	Data Monitoring Committee
ECG:	electrocardiogram
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOS:	end of study
EOSI:	events of special interest
EOT:	end of treatment
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
FSH:	follicle-stimulating hormone
GCP:	good clinical practice
GI:	gastrointestinal
GLP-1:	glucagon-like peptide-1
GU:	genitourinary
HbA1c:	hemoglobin A1C
HLGT:	high-level group term
HLT:	high level term
HRT:	hormone replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
ID:	identification

IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	intention-to-treat
MACE:	major adverse cardiac event
MDRD:	Modification of Diet in Renal Disease
MI:	myocardial infarction
N:	number (of observations)
NIMP:	noninvestigational medicinal product
NPH:	Neutral Protamine Hagedorn
OAD:	oral antidiabetes drug
OC:	observed cases
PCSA:	potentially clinically significant abnormality
P-gp:	P-glycoprotein
PK:	pharmacokinetic
PQAT:	Patient Qualitative Assessment of Treatment
PRO:	patient reported outcome
PT:	preferred term
PYY:	peptide YY
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	Steering Committee
SD:	standard deviation
SE:	standard error
SGLT:	sodium-glucose cotransporter
SGLT1:	sodium-glucose cotransporter type 1
SGLT2:	sodium-glucose cotransporter type 2
SMBG:	self-monitored blood glucose
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T1D:	type 1 diabetes
T2D:	type 2 diabetes
TEAE:	treatment-emergent adverse event
TRIM-D:	Treatment Related Impact Measure - Diabetes
UACR:	urinary albumin creatinine ratio
ULN:	upper limit of normal
US:	United States
UTI:	urinary tract infection
VTE:	venous thrombotic event
WOCBP:	women of childbearing potential

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: SOTAGLIFLOZIN AND DISEASE

Sotagliflozin is a dual inhibitor of the sodium-glucose cotransporters (SGLT) type 1 and 2 (SGLT1 and SGLT2). Sotagliflozin is being developed for use in type 2 diabetes (T2D), a metabolic disorder characterized by hyperglycemia that results from a combination of increased insulin resistance and beta cell dysfunction (1). The microvascular complications of diabetes are well known and can result in impaired renal function, retinopathy, and neuropathy, while results of macrovascular complications are coronary artery disease, peripheral arterial disease, and stroke (2). Other comorbidities that are frequently associated with diabetes are hypertension, obesity, and cardiovascular (CV) disease. According to the most recent International Diabetes Federation Diabetes Atlas, it was estimated in 2015 that 1 in 11 adults have diabetes, equivalent to 415 million people, which is estimated to rise to 642 million adults by 2040 (3).

According to the World Health Organization, there are about 60 million people with diabetes in the European Region, or about 10.3% of men and 9.6% of women aged 25 years and over (4). While these numbers include both people with T2D and type 1 diabetes (T1D), over 90% of adults with diabetes have T2D. Diabetes is among the leading causes of death by disease and is a leading cause of heart disease, stroke, blindness, kidney disease, and amputation (3, 4). Despite the fact that the population of people with diabetes is growing, none of the current therapies is curative and the results of treatment are variable.

Although lifestyle changes, including diet, exercise, and education, are valuable components of diabetes treatment, the vast majority of people with T2D must receive pharmacological therapy to control the disease. In the United States (US) and Europe, metformin is the standard first-line therapy in the absence of any contraindications or tolerability issues, as per guidance from the American Diabetes Association (5).

Despite the numerous treatment options available, monotherapy fails in many patients as beta cell function continues to deteriorate leading to progressively increasing hyperglycemia. Aggressive glycemic control with the currently available agents often leads to side effects, most notably weight gain and an increased frequency of hypoglycemia. These concerns emphasize the need to develop new agents that effectively and safely lower glucose in diabetic patients (6).

In patients with diabetes, it is desirable to maintain blood glucose in the normal range without exhausting the ability of the pancreatic beta-cells to produce insulin. Glucose is transported across the cell membrane by 2 different types of glucose transporters: glucose-facilitated transporters and SGLT proteins (7). In the kidney, after blood is filtered by the glomerulus, glucose passes into the urine, but 99% is reabsorbed, primarily via SGLT2, which is responsible for 90% of glucose reabsorption, while 10% is reabsorbed by SGLT1. When functional SGLT2 is lacking in humans, a significant amount of glucose remains in the urine and is removed from the body (8). This way of reducing blood glucose is an insulin-independent mechanism and therefore hyperglycemia may be reduced while the pancreas is spared from an increased demand for insulin production that is

caused by hyperglycemia. Since obesity is a significant comorbidity in T2D, and insulin resistance is increased in obesity, the caloric loss from glucose in the urine may represent an additional benefit resulting in decreased weight, which should result in decreased insulin resistance (8).

SGLT1 is expressed predominantly in the gastrointestinal (GI) tract and is responsible for the majority of glucose absorption by the small intestine (9). Inhibition of SGLT1 in the GI tract delays glucose absorption and lowers peak postprandial glucose levels (8). Additionally, there is accumulating evidence that SGLT1 inhibition stimulates secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), gut hormones involved in pancreatic beta cell function and appetite control, respectively. Reduced glucose absorption in the proximal intestine leads to more glucose being delivered distally, which allows L cells in both the ileum and the colon to sense glucose and its byproducts and, as a result, they secrete GLP-1 and PYY. Although a complete lack of functional SGLT1 may be associated with symptoms of glucose and galactose malabsorption (10), pharmacologic inhibition of SGLT1 by sotagliflozin has not produced these effects in preclinical models or patients with T2D. Selective inhibitors of the SGLT1 transporter are in early stages of development.

Extensive clinical studies conducted for selective SGLT2 inhibitors have established this class as effective agents for the treatment of T2D (6, 11) and have led to approvals by the US Food and Drug Administration (FDA) and the European Medicines Agency. Studies with sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, have shown that this agent produces significant glucosuria in preclinical animal models, healthy human volunteers, and patients with T2D. Single- and multiple-dose administration of sotagliflozin to healthy human patients has resulted in dose-dependent increases in glucosuria. Multiple-dose (28-day) administration in diabetic patients produced improvements in several metabolic parameters, including urinary glucose excretion, fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), GLP-1, and PYY (12). These data suggest that sotagliflozin should be of therapeutic benefit to patients with T2D.

4.2 CLINICAL TRIALS OF SOTAGLIFLOZIN IN HUMANS

Approximately 840 subjects (698 assigned to sotagliflozin and 229 assigned to placebo) have participated in completed 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. The most frequently reported TEAEs (≥2.0%) were headache, nausea, diarrhea, constipation, dizziness, and upper respiratory tract infection, all of which were reported at a frequency greater than placebo. However, the majority were described as mild to moderate, and most resolved spontaneously and without discontinuation of the study drug.

In completed and ongoing clinical trials, no additional safety issues beside those already described in the current Investigator's Brochure (IB) have been observed. In general, no significant imbalances of SAEs/AEs between sotagliflozin and comparators were observed in completed

studies. Cumulatively, across the completed studies, 8 SAEs were reported in 6 patients (4 patients with T2D and 2 with T1D), all of which were assessed as unrelated to study drug; those reported in 4 patients with T2D who received sotagliflozin included pulmonary embolism, deep vein thrombosis, bile duct stone, cholangitis and lower limb fracture, while a patient receiving placebo had a myocardial infarction (MI). Two SAEs of diabetic ketoacidosis (DKA) were reported in 2 patients with T1D in the ongoing (blinded) Phase 2 T1D study (LX4211.1-203-TIDM) using insulin pumps; in each case basal insulin was within 7% of Baseline, and both SAEs were assessed as due to failure of insulin delivery via insulin pump. 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.

A drug interaction study with digoxin, a sensitive P-glycoprotein (P-gp) substrate, indicated that sotagliflozin acts as a weak P-gp inhibitor. Thus, sotagliflozin increases systemic exposure of digoxin and could also increase the exposure of other P-gp substrates. Patients taking sotagliflozin with concomitant digoxin should have digoxin concentrations monitored and doses reduced as needed. In addition, other P-gp substrates may be affected and the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments.

Safety, tolerability, pharmacokinetic (PK) and pharmacodynamic effects of sotagliflozin are supported by Phase 1 and Phase 2 studies and animal toxicology data in rats up to 26 weeks and dogs up to 39 weeks as well as 2-year carcinogenicity data in rats.

More information on the safety of sotagliflozin and on the clinical program can be found in the IB.

4.3 RATIONALE FOR SELECTION OF DOSE

Both the 200 mg and 400 mg doses are being developed in the Phase 3 program for sotagliflozin for the treatment of T2D. These doses are being tested in several Phase 3 trials, including the current trial in patients with T2D and inadequate glycemic control.

The proposed sotagliflozin 200 mg and 400 mg once daily doses are based on the results of the Phase 2b study LX4211.1-202-DM. In this study sotagliflozin doses of 75 mg once daily, 200 mg once daily, 200 mg twice daily, and 400 mg once daily were tested over a 12-week, double-blind period. The sotagliflozin 200 mg and 400 mg once daily doses were chosen for further evaluation based on their HbA1c lowering effects and the overall safety and tolerability observed at these doses. At 12 weeks, the 200 mg and 400 mg once daily doses lowered HbA1c by a mean of 0.52% and 0.93%, respectively ($p < 0.001$ for both arms), while placebo lowered HbA1c by a mean of 0.14%. Sotagliflozin also produced statistically significant reductions in body weight (BW) (200 mg and 400 mg doses) and systolic blood pressure (SBP) (400 mg dose).

The overall incidences of AEs on sotagliflozin 200 mg and 400 mg once daily doses were similar to placebo.

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 T2D, 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.

4.4 RATIONALE FOR STUDY DESIGN AND CONTROL GROUPS

This study is designed to assess the efficacy and safety of sotagliflozin (compared to placebo) when used as add-on therapy to basal insulin (Lantus), alone or in combination with oral antidiabetes drugs (OADs). Patients will be switched from their current basal insulin to Lantus (1:1 dose conversion, or 20% reduction if on treatment with Toujeo or Neutral Protamine Hagedorn [NPH] twice daily) and will have a 4-week dose titration period to improve their basal insulin dose prior to Randomization, utilizing a standard titration algorithm. During this period, compliance with the algorithm will be reviewed by an internal group blinded to the treatment assignment and investigators will be contacted as needed to encourage adherence to titration algorithm. During this Lantus titration period, the dose of concomitant OADs should stay unchanged, except if decreases are needed due to hypoglycemia.

The primary endpoint is HbA1c reduction from Baseline to Week 18 because it is expected that sotagliflozin can provide significant additional glycemic efficacy even in an advanced T2D population with presumed beta cell failure. During the first 18 weeks no adjustment of Lantus is permitted (except for safety reasons or if rescue criteria are met) to enable the assessment of the effect of randomized treatment drug on top of a stable background therapy of insulin ±OADs. After Week 18, titration of Lantus may resume following the same titration algorithm utilized during the Run-in period. This will enable the assessment of the effect of the randomized study drug in a context of total dose of insulin being simultaneously adjusted and more typical of a real-world setting. Prandial insulin or GLP-1 agonists will be the recommended rescue therapy for patients on a stable regimen of oral antihyperglycemic agents who cannot adequately achieve glycemic control by up-titrating their Lantus dose, as per international diabetes treatment guidelines (13, 14). However, the investigator will be allowed to choose from any antidiabetic agent (with the exception of the SGLT2 inhibitors class) according to their clinical judgment and in line with the local standard of care. The protocol stipulates that patients be provided rescue therapy according to increasingly stringent hyperglycemia criteria (based on FPG and/or HbA1c) as aligned with regulatory guidance (15).

Randomization will be stratified based on HbA1c at Week -1 (≤8.5%, >8.5%), SBP at Week -1 (<130 mmHg, ≥130 mmHg), and use of sulfonylureas at Week -1 (yes, no), to achieve balanced randomization for assessment of the primary and main secondary study endpoints.

A placebo control will be used to allow for an unbiased assessment of treatment effects and safety data. Bias will be minimized by randomizing the patients to treatment groups, blinding the patients, the Investigators, and the Sponsor to the treatment allocations, and by adjudicating endpoints in a blinded fashion.

Two Patient Reported Outcomes (PROs) will be assessed in this trial. The Patient Qualitative Assessment of Treatment (PQAT) will be assessed at Week 18 and at the final on-treatment visit (Week 52). This instrument includes a 7-point Likert Scale for the patient to evaluate his/her subjective response to the treatment (-3 to +3 including 0 for a neutral response) and 2 free-text response questions to describe key advantages and disadvantages. The Treatment Related Impact Measure – Diabetes (TRIM-D) includes questions related to satisfaction with weight and hypoglycemia; it will be assessed at Screening, at Baseline (after the Lantus titration phase), and at several visits during the Treatment Period.

A continuous glucose monitoring (CGM) substudy is planned to include a subset of patients. This study will allow assessing the impact of sotagliflozin on additional parameters of glucose control and variability over 24 hours which cannot be inferred by the HbA1c as an aggregate measure of overall glycemic control. The details of the CGM substudy are specified in the separate substudy protocol.

4.5 BENEFIT/RISK OF SOTAGLIFLOZIN

Sotagliflozin is currently being investigated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The development program will also provide efficacy and safety data for sotagliflozin in combination with other antidiabetes medications. In addition, the program will evaluate clinical outcomes in patients with high CV risk and in patients with renal impairment. The use of sotagliflozin in the treatment of T1D is also being studied in a separate development program.

Sotagliflozin may benefit a wide variety of diabetic patients based on multiple potential beneficial effects of dual SGLT1/SGLT2 inhibition, and its insulin-independent mechanism of action. Improvements in HbA1c, FPG, and postprandial glucose were observed with sotagliflozin in multiple studies. As anticipated from the mechanism of action, treatment with sotagliflozin resulted in increased urinary glucose excretion (from inhibition of SGLT2) as well as increased levels of the intestinal peptides GLP-1 and PYY (from inhibition of SGLT1). In addition, the improvements in BW and blood pressure (BP) observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

Phase 2 data indicated that sotagliflozin may reduce SBP by 10 to 15 mmHg in patients with SBP ≥130 mmHg at Baseline, while having no significant effect in patients with SBP <130 mmHg, and did not induce hypotension in normotensive patients. Since this could be of benefit to patients with T2D, this finding is being followed up as a secondary objective in this trial.

Additionally, the insulin-independent glucose lowering mechanism can result in an insulin sparing effect and consequently reduce the insulin requirements of patients managed with basal insulin. This outcome can result in a clinical benefit in patients on insulin therapy by lowering the risk of

hypoglycemia and weight gain associated with higher insulin doses. Also, the reduction in glucose levels can also delay the need for initiation of rescue treatment, which can include prandial insulin and GLP-1 receptor agonists.

SGLT2 inhibitors class have been associated with small decreases of glomerular filtration rate and increased rate of genital infections, which are usually mild and well tolerated in clinical trials. Overall, sotagliflozin has been well-tolerated in all studies to date, with the majority of events assessed as mild to moderate; most of which resolved spontaneously. Serious AEs and discontinuations due to AEs have been limited and balanced between treatment and comparator groups.

Events of special interest (EOSI) are evaluated based on either their potential link to the drug's mechanism of action, events that occur in other SGLT-inhibitor drugs, or regulatory interest/guidance for diabetes products, but found not to be in imbalance in clinical trials. In addition to the identified and potential risks (genital mycotic infections [male and female], metabolic acidosis, DKA, urinary tract infections [UTIs], volume depletion, severe hypoglycemia) for the sotagliflozin program, other EOSI have been defined. These EOSI are: major adverse cardiac events (MACEs) and other CV events, venous thrombotic events (VTEs), drug-induced liver injuries (DILIs)/alanine aminotransferase (ALT) increase >3 times the upper limit of normal (ULN), diarrhea, pancreatitis, bone fractures, renal events, malignancies of special interest (including but not limited to: breast, bladder, renal cell, Leydig cell, pancreatic, prostate and thyroid cancer), and AEs leading to amputation.

However, reports of these events have been infrequent and have responded to standard treatment. The improvement in glycemic control, the reductions in weight and BP, and the tolerability and safety profile of sotagliflozin to date demonstrate a favorable benefit-risk assessment for sotagliflozin.

5 STUDY OBJECTIVES

5.1 PRIMARY

To demonstrate the superiority of sotagliflozin 400 mg versus placebo with respect to HbA1c reduction at Week 18 in patients with T2D who have inadequate glycemic control on basal insulin alone or with OADs.

5.2 SECONDARY

- To assess the effects of sotagliflozin 400 mg versus placebo on:
  - Change from Baseline to Week 18 in FPG
  - Change from Baseline to Week 18 in BW
  - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline to Week 12 in SBP for all patients
  - Change from Baseline to Week 52 in HbA1c
  - Change from Baseline to Week 52 in BW
- To assess the effects of sotagliflozin 200 mg versus placebo on:
  - Change from Baseline to Week 18 in HbA1c
  - Change from Baseline to Week 18 in BW
  - Change from Baseline to Week 18 in FPG.
  - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline to Week 52 in HbA1c
  - Change from Baseline to Week 52 in BW
- To evaluate the safety of sotagliflozin 400 mg and 200 mg versus placebo throughout the 52-week trial.

5.3 OTHER

- To assess the effects of sotagliflozin 400 mg versus placebo on the proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Weeks 18, 26, and 52
- To assess the effects of sotagliflozin 200 mg versus placebo on the proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Weeks 18, 26, and 52
- To assess the effects of sotagliflozin 200 mg versus placebo on the change from Baseline to Week 12 in SBP for all patients
- To assess the effects of sotagliflozin 400 mg and 200 mg versus placebo on:

- Change from baseline to Week 26 in HbA1c
- Change from Baseline to Weeks 26 and 52 in SBP in all patients and the subset of patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Weeks 12, 26, and 52 in SBP in patients with Baseline SBP <130 mmHg
- Change from Baseline to Weeks 12, 26, and 52 in diastolic blood pressure (DBP) for all patients and the subset of patients with Baseline DBP ≥80 mmHg
- Change from Baseline to Week 52 in the total daily insulin dose
- Proportion of patients requiring rescue therapy during the 52-week double-blind Treatment Period
- Change from Baseline to Weeks 18 and 52 on 7-point Self-Monitored Blood Glucose (SMBG) profile (mean daily value at each time point)
- Change from Baseline on estimated glomerular filtration rate (eGFR)
- Change from Baseline in urinary albumin creatinine ratio (UACR)
- Patient Qualitative Assessment of Treatment (PQAT) during the 52-week Treatment Period
- Patient perception of treatment impact and satisfaction using the TRIM-D during the 52-week Treatment Period.

