Official Title: A 26-week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study with a 78-week Extension Period to Evaluate the Efficacy and Bone Safety of Sotagliflozin in Patients 55 years or Older with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

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CLINICAL TRIAL PROTOCOL

COMPOUND: sotagliflozin/SAR439954

A 26-week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study with a 78-week Extension Period to Evaluate the Efficacy and Bone Safety of Sotagliflozin in Patients 55 years or Older with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

STUDY NUMBER: EFC15294

STUDY NAME: SOTA-BONE

Version Number:	1	EudraCT: IND Number(s): WHO universal trial number:	2017-002041-30 [redacted] U1111-1195-6371
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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
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.: EFC15294** **STUDY NAME: SOTA-BONE**
TITLE	A 26-week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 study with a 78-week Extension Period to Evaluate the Efficacy and Bone Safety of Sotagliflozin in Patients 55 years or older with Type 2 Diabetes Mellitus and Inadequate Glycemic Control.
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary objective:** The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo with respect to hemoglobin A1c (HbA1c) reduction at Week 26 in patients with Type 2 diabetes (T2D) who have inadequate glycemic control on diet and exercise only or with a stable antidiabetes regimen. **Secondary objective(s):** The secondary objectives of this study are: • To compare the effects of sotagliflozin 400 mg and 200 mg versus placebo with respect to the percent change from Baseline to Week 26 in bone mineral density (BMD) (lumbar spine, total hip, and femoral neck) measured by dual-energy X-ray absorptiometry (DXA) (key secondary safety objective). • To demonstrate the superiority of sotagliflozin 400 mg versus placebo on: - Change from Baseline to Week 26 in body weight (BW). - Change from Baseline to Week 26 in fasting plasma glucose (FPG). - Change from Baseline to Week 12 in systolic blood pressure (SBP) for all patients. - Proportion of patients with HbA1c <7.0% at Week 26. • To demonstrate the superiority of sotagliflozin 200 mg versus placebo with respect to: - HbA1c reduction from Baseline to Week 26. - Change from Baseline to Week 26 in BW. - Change from Baseline to Week 26 in FPG. - Change from Baseline to Week 12 in SBP for all patients. - Proportion of patients with HbA1c <7.0% at Week 26. • To evaluate the safety of sotagliflozin 200 mg and 400 mg compared with placebo over the 104 weeks of treatment. **Other objectives:** Other objectives of this study are: • To compare the effects of sotagliflozin 200 mg and 400 mg versus placebo with respect to: - Change from Baseline to Weeks 52 and 104 in HbA1c.

	- Change from Baseline to Weeks 52 and 104 in FPG. - Change from Baseline to Weeks 52 and 104 in BW. - Proportion of patients with HbA1c <7.0% at Weeks 52 and 104. - Proportion of patients starting rescue therapy during the 104 weeks of treatment. - Change from Baseline to Weeks 26 and 104 in SBP for all patients. - Change from Baseline to Weeks 12, 26, and 104 in SBP for the subset of patients with baseline SBP ≥130 mmHg and SBP <130 mmHg, respectively. - Change from Baseline to Weeks 12, 26, and 104 in diastolic blood pressure (DBP) for all patients and the subsets of patients with Baseline DBP ≥80 mmHg and <80 mmHg, respectively. - Changes from Baseline to Weeks 26, 52, and 104 in total body fat mass and total lean mass measured by DXA. - Changes from Baseline to Weeks 26, 52, and 104 in serum estradiol (only for women). - Changes from Baseline to Weeks 26, 52, and 104 in urinary albumin to creatinine ratio (UACR). - Changes from Baseline to Weeks 26, 52, and 104 on estimated glomerular filtration rate (eGFR).
STUDY DESIGN	This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that is anticipated to enroll approximately 360 patients. Patients with T2D who are 55 years of age or older currently managed with diet and exercise only or with a stable antidiabetes regimen in monotherapy or combination therapy (including oral antidiabetes medications, insulin, or glucagon-like peptide-1 [GLP-1] agonists) for more than 12 weeks are eligible for enrollment in the study. The study will consist of 4 periods: • A Screening Period of up to 4 weeks comprised of: - A Screening Phase of up to 2 weeks. - A 2-week single-blind placebo Run-in Phase. • A 26-week Randomized Double-blind Core Treatment Period. • A 78-week Randomized Double-blind Extension Period. • A 2-week, post-treatment Follow-up Period. To qualify for randomization, patients must demonstrate compliance based upon tablet count (≥80%) during the Run-in Phase. Randomization will be stratified by: • HbA1c at Screening (≤8.5%, >8.5%). • Sex (male, female). Patients will be randomized at a 1:1:1 ratio to the following 3 treatment groups: • Sotagliflozin 400 mg as two (2) 200 mg tablets, taken orally once daily (N=120).

	• Sotagliflozin 200 mg as one (1) 200 mg tablet and one (1) placebo tablet (identical to sotagliflozin 200 mg in appearance), taken orally once daily (N=120). • Placebo as two (2) placebo tablets, taken orally once daily (N=120). To avoid partial unblinding, HbA1c and FPG will be masked to study sites and patients after randomization. Additionally, urinalysis by dipstick will not include the measurement of urine glucose. **Early termination** If a patient discontinues treatment with the investigational medicinal product (IMP) at any time during the Randomized Double-blind Core Treatment Period or during the Randomized Double-blind Extension 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 Week 26 Visit and Week 104 Visit to perform the respective study assessments and collect safety data, emphasizing the measurement of HbA1c and BMD. If the patient does not agree to site visits, the patient will be contacted by respective sites by telephone to inquire about safety status. The study design is presented graphically in Section 1.1.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patient with T2D managed with diet and exercise only or with a stable antidiabetes regimen (in monotherapy or combination therapy that can include oral antidiabetes medications, insulin, or GLP-1 agonists). • Patient has given written informed consent to participate in the study in accordance with local regulations. **Major Exclusion criteria:** • Age <55 years at the Screening Visit. • Women who have been postmenopausal (or undergone bilateral oophorectomy) for less than 5 years. • Type 1 diabetes mellitus. • Body mass index ≤20 or >45 kg/m^2 at Screening or BW that exceeds the weight limits of the DXA scanner. • HbA1c <7.0% or HbA1c >11.0% via central laboratory test at the Screening Visit. • Not on stable prior antidiabetes treatment in the last 12 weeks prior to the Screening Visit (for prior insulin treatment: change of total daily dose of basal insulin by more than 20% within 8 weeks prior to the Screening Visit). • Use of a selective sodium-glucose cotransporter Type 2 (SGLT2) inhibitor or thiazolidinedione within 24 months prior to Screening. • Anatomical changes or conditions that interfere with accurate measurement of BMD by DXA.