- To assess plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multicenter, randomized, double-blind (with single-blind Run-in Phase), placebo-controlled, parallel-group study that is anticipated to enroll approximately 560 patients.

The study will consist of 3 periods: 1) an up to 6-week Screening Period comprised of a Screening phase of up to 2 weeks and a 4-week Lantus titration/single-blind placebo titration Run-in Phase; 2) a 52-week double-blind Treatment Period; and 3) a 2-week, post-treatment Follow-up Period. The study design is presented graphically in Section 1.1.

In the United States, a substudy employing CGM technology will be performed to assess detailed glycemic profiles. The details of the CGM substudy procedures, endpoints and statistical analyses will be provided in a separate substudy protocol.

6.1.1 Screening period

6.1.1.1 Screening phase (Visit 1)

The Screening phase will last up to 2 weeks. The period must be long enough to collect the data required to establish whether the patient satisfies the inclusion/exclusion criteria.

Patients with T2D (16) will be included in this study if at Screening they have inadequate glycemic control (as demonstrated by a mean HbA1c ≥7.5% or HbA1c ≤10.5%), despite use of basal insulin (at a total daily dose that has been stable within ±20% of the dose at Screening for 8 weeks inclusive). Patients may also be using up to any 2 OADs which may include metformin at a dose of at least 1500 mg/day or the maximum tolerated dose (documented).

At the Screening Visit after signing of the informed consent form (ICF), eligibility criteria will be assessed, and Screening assessments will be performed. Women of childbearing potential (WOCBP) not willing to use highly effective contraceptive method(s), and/or who are unwilling or unable to be tested for pregnancy during the study will be excluded; guidance on highly effective contraceptive methods and collection of pregnancy information is provided in Appendix A. If another contraceptive method is used (such as a barrier method), it should be used in combination with one of the highly effective methods described in Appendix A (such as an oral contraceptive).

The interactive response technology (IRT; either Interactive Voice Response System or Interactive Web Response System) will be contacted at Visit 1 for notification of Screening and for patient number allocation.

6.1.1.2 Run-in phase (Visits 2 to 5)

The Lantus titration/single-blind placebo Run-in Phase will last 4 weeks. If the patient satisfies the entry criteria during the Screening phase, the basal insulin that the patient is currently taking will be replaced by Lantus (Section 8.2.1) provided by the Sponsor. A 4-week Lantus optimization phase will commence.

During the 4-week Lantus titration/single-blind placebo Run-in Phase, patients will also take single-blind placebo (2 tablets, identical to sotagliflozin 200 mg in appearance) once daily before the first meal of the day, starting from Visit 2.

6.1.2 Double-blind Treatment Period (Day 1 to Week 52)

Eligible patients will be randomized on Day 1 (Visit 6). In order to qualify for randomization, patients must have an HbA1c value ≥7.0% at Week -1 (Visit 5) and must demonstrate compliance at the end of the single-blind placebo Run-in Phase based upon tablet count (≥80%), and as assessed at the Investigator's discretion.

Randomization will be stratified by:

- HbA1c at Week -1 (≤8.5%, >8.5%)
- SBP at Week -1 (<130 mmHg, ≥130 mmHg)
- Sulfonylureas use at Week -1 (yes, no).

Following randomization, patients will be treated in a double-blind manner for 52 weeks. A total of 560 patients ≥18 years of age (or ≥legal age of majority if greater) will be randomly assigned 2:1:1 to the following 3 treatment groups:

- Sotagliflozin 400 mg, given as two (2) 200-mg tablets, once daily before the first meal of the day (N = 280 patients)
- Sotagliflozin 200 mg, given as one (1) 200-mg tablet and one (1) placebo tablet (identical to sotagliflozin 200 mg in appearance), once daily before the first meal of the day (N = 140 patients)
- Placebo, given as two (2) placebo tablets (identical to sotagliflozin 200 mg in appearance), once daily before the first meal of the day (N = 140 patients).

The doses of the OADs (if applicable) should be held constant throughout the entire 52-week double-blind Treatment Period (ie, not changed except for safety reasons), and the dose of all antihypertensive medications should be held constant for the first 12 weeks (until Visit 11) except for safety reasons.

The dose of Lantus should be held constant for the first 18 weeks unless glycemic rescue criteria are satisfied (Section 8.2.1.4). Insulin titration resumes after Visit 12.

6.1.3 Follow-up period

A post-treatment Follow-up Visit should be scheduled for all patients 14 days (2 weeks) ± 3 days after last dose of the IMP (either as scheduled or prematurely).

[redacted]

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The total duration of the study for each patient will be up to 60 weeks, including a Screening phase of up to 2 weeks, a 4-week Lantus titration/single-blind placebo Run-in phase, a 52-week double-blind Treatment Period, and a 2-week post-treatment Follow-up Period.

6.2.2 Determination of end of clinical trial (all patients)

The end of study (EOS) is defined as being the "last patient last visit" planned with the protocol, including Follow-up visit.

The Sponsor can terminate the trial prematurely based on the advice of the independent Data Monitoring Committee (DMC) or other unforeseen developments.

6.3 STUDY COMMITTEES

6.3.1 Steering committee

The Steering Committee (SC) is composed of experts in diabetes and scientists with clinical and methodological expertise.

This committee, led by a Chair, is responsible for producing and conducting a scientifically sound study and for ensuring accurate reporting of the study. In that capacity, the SC must address and resolve scientific issues encountered during the study. The members will remain blinded until completion of the study.

Among its responsibilities, the SC will receive blinded study status reports from the Sponsor, and will review the recommendations from the DMC throughout the study. The SC members will participate in a face-to-face meeting at regular intervals throughout the study and in regularly scheduled teleconferences.

Detailed activities and responsibilities for the SC are provided in the SC Charter.

6.3.2 Data monitoring committee

A DMC with members who are independent from the Sponsor and the Investigators will meet on a regular basis, and will be responsible for:

- Review of accumulating clinical trial safety data by treatment
- Making a recommendation to the Sponsor regarding the study following each meeting.

Safety data to be reviewed will include events and outcomes described below for adjudication, as well as any additional safety data considered relevant. 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.

6.3.3 Clinical endpoint committee(s)

The Clinical Endpoint Committees (CECs) is/are comprised of experts in cardiology and nephrology (and other appropriate medical specialties such as neurology and endocrinology as needed) who are independent of the Sponsor and the contract research organization (CRO). The CEC(s) will review and adjudicate all deaths, MACE/selected CV events (MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), selected renal events, bone fracture, and DKA.

The details regarding the CEC processes and procedures will be outlined in the CEC Charter(s).

6.3.4 Safety adjudication of events requiring ongoing monitoring

Two independent committees will review safety events that require ongoing monitoring to ensure timing protocol amendments in case a safety signal is identified. These events are: 1) potential cases of DILI, and 2) cases of amputations.

The 2 committees will review the cases in a treatment-blinded manner and will present their assessment to the DMC.

The members, roles and responsibilities of the two committees will be described in a separate Charter.

7 SELECTION OF PATIENTS

Note: A patient should not be randomized more than once. In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the patient can be rescreened once prior to entering Run-in for this study.

7.1 INCLUSION CRITERIA

I 01. Patients with T2D using any types of basal insulin alone or in combination with up to 2 OADs

I 02. Patient has given written informed consent to participate in the study in accordance with local regulations.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. At the time of Screening age <18 years or <legal age of majority, whichever is greater.

E 02. Body Mass Index (BMI) ≤20 or >45 kg/m^2 at the Screening Visit.

E 03. Use of systemic glucocorticoids (excluding topical, intra-articular, or ophthalmic application, nasal spray or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit.

E 04. Use of weight loss medications within 12 weeks or weight change of 5 kg or more during the 12 weeks before Screening.

E 05. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol (eg, long-term systemic glucocorticoids) and refusing or unable to take alternative treatment.

E 06. Patients who have previously been randomized in any clinical trial of sotagliflozin/LX4211.

E 07. Patients with severe anemia, severe CV (including congestive heart failure New York Heart Association IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy that, according to the Investigator, will preclude their safe participation in this study, or will make implementation of the protocol or interpretation of the study results difficult.

E 08. Current diagnosis of chronic hepatitis, and/or other clinically active liver disease requiring treatment.

E 09. Known presence of factors that interfere with the Central Lab HbA1c measurement (eg, genetic Hb variants) compromising the reliability of HbA1c assessment or medical conditions that affect interpretation of HbA1c results (eg, blood transfusion or severe blood loss in the last 3 months prior to randomization, any condition that shortens erythrocyte survival).

E 10. History of drug or alcohol abuse within 6 months prior to Screening.

E 11. Patient is an employee of the Sponsor, or is the Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in conducting the study.

E 12. Patient who has taken other investigational drugs or prohibited therapy for this study within 12 weeks or 5 half-lives from prior to Screening, whichever is longer.

7.2.2 Exclusion criteria related to the diabetes history and treatment

E 13. Type 1 diabetes mellitus.

E 14. HbA1c <7.5% or HbA1c >10.5% measured by the central laboratory at Screening.

E 15. Use of a selective SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) within 3 months prior to the trial.

E 16. History of DKA or nonketotic hyperosmolar coma within 12 weeks prior to the Screening Visit.

E 17. History of severe hypoglycemia resulting in unconsciousness, seizure or hospitalization within 6 months prior to the Screening Visit.

E 18. For patients using metformin or other OADs, contraindication to metformin or the other OADs as per local labeling.

E 19. Use of injectable diabetes drugs other than basal insulin (eg, insulin glargine, NPH, detemir, or degludec), ie, prandial or rapid-acting insulins, short-acting insulins, GLP-1 receptor agonists, or inhaled prandial insulin (Afrezza) within 8 weeks of Screening.

E 20. OAD dose not stable for 8 weeks before Screening.

E 21. Use of basal insulin therapy (eg, insulin glargine, NPH, detemir, or degludec) for less than 6 months before Screening.

E 22. Dose of basal insulin (eg, insulin glargine, NPH, detemir, or degludec) not stable for 8 weeks before Screening (ie, total daily insulin dose increased or decreased by more than 20%).

E 23. Known unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema that is likely to require laser, surgical treatment during study period.

7.2.3 Exclusion criteria related to the current knowledge of sotagliflozin

E 24. Pregnant (confirmed by serum pregnancy test at Screening) or breastfeeding women.

E 25. Women of childbearing potential not willing to use highly effective method(s) of birth control during the study treatment period and follow-up period, or who are unwilling or unable to be tested for pregnancy (see Appendix A), during the study.

E 26. Mean of 3 separate BP measurements >180 mmHg (SBP) or >100 mmHg (DBP).

E 27. History of hypertensive emergency within 12 weeks prior to Screening.

E 28. History of gastric surgery including history of gastric banding or inflammatory bowel disease within 3 years prior to the Screening Visit. **Note**: Patients who have had bariatric surgery or gastric banding more than 3 years prior to the Screening Visit must have a stable weight (±10%) for 6 months prior to the Screening Visit.

E 29. Difficulty swallowing such that the patient cannot take the IMP.

E 30. Known allergies, hypersensitivity, or intolerance to SGLT2 inhibitor 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.

E 31. Renal disease as defined by eGFR of <30 mL/min/1.73m^2 at Screening by the 4 variable Modification of Diet in Renal Disease (MDRD) equation.

E 32. Laboratory findings with the central lab tests at Visit 1

- ALT or aspartate aminotransferase (AST) >3 times the ULN laboratory range
- Total bilirubin >1.5 times the ULN (except in case of Gilbert's syndrome)
- Neutrophils <1500/mm^3 (or according to ethnic group) and/or platelets <100 000/mm^3
- Amylase and/or lipase >3 times the ULN.

E 33. Any country-related specific regulation that would prevent the patient from entering the study (eg, individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities).

7.2.4 Additional exclusion criteria during or at the end of the Run-in Phase before Randomization

E 34. Patients unwilling or unable to perform SMBG (failure to perform at least 3 fasting SMBG per week during Run-in), complete the patient diary, or comply with study visits and other study procedures as required per protocol.

E 35. HbA1c <7% measured by the central laboratory at Visit 5 (Week -1).

E 36. Informed consent withdrawal before randomization (patient who is not willing to continue or fails to return).

E 37. Any clinically significant abnormality identified on physical examination, laboratory tests, electrocardiogram (ECG) or vital signs at the time of screening or any AE during screening period which, in the judgment of the Investigator or any Sub-investigator, would preclude safe completion of the study or constrains efficacy assessment.

E 38. Patient insufficiently compliant during Run-in Phase based upon tablet count (<80%) or in the opinion of the Investigator.

E 39. Lower extremity complications (such as skin ulcers, infection, osteomyelitis and gangrene) identified during the Screening period, and still requiring treatment at Randomization.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The IMPs are sotagliflozin 400 mg, sotagliflozin 200 mg, and matching placebo. Patients will be provided with kits containing wallets of sotagliflozin or sotagliflozin-matching placebo (supplied as tablets identical to sotagliflozin 200 mg in appearance).

Each patient will be supplied with the appropriate number of kit according to the dispensing scheme indicated in the study flowchart (see Section 1.2).

A summary of the IMP (dose and timing) is provided in Table 1.

Table 1 – Summary of investigational medicinal products

IMP:	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo group
Name of IMP	Sotagliflozin (SAR439954)	Sotagliflozin (SAR439954)	Placebo
Pharmaceutical form	Sotagliflozin (SAR439954) will be supplied as 200-mg tablets	Sotagliflozin (SAR439954) will be supplied as 200-mg tablets	Placebo will be supplied as tablets (identical to sotagliflozin 200 mg in appearance)
Dose, timing, and route of administration	**Sotagliflozin 200 mg group:** One 200-mg tablet, taken orally once daily, before the first meal of the day One placebo tablet, taken orally once daily, before the first meal of the day	**Sotagliflozin 400 mg group:** Two 200-mg tablets, taken orally once daily, before the first meal of the day	**Placebo group:** Two placebo tablets, taken orally once daily, before the first meal of the day
Duration of treatment	52-week double-blind Treatment Period following randomization	52-week double-blind Treatment Period following randomization	4 weeks Run-in and 52 weeks following randomization
Storage conditions	Store between +15°C and +30°C (59°F and 86°F)		

IMP = Investigational medicinal product

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT

Noninvestigational medicinal product (NIMP) treatment is defined as the rescue medication that will be used to treat hyperglycemia when a patient's hyperglycemia reaches the rescue threshold and the mandatory background therapy (Lantus [see Section 8.2.1]), and/or the patients' existing OADs (metformin [see Section 8.2.2]; other OADs [see Section 8.2.3]). The recommended rescue medication is the initiation of prandial injection of short-acting insulin or GLP-1 agonists, or another antidiabetic agent (except SGLT2 inhibitors) as per the Investigator's discretion and in line with local treatment guidelines (see Section 8.2.4).

8.2.1 Lantus (insulin glargine 100 U/mL)

All patients will use the study provided basal insulin, Lantus (insulin glargine 100 U/mL), starting from Visit 2 (beginning of the single-blind Run-in Phase) and continuing throughout the entire Run-in Phase and double-blind Treatment Period. Lantus will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the marketed Lantus SoloStar prefilled (disposable) pen (insulin glargine 100 U/mL solution for subcutaneous injection) specifically labeled for use in this study. The disposable self-injector prefilled pens will be provided to each patient entering in the single-blind Run-in Phase at Visit 2.

Each Lantus SoloStar contains 300 units of insulin glargine (3.0 mL of 100 U/mL insulin glargine solution) in total. This pen allows dose setting in the range of 1 to 80 units with a minimum increment of 1 unit. Dosing and dose adjustments should be performed according to details provided in Section 8.2.1.1, Section 8.2.1.2, Section 6.1.1.2 and Section 6.1.2. Each patient will be supplied with the appropriate number of pens according to the dispensing scheme indicated in the study flow chart (see Section 1.2). (Patients will be provided with kit containing 5 prefilled pens.)

Pen-device related issues (malfunctions) should be reported to the Sponsor by the means of a procedure on Product Technical Complaint forms, which are described in a separate manual.

8.2.1.1 Dosage schedule

Lantus will be administered once a day. Patients should keep their existing basal insulin administration time (eg, morning or evening dosing) for Lantus dosing time. If a dose greater than 80 units is required, it may be given as two or more consecutive subcutaneous injections at the same dosing time with daily dose split in equal or close to equal doses. Patients who are receiving NPH (or any other basal insulin) twice daily prior to Screening should administer Lantus once a day either in the morning or evening, following the Investigator's advice since the beginning of Run-In. However, once the NIMP Lantus starts, the patients should not change the injection time during the study course. Lantus should be given at the same time daily within a ±1 hour window, which should be maintained for the duration of the study.

Lantus should be administered by deep subcutaneous injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall or thighs or upper arms. Within a given area, location should be changed (rotated) at each time to prevent injection site skin reactions.

8.2.1.2 Starting dose

From Visit 2 (start of the single-blind Run-in period) all patients will receive Lantus as basal insulin. Patients who are already receiving Lantus prior to the study will start Run-in (Visit 2) at their pre-study dose level.

Patients who are receiving any basal insulin other than Lantus before Screening will switch to Lantus once a day. For patients who are using long-acting insulin analogs other than Lantus (eg, Levemir, Tresiba, Basaglar) the existing basal insulin will be converted to an equivalent dose of Lantus on a 1:1 unit basis (ie, the same dose on the day before Visit 2). If the patient is using Toujeo (glargine U-300/mL), the initial Lantus dose is 80% of the existing Toujeo dose as recommended in the Lantus label. If the patient is using NPH twice daily, it's recommended that the converted Lantus dose should be reduced by 20% and given once daily. (If using NPH once a day, it can be converted to Lantus unit-to-unit.)

8.2.1.3 Dose titration and modification

Lantus will be titrated during the 4-week single-blind Run-in Phase and if necessary after 18 weeks of the core Treatment Period to reach and maintain the target fasting glucose.

The target range for fasting (pre-breakfast/pre-injection if available) blood glucose is 80-100 mg/dL (4.4 to 5.6 mmol/L) avoiding hypoglycemia.

During Run-in (Week -4 to Week -1): after initiating the study provided basal insulin, Lantus, the insulin dose will be up-titrated every 3 days (twice per week) until the patient reaches the target fasting blood glucose according to the recommended regimen (Table 2). The dose adjustments will be made in consultation with the study site either at site visits, phone visits, or unscheduled phone contacts. At the end of Run-in, patients with HbA1c ≥7.0% measured at Visit 5 (Week -1) are eligible to be randomized to receive the IMP treatment (sotagliflozin 200 mg, sotagliflozin 400 mg or placebo) on top of Lantus.