	• BMD T-score <-2.0 at any site (ie, lumbar spine, total hip, or femoral neck) measured by DXA during the Screening Period (determination of eligibility based on this test can be made until the time of randomization). • Hypercalcemia based on total serum calcium level >10.5 mg/dL (2.63 mmol/L) at Screening by central laboratory. • Serum 25-hydroxyvitamin D levels ≤20 ng/mL (≤50 nmol/L) at the Screening Visit by central laboratory (determination of eligibility based on this test can be made until the time of randomization). • History of fracture within 12 months prior to the Screening Visit (except for fractures of the hand/fingers, foot/toes, facial bones, and skull). • Treatment with medications known to affect bone mass or modify the risk of fractures within 36 months prior to the Screening Visit (eg, bisphosphonates, selective estrogen-receptor modulators, calcitonin, teriparatide, denosumab, strontium ranelate, growth hormone, aromatase inhibitors, androgen deprivation therapy, carbamazepine, phenytoin, phenobarbital). Use of hormonal replacement that includes systemic or transdermal estrogen and testosterone is excluded unless is stable for at least 24 months prior to Screening. • 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 Screening. • Use of weight loss medication within 12 weeks or weight change of 5 kg or more during the 12 weeks prior to Screening. • History of gastric surgery including history of gastric banding or surgery for inflammatory bowel disease within 3 years prior to Screening. • History of diabetic ketoacidosis or nonketotic hyperosmolar coma within 12 weeks prior to Screening. • History of severe hypoglycemia resulting in unconsciousness, seizure, or hospitalization within 6 months prior to Screening. • Lower extremity complications (such as skin ulcers, infection, osteomyelitis and gangrene) identified during the Screening Period, and still requiring treatment at Randomization. • Mean of 3 separate measurements SBP >180 mmHg or DBP >100 mmHg at the Screening Visit. • History of hypertensive emergency within 12 weeks prior to Screening. • Patients with severe anemia, severe cardiovascular disease (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.

	• Aspartate aminotransferase and/or alanine aminotransferase >3 times the upper limit of the normal laboratory range (ULN). • Total bilirubin >1.5 times the ULN (except in case of Gilbert's syndrome). • Alkaline phosphatase >1.5 times the ULN. • Renal disease as defined by eGFR <30 mL/min/1.73m² at the Screening Visit by the 4 variable Modification of Diet in Renal Disease equation. • Patient is unwilling or unable to perform self-monitoring of blood glucose (SMBG), complete the patient diary, or comply with study visits and other study procedures as required per protocol. • Patient who has taken other investigational drugs or prohibited therapy for this study within 12 weeks or 5 half-lives from Screening or randomization, whichever is longer.
Total expected number of patients	360
STUDY TREATMENTS	
Investigational medicinal product(s)	During the single-blind Run-in period all patients will receive two (2) placebo tablets (identical to sotagliflozin 200 mg in appearance). During the Randomized Double-blind Core Treatment Period and Double-blind Extension Period, the patients will receive treatment with the IMP, as follows: • Sotagliflozin 400 mg given as two (2) 200-mg tablets, or, • Sotagliflozin 200 mg given as one (1) 200-mg sotagliflozin tablet and one (1) sotagliflozin-matching placebo tablet, or, • Placebo, given as two (2) sotagliflozin-matching placebo tablets.
Formulation	Tablet
Routes of administration	Oral
Dose regimen	Once daily before the first meal of the day
Noninvestigational medicinal product(s)	Dose of background antidiabetes medication (if any) should be stable throughout the study, unless a change is required for safety reasons or if hyperglycemia rescue criteria are satisfied. For patients on insulin therapy, the total daily dose of basal insulin should remain within 20% of the randomization dose, unless changes are needed for safety reasons or hyperglycemia rescue criteria are met. **Rescue Therapy** The threshold values for rescue are defined as follows, depending on study period: • From Baseline visit (Visit 3, Day 1) to Visit 5 (Week 6), inclusive: FPG >270 mg/dL (15.0 mmol/L). • From Visit 5 (Week 6) to Visit 6 (Week 12), inclusive: FPG >240 mg/dL (13.3 mmol/L). • From Visit 6 (Week 12) up to Visit 8 (Week 26), inclusive: 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 ≥1.0%).

	• From Visit 8 (Week 26) up to Visit 10 (Week 52), inclusive: 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 ≥1.0%). • From Visit 10 (Week 52) up to the EOT Visit 13 (Week 104): FPG >160 mg/dL (8.9 mmol/L) or HbA1c ≥7.5%. The HbA1c and FPG results will be masked to study sites and patients after randomization and until study end. Routine fasting SMBG and central laboratory alerts on FPG and/or HbA1c 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 as soon as possible, preferably within 7 days, by unscheduled visit. Likewise, patients will be 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 laboratory re-test confirmation should be performed as soon as possible, preferably within 7 days, by unscheduled visit. Open-label rescue treatment may be added at the Principal Investigator's discretion (with exception of treatment with SGLT2 inhibitors or thiazolidinediones). If a patient requires rescue, the IMP received at Randomization should continue and must remain blinded until the end of the study.
ENDPOINT(S)	**Primary endpoint:** • Change from Baseline to Week 26 in HbA1c (sotagliflozin 400 mg). **Secondary endpoint(s):** **Key secondary safety endpoint:** • Percent change from Baseline to Week 26 in BMD (lumbar spine, total hip, and femoral neck). **Secondary efficacy endpoints**: • Change from Baseline to Week 26 in HbA1c (sotagliflozin 200 mg only). • Change from Baseline to Week 26 in BW. • Change from Baseline to Week 26 in FPG. • Change from Baseline to Week 12 in SBP for all patients. • Proportion of patients with HbA1c <7.0% at Week 26. **Other efficacy endpoint(s):** • Change from Baseline to Weeks 52 and 104 in HbA1c. • Change from Baseline to Weeks 52 and 104 in FPG. • Change from Baseline to Weeks 52 and 104 in BW. • Proportion of patients with HbA1c <7.0% at Weeks 52 and 104. • Proportion of patients starting rescue therapy during the 104 weeks of treatment.

	• Change from Baseline to Weeks 26 and 104 in SBP for all patients. • Change from Baseline to Weeks 12, 26, and 104 in SBP for the subset of patients with baseline SBP ≥130 mmHg and SBP<130 mmHg, respectively. • Change from Baseline to Weeks 12, 26, and 104 in DBP for all patients and the subsets of patients with Baseline DBP ≥80 mmHg and <80 mmHg, respectively. • Change from Baseline to Weeks 26, 52, and 104 in total body fat mass and total lean mass measured by DXA. • Change from Baseline to Weeks 26, 52, and 104 in serum estradiol (only for women). • Change from Baseline to Weeks 26, 52, and 104 in UACR. • Change from Baseline to Weeks 26, 52, and 104 in eGFR. **Other safety endpoints:** • Percent change from Baseline to Week 52 and 104 in BMD (lumbar spine, total hip, and femoral neck). • Proportion of patients with adjudicated bone fractures over 104 weeks. • Proportion of patients with ≥3% decline in BMD at Week 104. • Changes from Baseline to Week 26, 52, and 104 in bone turnover markers (serum bone resorption markers: N-terminal telopeptide of Type 1 collagen (NTX) and beta C-terminal telopeptide of Type 1 collagen (β-CTX-1); serum bone formation markers: Type 1 procollagen N-terminal propeptide [P1NP] and osteocalcin). • Changes from Baseline to Week 26, 52, and 104 in markers of calcium metabolism (serum: calcium, phosphorus, magnesium, parathyroid hormone [iPTH], 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D; urinary: calcium, phosphorus and magnesium). • Clinical laboratory results, vital signs results, and 12-lead electrocardiogram (ECG). • Adverse events (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.
ASSESSMENT SCHEDULE	See Study Flow Chart in Section 1.2
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size/power calculations were performed based on the primary variable of change from Baseline to Week 26 in HbA1c. Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 360 patients (120 patients per arm) will have 97% power to detect a treatment difference of -0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

	This sample size will also allow to exclude a decline in BMD from Baseline of >2% with a 95% power, assuming a missing rate of 30% and an SD of 3.5%. **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 for efficacy analyses according to the treatment group to which they are randomized. The safety analysis will be conducted on the safety population, defined as all randomized patients who did actually receive at least one dose of study treatment during the Treatment Period (regardless of the amount of treatment administered). Patients will be analyzed according to the treatment actually received. The analyses will be conducted in 2 steps: • **First step**: Efficacy analyses up to Week 26, and interim safety analysis. The first step analyses will be conducted when all randomized patients have at least all their data up to Week 26 (Visit 8) collected and validated. The first step analyses will consist of efficacy analyses up to Week 26 and analysis for key secondary safety endpoint of BMD at Week 26, which are considered as the final analyses for the primary and secondary endpoints. The other safety analysis will be performed on all safety data collected and validated at the time of the first step analysis. The results of the first step analyses will not be used to change the conduct of the ongoing study in any aspect. Since primary efficacy, secondary efficacy, and key safety analyses will have been concluded in all patients at the time of this first step analyses, the significance level for the study remains at 0.05. The first step analyses plan will be used for the submission dossier to health authorities. • **Second step**: Final analyses The second step analyses will be conducted at the end of the study and will include the efficacy endpoints analysis at Week 52 and Week 104, which will be descriptive only. The second step analysis will also include safety analysis for the entire Week 104 Treatment Period. **Analysis of the primary efficacy endpoint:** Analysis of the primary efficacy endpoint (change from Baseline to Week 26 in HbA1c) will be performed on the ITT population, using HbA1c measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy (de facto estimand). The primary efficacy endpoint of change in HbA1c from Baseline to Week 26 will be analyzed with missing values imputed by control-based copy reference multiple imputation method under the missing not at random framework for the active treatment group: • For placebo patients, missing data will be imputed based on the placebo group data.

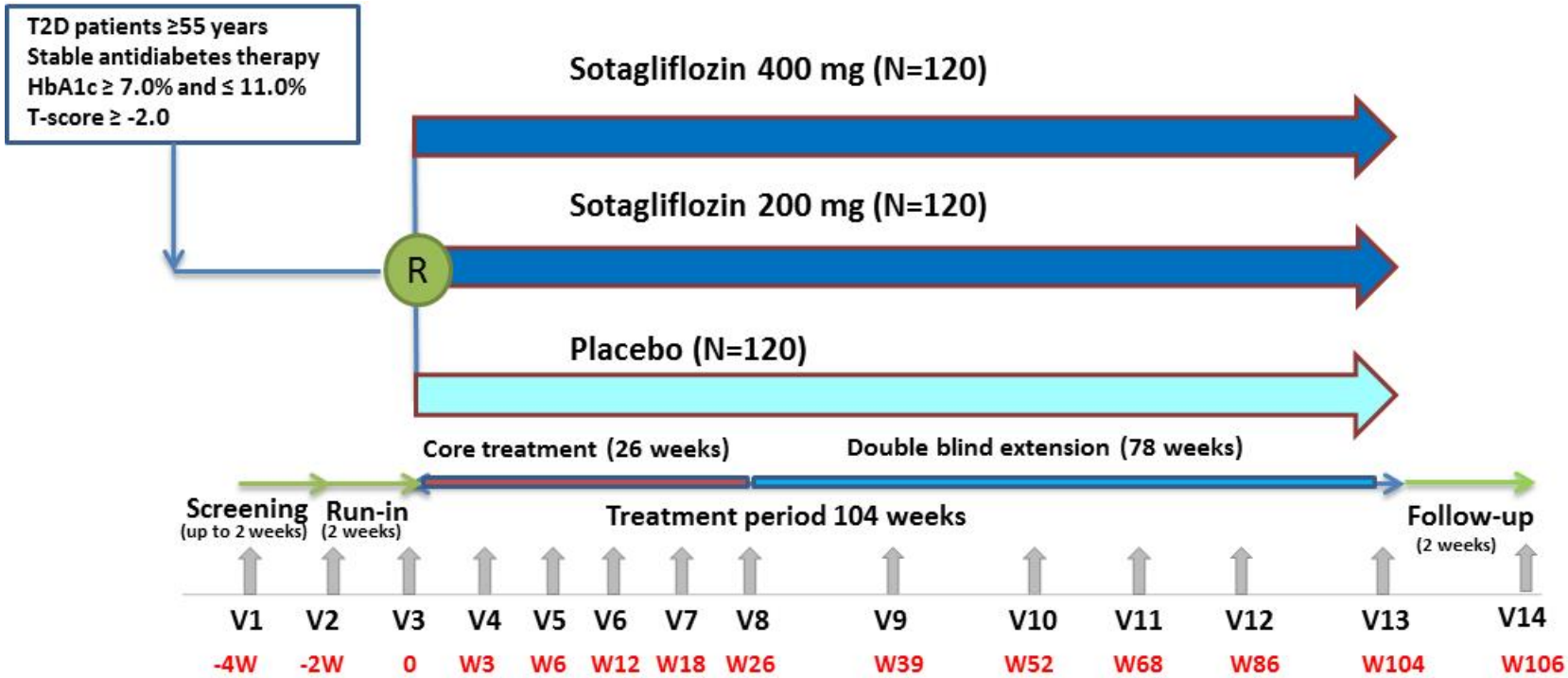
	• For patients in the sotagliflozin groups, missing data will be imputed as if the patients were on placebo throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model. Each 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 stratum of HbA1c (≤8.5%, >8.5%) at Screening, randomization stratum sex (male, female) and country as fixed effects, and Baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted least squares (LS) mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg versus placebo) and the 95% confidence intervals (CIs) for the difference. 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]). **Analysis of secondary endpoints:** The secondary efficacy endpoints 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. For each of the continuous secondary endpoints, each of the complete datasets will be analyzed by the ANCOVA model. The model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of HbA1c (≤8.5%, >8.5%) at Screening, sex (male, female) 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 LS mean change from Baseline to Week 26 (respectively Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing each sotagliflozin group versus placebo group) and the 95% CI for the difference. The categorical secondary efficacy variables of HbA1c <7.0% at Week 26 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization strata of HbA1c (≤8.5%, >8.5%) at Screening and sex (male, female). Analysis of the key secondary safety endpoint of percent change from Baseline to Week 26 in BMD will be performed on the safety population, using an ANCOVA model. To compare sotagliflozin 400 mg and 200 mg versus placebo, the model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of HbA1c