During the randomized core Treatment Period (Weeks 0 to 18): no insulin titration should be implemented.

For patients with HbA1c <7.5% measured at Week-1, a 10% reduction in the Lantus dose at the randomization may be considered by the Investigator as needed, to reduce a potential risk of hypoglycemia.

Lantus daily dose will remain stable (< ±10% from the dose at randomization, or < ±4 units, whichever is less) unless it is deemed necessary by the investigator to reduce or increase the dose for safety reasons (ie, severe hypoglycemia or AE/SAE) or the patient has met the hyperglycemic threshold for rescue therapy. In such a case, rescue assessment will apply and be implemented (Section 8.2.4). Increase and optimization in Lantus dose will be the first step of rescue therapy prior to initiation of prandial insulin or GLP-1 receptor agonists.

After the core Treatment Period (Weeks 19 to 52): if the target fasting SMBG level is not achieved at the end of Week 18, insulin dose should be continuously up-titrated to maintain the fasting SMBG in the target range until the EOT. Titration will be done on a weekly basis, or as frequently as deemed necessary by the Investigator.

Lantus dose adjustment is based on fasting SMBG values using study glucose meter that displays results already converted to plasma glucose concentration. Regular self-monitoring of plasma glucose is very important in order to achieve the blood glucose targets. It is recommended to

perform daily fasting/pre-breakfast SMBG to support Lantus titration process during the 4-week Run-in period and less frequent afterward during the Treatment Period (Section 8.2.1.4 and Table 3).

The recommended Lantus titration regimen is outlined in Table 2, based on the mean of the 3 most recent fasting pre-breakfast SMBG values, as measured by the patients.

Table 2 – Lantus titration regimen

Mean of 3 most recent fasting SMBG values[a]	Lantus dose adjustments (IU/day)
≥140 mg/dL (≥7.8 mmol/L)	Increase Lantus by 4 units, or split to 2 x 2 units
≥120 mg/dL and <140 mg/dL (≥6.7 mmol/L and <7.8 mmol/L)	Increase Lantus by 2 units
>100 mg/dL and <120 mg/dL (>5.6 mmol/L and <6.7 mmol/L)	Increase Lantus by 1 unit
80 mg/dL and 100 mg/dL (4.4 and 5.6 mmol/L), inclusive	No change in dose
<80 mg/dL (<4.4 mmol/L)	Decrease Lantus by 2 units

a The glucometers, used for SMBG, display results already calibrated to plasma glucose concentrations, thus no conversion is required.
SMBG = self-monitored blood glucose

In addition:

1. Lantus dose titration may be withheld for a week or reduced in a patient who experiences two or more episodes of symptomatic hypoglycemia (with symptoms of hypoglycemia and an SMBG reading ≤70 mg/dL [≤3.9 mmol/L]) or one episode of severe hypoglycemia (patient required assistance from others to treat the hypoglycemic event; see Section 10.6.1).
2. In both Run-in phase or post-Week 18 Treatment Phase, Investigators are allowed to modulate or stop titration or temporarily reduce dosage if they believe further titration would be hazardous to the patient (eg, due to age, comorbid conditions, individual patient considerations, other than hypoglycemia). In such a case the reason for the exceptions should be recorded in the source document.

Good clinical judgment is to be exercised while titrating the insulin dose. For example, when implementing the weekly Lantus titration dose, a dose increase could be split into two incremental increases over the course of the week, rather than implementing the entire dose increase at one time, if it was concluded by the investigator or medically qualified designee to be in the best interest of the patient to do so.

Patients will be familiarized with the titration schedule so that they would be able to monitor the titration with the assistance of the investigator or medically qualified designee. All dose adjustments must be discussed between the patient and appropriate site personnel.

Patients who experienced mild to moderate hypoglycemia as a result of a missed meal, unusual exercise, or alcohol use will be counseled on the correction of those behaviors and may not need to have their insulin dose decreased.

8.2.1.4 Self-monitoring of blood glucose (SMBG)

Self-monitoring of blood glucose measured by patients will be used for investigators to guide Lantus dose modification and monitor for hypoglycemia or hyperglycemia.

A meter for self-assessment of blood glucose will be dispensed at the Week -4 Run-in visit (Visit 2). Patients will be trained on how to accurately measure plasma glucose values with the blood glucose meter. The study provided glucose meter will be used over the course of the study period. The investigator or site study staff will explain the need to measure glucose at the times requested for profiles and how to correctly record the values and times in the diary. Training is repeated as often as necessary at the study visits and the site study staff reviews the patient's diary at each on-site visit.

Patients will also receive a patient diary at all on-site visits with the exception of Visit 5 and Follow-up (Visit 16). The diary will be reviewed at all on-site visits from Visit 2 to Visit 16.

The performance of SMBG is outlined in Table 3 and is also specified in Section 1.2.

Table 3 – Instruction for SMBG performed during the study

SMBG	Definition	Frequency		Weeks/Visits
		Recommended	Mandatory	
Fasting SMBG	Overnight fasting pre-breakfast and before Lantus injection or any OAD intake	Daily until achieving fasting SMBG target	Daily SMBG	Week -4 to Week -1
		5 days per week	3 days per week	Week 0 to Week 18
		5 days per week until achieving fasting SMBG target	3 days during the week prior to study visit	Week 19 to Week 52
7-points	Before and 2 hours after breakfast, lunch and dinner, and bedtime	As needed	1 day during the weeks prior to Weeks 0, 18, and 52	Visit 6, 12, and 15

OAD = oral antidiabetes drugs; SMBG = self-monitored blood glucose.

Fasting SMBG readings will be used to guide the Lantus dose modification to reach and maintain the glucose targets. The investigators should review the SMBG records at each study visit including the phone visits so that they can provide instruction to the patients for appropriate insulin dose adjustment.

Fasting SMBG

Fasting SMBG should be tested in the morning before breakfast and before Lantus injection (for morning regimen) and taking any antidiabetic oral medications (if applicable). Patients should be instructed to check the fasting SMBG without food intake (except for water) for at least 8 hours (overnight) if possible. Patients should also be advised that a SMBG value should be excluded for insulin dose titration if the data were measured after taking food.

SMBG during hypoglycemic event

Patients will also be requested to self-assess blood glucose levels whenever they experience any illnesses (eg, cold, flu), 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 should be instructed to measure blood glucose prior to carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue prior to confirmation with the SMBG.

Patients will be instructed to record the presence or absence of hypoglycemic episodes or hypoglycemic symptoms in the patient diary provided.

All hypoglycemia episodes will be documented on the "hypoglycemia specific form" in the electronic case report form (eCRF). This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia.

Hypoglycemia events fulfilling the criteria of a SAE will be documented on the SAE form in the eCRF.

SMBG for monitoring hyperglycemia

Patients should be instructed to contact the site if the fasting SMBG values over 3 consecutive days are:

- From Baseline Visit (Visit 6, Day 1) to Visit 10 (Week 8): fasting SMBG >270 mg/dL (15.0 mmol/L)
- From Visit 10 (Week 8) to Visit 11 (Week 12): fasting SMBG >240 mg/dL (13.3 mmol/L)
- From Visit 11 (Week 12) up to Visit 12 (Week 18): fasting SMBG >200 mg/dL (11.1 mmol/L)
- From Visit 12 (Week 18) up to the EOT Period Visit 15 (Week 52): fasting SMBG >170 mg/dL (9.4 mmol/L)

8.2.2 Metformin

Patients may use metformin at a dose of ≥1500 mg/day or maximum tolerated dose (as documented). Use of metformin is not required but the dose should be stable throughout the study; a dose decrease is allowed only for safety reasons.

Metformin tablets are administered as per Investigator and in accordance with local labeling.

8.2.3 Other oral antidiabetes drugs

Patients may use up to 2 OADs (including metformin). Other OADs are administered as per Investigator and administered in accordance with local labeling. Doses of OADs should be kept

constant during the trial, but decrease for safety reasons during the insulin titration period is allowed.

8.2.4 Rescue therapy

If a patient needs to receive rescue antidiabetes medication, assessment of HbA1c should be performed before the introduction of the rescue medication.

The threshold values for FPG and HbA1c are defined as follows, depending on study period:

- From Baseline Visit (Visit 6, Day 1) to Visit 10 (Week 8) (including value at Visit 10): FPG >270 mg/dL (15.0 mmol/L)
- From Visit 10 (Week 8) to Visit 11 (Week 12) (including value at Visit 11): FPG >240 mg/dL (13.3 mmol/L)
- From Visit 11 (Week 12) up to Visit 12 (Week 18): FPG >200 mg/dL (11.1 mmol/L) or HbA1c ≥8.5% (the 8.5% criteria does not apply if the HbA1c decrease from Baseline was ≥1.5%)
- From Visit 12 (Week 18) up to the EOT Period Visit 15 (Week 52): FPG >170 mg/dL (9.4 mmol/L) or HbA1c ≥8.0% (the 8.0% criteria does not apply if the HbA1c decrease from Baseline was ≥1.5%).

Routine fasting SMBG and central laboratory alerts on FPG (and HbA1c at Week 12 and onwards) are set up to ensure that glycemic parameter results remain within predefined thresholds.

- If one fasting SMBG value exceeds the specific glycemic limit on one day, the patient will check again during the two following days. If all the values in 3 consecutive days exceed the specific limit, the patient should contact the Investigator and a central laboratory FPG measurement (and HbA1c at Week 12 and onwards) will be performed as soon as possible, preferably within 7 days, to confirm the hyperglycemia.
- Likewise, upon receipt of a central laboratory rescue alert, a central laboratory re-test **must** be completed and confirmed as exceeding the criterion for rescue before rescue therapy is initiated. The re-test confirmation should be performed as soon as possible, but within 7 days of receipt, by unscheduled visit.

In the event that a confirmatory FPG and/or HbA1c exceed the threshold, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- The increased FPG has been tested at a fasting status (ie, no food intake for ≥8 hours)
- IMP is given at the maximum planned dose and the basal insulin is titrated according to the titration algorithm
- Lantus is appropriately titrated, according to the titration algorithm, during the Run-in Phase and from Week 18 to EOT
- There is no intercurrent disease, which may jeopardize glycemic control (eg, infectious disease)
- Compliance to treatment is appropriate

- Compliance to diet and lifestyle is appropriate. During these phases, increase in Lantus dose is the first choice prior to initiating prandial insulin or a GLP-1 receptor agonist.

If any of the above can reasonably explain insufficient glycemic control, the Investigator should consider not initiating rescue medication and should undertake appropriate action, ie:

- Assess plasma glucose in fasting condition (ie, after at least 8-hour fast)
- Initiate an evaluation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the eCRF and the medical record)
- Stress the absolute need to be compliant with treatment. Increase in Lantus dose is the first choice prior to initiating prandial insulin
- Organize a specific interview with the patient and a Registered Dietician or other qualified nutrition professional and to reinforce on the absolute need to be compliant to diet and lifestyle recommendations, and schedule an FPG/ HbA1c assessment at the next visit (in case the next visit is a phone call, it should be replaced by an on-site visit).

If none of the above mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, rescue medication may be introduced. However, patients exceeding glucose rescue limits should have their Lantus dose up-titrated without a maximum limit as a first approach. If up-titration of the Lantus regimen has been unsuccessful (ie, increase in basal insulin is associated with low FPG values despite high HbA1c or elevated post-prandial values), it is appropriate to initiate rescue therapy.

The recommended approach to rescue, if rescue thresholds have reached despite up-titration of the Lantus dose, is to initiate a prandial insulin, or a GLP-1 agonist or another antidiabetic agent (except SGLT2 inhibitors) as per the Investigator's discretion and in line with local treatment guidelines. The prandial insulin can be any injectable short-acting insulin including fast-acting insulin analogs (such as, Humalog, Novolog, Apidra, and Fiasp) or regular insulin (eg, Humulin) or inhaled insulin (Afrezza).

If a patient requires glycemic rescue, the IMP received during the randomized, double-blind Treatment Period should continue and must remain blinded until the EOS. The dose of the existing OAD may be adjusted after rescue therapy.

Rescue therapy is considered an NIMP. Rescue therapy is to be reported in the eCRF. This information should include specific drug name, dose, route of administration, and frequency.

If not covered by health insurance, the cost of rescue therapy will be reimbursed by the Sponsor where permitted by local regulations.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

To maintain blinding, sotagliflozin and the matching placebo tablets and packaging will be blinded and indistinguishable.

During the double-blind Treatment Period, each treatment package will be labeled with a number, which is generated by a computer program from Sanofi. Investigators will not have access to the randomization (treatment) code except under circumstances described in Section 8.3.2.

The randomization and the treatment allocation will be performed centrally by an IRT. The study biostatistician provides the randomization scheme to the IRT. Then, the IRT generates the patient randomization list from which it allocates treatment arms to the patients.

Fasting glucose (plasma or serum) and HbA1c will be masked to study sites and patients after randomization and until study end. Additionally, the central laboratory urinalysis by dipstick will not include the measurement of urine glucose.

The CEC members will perform adjudication in a blinded manner.

8.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. Code breaking can be performed by a local study Investigator, sponsor physician or healthcare professional with direct responsibility for patient care. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking. The identity of the unblinded personnel, how the code was broken, and the treatment kit number should also be recorded. The Sponsor should also be informed. If the code is broken by the Investigator (or other medical doctor in emergency situation), the patient must be withdrawn from IMP administration.

Refer to Section 10.5 for suspected unexpected serious adverse reaction (SUSAR) unblinding by the Sponsor.

Randomization code breaking will also be performed during the analysis of the Pharmacokinetic plasma concentration samples. Only the Project manager and lead scientist at the Bioanalytical laboratory will have access to the randomization code to allow for the sorting of the sotagliflozin plasma samples. The Bioanalytical lab and responsible personnel will follow the standard procedures (SOP) to ensure the protection of the blind within the Sponsor's clinical team. The randomization code or the individual analytical results will not be disclosed to any clinical team personnel prior to the database lock.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number is generated centrally by Sanofi. The IMPs are packaged in accordance with this list.

Patients will be randomized to receive either sotagliflozin (200 mg or 400 mg) or placebo once daily during the randomized, double-blind Treatment Period. Randomization (ratio 2:1:1) will be stratified by HbA1c at Week -1 (≤8.5, >8.5%), SBP at Week -1 (<130 mmHg, ≥130 mmHg), and use of sulfonylureas at Week -1 (yes, no).

The randomization and the treatment package allocation are performed centrally by an IRT. At the Screening Visit, the Investigator or designee has to contact the IRT to receive the patient number. [redacted] At Visit 2 (Run-in), the IRT will be contacted for dispensing single-blinded placebo Run-in kit and Lantus kit. At Visit 6 (Baseline), assessment results are reviewed and Baseline assessments are completed, the IRT is contacted for randomization and corresponding allocation of treatments package (Treatment kit and Lantus kit). After Visit 6 (Baseline) the IRT is contacted again each time new treatment packages allocation is required per the protocol. For each randomized patient, the IRT will allocate a treatment package number corresponding to the treatment group assigned.

Treatment packages are allocated by the IRT using their treatment kit number.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the IRT, as documented in IRT.

A patient may not be randomized in this study more than once. In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the patient can be rescreened prior to entering Run-in once for this study. In these cases, a patient will need to sign a new ICF, be registered as a new patient in IRT, and assigned a new patient number in IRT (first Screening Visit is to be registered as a screen failure in IRT), and complete the Screening Visit procedures/assessments again.

8.5 PACKAGING AND LABELING

Packaging will be undertaken in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The appropriate number of packages will be dispensed to cover up to the next dispensing visit (please refer to Section 1.2). Storage conditions and use-by-end date are part of the label text.

Treatment labels will indicate the treatment number (used for treatment allocation and reported in the eCRF).

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP and Lantus in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP and Lantus storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The expiry date and storage conditions are written on the IMP and Lantus labels.

The treatment kit containing sotagliflozin 400 mg, sotagliflozin 200 mg, or placebo should be stored between +15°C and +30°C (59°F and 86°F).

For the Lantus, prior to the first use, the disposable pens are to be stored between +2°C and +8°C, protected from light, and must not be frozen. In-Use Lantus disposable pens are to be stored below +25°C (not refrigerated) protected from light. Each pen should not be used for more than 28 days after the first use.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP and Lantus supplied by sponsor will be responsible for ensuring that the IMP and Lantus used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs and Lantus will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP and Lantus issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP and Lantus (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP and Lantus may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor or Delegate, in order to recall the IMP and Lantus and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP and Lantus to a third party (except for direct-to-patient shipment, for which a courier company has been approved by the Sponsor), allow the IMP and Lantus to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Accounting and compliance for IMPs and Lantus will be performed at Visit 5 and all subsequent on-treatment visits (excluding telephone visits).

The Investigator will check the compliance to the study treatments based on the patient diary and will then complete the appropriate site treatment and patient treatment log forms. Returned IMP and Lantus NIMP (unused, in-use, or used wallets and pens) should be counted by site staff. In addition, the dosing information will be recorded on the appropriate pages of the eCRF.

An internal group will review compliance with the fasting SMBG algorithm for Lantus titration in a blinded manner during the study. Mean fasting SMBG and insulin doses over time will be used to identify the out of the target values (within the range of 4.4 to 5.6 mmol/L [80-100 mg/dL]) via a pre-set program. The identified issues will be sent to the Investigators for their actions on the refinement of the titration schedule as needed.

For other NIMPs (metformin, and other OADs), name, start and end date of treatment, total daily dose, etc, will be documented in the source documents. Compliance to NIMPs will be checked by interviewing the patient and reviewing diary at each on-treatment visit and be documented in the source documents and in the eCRF.

If compliance is inadequate as determined by the Principal Investigator, patients will be trained again and mentored. If sub-optimal compliance continues after training and mentoring, patients may be discontinued at the discretion of the Investigator after discussion with the Sponsor's medical monitor.

8.7.2 Return and/or destruction of treatments

Patients are to return all IMP and Lantus NIMP (unused, in-use, or used wallets and pens) at each on-site visit (or final assessment on-treatment visit, in the case of permanent premature discontinuation), as described in Section 1.2). IMP accounting is not required at telephone visits.

Patients are to return all IMP and Lantus NIMP (unused, in-use, or used wallets and pens) at Visit 15 (or final assessment on-treatment visit, in the case of permanent premature discontinuation).

All used wallets and pens, partially-used, or unused IMPs, and basal Lantus NIMP will be retrieved by the sponsor or delegate. A detailed site and patient treatment log of the returned IMP and basal Lantus NIMP will be established with the Investigator and countersigned by the Investigator and the monitoring team.

For NIMP not provided by the Sponsor (ie, metformin or other OAD), tracking and reconciliation is to be undertaken by the Investigator (or pharmacist if appropriate) according to the system proposed by the CRO.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). The IMP includes placebo and sotagliflozin 400 mg and 200 mg.

All concomitant medications should be documented on the Medications page of the eCRF. This includes all NIMP treatments that are taken by the patients at any time during the clinical study, beginning at Visit 1.

Additionally, all medications in the 3 months prior to Visit 1 and prior use of SGLT1/SGLT2 inhibitor should be reported.

8.8.1 Prohibited prior and concomitant medications

During the study Treatment Period, the following medications are prohibited:

- Initiation of any antidiabetic agents, including oral, inhaled, or injectable antihyperglycemic agents other than the IMP and NIMP is not allowed before the rescue therapy. The existing background medication (NIMP) should not be modified before the rescue.
- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin) are not allowed for rescue.
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, intra-articular, ophthalmic, nasal spray, or inhaled applications are allowed).
- IMPs in any other clinical study.
- Modification of any antihypertensive medication before Week 12 is not allowed unless for safety reasons.
- Initiation of any weight loss drugs (eg, phentermine, orlistat).

Patients taking sotagliflozin with concomitant digoxin should have digoxin concentrations monitored and doses reduced as needed. In addition, other P-gp substrates may be affected and the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments.

Note: short-term use (<10 consecutive days) of the prohibited medication, eg, short-acting insulin for treatment of acute illness or surgery is allowed.

Other medications which are unlikely to interfere with the PK or pharmacodynamics of the IMP or confound interpretation of the study endpoints are allowed as needed and following discussion between the Investigator and the Sponsor/CRO. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

The dose of all antihypertensive agents should be kept constant during the 12 weeks following randomization and no antihypertensive agents should be added or withdrawn for the 12 weeks following randomization unless it is considered necessary for safety reasons. During the Run-in

Phase, adjustments to antihypertensive therapy can be made as needed. After randomization, antihypertensive regimen should be kept constant during the following 12 weeks.

8.8.2 Concomitant diabetes therapy

Noninvestigational medicinal product (see Section 8.2) treatment is defined as the rescue medication that will be used to treat hyperglycemia when a patient's hyperglycemia reaches the rescue threshold, plus the protocol-specified background therapy (Lantus), and/or up to 2 OADs (metformin and/or other OADs). The recommended approach to rescue, if rescue thresholds have been reached despite up-titration of the Lantus dose, is to initiate a prandial insulin, or a GLP-1 agonist or another antidiabetic agent (except SGLT2 inhibitors) as per the Investigator's discretion and in line with local treatment guidelines.

8.9 POST-STUDY TREATMENT

As sotagliflozin may reduce BP, decrease of antihypertensive medication may be needed during the study in patients with hypertension. Conversely, monitoring for an increase in BP should be performed after withdrawal of study medication. If the BP is elevated after withdrawal of study treatment, the Investigator should consider adding or adjusting antihypertensive medication. Sotagliflozin will not be provided after EOT. Patient's further treatment, for diabetes and other pathologies will be at the Investigator's discretion based on his/her clinical judgment.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

The methods of assessment of efficacy endpoints are detailed in Section 9.1.4.

9.1.1 Primary efficacy endpoint (sotagliflozin 400 mg dose)

- Change from Baseline to Week 18 in HbA1c.

9.1.2 Secondary efficacy endpoints

Continuous secondary efficacy endpoints for the sotagliflozin 400 mg dose:

- Change from Baseline to Week 18 in FPG
- Change from Baseline to Week 18 in BW
- Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Week 12 in SBP for all patients
- Change from Baseline to Week 52 in HbA1c
- Change from Baseline to Week 52 in BW

Continuous secondary efficacy endpoints for the sotagliflozin 200 mg dose:

- Change from Baseline to Week 18 in HbA1c
- Change from Baseline to Week 18 in BW
- Change from Baseline to Week 18 in FPG
- Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Week 52 in HbA1c
- Change from Baseline to Week 52 in BW

9.1.3 Other efficacy endpoints (sotagliflozin 400 mg and 200 mg doses)

- The proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Weeks 18, 26, and 52
- Change from baseline to Week 26 in HbA1c
- Change from Baseline to Week 12 in SBP for all patients in the sotagliflozin 200 mg arm, and from Baseline to Weeks 26 and 52 in SBP for all patients and the subset of patients with Baseline SBP ≥130 mmHg in the sotagliflozin 400 mg and 200 mg arms
- Change from Baseline to Weeks 12, 26, and 52 in SBP in patients with Baseline SBP <130 mmHg

- Change from Baseline to Weeks 12, 26, and 52 in DBP for all patients and for the subset of patients with Baseline DBP ≥80 mmHg
- Change from Baseline to Week 52 in total daily insulin dose
- Proportion of patients requiring rescue therapy during the 52-week double-blind Treatment Period
- Change from Baseline to Weeks 18 and 52 in 7-point SMBG profile (mean daily value and at each time point)
- Change from Baseline in eGFR
- Change from Baseline in UACR during the 52-week Treatment Period
- PQAT at Weeks 18 and 52
- Change in TRIM-D from Baseline to Week 52 for total score and 5 domain scores. There will be a particular focus on the Diabetes Management domain score, to evaluate patient satisfaction of ability of treatment to control diabetes and its effects.

9.1.4 Assessment methods of efficacy endpoints

9.1.4.1 Hemoglobin A1c

Hemoglobin A1c will be assessed at Screening (Visit 1), Week -1 (Visit 5), and all on-site visits during the double-blind Treatment Period.

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I "National Glycohemoglobin Standardization Program" central laboratory to allow estimation of the change from Baseline to Week 18 in HbA1c and the proportion of patients with HbA1c <6.5%, <7.0% at Week 18.

If a patient needs to receive rescue antidiabetes medication, assessment of HbA1c should be performed before the introduction of the rescue medication.

9.1.4.2 Fasting plasma glucose measurement

Plasma glucose is measured in the fasting state at Screening (Visit 1) and all on-site visits during the Treatment Period. Fasting plasma glucose will be performed in fasting state, ie, without any food intake (except for water) for at least 8 hours. For the eligibility and efficacy assessments of the study, FPG is measured at a central laboratory to allow estimation of change from Baseline to Week 18 in FPG.

9.1.4.3 Blood pressure measurements

Systolic BP and DBP will be assessed at all on-site visits. Blood pressure measurements taken as described in Section 9.2.1.5 with details provided in Appendix D.

9.1.4.4 Body weight measurement

Body weight is measured at all on-site visits to allow the estimation of change from Baseline to Week 52 in BW. Change from Baseline to Week 18 in BW will also be assessed (secondary endpoint).

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. Calibration should be documented in source documents. The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The patient should stand in the center of the platform as standing off-center may affect measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded in the eCRF and source data. Self-reported weights are not acceptable; patients must not read the scales themselves.

9.1.4.5 Kidney function parameter measurement

Serum creatinine will be assessed at Screening (Visit 1), Week -1 (Visit 5), Baseline (Visit 6), and all subsequent on-site visits. Urinary albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine) and glucose will be assessed from overnight urine samples taken at Weeks 0, 12, 26, and 52. A central laboratory will analyze samples and estimate change from Baseline in serum UACR.

9.1.4.6 7-point SMBG profiles

Before (pre-injection after randomization) and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner and at bedtime: at least one day in the week before the Baseline visit (Visit 6), and before Visit 12 (Week 18) and Visit 15 (Week 52).

Note: Patients should be reminded at the preceding visit to perform at least one day 7-point SMBG in the week prior to above study visits. If found missing performance (or any missing point), the visit should be postponed to allow the patient for repeating the performance.

9.1.4.7 Proportion of patients starting rescue therapy

The use of rescue medication for hyperglycemia will be assessed and reported throughout the Treatment Period. Routine alerts on FPG and/or HbA1c will be sent to the Investigator from the central laboratory to ensure that glycemic parameter results remain within predefined thresholds. For details and further actions should FPG values fall above thresholds, refer to Section 8.2.4.

9.1.4.8 Insulin dose

Patients will record their Lantus daily dose in the diary since Visit 2 at the beginning of Run-in and throughout the Treatment Period. In case of rescue therapy with prandial insulin, the meal-time insulin will also be recorded in the patient's diary. The insulin doses will be reviewed and verified by the investigator and site study staff, and then be documented onto the eCRF.

The total daily insulin dose (Lantus and prandial, if applicable) will be analyzed by treatment groups.

9.2 SAFETY ENDPOINTS

Assessments for safety include AEs, SMBG, clinical laboratory assessments, physical examination, 12-lead ECG, weight, and vital signs. An independent DMC will meet on a regular basis to review accumulating clinical trial safety data.

Adjudication of all deaths, MACE/other selected CV events, selected renal events, bone fracture, and DKA will be performed in a blinded manner by a CEC(s) comprised of experts. Details will be provided in the charter of the CEC(s). Further details are available in Section 6.3.3.

Two expert committees will review all potential cases of DILIs and cases of amputation in a treatment-blinded manner.

The following safety endpoints will be assessed throughout the 52-week double-blind Treatment Period:

- Adverse events, AEs leading to discontinuation from the IMP, adverse events of special interest (AESI), EOSI, SAEs, and deaths
- Hypoglycemia (all, severe and/or documented symptomatic)
- Markers of calcium metabolism
- Safety laboratory results (including amylase, lipase, and fasting lipids; see Section 9.2.1.3), vital signs results, and 12-lead ECG results.

Observation period of safety endpoints

The observation period of safety data will be divided into 3 segments:

- The pre-Treatment Period is defined as the time between the date of informed consent and the first dose of double-blind IMP.
- The on-Treatment Period (TEAE period) is defined as the time from the first dose of double-blind IMP up to 10 days (1 day for hypoglycemia) after the last dose of double-blind IMP, regardless of the introduction of rescue therapy. The 10-day interval is chosen based on the half-life of the IMP (approximately 5 times the half-life of sotagliflozin) in patients with moderate renal dysfunction.
- The post-Treatment Period is defined as the time starting 11 days after the last dose of double-blind IMP (after the on-Treatment Period).

The Baseline value for safety endpoints in the safety population is the last available value (or the average of all values for creatinine or eGFR) prior to the first administration of the double-blind IMP.

9.2.1 Assessment methods of safety endpoints

9.2.1.1 Adverse events

Adverse events including SAEs, AESI, and EOSI will be assessed. Refer to Section 10.4 to Section 10.7 for details.

9.2.1.1.1 Adverse events of special interest

Adverse events of special interest are listed in Section 10.4.1.3; reporting requirements for AESI are presented in Section 10.4.4.

9.2.1.1.2 Events of special interest

Events of special interest are separate from AESI. For a list of events defined as EOSI and their reporting requirements see Section 10.4.1.4 and Section 10.4.5, respectively.

9.2.1.2 Hypoglycemia

Hypoglycemia (all, severe and/or documented symptomatic hypoglycemia) will be assessed starting with signing of the ICF and continue until 2 weeks after the last dose of IMP (**Note**: for patients who discontinue treatment >2 weeks before Week 52, safety data will be collected until scheduled study end). Patients will also complete the patient diary, which will be regularly viewed by Investigators. See Section 10.6.1 for further details.

9.2.1.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry, amylase, lipase, and fasting lipids) and urinalysis, according to the schedule presented in Section 1.2. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Table 4 lists the hematology, clinical chemistry, and other blood safety parameters to be assessed by the central laboratory.

In addition, for WOCBP a serum pregnancy test is performed at Screening and urine pregnancy tests are taken at all on-site visits during the double-blind Treatment Period. Any positive urine test results must be confirmed by a serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

For women of nonreproductive potential (Appendix A), follicle-stimulating hormone (FSH) and/or estradiol levels should be tested if the definition of postmenopausal or premenopausal

cannot be satisfied, eg, no medical document of hysterectomy or cessation of menses <12 months without an alternative medical cause.

Table 4 – Blood safety parameters

Clinical chemistry	Hematology	Other blood parameters
Sodium	Complete blood count (CBC)	**Lipid profile**
Potassium	Differential	Total cholesterol (TC)
Calcium	Platelet count	High-density lipoprotein cholesterol (HDL-C)
Chloride		
Carbon dioxide (bicarbonate)	Hemoglobin	Low-density lipoprotein cholesterol (LDL-C) will be calculated by Friedwald equation
Blood urea nitrogen (BUN)	Hematocrit	Non-HDLC will be calculated as the difference between TC and HDLC
Creatinine (eGFR will be calculated[a])		Triglycerides (TG)
Glucose (serum)		
Alanine aminotransferase (ALT)		**Markers of calcium metabolism**[b]
Aspartate aminotransferase (AST)		25-hydroxyvitamin D
Total bilirubin (TB)		1,25-dihydroxyvitamin D
Alkaline phosphatase (ALP)		Parathyroid hormone (PTH)
Uric acid		
Phosphorus		
Total protein		
Albumin		
Magnesium		
Creatine phosphokinase (CPK)		
Lactic acid dehydrogenase (LDH)		
Amylase		
Lipase		
Beta-hydroxybutyrate (BHB)[c]		

All assessments to be performed by central laboratory. All assessments measured in serum.

a The recommended equation for estimating eGFR from serum creatinine is the 4 variable MDRD study equation (17, 18). The isotope dilution mass spectrometry (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 Standardized International (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.

b To be collected at Baseline (Visit 6) and Week 26 (Visit 13).

c Serum BHB to be assessed (central lab determination) at Baseline (Visit 6), Week 4 (Visit 8), Week 8 (Visit 10), Week 18 (Visit 12), Week 26 (Visit 13), Week 39 (Visit 14), and Week 52 (Visit 15).

9.2.1.4 Urinalysis

Urinalysis (urine dipstick with microscopy) will be performed by central laboratory at Screening (Visit 1), Baseline (Visit 6), and Week 26 (Visit 13). To prevent partial unblinding the central laboratory urinalysis by dipstick will not include the measurement of urine glucose. Central urinalysis includes:

- Urine dipstick includes: specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase
- Urine microscopy includes, but is not limited to: detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment.

In the event of abnormal urinalysis findings suspicious of UTI, urine culture should be performed. Positive urine culture determination will be based upon the criteria of the reporting laboratory. Additionally, urine culture should be performed if at any point the Principal Investigator suspects the presence of a UTI.

If the urine dipstick is positive for blood, the central laboratory will perform reflexive testing to include microscopy. Additional testing will be performed according to the judgment of the Investigator. Referral to urology/urologic evaluation is recommended for new or unexplained cases of confirmed hematuria (urology/urologic evaluation is not required where hematuria is considered to be related to diabetic nephropathy).

9.2.1.5 Vital signs

A complete physical exam (including sitting BP and heart rate, temperature and respiratory rate) will be performed at Visit 1 (Screening) and Week 26 (Visit 13). Abbreviated physical exams (including sitting BP and heart rate) will be performed at all other on-site visits. The abbreviated physical exam should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs if necessary.

Three separate seated BPs and heart rate measurements should be taken with at least 1 minute between measurements following a 5-minute rest period, and prior to phlebotomy. Full details and directions for the measurement of BP are presented in Appendix D.

9.2.1.6 Electrocardiogram variables

The ECG assessment of “normal” or “abnormal” will be analyzed.

A 12-lead ECG record is performed locally at Screening (Visit 1), Baseline (Visit 6), and Week 26 (Visit 13).

The 12-lead ECG should be performed after at least 10 minutes in a supine position and prior to the morning IMP administration. The Investigator should review the ECG and the document the interpretation, and sign and date it on the ECG print out and on the eCRF. Each ECG trace is analyzed in comparison with the Screening recorded trace. All original traces are kept as source data.

Note: any new ECG abnormality should be rechecked for confirmation and reported as appropriate for that finding.

9.2.1.7 Diabetic ketoacidosis

During the Run-in Phase patients will be provided meters and test strips for monitoring capillary blood beta-hydroxybutyrate (BHB). Patients will be instructed to measure their BHB levels by fingerstick if they experience any symptoms consistent with ketosis/ketoacidosis throughout the Lantus titration phase/Run-in Phase and randomized Treatment Period. Patients will be instructed on how to respond (seek help, hydrate, ingest carbohydrates, etc) if they present with possible ketoacidosis symptoms and the BHB value is abnormal (>0.6 mM/L) (see Appendix C).

Patients will be provided with instructions on how to recognize the symptoms of DKA and perform the BHB measurement at home in these situations, and will be instructed to contact the site (or seek emergency medical services if after business hours) if these symptoms develop. Patients should have a full clinical evaluation with laboratory testing for possible DKA by the Investigator or emergency medical services physician. If such an evaluation and laboratory testing confirm the presence of metabolic acidosis, then appropriate treatment should be implemented and the "Possible DKA" eCRF should be completed.

In addition, serum BHB will be assessed at the study site via a central lab determination at Baseline (Visit 6), Week 4 (Visit 8), Week 8 (Visit 10), Week 18 (Visit 12), Week 26 (Visit 13), Week 39 (Visit 14), and Week 52 (Visit 15) and a capillary BHB measurement will also be done at the study site at these same visits. An alert will be sent to the investigator if the serum BHB measured by central lab value is ≥1.5 mM/L. Upon receiving the alert, investigator/designees should call the patient to assess if the patient experiences a suspected DKA, insulin dosing compliance, and any action to take, eg, seek urgent care or unscheduled site visit for further evaluation.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

The PK endpoint for sotagliflozin is:

- Plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite.

Pharmacokinetic sotagliflozin data may be subjected to a population PK analysis, which will be reported separately to the clinical study report (CSR).

9.3.1.1 Sampling time

At Weeks 4, 18, 26, and 52 (Visits 8, 12, 13, and 15, respectively) blood samples for PK assessment are to be drawn with the other laboratory assessments, prior to administration of IMP. Pharmacokinetic samples **must** be collected before administration of IMP. The date and time of the last intake of study drug prior to visits when PK samples are taken should be recorded by the

patient in the patient diary. Patients should be reminded of this at visits preceding PK time points to ensure these details are captured. In the case of premature IMP discontinuation, PK samples should not be drawn at the Premature EOT visit, or at subsequent visits. See Table 5 for identification of samples.

Table 5 – Samples identification

Visit	Week	Relative to dosing	PK
Visit 8	Week 4	Pre-dose	P00
Visit 12	Week 18	Pre-dose	P01
Visit 13	Week 26	Pre-dose	P02
Visit 15	Week 52	Pre-dose	P03

PK = pharmacokinetic

9.3.1.2 Pharmacokinetic handling procedure

Detailed procedures for sample preparation, storage, and shipment are described in the specific laboratory manual.