	(≤8.5%, >8.5%), sex (male, female) and country as fixed effects, and Baseline BMD value as a covariate, providing the adjusted LS mean percent change from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing each sotagliflozin group vs placebo group) and the 95% CI for the difference. The last-observation-carried-forward (LOCF) approach will be applied for the missing data imputation of the key safety endpoint of percent change in BMD from Baseline to Week 26. As the Week 26 Visit is the first post-Baseline scheduled visit for BMD measurement, if a patient withdraws early from the study before Week 26, the BMD measurement collected at the withdrawal visit will be used carrying forward to Week 26 in analysis. **Multiplicity considerations** To control the family-wise Type I error, a fixed sequence testing approach will be used to test primary and secondary endpoints. Only if the difference in mean change from Baseline to Week 26 in HbA1c of sotagliflozin 400 mg versus placebo is statistically significant at α=0.05 (2-sided), a hierarchical testing procedure will be performed to test the secondary endpoints in the following prioritized order: Superiority of sotagliflozin 400 mg versus placebo with respect to: • Change from Baseline to Week 26 in BW. • Change from Baseline to Week 26 in FPG. • Change from Baseline to Week 12 in SBP for all patients. Superiority of sotagliflozin 200 mg versus placebo with respect to: • Change from Baseline to Week 26 in HbA1c. • Change from Baseline to Week 26 in BW. • Change from Baseline to Week 26 in FPG. • Change from Baseline to Week 12 in SBP for all patients. Superiority tests will be tested at 2-sided 5% significant level. If any of the endpoints is found to be not statistically significant, the testing procedure will be stopped and the following endpoints will not be tested. Multiplicity adjustment will not be performed on other secondary endpoints not mentioned above. **Analysis of other efficacy endpoints:** The analysis of other efficacy 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. **Analysis of other safety endpoints:** The percent change from Baseline to Week 52 (or Week 104) in BMD will be analyzed using a mixed-effect model with repeated measures (MMRM). The MMRM model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of HbA1c (≤8.5%, >8.5%), sex (male, female), visit, treatment-by-visit interaction and country as fixed effects, and Baseline BMD value-by-visit interaction as covariate, providing the

	adjusted LS mean percent change from Baseline to Week 52 (or Week 104) for each treatment group, as well as the between-group difference (comparing each sotagliflozin group vs placebo group) and the 95% CI for the difference. No statistical significance tests will be performed on safety endpoints. These analyses will be based on the Safety Population.
DURATION OF STUDY PERIOD (per patient)	Up to 110 weeks, including a 4-week Screening Period (comprised of a Screening Phase of up to 2 weeks and a 2-week single-blind placebo Run-in Phase), a 26-week Randomized Double-blind Core Treatment Period, a 78-week Randomized Double-blind Extension Period, and a 2-week post-treatment Follow-up Period.
STUDY COMMITTEES	**Steering Committee:** ☒ Yes ☐ No **Data monitoring committee:** ☒ Yes ☐ No **Clinical Endpoint Committees:** ☒ Yes ☐ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Abbreviations: HbA1c = hemoglobin A1c; N = number; R = randomization; T2D = Type 2 Diabetes; V = visit; W = week.

1.2 STUDY FLOW CHART

	Screening Period		Double-blind Treatment Period[a]											Follow-up Period[b]
	Screening	Run-in	Randomized Double-blind Core Treatment Period						Randomized Double-blind Extension Period					
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-4**	**-2**	**0**	**3**	**6**	**12**	**18**	**26**	**39**	**52**	**68**	**86**	**104**	**106**
Day (window [days])	**-28**	**-14 (±3)**	**1**	**21 (±3)**	**42 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**476 (±7)**	**602 (±7)**	**728 (±3)**	**742 (±3)**
Informed consent	X													
Inclusion criteria	X													
Exclusion criteria	X	X	X											
Patient demography	X													
Medical/surgical history	X													
Prior medication history	X													
Body weight, height[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination:														
Complete	X							X					X	
Abbreviated[e]		X	X	X	X	X	X		X	X	X	X		X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SMBG[f]			X	X	X	X	X	X	X	X	X	X	X	X
Diet & exercise instruction		X	X					X		X	X	X		
Instruction on basic GU hygiene & hydration		X	X	X	X	X	X	X	X	X	X	X		
IRT contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X											

	Screening Period		Double-blind Treatment Period[a]											Follow-up Period[b]
	Screening	Run-in	Randomized Double-blind Core Treatment Period						Randomized Double-blind Extension Period					
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-4**	**-2**	**0**	**3**	**6**	**12**	**18**	**26**	**39**	**52**	**68**	**86**	**104**	**106**
Day (window [days])	**-28**	**-14 (±3)**	**1**	**21 (±3)**	**42 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**476 (±7)**	**602 (±7)**	**728 (±3)**	**742 (±3)**
Dispense glucose meter		X												
Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review diary			X	X	X	X	X	X	X	X	X	X	X	X
Dispense single-blind placebo		X												
Dispense double-blind IMP			X	X	X	X	X	X	X	X	X	X		
IMP accounting & compliance			X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[g]		X						X					X	
Laboratory assessments[h]														
Serum 25 hydroxyvitamin D screening	X													
FPG[i]			X	X	X	X		X		X		X	X	
HbA1c	X		X			X		X		X		X	X	
Safety laboratory	X		X	X	X	X		X		X		X	X	X
Hematology	X		X			X		X		X		X	X	X
Fasting lipids			X					X					X	
FSH and estradiol for documentation of menopausal status[j]	X													
Estradiol (only for women)			X					X		X			X	
Bone turnover markers[k]			X					X		X			X	

	Screening Period		Double-blind Treatment Period[a]											Follow-up Period[b]
	Screening	Run-in	Randomized Double-blind Core Treatment Period						Randomized Double-blind Extension Period					
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-4**	**-2**	**0**	**3**	**6**	**12**	**18**	**26**	**39**	**52**	**68**	**86**	**104**	**106**
Day (window [days])	**-28**	**-14 (±3)**	**1**	**21 (±3)**	**42 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**476 (±7)**	**602 (±7)**	**728 (±3)**	**742 (±3)**
Markers of calcium metabolism[l]			X					X		X			X	
Collection of home 24-hour urine for albumin, creatinine, albumin-creatinine ratio, calcium, magnesium, and phosphorus[m]			X					X		X			X	
Urinalysis w/microscopy[n]	X		X			X		X		X		X	X	
DXA scan [o]		X						X		X			X	
[redacted]														
Evaluate for glycemic rescue	To be assessed and reported throughout the Treatment Period													
Hypoglycemia	To be assessed and reported throughout the study													
AE/SAE/AESI/EOSI recording[p]	To be assessed and reported throughout the study													