9.3.1.3 Bioanalytical method

Concentration of sotagliflozin and its 3-O-glucuronide

Plasma samples will be analyzed at Covance US using a validated high performance liquid chromatography-tandem mass spectrometry, with lower limit of quantification of 2 ng/mL for sotagliflozin and lower limit of quantification of 10 ng/mL for sotagliflozin 3-O-glucuronide.

[redacted]

[redacted]

9.3.3 Patient reported outcomes assessments

9.3.3.1 Patient's qualitative assessment of treatment

The PQAT aims to understand patient perspective on benefit/risk of the IMP during the Treatment Period. This instrument includes a 7-point Likert Scale for the patient to evaluate his/her subjective response to the treatment (-3 to +3 including 0 for a neutral response) and 2 free-text response questions to describe key advantages and disadvantages (Appendix F).

The PQAT will be administered to approximately 70 English-speaking patients at sites in English-speaking countries. This should take between 10 and 30 minutes for patients to complete.

The patients will be asked to complete it electronically from home just before the on-site visits planned at Weeks 18 (Visit 12) and 52 (Visit 15). They will be asked to do it by themselves without any help from friends or relatives.

At the beginning of the Weeks 18 (Visit 12) and 52 (Visit 15) patient visits, Investigators will have to review patient answers (accessible on a web platform) in order to identify any potential AEs reported by patients within the open-ended questions. Investigators will discuss with the patient potential AEs identified; Investigators will not discuss any other aspects of the answers with the patients, and will not ask patients to change their answers. If AEs that were previously not captured are identified during this process, they should be reported as described in Section 10.4.2.

All patients' answers will be analyzed qualitatively and quantitatively, as relevant, using appropriate data analysis software.

The analysis method for this exploratory analysis will be provided in a separate statistical analysis plan (SAP) and the analyses results will be documented in a separate report.

If a patient discontinues treatment with IMP during the Treatment Period, the patient will be asked to complete this qualitative assessment of treatment at time of discontinuation.

9.3.3.2 Treatment related impact measure for diabetes (TRIM-D)

The TRIM-D is a validated questionnaire assessing the treatment-related impact on patients of diabetes medication (19). The TRIM-D questionnaire (Appendix B) is a 28-item measure with 5 domains assessing Treatment Burden, Daily Life, Diabetes Management, Compliance, and Psychological Health. The Diabetes Management domain evaluates the patient satisfaction with his/her medication's ability to control their diabetes, hyperglycemia, hypoglycemia, weight, and fatigue. A total score as well as 5 domain scores can be calculated. After reverse coding of some items, raw scores are calculated by summing the items. Then, the raw scores can be transformed to scores ranging from 0 to 100 with higher scores indicating less treatment impact.

The TRIM-D includes questions related to satisfaction with weight and hypoglycemia

The TRIM-D will be completed by all patients in the local language. The patients will be asked to complete the TRIM-D at Screening (Visit 1), Baseline (Visit 6, Day 1), Week 18 (Visit 12), Week 26 (Visit 13), Week 39 (Visit 14), and Week 52 (Visit 15). This should take less than 5 minutes for patients to complete.

The patients will be requested to complete the TRIM-D questionnaire by themselves during the selected clinical visits, independently from investigator, site staff, and any help from friends or relatives. For validity purposes, patients will be asked to answer all the questions of the questionnaires at the start of the visit before any other procedures or tests, in a quiet place, and while on site to return the completed questionnaires to the investigator or his/her designee on the same day.

9.5 APPROPRIATENESS OF MEASUREMENTS

The addition of sotagliflozin to background therapy consisting of Lantus with or without up to 2 OADs (which may include metformin) is expected to lower HbA1c over 18 weeks of treatment (primary efficacy analysis). Sotagliflozin treatment for 18 weeks is likely to be of sufficient duration to observe effects on reduction of HbA1c, FPG, BP, and BW, and is therefore selected as the time point for assessment of the primary endpoint HbA1c. Treatment up to 52 weeks will provide additional long-term data on safety and efficacy.

The concentration of HbA1c reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2 to 3 months. Hemoglobin A1c has also been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. The duration of study treatment (18 weeks for the primary HbA1c endpoint) is considered to be sufficient for achieving stable conditions with IMP and for enabling an adequate assessment of time-dependent changes in HbA1c.

The problem of weight gain in T2D is widely recognized. More than 80% of individuals with T2D are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. Therefore, in this study, assessing change in BW from Baseline to Week 18 is a secondary endpoint.

Potential therapeutic effect of sotagliflozin on BP reduction will be assessed in all trial patients and in patients with a mean SBP ≥130 mmHg at Baseline. To avoid confounding factors, modification of antihypertensive medications is not allowed during the first 12 weeks of Treatment Period (Section 8.8.1). The beneficial effect of sotagliflozin to patients with inadequately controlled hypertension could be best assessed by the key secondary endpoint, “the change in the SBP from Baseline to Week 12 for patients with Baseline SBP ≥ 130 mmHg”. In addition, the effect of sotagliflozin on BP will be evaluated in all patients, including normotensive individuals.

Improvement in FPG has been observed with sotagliflozin in multiple studies. Therefore assessment of FPG is relevant in this study. This parameter is also considered by regulatory agencies to be supportive of the efficacy of an antidiabetes agent.

The other efficacy and safety assessments in this study are standard, well established measurements for a Phase 3 study evaluating the treatment of T2D in adult patients. Safety laboratory parameters include BHB (beta-hydroxybutyrate), which is considered as a sensitive indicator for DKA diagnosis and monitoring (20). The values measured during study course will be analyzed between the treatment groups.

The length of the study is considered appropriate for detection of efficacy endpoints given the power estimates (see Section 11).

Phase 2 data indicated that sotagliflozin may reduce SBP by 10 to 15 mmHg in patients with SBP ≥130 mmHg at Baseline, while having no significant effect in patients with SBP <130 mmHg, and did not induce hypotension in normotensive patients. Since this could be of benefit to patients with T2D, this finding is being followed up as a secondary objective in this trial, as well as the potential in patients with DBP ≥80 mmHg. Although effects on BP in Phase 2 data were observed with the 400 mg dose at 12 weeks, the effects will be examined at Weeks 12, 26, and 52.

Because of potential effects on calcium metabolism, specific biomarkers for calcium metabolism will be assessed at regular time points.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments are listed in the Study Flow Chart (Section 1.2). The aim of this section is to provide details on how some of the procedures/assessments should be performed.

This is an out-patient study and consists of 12 on-site visits and 4 telephone visits, although optional on-site and/or telephone visits can be scheduled at any time for any reason during the study whenever considered necessary by the Investigator.

The patients need to be fasting for on-site visits Visit 1 through Visit 15 (Week -6 through Week 52), unless otherwise instructed by the Investigator. Throughout the study, "fasting" is defined as at least 8 hours without any food intake (except for water). **Note:** if the patient is not fasting at the visits specified above, the blood sample will not be collected and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted (other procedures can be performed as scheduled). The first Run-in Visit (Visit 2) can be performed as soon as the results of all Screening tests are available and the patient is confirmed to be eligible for participation in the study. The visit window for Visit 5 is ±2 days, and Visits 7 through 13 should occur within ±3 days. Visits 14 and 15 should occur at the scheduled time point ±7 days. Visit 15 (EOT) should occur from Day 357 to Day 371. For the Follow-up Visit (Visit 16), the visit should occur within a window of ±3 days, 2 weeks after the last dose of IMP. If one date is changed, the next visit should occur according to the original schedule, ie, calculated from the date of Baseline Visit (Visit 6, Day 1).

For a complete list of procedures scheduled for each study visit, please refer to the Study Flow Chart (Section 1.2), which details the procedures to be performed.

All data obtained during the trial visits are reviewed by the Investigator and/or Sub-investigators who are qualified in the treatment of T2D and are trained on the study.

10.1.1 Screening Period

The Screening Period is up to 6 weeks in duration and includes the Screening phase and the Run-in phase.

10.1.1.1 Screening phase (Visit 1)

The Screening phase will be up to 2 weeks in duration and includes Visit 1 (Week -6) only. It must be long enough to collect the data to establish whether the patient satisfies the inclusion/exclusion criteria.

Patients will undergo Screening assessments at Visit 1 (Week -6) following signing of the ICF. Patients who meet the inclusion criteria as noted in Section 7.1 and have no exclusion criteria as noted in Section 7.2 will be randomized at Visit 6 (Day 1).

The IRT will be contacted at Visit 1 for notification of the Screening Visit and to obtain the patient number.

In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the patient can be rescreened once prior to entering Run-in for this study. In these cases, a patient will need to sign a new ICF, be registered as a new patient in the IRT, and assigned a new patient number (first Screening Visit is to be registered as a screen failure in the IRT), and again complete the Screening Visit procedures/assessments.

10.1.1.1.1 On-site Visit 1 (Week -6) Screening Visit

The following procedures/assessments will be performed at Visit 1 (Week -6):

- Obtain the informed consent:
  - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration. Written information will be provided to the patient. Written informed consent must be given by the patient and Investigator prior to any investigations.

- IRT to be notified (allocation of ID, registration of Screening)
- Assessment of all inclusion/exclusion criteria
- Collection of demographic data (age, gender, race, and ethnic origin)
- Assessment of the patient's medical and surgical history: to include history of T2D, treatment, and complications (eye, kidney, amputations, etc); history of smoking/tobacco use; history of alcohol and drug abuse
- Concomitant medication and medication history, including any prior medications for T2D
- Complete physical examination including height, weight, and vital signs (SBP and DBP, temperature, heart rate, and respiratory rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix D for details).
- Patient diary is dispensed and instructions/training are provided
- 12-lead ECG

- The following laboratory testing (by the central laboratory):
  - HbA1c
  - Safety laboratory, including amylase and lipase
  - Hematology
  - Serum pregnancy testing for WOCBP or serum FSH and estradiol (for women of nonreproductive potential if definition of postmenopausal or premenopausal cannot be satisfied; see Appendix A)
  - Urinalysis (dipstick and microscopy)
- PRO: TRIM-D
- Patients are instructed to return to the site in the fasting state for Visit 2 (Week -4).

10.1.1.2 Run-in phase (Visits 2 to 5)

The Run-in phase is 4 weeks in duration and includes Visits 2 to 5 (Weeks -4 to -1, inclusive).

10.1.1.2.1 On-site Visit 2 (Run-in, Week -4)

The following procedures/assessments will be performed at Visit 2 (Week -4):

- Assessment of exclusion criteria
- Measurement of BW
- Abbreviated physical examination including vital signs (SBP, DBP, and heart rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix D for details).
- Diet and exercise instruction
- Blood glucose and BHB meters are dispensed and instructions/training is provided
- Glucose test strips and BHB strips are dispensed
- IRT to be notified (registration of Run-in, allocation of single-blind placebo Run-in kit and Lantus kit)
- Instruction on DKA symptoms and glucose testing is provided
- Patient diary is collected and reviewed and a new one dispensed. Instructions/training are provided as needed.
- AEs/SAEs/AESI/EOSI and hypoglycemia occurring since Visit 1 (if any) are reported
- Run-in kit/placebo (IMP) and Lantus are dispensed
- Treatment with study provided Lantus is started either on evening of Visit 2 (if evening dose) or the following morning (if morning dose)
- Changes in concomitant medication are reported
- Fasting SMBG is assessed and Lantus dose adjustments are made as necessary

- Patients are instructed to return to the site for Visit 5.

10.1.1.2.2 Telephone Visits 3 and 4 (Run-in Weeks -3 and -2)

The following will be performed at this visit:

- Assessment of exclusion criteria
- Fasting SMBG is reviewed from diary and Lantus dose adjustments are made as necessary (Section 8.2)
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are instructed to return to the site for Visit 5.

10.1.1.2.3 On-site Visit 5 (Run-in, Week -1)

The following procedures/assessments will be performed at Visit 5 (Week -1):

- Assessment of exclusion criteria
- Measurement of BW
- Abbreviated physical examination including vital signs (SBP, DBP, and heart rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix D for details).
- Diet and exercise instruction
- Instruction on DKA symptoms, glucose testing, and basic genitourinary (GU) hygiene and hydration (see Appendix C) is provided
- Patient diary is collected/reviewed. Instructions/training are provided as needed.
- IMP and Lantus accountability and compliance
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Changes in concomitant medication are reported
- Fasting SMBG is assessed and Lantus dose adjustments are made as necessary (Section 8.2)
- Patients are instructed to return to the site in the fasting state for Visit 6 (Randomization)
- The following laboratory testing (by the central laboratory):
  - HbA1c
  - Clinical chemistry, including amylase and lipase.

10.1.2 Double-blind Treatment Period (Day 1 to Week 52)

Upon successful completion of the Run-in phase, patients will be randomly allocated to sotagliflozin 400 mg, sotagliflozin 200 mg, or placebo for the double-blind Treatment Period. All

randomized patients will be followed at regular on-site visits for the duration of the Treatment Period. Visit 7 (Week 2) and Visit 9 (Week 6) are telephone visits.

Patients will be instructed that their Lantus dose should remain unchanged (< ±10% of the randomization dose, or < ±4 units, whichever is less) until after Week 18 unless for safety reasons (eg, hypoglycemia, during treatment of an SAE) or meet the rescue criteria. After Week 18, Lantus dose may be adjusted if deemed necessary by the Investigator.

In addition to routine laboratory testing, the following will be performed at specified time points: plasma concentration, serum and capillary BHB, hematology, fasting lipids, urinalysis, complete physical examination, diet and exercise instruction, [redacted], PQAT, and TRIM-D.

The date and time of the last intake of IMP prior to visits where PK samples are taken should be recorded by the patient in the patient diary. Patients should be reminded of this at visits preceding PK time points to ensure these details are captured.

In the event of abnormal urinalysis findings suspicious of UTI, urine culture should be performed. Positive urine culture determination will be based upon the criteria of the reporting laboratory. Additionally, urine culture should be performed if at any point the Principal Investigator suspects the presence of a UTI.

10.1.2.1 On-site Visits 6, 8, 10, 11, 12, 13, and 14 (Weeks 0, 4, 8, 12, 18, 26, and 39)

The following procedures will be performed at these visits:

- Exclusion criteria are to be reviewed, including assessment of compliance during the Run-in phase (Visit 6 only)
- Randomization (Visit 6 only)
- Measurement of BW (all visits)
- Abbreviated physical examination including vital signs (SBP and DBP, and heart rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix D for details) (all visits except Visit 13, where a complete physical examination will be performed).
- Concomitant medications are assessed (all visits)
- Glucose test strips and BHB strips are dispensed (all visits)
- Measurement of capillary BHB (all visits, except Visit 11)
- Diet and exercise instruction (Visits 6 and 13 only)
- Instruction on DKA symptoms, glucose testing, and basic GU hygiene and hydration (see Appendix C) is provided (all visits)
- IRT to be notified, IMP and Lantus for resupply (all visits)
- Patient diary is collected/ reviewed and new diary dispensed. Instructions/training are provided as needed (all visits).

- IMP and Lantus are dispensed (all visits)
- IMP and Lantus accountability and compliance (all visits)
- Fasting SMBG is assessed and Lantus dose adjustments are made as necessary (all visits)
- Record results of 7-point SMBG (Visits 6 and 12 only)
- Patients are evaluated for glycemic rescue (see Section 9.1.4.7) (all visits)
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- The following laboratory testing (by the central laboratory):
  - FPG (all visits)
  - BHB (all visits except Visit 11)
  - HbA1c (all visits)
  - Clinical chemistry, including amylase and lipase (all visits)
  - Hematology (Visits 6, 11, 13, and 14 only)
  - Fasting lipids (Visits 6, and 12 only)
  - Urine pregnancy testing for WOCBP (all visits)
  - Pre-dose plasma concentration samples are collected and sent to the appropriate laboratory (Visits 8, 12, and 13 only)
  - Markers of calcium metabolism (Visits 6 and 13 only)
  - Urinalysis (dipstick and microscopy) (Visits 6 and 13 only)
  - Overnight urine collection for albumin, protein, creatinine, calcium, phosphorus, magnesium, glucose, and albumin-creatinine ratio (Visits 6, 11, and 13 only)

    [redacted]
- PRO: PQAT (Visit 12 only)
- PRO: TRIM-D (Visits 6, 12, 13, and 14 only)
- 12-lead ECG (Visits 6 and 13 only)
- Patients are instructed to return to the site in the fasting state for their next visit (all visits except Visits 6 and 8, which precede telephone visits). They should be reminded to record in the diary the date and time of IMP intake on the day before their next visit (reminder at Visits 7, 11, and 12 only).
- For accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use, and used wallets and pens at the next on-site visit (all visits).

10.1.2.2 Telephone Visits 7 and 9 (Weeks 2 and 6)

The following will be performed at this visit:

- Fasting SMBG is assessed and Lantus dose adjustments are made as necessary
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are evaluated for glycemic rescue (see Section 9.1.4.7)
- Patients are instructed to return to the site in the fasting state for Visits 8 and 10.

10.1.2.3 On-site Visit 15 (Week 52) - end of treatment

The following procedures will be performed at this visit:

- Measurement of BW
- Abbreviated physical examination including vital signs (SBP and DBP, and heart rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix D for details).
- Concomitant medications are assessed
- Glucose test strips and BHB strips are dispensed
- Diet and exercise instruction
- Instruction on DKA symptoms, glucose testing, and basic GU hygiene and hydration (see Appendix C) is provided
- IRT to be notified
- Patient diary is collected and reviewed and new diary dispensed. Instructions/training are provided as needed
- IMP and Lantus accountability and compliance
- Fasting SMBG is assessed and Lantus dose adjustments are made as necessary
- Record results of 7-point SMBG
- Measurement of capillary BHB at the site using the meter
- Patients are evaluated for glycemic rescue (see Section 9.1.4.7)
- The following laboratory testing (by the central laboratory):
  - FPG
  - BHB
  - HbA1c
  - Clinical chemistry, including amylase and lipase
  - Hematology
  - Fasting lipids

- Urine pregnancy testing for WOCBP
- Plasma concentration of sotagliflozin and its 3 O-glucuronide metabolite
- Overnight urine collection for albumin, protein, creatinine, calcium, phosphorus, magnesium, glucose, and albumin-creatinine ratio

- PRO: PQAT
- PRO: TRIM-D
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are instructed to return to the site in the fasting state for their next visit (Visit 16)
- For accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use, and used wallets and pens at the next visit.

10.1.3 Post-treatment follow-up period

The post-treatment Follow-up Period (EOS) will include an on-site visit 14 days (2 weeks) ±3 days after the last dose of IMP.

10.1.3.1 On-site Follow-up Visit 16 (Week 54)

The following will be performed at this visit:

- Measurement of BW
- IRT notified for EOS
- Patient diary is collected and reviewed
- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Abbreviated physical examination including vital signs (SBP, DBP, and heart rate). After 5 minutes resting, seated SBP, DBP and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix D for details).
- Fasting SMBG is assessed and Lantus dose adjustments are made as necessary.
- The following laboratory testing (by the central laboratory):
  - Clinical chemistry, including amylase and lipase.
- The patient is instructed to schedule future follow-up with their own personal physician.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient's file

Evaluations recorded in the eCRF must be supported by appropriately signed source documentation related but not limited to the following:

- Agreement and signature of ICF with the study identification
- Study identification (name)
- Patient number, confirmation of randomization, treatment batch number, dates, and doses of study medication administration
- Medical, surgical, diabetes history, including information on:
  - Demography, inclusion, and exclusion criteria
  - Last participation in a clinical trial
  - Contraception method for WOCBP
  - Previous and concomitant medication.
- Dates and times of visits and assessments including examination results
- Vital signs, height, BW, laboratory reports, Investigation results (eg, ECG traces, imaging reports)
- Adverse events and follow-up:
  - In case of an SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature treatment discontinuation (if any) and reason
- Date of premature study discontinuation (if any) and reason
- Nursing notes
- Dietician's notes
- Physician's notes.

10.2.2 Source data verification requirements for screen failures

For screen failure patients, the following source data must be verified: patient's ID details, the informed consent signed by the patient, the study identification (name), dates of study visits, and the main reasons for screen failure.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporary; permanent IMP discontinuation should be a

last resort. Any IMP discontinuation should be fully documented in the eCRF. In any case, the patient should remain in the study and followed for the remainder of the study to collect vital safety status and endpoint data.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Low extremity complications (such as skin ulcers, infection, osteomyelitis and gangrene) requiring treatment should lead to temporary discontinuation of IMP. Re-initiation of treatment with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment, that the occurrence of the concerned event was unlikely to be related to the IMP.

It is in the interest of the patient to monitor their blood glucose during the temporary discontinuation period, therefore regular determination of SMBG is to be performed and documented (see Section 8.2.1.4).

For all temporary treatment discontinuations, the duration should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

Temporary treatment discontinuation, as decided by the Investigator, corresponds to more than 1 dose not administered to the patient.

Use of any other antihyperglycemic medication during the time of temporary treatment discontinuation (ie, insulin during a hospitalization) is recorded as concomitant medication with the name and doses recorded in the eCRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is defined as any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

Patients may withdraw from treatment with the IMP at any time for any reason or this may be the Investigator's decision. Patients should discuss stopping study medication with the site before doing so in order that questions can be addressed, glycemic therapy adjusted, and a follow-up assessment arranged. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the eCRF.

The following reasons lead to permanent discontinuation:

- At the patient's own request (ie, withdrawal of consent for treatment)
- If, in the Investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's well-being

- Intercurrent condition that requires permanent discontinuation of the study treatment as long as the abnormality persists and if the causal relationship of the concerned event and the IMP is possible (according to the Investigator's best medical judgment)
- Pregnancy (in female patients)
- Specific request of the Sponsor.

Any abnormal laboratory value will be immediately rechecked to confirm the result before a decision is made to permanently discontinue IMP for the concerned patient.

For patients who prematurely discontinue the IMP, the assessments planned at the EOT Visit (see Section 10.1.2.3) will be performed at the Premature EOT Visit scheduled preferably prior to treatment discontinuation or as soon as possible after the time of discontinuation (at the latest at the next scheduled on-site visit). In the case of premature IMP discontinuation, PK samples should not be drawn at the Premature EOT Visit, or at any subsequent visit. The reason(s) for IMP discontinuation will be clearly specified. This EOT assessment may occur at a regularly scheduled or unscheduled visit.

10.3.4 Handling of patients after permanent treatment discontinuation

Every effort should be made to maintain patients in the study. Patients should be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last.

If a patient decides to discontinue study treatment early, a Premature EOT Visit (see Section 10.1.2.3) should be scheduled prior to treatment discontinuation, if possible. If not possible, the Premature EOT Visit should be scheduled as soon as possible after treatment discontinuation. In the case of premature IMP discontinuation, PK samples should not be drawn at the Premature EOT Visit, or at any subsequent visits. For patients that discontinue treatment but remain in the study, remaining study visits should occur as scheduled where possible. The IRT should be notified of EOT.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF.

10.3.5 Procedure and consequence for patient withdrawal from study

Patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits. Patients will be told that they are free to withdraw from the study at any time without any adverse effect on their care. However, if they no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining study visits. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the EOT Visit.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All confirmed study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to re-contact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts (3 phone call attempts followed by a certified letter) to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **AE** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

An **SAE** is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid notification by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

The AESI for this study are:

- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP:
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2)
  - In the event of pregnancy in a female participant, IMP should be discontinued
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix A).

- Symptomatic overdose with IMP/ NIMP
  - A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and resulting in clinical symptoms and/or signs accompanied by administration of more than twice the intended daily dose within a 24-hour period. It will be recorded in the eCRF as an AESI with immediate notification "Symptomatic OVERDOSE (accidental or intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria
  - (Please note that an asymptomatic overdose with the IMP/NIMP, accidental or intentional, defined administration of more than twice the intended daily dose within a 24-hour period, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient, not based on accountability assessment. It will be recorded as an AE "Asymptomatic OVERDOSE, accidental or intentional").
- ALT increase >3 × ULN (refer to related flow chart, Appendix E).

10.4.1.4 Events of special interest

An EOSI is a serious or non-serious AE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. These events should be reported on the specific eCRF page and will only qualify for expedited reporting when serious (fulfilling SAE criteria).

The EOSI for this study are:

- MACE (CV death, MI, or stroke) and other specific CV events (eg, heart failure leading to hospitalization)
- Severe hypoglycemia (see Section 9.2.1.2)
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candidal balanitis in males)
- UTIs
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Diarrhea
- Pancreatitis
- Bone fractures
- Venous thrombotic events to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- DKA
- Renal events to include 50% decline in eGFR, end stage kidney disease, renal death

- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid carcinoma)
- Adverse events leading to an amputation.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the ICF until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- In this study, the use of concomitant medications including antidiabetes medications may make it difficult to assess the causal relationship, particularly for hypoglycemia. The Global Safety Officer, with input from other appropriate study team members, will determine the causal relationship when it is not clearly provided by the Investigator.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant based on the investigator's' medical judgment, eg:
  - Symptomatic, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI or EOSI.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the Monitoring team and Pharmacovigilance after approval of the Investigator within the eCRF
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring

team whose name, fax number, and e-mail address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper case report form [CRF] process) is available and should be used when the eCRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESI, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the eCRF.

10.4.5 Guidelines for reporting events of special interest

If an EOSI fulfills the criteria of an SAE, reporting should be performed according to the instructions for reporting of SAEs (see Section 10.4.3). Otherwise, reporting should follow the instructions for an AE (see Section 10.4.2).

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix E.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSARs), to the regulatory authorities, and Independent Ethics Committee (IECs)/Institutional Review Board (IRBs) as appropriate and to the Investigators
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations
- The following AESI to those regulatory authorities who require such reporting:
  - Pregnancy
  - Symptomatic overdose
  - ALT increase >3 × ULN.

Adverse events that are considered expected will be specified by the reference safety information provided in the current IB.

If required, unblinding of SUSARs will be the responsibility of the Sponsor.

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

10.6 SAFETY INSTRUCTIONS

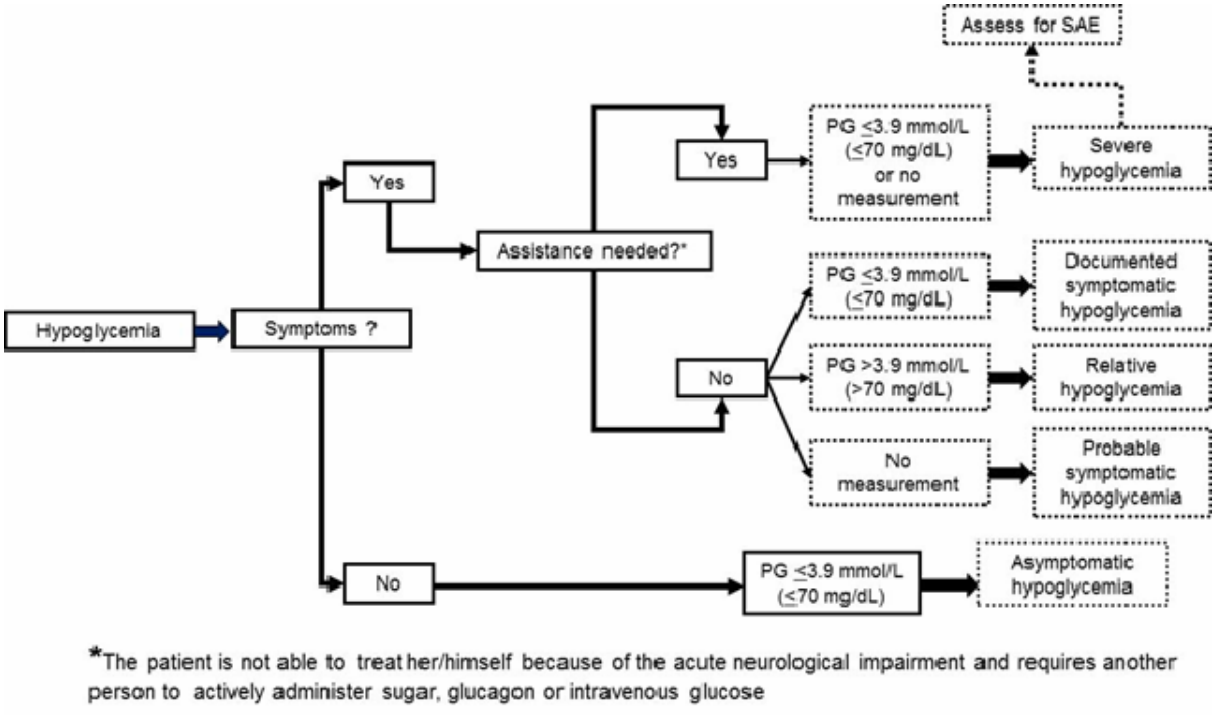
10.6.1 Hypoglycemia

During the study, patients are instructed to document the presence or absence of hypoglycemic episodes or hypoglycemic symptoms in their study diary. The hypoglycemia will be reported in the specific eCRF page with onset date and time, symptoms and/or signs, the SMBG value if available, and the treatment. If the event fulfills SAE criteria, hypoglycemia will also be reported as an SAE.

Hypoglycemia is categorized according to the American Diabetes Association workgroup on hypoglycemia classification (21) and summarized in Figure 1.

In addition to the threshold of ≤3.9 mmol/L (≤70 mg/dL), hypoglycemia episodes with a plasma glucose of <3.0 mmol/L (<54 mg/dL) will be analyzed separately.

Figure 1 - Hypoglycemia classification in Study EFC14868



PG = plasma glucose; SAE = serious adverse event

Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate (sugar), glucagon, intravenous glucose, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness, or coma. Self-monitored plasma glucose values may not be available, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Note: "Requiring assistance of another person" means that the patient could not help himself or herself to treat the hypoglycemia. Assisting a patient out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Any hypoglycemic event which leads to unconsciousness, coma, or seizure should also be reported as an **SAE.**

Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤3.9 mmol/L (≤70 mg/dL).

Clinical symptoms that are considered to result from a hypoglycemic episode include increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.

Asymptomatic hypoglycemia

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤3.9 mmol/L (≤70 mg/dL).

Note: low plasma glucose values without symptoms or signs should not be reported more than once within 30 minutes. Repeated low glucose values within a short period could be due to malfunction of the device, error testing or following up a low glucose reading. The Investigator should try not to document false low SMBG values or redundant low glucose values as asymptomatic hypoglycemic events. Further clarification with the patients is needed.

Probable symptomatic hypoglycemia

Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, (but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/L [≤70 mg/dL]), ie, symptoms treated with oral carbohydrate **without** a test of plasma glucose.

Relative hypoglycemia

Relative hypoglycemia recently termed “pseudo-hypoglycemia” (21) is an event during which the patient reports typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >3.9 mmol/L (>70 mg/dL).

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations were performed based on the primary endpoint. Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 280 patients in the sotagliflozin 400 mg arm and 140 patients in the placebo arm will provide at least 95% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 18 between sotagliflozin 400 mg and placebo.

A sample size of 140 patients in the sotagliflozin 200 mg arm and 140 patients in the placebo arm will provide 80% power to detect a treatment difference of 0.4% in mean HbA1c change from Baseline to Week 18 between sotagliflozin 200 mg and placebo (SD 1.2%; 5% significance level 2-sided).

The total sample size will be 560 patients to be randomized (280 patients in the sotagliflozin 400 mg arm; 140 patients in the sotagliflozin 200 mg arm; 140 patients in the placebo arm).

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented in the CSR:

- Screened patients: patients who have signed the ICF
- Run-in patients
- Randomized patients: patients with a treatment kit number allocated and recorded in IRT database, regardless of whether the treatment kit was used or not
- The safety population (ie, randomized and treated patients).
- The intention to treat (ITT) population (as defined in Section 11.3.2 and analyzed as randomized)
- The randomization strata (HbA1c at Week -1 [≤8.5%, >8.5%], SBP at Week -1 [<130 mmHg, ≥130 mmHg], and sulfonylureas use at Week -1 [yes, no]). The discrepancy between the strata assigned by IRT and the information reported on eCRF will be listed for all randomized patients.
- Patients who have completed the 18-week randomized core Treatment Period
- Patients who discontinued the IMP during the 18-week randomized core Treatment Period, and the reasons for treatment discontinuation
- Patients who have completed the entire 52-week double-blind Treatment Period
- Patients who discontinued the IMP during the entire 52-week double-blind Treatment Period, and the reasons for treatment discontinuation

- Patients who have completed the study
- Patients who discontinued the study, and the reasons for study discontinuation.

For all categories of patients except screened, percentages will be calculated using the number of randomized patients as denominator for each treatment group.

A list of patients prematurely discontinued from the treatment, along with reasons for discontinuation, will be provided. Similarly, a list of patients prematurely discontinued from the study, along with reasons for discontinuation, will be provided.

Patients treated but not randomized, patients randomized but not treated and patients randomized but not treated as randomized will be identified and described in separate listings. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Efficacy analyses will be based on the treatment group allocated by the IRT according to the schedule at Randomization Visit (as randomized), irrespective of the treatment group actually received.

11.3.2 Intent-to-treat population

Efficacy analyses will be based on the ITT population, defined as all randomized patients irrespective of compliance with the study protocol and procedures. Patients will be analyzed for efficacy analyses according to the treatment group to which they are randomized.

11.3.3 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least 1 dose of double-blind IMP (regardless of the amount of treatment administered). Patients will be analyzed for safety analyses according to the treatment actually received.

In addition:

- Non-randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- When a patient is exposed to both sotagliflozin and placebo, the patient will be analyzed in the sotagliflozin group (depending on the treatment kit taken [400 mg or 200 mg]).
- When a patient is exposed to both sotagliflozin 400 mg (treatment kit) and 200 mg (treatment kit), the patient will be analyzed in the sotagliflozin 200 mg group.

- Randomized patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study medication.

11.4 STATISTICAL METHODS

Continuous data will be summarized by treatment group using the number of observations available (N), mean, SD, minimum, median, and maximum. Categorical data will be summarized by treatment group using count and percentage.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from Baseline) by scheduled visits will be provided on observed cases (OC), ie, inclusion of only patients having non-missing assessments at a specific visit.

The Baseline value is defined generally as the last available value before the first dose of double-blind IMP or the last available value prior to Randomization for patients who were randomized but never exposed to IMP.

For serum creatinine and eGFR, the Baseline value is defined as average of all values before the first dose of double-blind IMP for those patients randomized and exposed or before randomization for those patients who were randomized but never exposed to IMP.

Analysis of demographics and Baseline characteristics, prior and concomitant medications will be provided in detail in the SAP.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received in the Safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed by the duration of treatment exposure during the study.

The duration of treatment exposure will be the total number of days of administration of the double-blind IMP, regardless of unplanned intermittent discontinuations. The duration of IMP exposure will be calculated as:

(Date of the last double-blind IMP taken – Date of the first double-blind IMP taken) + 1

The number (%) of patients randomized and exposed to double-blind IMP will be presented by specific time periods for each treatment group. The time periods of interest will be defined in the SAP.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in patient year will also be presented by treatment group in the Safety population.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, mean, SD, median, min, and max). The percentage of patients with compliance <80% will be summarized. In addition, the number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, 0 to 20%, and >20% under-planned dosing administrations.

11.4.2 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population.

Statistical testing will be performed for primary endpoint at Week 18, and at Week 12 (for SBP) and Week 18 and Week 52 (for HbA1c and BW) for secondary endpoints. All other efficacy variables will only be summarized by descriptive statistics without formal statistical testing.

11.4.2.1 Analysis of primary efficacy endpoint

The statistical test will be two-sided tests at a nominal 5% significance level.

Analysis of the primary efficacy endpoint (change from Baseline to Week 18 in HbA1c) will be performed using the ITT population, using HbA1c measurements obtained from visits during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

The primary efficacy endpoint of change in HbA1c from Baseline to Week 18 will be analyzed with missing values imputed by control-based multiple imputation method under the missing not at random framework.

- For placebo patients, missing data will be imputed based on the placebo group data
- For patients in the sotagliflozin groups, missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model.

Each of the complete datasets will be analyzed by the analysis of covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and Baseline HbA1c value as a covariate. Results from each complete dataset will be

combined to provide the adjusted mean change in HbA1c from Baseline to Week 18 for the sotagliflozin 400 mg arm and placebo arm, as well as the between-group difference (comparing sotagliflozin 400 mg arm versus placebo) and the 95% confidence interval (CI) using contrast statements.

Summary statistics (for Screening value, Baseline value, observed values, and observed changes from Baseline) at scheduled visits will be provided for each treatment group. The summary will include the number of observations, mean, SD, standard error (SE), minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from Baseline (±SE) at each of the scheduled visits (using OC).