Abbreviations: AE = adverse event, AESI = adverse event of special interest, BMD = bone mineral density, BP = blood pressure, DXA = dual-energy X-ray absorptiometry, ECG = electrocardiogram, EOSI = event of special interest, EOT = End of Treatment, FPG = fasting plasma glucose, FSH = follicle-stimulating hormone, GU = genito-urinary, HbA1c = hemoglobin A1C, HR = heart rate, IMP = investigational medicinal product, iPTH = parathyroid hormone, IRT = Interactive Response Technology, NIMP = noninvestigational medicinal product, NTX = N-terminal telopeptide of Type 1 collagen, P1NP = Type 1 procollagen N-terminal propeptide, SAE = serious adverse event, SMBG = self-monitoring of blood glucose, β-CTX-1 = beta C-terminal telopeptide of Type 1 collagen.

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 26 (Visit 8) and Week 104 (Visit 13). If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status.

b The Follow-up Visit will take place 2 weeks ± 3 days after the last dose of IMP. All attempts will be made to contact the patient to inquire about safety status.

c Height to be measured only at Screening, Week 52, Week 104, and at the Premature EOT Visit.

d Vital sign measurements (sitting BP and HR): 3 separate seated BP and HR measurements should be taken with at least 1 minute between readings, following a 5-minute rest period and prior to phlebotomy (see Appendix C).

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

f Patients will be instructed to measure their fasting glucose levels via SMBG and discuss results with site personnel at clinic visits or phone contacts. The frequency of the fasting SMBG measurements will be determined by the Investigator according to the clinical need and background diabetes treatment, but it is recommended to be done at least once a week. Patients will also be instructed to self-assess blood glucose levels whenever they experience any illnesses (eg, cold, flu), or symptoms of hyperglycemia or hypoglycemia. Note that the SMBG measurements obtained with glucose meters are displayed as plasma glucose concentration. The SMBGs ≤70 mg/dL will be reported on the hypoglycemia specific electronic case report form page.

g The 12-lead ECG recordings should be obtained prior to IMP administration. The ECG will be evaluated as “normal” or “abnormal”.

h All laboratory assessments occur prior to dose of double-blind IMP and NIMP.

i The FPG is performed in fasting status, ie, without any food intake (except for water) for at least 8 hours.

j The FSH and serum estradiol is performed in all women at Screening to confirm menopausal status as needed.

k Markers of bone turnover include: markers of bone resorption (serum NTX, serum β-CTX-1) and bone formation (serum P1NP and osteocalcin).

l Markers of calcium metabolism include: serum and urinary calcium (adjusted for creatinine), serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum and urinary phosphorus (adjusted for serum phosphorus, and creatinine), serum and urinary magnesium (adjusted for serum magnesium and creatinine), serum iPTH.

m 24-hour urine samples for calcium, phosphorus, and magnesium will be collected at Weeks 0, 26, 52, and 104. Patients will be instructed to initiate the 24-hour urine collection on the day before the visits. In exceptional situations, the 24-hour urine collection can be done up to 2 days maximum prior to or after the visit, and the specimen should be sent to the study site as soon as possible.

n Urinalysis will be done at central laboratory and includes urine dipstick and microscopy. Dipstick includes assessment of specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. Microscopy includes detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment. In the event of abnormal urinalysis findings, urine cultures should be performed (microbial testing). Additionally, urine cultures should be performed if at any point the Principal Investigator suspects the presence of a urinary tract infection.

o Baseline DXA scans for BMD assessment will be performed during Run-in and centrally reviewed for eligibility assessment. All BMD assessments will be performed locally with a central review. Post-Baseline DXA scans will be performed within 2 weeks prior to the on-site visits at Weeks 26, 52, and 104, or no later than 7 days after the visit. Body composition by DXA will be performed at the same visits when the BMD is measured.

p All SAEs, AEs, AESI, and 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.

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3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BMD:	bone mineral density
BMI:	body mass index
BP:	blood pressure
BW:	body weight
CEC:	Clinical Endpoint Committee
CI:	confidence interval
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
DNA:	deoxyribonucleic acid
DXA:	dual-energy X-ray absorptiometry
ECG:	electrocardiogram
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
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
GLP-1:	glucagon-like peptide-1
GU:	genito-urinary
HbA1c:	hemoglobin A1c
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID:	identification

IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
iPTH:	parathyroid hormone
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	Intention-to-Treat
LS:	least squares
MACE:	major adverse cardiovascular event
MDRD:	modification of diet in renal disease
MI:	myocardial infarction
MMRM:	mixed-effect model with repeated measures
NIMP:	noninvestigational medicinal product
NTX:	N-terminal telopeptide of type 1 collagen
OC:	observed cases
P1NP:	type 1 procollagen N-terminal propeptide
PCSA:	potentially clinically significant abnormality
P-gp:	P-glycoprotein
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
SERM:	selective estrogen receptor modulator
SGLT1:	sodium-glucose cotransporter type 1
SGLT2:	sodium-glucose cotransporter type 2
SMBG:	self-monitored/monitoring of 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
UACR:	urinary albumin to creatinine ratio
ULN:	upper limit of the normal laboratory range
US:	United States
UTI:	urinary tract infection
β-CTX-1:	beta C-terminal telopeptide of type 1 collagen

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: SOTAGLIFLOZIN AND DISEASE

Sotagliflozin is being developed as a therapy to improve glycemic control 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 macrovascular complications result in coronary artery disease, peripheral arterial disease, and stroke (2). 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). 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 (5).

While these numbers include both people with T2D and Type 1 diabetes (T1D), over 90% of adults with diabetes have T2D. 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 diabetes education, are important components of diabetes treatment, the vast majority of people with T2D need to receive pharmacological therapy to control the disease. Despite the numerous treatment options available (3), a large proportion of patients fail to achieve the glycemic control targets as beta cell function continues to deteriorate leading to progressively increasing hyperglycemia. Concerns with side effects of currently available agents, most notably hypoglycemia and weight gain, also 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 and avoiding hypoglycemia. Sotagliflozin is being investigated as a novel antidiabetic agent that can improve glycemic control by an insulin-independent mechanism of dual inhibition of sodium-glucose cotransporters Type 1 and 2 (SGLT1 and SGLT2). 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 excreted from the body, rather than being reabsorbed (8). This mechanism of reducing blood glucose is insulin-independent, sparing the pancreas from an increased demand for insulin production, and therefore hyperglycemia is controlled with little or no risk of hypoglycemia. 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).