Assessment of treatment effect by subgroup

Descriptive analyses will be performed on the primary endpoint to summarize the treatment effects across subgroups defined by the following Baseline or Screening factors:

- Race
- Ethnicity (Hispanic, Not Hispanic)
- Age group (<50 years, ≥50 to <65 years, ≥65 years)
- Gender
- Baseline BMI level (<30, ≥30 kg/m^2)
- Baseline HbA1c (≤8.5%, >8.5%)
- Baseline SBP (<130 mmHg, ≥130 mmHg)
- Country
- Use of sulfonylureas at Week -1 (yes, no).

The treatment effects across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 18 in HbA1c in the ITT population, and using a similar approach to the analysis for the primary efficacy endpoint. The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus placebo) with SE and 95% CIs will be provided as appropriate across the subgroups.

In the event that the subgroup factor is identical or similar to a randomization strata factor (eg, Baseline HbA1c category, Baseline SBP category, or sulfonylurea use), only the subgroup factor will be included in the model in order to avoid the issue of co-linearity in the analysis.

Baseline definition

The Baseline value is defined generally as the last available value before the first dose of double-blind IMP or the last available value prior to Randomization for patients who were randomized but never exposed to IMP.

11.4.2.2 Analyses of secondary efficacy endpoints

The secondary endpoints (Section 9.1.2) will be analyzed using a similar approach to the primary efficacy endpoint, with missing values imputed by the control-based multiple imputation method under the missing not at random framework.

- For placebo patients, missing data will be imputed based on the placebo group data
- For patients in the sotagliflozin groups, missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model.

For each of the continuous secondary endpoints, each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and Baseline secondary endpoint value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 18 (Week 12 for SBP endpoints) for each treatment group, as well as the between-group difference (comparing each sotagliflozin group versus placebo) and the 95% CI using contrast statements. For HbA1c endpoint, results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 18 for sotagliflozin 200 mg arm and placebo arm, as well as the between group difference (comparing the sotagliflozin 200 mg arm versus placebo arm) and the 95% CI using contrast statements.

Summary statistics for the secondary endpoints at scheduled visits will be provided for each treatment group. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (± SE) and mean changes from Baseline (± SE) at each of the scheduled visits (using OC).

11.4.2.3 Analysis of other efficacy endpoints

Except for PRO endpoints, the analysis of other endpoints (see Section 9.1.3) will be descriptive with no formal testing. Summary statistics at scheduled visits using OC will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time.

The analysis of the TRIM-D PRO scores will be conducted on the ITT population.

For TRIM-D scores (total and domain scores), descriptive statistics will be presented by treatment group per visit. The change in TRIM-D scores from Baseline to endpoint will be analyzed using a similar approach to the primary efficacy endpoint, with missing values imputed by control-based multiple imputation method under the missing not at random framework.

Each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), and

randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and TRIM-D scores at Baseline as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 52 for each treatment group, as well as the between-group difference (comparing sotagliflozin group versus placebo) and the 95% CI using contrast statements.

The number (%) of patients achieving HbA1c response (<6.5%, <7% at Week 18 and Week 52, respectively) will be descriptive summarized at each scheduled visit.

Sensitivity analysis may be performed as appropriate.

11.4.2.4 Multiplicity considerations

To control for the family wise type I error, a fixed-sequence testing procedure will be applied to the primary and key secondary endpoints to the following order:

Once the main study primary variable (change from Baseline to Week 18 in HbA1c comparing sotagliflozin 400 mg versus placebo) is statistically significant at $\alpha = 0.05$ (2-sided), a hierarchical testing procedure will be performed to test the following main study secondary efficacy variables by the following prioritized order. The testing will stop as soon as an endpoint is found to be not statistically significant at $\alpha = 0.05$ (2-sided).

- Comparing sotagliflozin 400 mg versus placebo:
  - Change from Baseline to Week 18 in FPG
  - Change from Baseline to Week 18 in BW
  - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline to Week 12 in SBP for all patients
  - Change from Baseline to Week 52 in HbA1c
  - Change from Baseline to Week 52 in BW
- Comparing sotagliflozin 200 mg versus placebo:
  - Change from Baseline to Week 18 in HbA1c
  - Change from Baseline to Week 18 in BW
  - Change from Baseline to Week 18 in FPG
  - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline to Week 52 in HbA1c
  - Change from Baseline to Week 52 in BW

No multiplicity adjustment will be made on other secondary efficacy variables than mentioned above.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. All safety summaries will be descriptive; no statistical significance tests will be performed on safety data.

Safety endpoints are presented in Section 9.2. These analyses will be based on the safety population as defined in Section 11.3.3. Patients will be analyzed for safety analyses according to the treatment actually received. The safety analyses will be provided for the 18-week randomized core Treatment Period and for the entire 52-week double-blind Treatment Period, unless specified otherwise.

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant abnormality (PCSA) values for clinical laboratory tests and vital signs are defined as abnormal values considered medically important by the Sponsor's Global Pharmacovigilance and Epidemiology department and in effect at the time of the final SAP approval. The PCSA criteria for parameters not cited in the protocol as safety parameters will not be analyzed.
- The PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

The "observation periods" defined in Section 9.2 are applicable for classification of AEs, determination of on-treatment PCSA values and the last on-treatment value for the laboratory, vital sign and ECG parameters.

11.4.3.1 Analysis of adverse events

Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-Treatment Period.

Treatment-emergent AEs are AEs that developed or worsened (according to the Investigator's opinion) or became serious during the on-Treatment Period.

Post-treatment AEs are AEs that developed or worsened or became serious during the post-Treatment Period.

The primary focus of AE reporting in the CSR will be on TEAEs. Pre- and post-treatment AEs will be described separately.

All adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the N and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be

counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Summaries of all TEAEs in each treatment group will include:

- The overview of AEs, summarizing number (%) of patients with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation.
- The N and percentage (%) of patients with at least one TEAE by primary SOC, HLGT, HLT, and PT
- Summary of TEAEs by maximal severity (severe, moderate, mild), presented by primary SOC and PT
- Summary of TEAEs possibly related to IMP, presented by primary SOC, HLGT, HLT, and PT.

A detailed listing of TEAE summaries will be provided in the SAP.

Death and serious adverse events

Death and treatment-emergent SAEs will be summarized and presented as number and percent of patients in each treatment group.

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) summarized on the safety population by treatment received
- Death in non-randomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adverse events leading to permanent treatment discontinuation

Treatment-emergent AEs leading to permanent treatment discontinuation will be summarized and presented as number and percent of patients in each treatment group.

11.4.3.2 Analysis of hypoglycemia

The number (%) of patients and rate in patient years (2 types: the number of patients with events or the number of events per 100 patient-years) of all, severe and/or documented symptomatic hypoglycemia, will be summarized by treatment group respectively. In addition, documented

hypoglycemia will also be analyzed by using a threshold of plasma glucose of <54 mg/dL (3.0 mmol/L).

Their pattern of occurrence over time will also be assessed, as appropriate.

11.4.3.3 Analysis of adverse events of special interest

Pregnancy and overdose will be included in overall AE summaries if any are reported. Alanine aminotransferase increase >3 × ULN is included in laboratory PCSA summary, if any.

11.4.3.4 Analysis of events of special interest

The number (%) of patients with each EOSI event will be summarized by treatment group. All events reported by the Investigators on the AE forms for special interest will be listed along with the adjudication outcome (if applicable).

11.4.3.5 Analysis of laboratory variables

The number and percentage of patients with PCSA or by the predefined categories (if no PCSA criterion is defined) at any evaluation during the on-Treatment Period will be summarized for each clinical laboratory test within each treatment group. The summaries will include patients in the safety population who have at least one laboratory test performed during the on-Treatment Period and, when required by the definition of the abnormality, with an available Baseline value and available laboratory normal ranges.

Descriptive statistics will be used to summarize the laboratory results and the changes from Baseline by visit and for the last on-treatment value within each treatment group. Shift tables and other tabular and graphical methods may be used to present the results for laboratory tests of interest. Listings will be provided with flags indicating the out of laboratory range values as well as the PCSA values.

The liver function tests, namely ALT, AST, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-Baseline visit by Baseline status will be displayed by treatment group for each parameter.

11.4.3.6 Analyses of vital sign variables

The number and percentage of patients with PCSA at any evaluation during the on-Treatment Period will be summarized for each vital sign parameter within each treatment group. The summaries will include patients in the safety population who have at least one parameter to be analyzed during the on-Treatment Period. Descriptive statistics will be used to summarize the results and the changes from Baseline by visit and for the last on-treatment value within each treatment group. Tabular and graphical methods may be used to present the results for parameters of interest. Listings will be provided with flags indicating the PCSA values.

11.4.3.7 Analyses of 12-lead electrocardiogram status

A shift table will be provided to present the ECG on-treatment status according to the Baseline status within each treatment group.

11.4.3.8 Analyses of pharmacokinetic variables

The PK endpoint is presented in Section 9.3.1. Individual plasma concentrations of sotagliflozin and of its 3-O-glucuronide at nominal sampling times will be listed.

Concentration data will be summarized by visit and, if appropriate, within visit by nominal sampling times (pre-dose), using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum, and maximum at each visit/nominal sampling time point for sotagliflozin-treated patients.

11.5 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned for this study. The study will not be terminated early for excellent efficacy.

An independent DMC will monitor and assess the safety of patients from this trial through periodic review of the accumulated safety data provided by an independent statistical group.

Related details are provided in separate documents (DMC charter and DMC SAP).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written ICF should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

[redacted]

The ICF used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title, and version number), the documents reviewed (clinical trial protocol, ICF, IB with any addenda or labeling documents [summary of product characteristics, package insert], Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor and/or service provider of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters, or telephone calls, by a representative of the monitoring team to review study progress, Investigator, and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE and EOSI documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the

ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data will be available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor/service provider may generate additional requests (Discrepancy Resolution Form) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor/service provider and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification, and training of each Investigator and Sub-investigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to the clinical trial protocol, personal data in relation to the patients, the eCRFs, the IB, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents, and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub-investigator not to mention any information or the product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.6 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race and ethnicity (race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, unknown; ethnicity:

Hispanic, Not Hispanic) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for FDA, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on Chinese population for the Chinese FDA).

[redacted]

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator or Sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients is included earlier than expected.

In any case, the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway,

or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor, and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be re-collected if necessary.

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Non-reproductive potential

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Women of reproductive potential (WOCBP) must use a highly effective method of contraception during the treatment period and the post-treatment follow up period (14 ± 3 days). If another contraceptive method is used (such as a barrier method), it should be used in combination with one of the highly effective methods (such as an oral contraceptive).

Female patients:

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - Oral - Intravaginal - Transdermal.
• Progestogen-only hormone contraception associated with inhibition of ovulation – Oral – Injectable.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.)*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION

Male patients with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. This applies only to patients who receive study treatment
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female patients who become pregnant

- The Investigator will collect pregnancy information on any female patient, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE
- A spontaneous abortion is always considered to be an SAE and will be reported as such

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.3. While the Investigator is not obligated to actively seek this information in former study patients, he/she may learn of an SAE through spontaneous reporting.

Appendix B Treatment Related Impact Measure - Diabetes (TRIM-D)

The following questions are concerned with the **MEDICATION that you take for your diabetes**. If you take more than one medication for your diabetes, or take medication for other conditions, please consider only your MEDICATION when answering these questions.

Please circle the response that most closely represents how you have felt about your MEDICATION over the PAST TWO WEEKS. Please mark only one number for each question. Remember there are no right or wrong answers to these questions.

1.	**How satisfied or dissatisfied have you been with:**	*Not at all satisfied*	*A little satisfied*	*Somewhat satisfied*	*Very satisfied*	*Extremely satisfied*
	a. The ease and convenience of your medication……	1	2	3	4	5
2.	**How convenient or inconvenient is it for you to:**	*Not at all convenient*	*A little convenient*	*Somewhat convenient*	*Very convenient*	*Extremely convenient*
	a. Carry your medication and supplies around with you……	1	2	3	4	5
	b. Store your medication……..	1	2	3	4	5
	c. Take your medication at the right time…	1	2	3	4	5
	d. Prepare your medication for use……..	1	2	3	4	5
	e. Monitor your blood sugar as often as necessary……..	1	2	3	4	5
3.	**How often does taking your MEDICATION interfere or not interfere with your:**	*Never/ Almost never interferes*	*Rarely interferes*	*Sometimes interferes*	*Often interferes*	*Almost always/ Always interferes*
	a. Meal time planning……..	1	2	3	4	5
	b. Social activities……..	1	2	3	4	5
4.	**How satisfied or dissatisfied are you with your MEDICATION'S ability to:**	*Not at all satisfied*	*A little satisfied*	*Somewhat satisfied*	*Very satisfied*	*Extremely satisfied*
	a. Help you control your diabetes……	1	2	3	4	5
	b. Help you avoid high blood sugar (hyperglycemia)……	1	2	3	4	5
	c. Help you avoid low blood sugar (hypoglycemia)……	1	2	3	4	5
	d. Help you manage your weight……..	1	2	3	4	5
	e. Help you prevent feeling tired or a lack of energy……..	1	2	3	4	5

5.	**Because of your MEDICATION, how <u>OFTEN</u>:**	*Never/ Almost never*	*Rarely*	*Sometimes*	*Often*	*Almost always/ Always*
a.	Do you have to limit your daily activities	1	2	3	4	5
b.	Do you accomplish less than you would like to……	1	2	3	4	5
c.	Do you feel tension in your relationships with friends or family……..	1	2	3	4	5

6.	**Thinking about your MEDICATION, how often do you:**	*Never/ Almost never*	*Rarely*	*Sometimes*	*Often*	*Almost always/ Always*
a.	Miss a dose……...	1	2	3	4	5
b.	Delay or postpone taking your medication……	1	2	3	4	5
c.	Take your medication at a different time than prescribed……	1	2	3	4	5
d.	Feel embarrassed or awkward when taking your medication……	1	2	3	4	5
e.	Worry that you forgot to take/or missed your last dose of medication…….	1	2	3	4	5

7.	**When I take diabetes MEDICATION I feel:**	*Never/ Almost never*	*Rarely*	*Sometimes*	*Often*	*Almost always/ Always*
a.	Depressed……	1	2	3	4	5
b.	Worried that the medication is not helping to slow down or prevent complications from my diabetes……...	1	2	3	4	5
c.	Nervous or anxious……...	1	2	3	4	5
d.	Worried about my blood sugar control….	1	2	3	4	5
e.	Unhealthy……	1	2	3	4	5
f.	Angry……	1	2	3	4	5
g.	Worried about side effects from my medication……	1	2	3	4	5

Thank You!

Appendix C Recommendations on basic genitourinary hygiene, maintaining hydration, and recognizing diabetic ketoacidosis

Patients with T2D 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 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 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. Before initiating study drug (at Screening, Run-in and Randomization) and during all on-site study visits thereafter, assess volume status in patients with renal impairment, the elderly, in patients with low SBP, or if receiving diuretics, angiotensin-converting-enzyme inhibitors, or angiotensin receptor blockers. 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 T2D:

"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

- 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."

Recognizing diabetic ketoacidosis

Potential GI AEs occurring with sotagliflozin may mask presenting symptoms of DKA. Patients will be provided with the BHB meter and instructions for use at the start of the Run-in Phase at Visit 2 (Week -4). Patients will be instructed to measure their BHB levels by fingerstick if they experience any symptoms consistent with ketosis/ketoacidosis throughout the entire study period. Patients will be instructed on how to respond (seek help, hydrate, ingest carbohydrates, etc) if they present with potential ketoacidosis symptoms and the BHB value is abnormal (>0.6 mM/L).

Patient communication cards will be printed with the following:

"If you have any of these symptoms on the list, measure your glucose and BHB by fingerstick, and then contact your study site immediately for assistance with managing your diabetes:

- 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 contact your study site regarding the need to be evaluated for possible DKA, which will include specific blood testing. If your study site is closed and your study doctor is not available, go to the nearest emergency room for evaluation.

If your blood BHB reading is >0.6 mM/L and you have symptoms of ketoacidosis, seek help, hydrate, ingest carbohydrates, etc, as described above.

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."

Whenever AE data is collected or the patient reports DKA or intercurrent illness (including infections), generalized weakness, increased weight loss, GI symptoms including nausea, vomiting, or abdominal pain or other symptoms or signs that the Investigator believes may be consistent with DKA, then the site will determine if an assessment for DKA is appropriate. If laboratory testing confirms presence of metabolic acidosis, then the "Possible DKA" eCRF will be completed.

Appendix D Measurement of blood pressure and heart rate

Equipment

1. Blood pressure measurements will be taken by an automated BP monitor or a manual sphygmomanometer. Same equipment should be used throughout the study and should be calibrated as per manufacturer recommendation.
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 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/her muscles.

Determination of the reference arm

At Visit 1 (Week -6), seated BP should be measured in both arms after 5-minute rest period, and then again after 1 minute in both arms in seated position. The arm with the highest SBP will be determined at this visit, and BP should be measured always in this same arm throughout the study.