The SGLT1 is expressed predominantly in the gastrointestinal tract and is responsible for the majority of glucose absorption by the small intestine (9). Inhibition of SGLT1 in the gastrointestinal 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.

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 United States (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

As of December 2016, approximately 840 subjects (including 698 subjects assigned to sotagliflozin and 229 assigned to placebo) have participated in 19 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. 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 leading to discontinuation from the study. Genital mycotic infections have occurred with more frequency in subjects taking sotagliflozin than with placebo, although the majority of the events were mild and all events resolved with usual standard of care therapy.

In completed and ongoing clinical trials, no additional safety issues beside those already described in the current Investigator's Brochure (IB) were observed. In general, no significant imbalances of serious adverse events (SAEs)/adverse events (AEs) between sotagliflozin and comparators were observed in completed studies. Cumulatively, during the clinical trial program, 8 SAEs were reported by 6 patients (4 patients with T2D and 2 with T1D), all of which were assessed as unrelated to study drug; those reported by 4 patients with T2D who received sotagliflozin included pulmonary embolism, deep vein thrombosis, bile duct stone, cholangitis, and lower limb

fracture, while a myocardial infarction (MI) was experienced by a patient receiving placebo. Two SAEs of diabetic ketoacidosis (DKA) were reported in 2 patients with T1D receiving sotagliflozin 400 mg once daily in the Phase 2 T1D study LX4211.1-203-T1DM (13); both SAEs were assessed as due to failure of insulin delivery via insulin pump.

Study LX4211.1-114-NRM, a drug interaction study with digoxin, a sensitive P-glycoprotein (P-gp) substrate, indicated that sotagliflozin acts as a weak P-gp inhibitor (14). Thus, sotagliflozin increases systemic exposure of digoxin and could also increase the exposure of other P-gp substrates. The efficacy of sotagliflozin has been shown in other studies in T2D patients. Study LX4211.1-202-DM was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the safety, and efficacy of sotagliflozin in combination with metformin in patients with T2D who had inadequate glycemic control on metformin monotherapy (N = 299) (12). All 4 dosing regimens of sotagliflozin (75 mg once daily, 200 mg once daily, 400 mg once daily, and 200 mg twice daily given as oral tablets) reduced mean HbA1c from Baseline to Week 12 to a statistically and clinically significant degree compared to placebo ($p = 0.025$, $p = 0.018$, $p < 0.001$, and $p < 0.001$), respectively. The arithmetic mean change from Baseline in HbA1c was greatest for the 400 mg once daily group (-0.92%), followed by the 200 mg twice daily group (-0.80%). The least squares (LS) mean difference from placebo was also greatest for the 400 mg once daily group (-0.79%; $p < 0.001$), followed by the 200 mg twice daily group (-0.61%; $p < 0.001$). The LS mean differences from placebo were similar for the 200 mg once daily group (-0.34%) and the 75 mg once daily group (-0.33%). Significant reductions were seen also in body weight (BW) (mean loss of 2 kg or more) with the top three dosing regimens and a dose-dependent reduction in systolic blood pressure (SBP; -5.7 mmHg with the 400 mg once daily dose), while diastolic blood pressure (DBP) was unchanged (12).

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 sotagliflozin 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 T2D patients with impaired renal function, and the special population of the current trial represented by T2D patients aged more than 55 years 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 (15). 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 effect 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 0.92%, respectively ($p <0.001$ for both arms), while placebo lowered HbA1c by a mean of 0.09%. Sotagliflozin also produced statistically significant reductions in BW (with 200-mg and 400-mg doses) and SBP (with 400-mg dose).

From a safety perspective, sotagliflozin was well tolerated across studies. The overall incidence of AEs on sotagliflozin 200-mg and 400-mg once daily doses was similar to placebo. Evaluation of safety during long-term treatment with sotagliflozin 400 mg and 200 mg in this study will allow to further characterize the bone safety profile of both doses and assess the effect of each dose on bone and calcium metabolism.

4.4 RATIONALE FOR THE STUDY AND OBJECTIVES

The primary objective is to assess the efficacy and safety of sotagliflozin compared to placebo in a population of T2D patients 55 years or older in inadequate control on a stable antidiabetes regimen. This study will enable to evaluate the glucose lowering efficacy of sotagliflozin in the context of a broad range of background antidiabetes therapies and in an aging population with potentially longer duration of diabetes. Additionally, this study will assess the effects of sotagliflozin in reducing SBP, which is another important health issue for people with diabetes and in particular this age group.

This study is also being specifically designed to evaluate the effects of sotagliflozin on bone health with a key secondary safety objective of evaluating the changes in bone mineral density (BMD) with sotagliflozin treatment. Evaluation of bone safety is relevant due to findings of hyperostosis and decreases in bone turnover observed in animal studies with other compounds in the class (16, 17). These effects have been hypothesized to be associated with SGLT1 inhibition leading to an off-target increase in intestinal calcium absorption and changes in calcium homeostasis and vitamin D metabolism (16, 17). Small and inconsistent changes in bone biomarkers and no imbalance in fracture rate were reported in clinical trials with dapagliflozin and empagliflozin (18, 19). Changes in bone markers (increase in beta C-terminal telopeptide of Type 1 collagen [β-CTX-1]) after 1 year and a small decrease in BMD after 2 years (placebo subtracted changes of -0.9% and -1.2% with canagliflozin 100 and 300 mg, respectively) were reported with canagliflozin treatment (20), although the clinical significance is unknown. These clinical findings were inconsistent with the preclinical data and could be explained at least in part by the weight loss occurred with canagliflozin treatment (20). An increased risk of fractures following treatment with other SGLT2 inhibitors was observed in patients with high risk of cardiovascular (CV) disease participating in the canagliflozin CV outcomes trial (21, 22) and in a 2-year study with dapagliflozin in patients with renal impairment (23), but in both cases, the findings were not seen in the pooled data from Phase 3 studies. It is possible that these subgroups present higher susceptibility to hemodynamic events or falls, which could be associated with fractures (23, 24). Of note, upon the US FDA review of clinical data at the time of New Drug Application submission, the agency concluded that there was no indication of a clinically significant effect of dapagliflozin on bone loss or fracture. Canagliflozin remains the only SGLT2 inhibitor that carries a label warning related to the increased risk of bone fractures in patients with T2D.

Preclinical studies with sotagliflozin in rats showed increase in trabecular bone and small reversible decreases in calciotropic hormone and bone markers (Type 1 procollagen N-terminal propeptide [P1NP], osteocalcin, 1,25-dihydroxyvitamin D), which were not considered biologically significant. No clinically significant changes in calcium and bone biomarkers have been observed in clinical studies with sotagliflozin. However, as changes in bone markers and

BMD were reported in clinical studies with canagliflozin (17), this study is also planned to further assess the effects of sotagliflozin on bone mass, markers of calcium metabolism and bone turnover over 104 weeks of treatment in this aging group of patients at higher risk for osteoporosis and fractures. To assess the risk of fractures with sotagliflozin treatment, the number of fractures will be evaluated and independently adjudicated in this study and in the totality of sotagliflozin Phase 3 studies, including in patients with various degrees of renal impairment.

This study will also include an evaluation of body composition by dual-energy X-ray absorptiometry (DXA) to assess the changes in total body fat mass and lean mass with sotagliflozin treatment. Clinically meaningful weight loss is observed with SGLT2 inhibitors (25) and a significant weight reduction is expected as a result of the dual SGLT1 and SGLT2 inhibition with sotagliflozin (26). Body composition study will enable to assess the differential changes in lean mass as compared to fat mass as part of the total weight reduction observed with sotagliflozin in this population. Reduction of BMD is reported following weight loss interventions and mechanical as well hormonal factors have been implicated (27, 28, 29). Adipose tissue is a source of multiple adipokines, inflammatory agents, and estrogen, all of them with different impact on bone mass. Decline in estradiol levels, which is observed in association with weight loss in women treated with canagliflozin in a 2-year study (20). Decrease in estradiol levels affects bone turnover and can represent an additional negative effect on bone mass. For this reason, changes in estradiol levels in women will also be evaluated during the study, which can be of additional interest for the understanding of any changes in bone density with sotagliflozin treatment. Selected markers of bone formation and resorption and other biochemical parameters of relevance to bone metabolism will also be evaluated in this trial.

4.5 RATIONALE FOR THE STUDY DESIGN AND CONTROL GROUP

A parallel-group, randomized, controlled design was selected because trial participants are exposed to a single treatment and assignment to that treatment is based solely on chance. This design is free of the limitations of competing designs such as crossover in which there may be a carryover effect from one treatment to the following treatment, which can confound interpretation of efficacy and safety, especially in regards to some longer term effects, such as bone mass.

Randomization will be stratified by HbA1c at Screening (≤8.5%, >8.5%) and sex (male, female) to enable a balanced treatment assignment considering factors that can impact the primary and key secondary safety study endpoint. 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. A 2-week Run-in Phase has been implemented to stabilize HbA1c and minimize response to placebo and effects inherent to participation in a controlled clinical trial.

Sotagliflozin treatment for 26 weeks is considered to be of sufficient duration to observe effects on reduction of HbA1c, blood pressure (BP), and BW, and is, therefore, selected as the time point for assessment of the primary endpoint HbA1c. The double-blind controlled extension up to 104 weeks will provide additional long-term data on efficacy and safety, including long-term assessment of bone safety with sotagliflozin treatment.

4.6 BENEFIT/RISK OF SOTAGLIFLOZIN

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 PPG 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 incretin levels (from inhibition of SGLT1). In addition, the improvements in BW, BP, and triglycerides observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

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. No imbalance was observed in the events of hypoglycemia in the sotagliflozin clinical program, and there have been no events of severe hypoglycemia or SAEs related to hypoglycemia in completed clinical trials. Serious adverse events and discontinuations due to AEs have been infrequent and balanced between treatment and comparator groups.

Based on evaluation of the cumulative safety data for the sotagliflozin clinical program, genital infections are monitored closely as an important identified risk. However, reports of these events have been infrequent and have responded to standard treatment. Diabetes ketoacidosis has been reported with treatment with other SGLT2 inhibitors and for this reason is identified as a potential risk. As of December 2016, two SAEs of DKA were reported in 2 patients with T1D and receiving sotagliflozin. Both SAEs were considered by the investigator to be due to insulin pump failure and unrelated to study treatment. Other potential risks are defined based on either their potential link to sotagliflozin mechanism of action, or because occurred during treatment with other SGLT2 inhibitor drugs. These potential risks have not been found to be in imbalance in sotagliflozin clinical trials, but will be also monitored in the study as events of special interest (EOSI), including urinary tract infections (UTI), diarrhea, pancreatitis, CV and renal events, drug-induced liver injuries (DILI), malignancies, volume depletion, and amputation. Evaluation of bone fractures will be of special relevance in this study as it includes a population of patients at increased risk for fractures.

Risks specific to this study are associated with the placebo-controlled design and long treatment duration. There is potential risk of insufficient glucose control, especially in the placebo arm during this 2-year study. Investigators will monitor regularly the glucose control at regular study visits by reviewing patients' fasting self-monitored blood glucose (SMBG) in conjunction with central laboratory alerts for FPG and HbA1c programed based on progressively stricter hyperglycemic thresholds. In case patients develop uncontrolled hyperglycemia during the study, Investigators will provide open-label antidiabetes rescue treatment and continue monitoring the patients as part of the study. Additionally, investigators can also provide rescue treatment at any time if medically indicated.

Patients may experience some discomfort associated with study procedures, such as blood draws, electrocardiogram (ECG), and fingersticks for SMBG. The Investigators will monitor for any possible occurrence of side effects related to these procedures.

During the study, the patients will perform DXA scans at four different occasions for monitoring of bone mass and changes in body composition. This diagnostic procedure is painless and carries very low risk of side effects. There is a small increase in radiation exposure with each DXA scan and the radiation exposure for the entire study is estimated to be around 56 µSv. This amount is equivalent to 9 days of average exposure to background radiation (30, 31). The procedures will be performed at qualified centers following standard procedures to ensure patient safety.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo with respect to HbA1c reduction at Week 26 in patients with T2D who have inadequate glycemic control on diet and exercise only or with a stable antidiabetes regimen.

5.2 SECONDARY

The secondary objectives of this study are:

- To compare the effects of sotagliflozin 400 mg and 200 mg versus placebo with respect to the percent change from Baseline to Week 26 in BMD (lumbar spine, total hip, and femoral neck) measured by DXA (key secondary safety objective).
- To demonstrate the superiority of sotagliflozin 400 mg versus placebo on:
  - Change from Baseline to Week 26 in BW.
  - Change from Baseline to Week 26 in FPG.
  - Change from Baseline to Week 12 in SBP for all patients.
  - Proportion of patients with HbA1c <7.0% at Week 26.
- To demonstrate the superiority of sotagliflozin 200 mg versus placebo with respect to:
  - HbA1c reduction from Baseline to Week 26.
  - Change from Baseline to Week 26 in BW.
  - Change from Baseline to Week 26 in FPG.
  - Change from Baseline to Week 12 in SBP for all patients.
  - Proportion of patients with HbA1c <7.0% at Week 26.
- To evaluate the safety of sotagliflozin 200 mg and 400 mg compared with placebo over the 104 weeks of treatment.

5.3 OTHER

Other objectives of this study are:

- To compare the effects of sotagliflozin 200 mg and 400 mg versus placebo with respect to:
  - Change from Baseline to Weeks 52 and 104 in HbA1c.
  - Change from Baseline to Weeks 52 and 104 in FPG.
  - Change from Baseline to Weeks 52 and 104 in BW.