Measurement technique

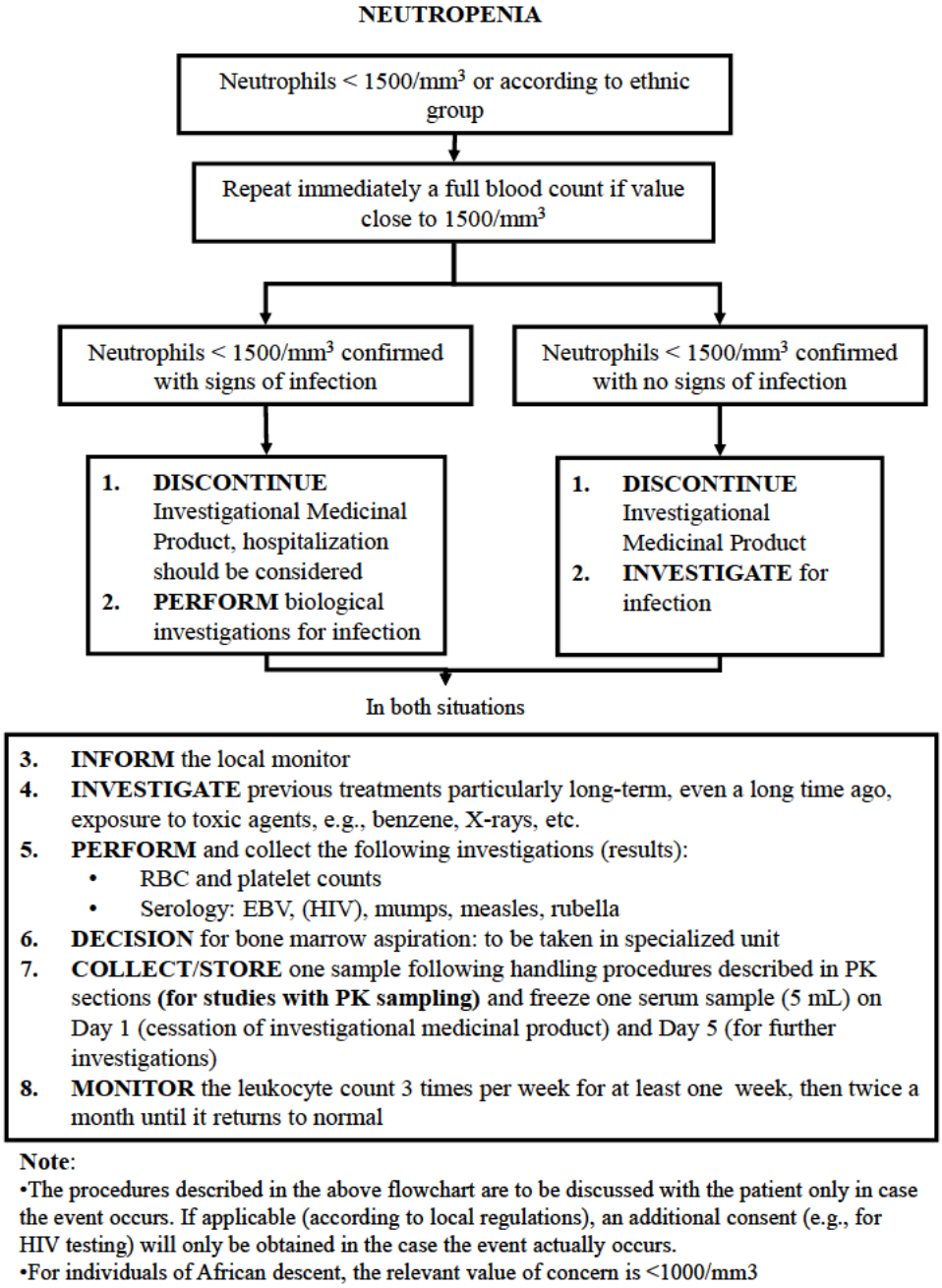
At Visit 1, immediately following arm selection, with the patient in the same position, an additional seated BP should be measured in the selected arm (at least 1 minute after last measurement).

At all other on-site visits, following the 5-minute rest period, 3 separate seated BPs should be measured in the selected arm with at least 1 minute between BP measurements and with the cuff fully deflated between measurements.

All 3 BPs will be recorded in the patient's eCRF. The mean of the 3 seated BPs will constitute the BP value for that visit.

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

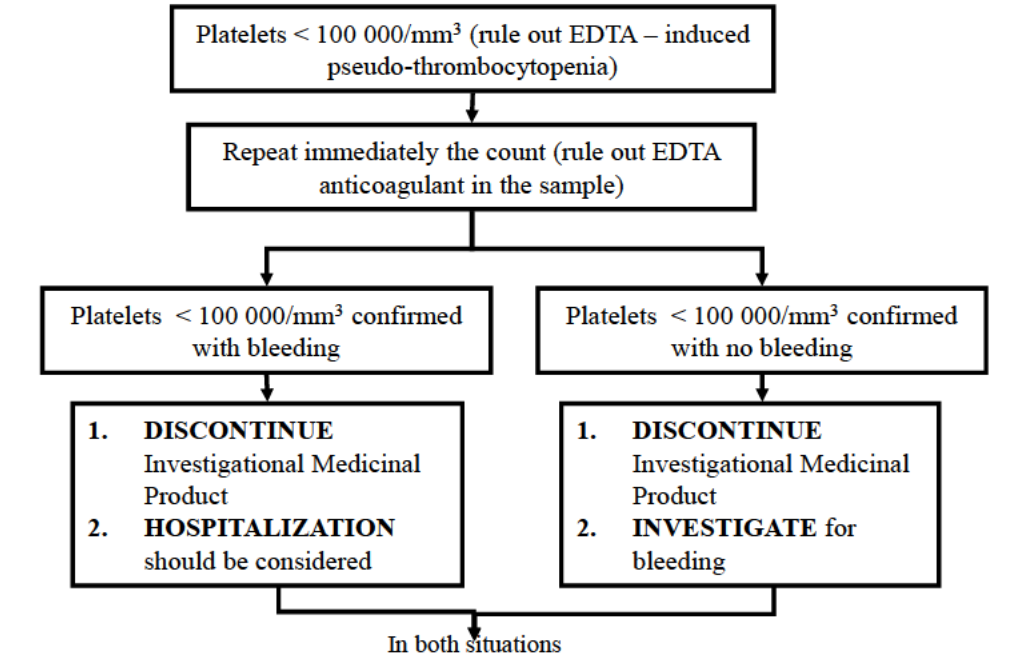
Appendix E General guidance for the follow-up of laboratory abnormalities by Sanofi



Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

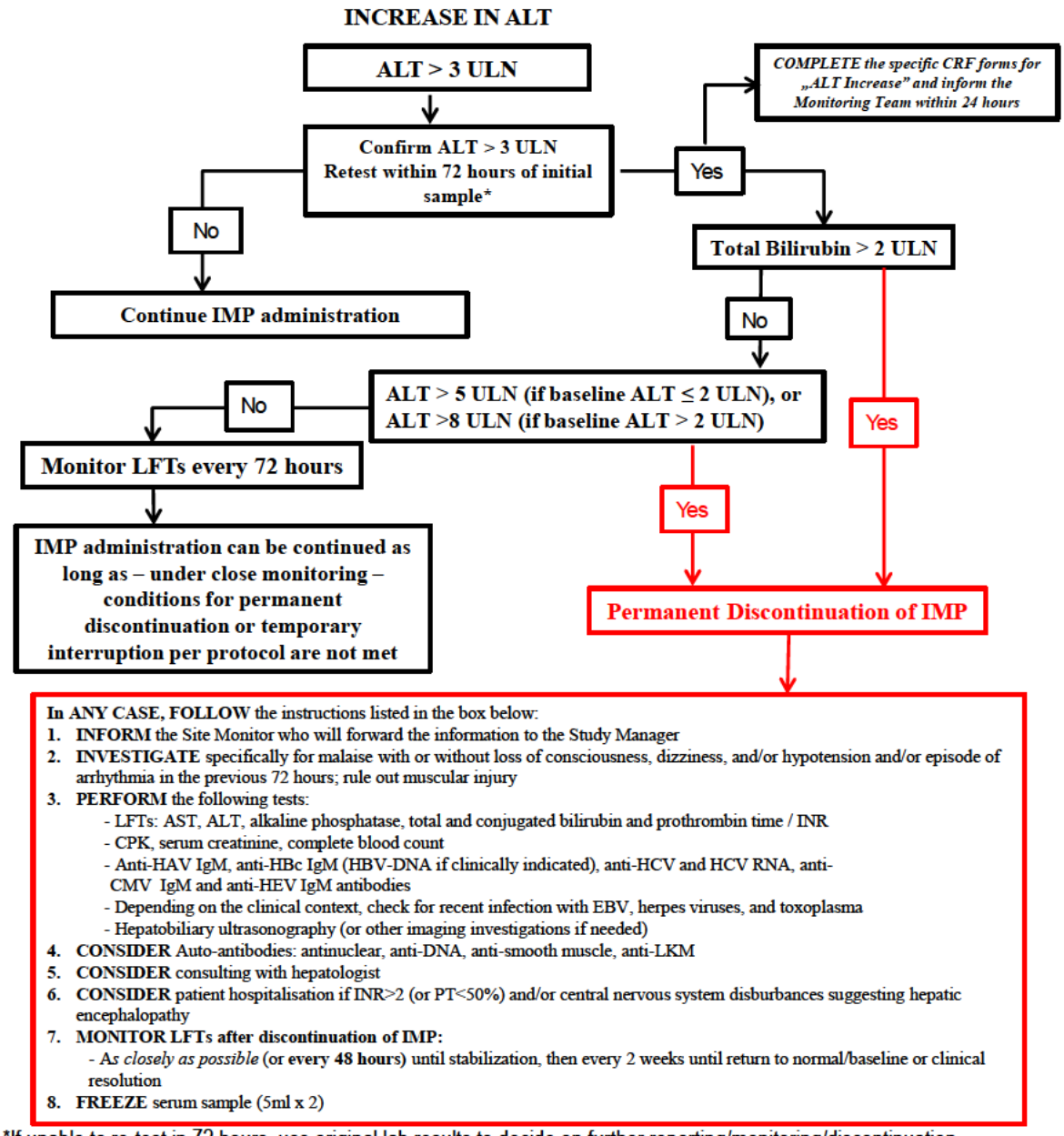
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if platelets remain < 50 000/mm³
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

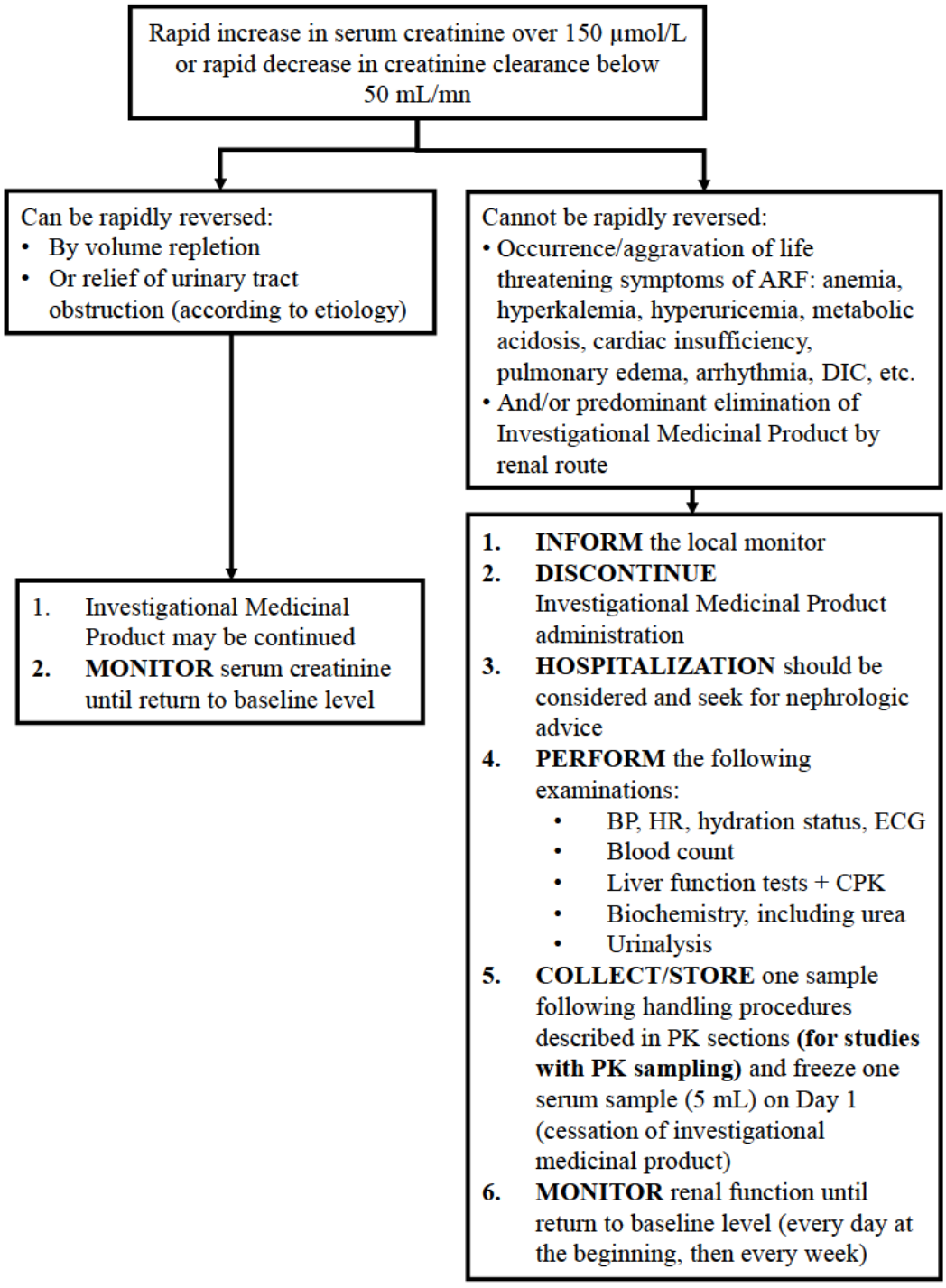


*If unable to re-test in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

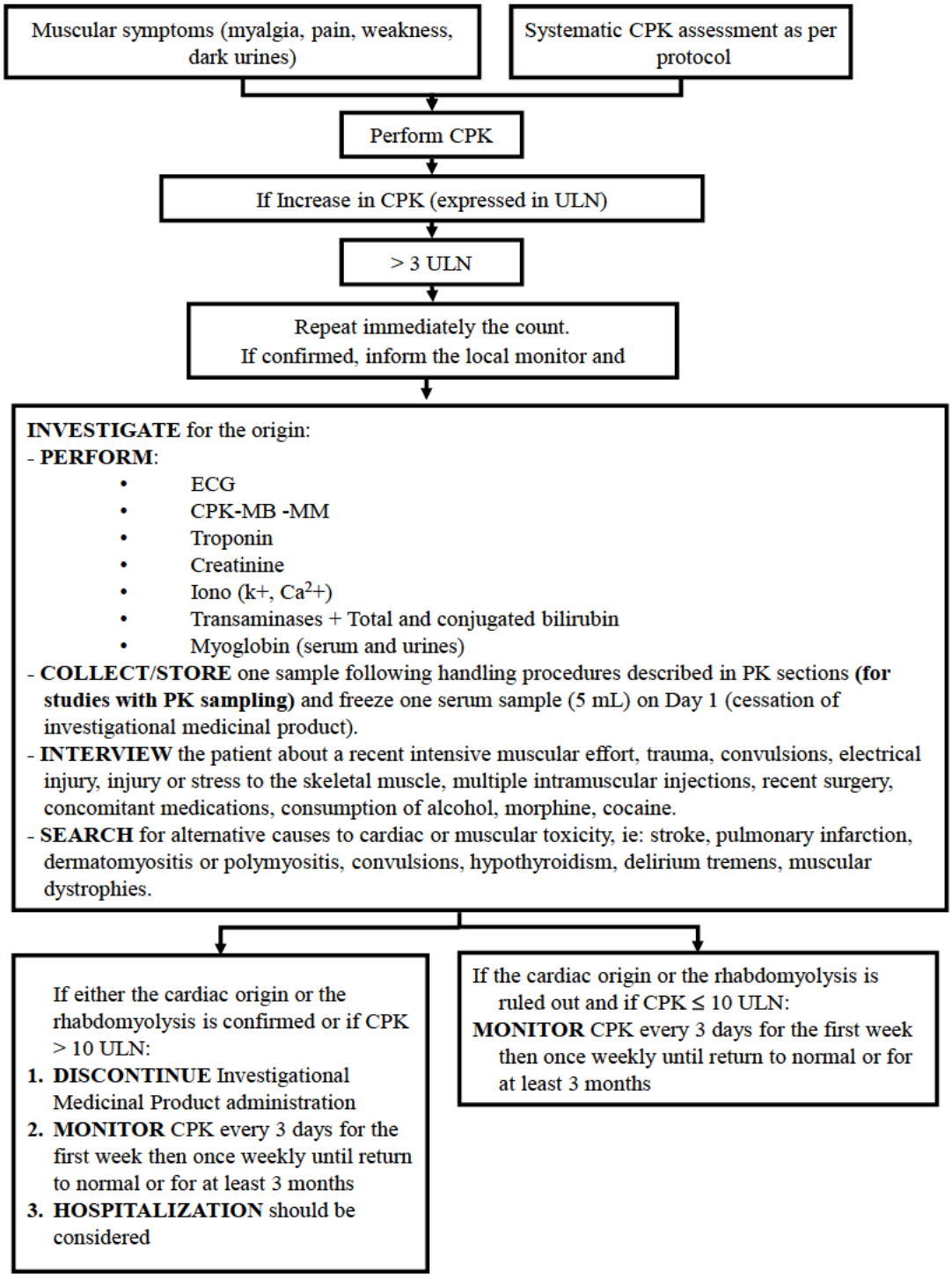
- "Baseline" refers to ALT sampled at Baseline Visit; or if Baseline value unavailable, to the latest ALT sampled before the Baseline Visit. The algorithm does not apply to the instances of increase in ALT during Screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ ULN or Baseline value, if Baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.2 is met.

Appendix F Patient Qualitative Assessment of Treatment (PQAT)

Week 18 Assessment

The following questions ask for your opinion **on the drug you received during this clinical study**.
There are no right or wrong answers; we would like to better understand your own experience of the drug.

1. **During this trial, so far, what were the main benefits you experienced with the drug you received?**

2. **During this trial, so far, what were the main disadvantages you experienced with the drug you received?**

3. **After this trial, would you be willing to continue using the drug you received during this trial?**

Yes ☐ No ☐

Please explain why?

4. **Based on your own experience in this trial so far, please select a response on the scale below**

The disadvantages of the drug I received significantly outweigh the benefits			There were equal benefits and disadvantages of the drug I received			The benefits of the drug I received significantly outweigh the disadvantages
☐ - 3	☐ - 2	☐ - 1	☐ 0	☐ 1	☐ 2	☐ 3

Week 52 Assessment

The following questions ask for your opinion **on the drug you received during this clinical study**.
There are no right or wrong answers; we would like to better understand your own experience of the drug.

1. **In the past 6 months, what were the main benefits you experienced with the drug you received?**

2. **In the past 6 months, what were the main disadvantages you experienced with the drug you received?**

3. **After this trial, would you be willing to continue using the drug you received during this trial?**
Yes ☐ No ☐

Please explain why?

4. **Based on your own experience in the past 6 months, please select a response on the scale below**

The disadvantages of the drug I received significantly outweigh the benefits			There were equal benefits and disadvantages of the drug I received			The benefits of the drug I received significantly outweigh the disadvantages
☐ - 3	☐ - 2	☐ - 1	☐ 0	☐ 1	☐ 2	☐ 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	10-Mar-2018 17:36 GMT+0100
[redacted]	Regulatory Approval	11-Mar-2018 17:30 GMT+0100
[redacted]	Clinical Approval	12-Mar-2018 12:15 GMT+0100