- Proportion of patients with HbA1c <7.0% at Weeks 52 and 104.
- Proportion of patients starting rescue therapy during the 104 weeks of treatment.
- Change from Baseline to Weeks 26 and 104 in SBP for all patients.
- Change from Baseline to Weeks 12, 26, and 104 in SBP for the subsets of patients with Baseline SBP ≥130 mmHg and <130 mmHg, respectively.
- Change from Baseline to Weeks 12, 26, and 104 in DBP for all patients and the subsets of patients with Baseline DBP ≥80 mmHg and <80 mmHg, respectively.
- Changes from Baseline to Weeks 26, 52, and 104 in total body fat mass and total lean mass measured by DXA.
- Changes from Baseline to Weeks 26, 52, and 104 in serum estradiol (only for women).
- Changes from Baseline to Weeks 26, 52, and 104 in urinary albumin to creatinine ratio (UACR).
- Changes from Baseline to Weeks 26, 52, and 104 on estimated glomerular filtration rate (eGFR).

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a Phase 3, multicenter, 1:1:1 randomized, double-blind (single-blind Run-in Phase), placebo-controlled, parallel-group study that is anticipated to enroll approximately 360 patients.

The trial will consist of 4 periods:

- A Screening Period of up to 4 weeks comprised of:
  - A Screening Phase of up to 2 weeks.
  - A 2-week Single-blind placebo Run-in Phase.
- A 26-week Randomized Double-blind Core Treatment Period.
- A 78- week Randomized Double-blind Extension Period.
- A 2-week, post-treatment Follow-up Period.

To qualify for randomization, patients must demonstrate compliance based upon tablet count (≥80%) during the Run-in Phase.

The study design is presented graphically in Section 1.1.

6.1.1 Screening period

6.1.1.1 Screening Phase

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

Patients with T2D, who are 55 years of age or older, currently managed with diet and exercise only or with a stable antidiabetes regimen in monotherapy or combination therapy (including oral antidiabetes medications, insulin, or GLP-1 agonists) for more than 12 weeks prior to Screening are eligible for enrollment in this study.

At the Screening Visit (Visit 1), after signing the informed consent form (ICF), eligibility criteria will be assessed and Screening assessments will be performed.

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 Single-blind Run-in-Phase

Patients who satisfy the entry criteria during the Screening phase will continue in the study and enter the Run-in Phase. The single-blind placebo Run-in Phase will last 2 weeks. During this phase, patients will be treated in a single-blind manner with placebo, given as 2 placebo tablets (identical to sotagliflozin 200 mg in appearance), taken orally once daily before the first meal of the day starting from Visit 2, to assess patients' compliance to the study medication.

During the Run-in Phase, patients will receive a glucose meter and study diary and will be trained to perform blood glucose measurements and complete the study diary correctly. During this period, patients will also have an assessment of BMD and body composition by DXA.
In exceptional circumstances, the Run-in Phase may be extended up to a maximum of 14 additional days, if necessary to obtain appropriate BMD measurements prior to randomization.

6.1.2 Randomized Double-blind Core Treatment Period (Week 0 to Week 26)

Eligible patients will be randomized on Day 1 (Visit 3). To qualify for randomization, patients must demonstrate compliance with the single-blind treatment at the end of the Run-in phase, based upon tablet count (≥80%) and, as assessed, at the Investigator's discretion. Additionally, only patients with BMD T-score ≥-2.0 measured by DXA during the Run-in Phase will be allowed to be randomized.

Randomization will be stratified by:

- HbA1c at Screening (≤8.5%, >8.5%).
- Sex (male, female).

Approximately 360 patients will be randomized at a 1:1:1 ratio to the following 3 treatment groups:

- Sotagliflozin 400 mg arm (estimated N = 120): sotagliflozin 400 mg given as two (2) 200-mg tablets, taken orally once daily.
- Sotagliflozin 200 mg arm (estimated N = 120): sotagliflozin 200 mg given as one (1) 200-mg tablet and one (1) placebo tablet (identical to sotagliflozin 200 mg in appearance), taken orally once daily).
- Placebo arm (estimated N = 120): placebo given as two (2) placebo tablets, taken orally once daily.

Following randomization, patients will be treated in a double-blind manner for 104 weeks.
The first 26 weeks after the randomization correspond to the Randomized Double-blind Core Treatment Period. The doses of the background antidiabetic treatments (if applicable) should be held constant throughout the entire 104 weeks of Double-blind treatment (ie, not changed except for safety reasons or in case patient meets glycemic rescue criteria). The dose of all antihypertensive medications should also be held constant for the first 12 weeks (until Visit 6) except for safety reasons.

The HbA1c and FPG results will be masked to study sites and patients after randomization and until study end. Additionally, the central laboratory urinalysis by dipstick will not include measurement of urine glucose.

6.1.3 Double-blind, Randomized Extension Period (Week 27 to Week 104)

Patients who remain in the study after Week 26 will continue double-blind treatment from Week 27 to Week 104 in a 78-week Double-blind Extension Period. Patients will continue to receive the blinded medication (sotagliflozin 400 mg, sotagliflozin 200 mg or placebo) to which they were randomized on Day 1. Patients who received rescue medication during the 26-week Randomized Double-blind Core Treatment Period will continue on the same rescue medication during the Double-blind Extension Period (unless the Investigator considers a change necessary for safety reasons). The criteria for initiation of rescue therapy will be indicated in Section 8.2.2.

6.1.4 Follow-up period

Following the last dose of the investigational medicinal product (IMP) and after the End of Treatment (EOT) visit (either as scheduled or prematurely), a post-treatment Follow-up Visit should be scheduled for all patients 14 days ±3 days after permanent IMP discontinuation to collect safety information.

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 110 weeks and will include a 4-week Screening Period (comprised of a Screening Phase of up to 2 weeks and a 2-week single-blind placebo Run-in Phase), a 26-week Randomized Double-blind Core Treatment Period, a 78-week Randomized Double-blind Extension Period, and a 2-week post-treatment Follow-up Period.

6.2.2 Early termination

If a patient discontinues treatment with the IMP at any time during the Randomized Double-blind Core Treatment Period or during the Randomized Double-blind Extension Treatment Period, the patient will have a Premature 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 Week 26 Visit and Week 104 visit to perform the respective study assessments, emphasizing the measurement of HbA1c and BMD. If the patient does not agree to site visits, he or she will be contacted by respective sites by telephone to inquire about safety status.

6.2.3 Determination of end of clinical trial (all patients)

The end of the study is defined as being the “last patient last visit” planned with the protocol, including the 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 (see Section 6.4.2).

6.3 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned. See Section 11.5 for more details.

6.4 STUDY COMMITTEES

6.4.1 Steering Committee

The Steering Committee (SC) is composed of experts in diabetes and scientists with clinical and methodological expertise and will serve in an advisory capacity to the Sponsor on the study.

This committee, led by a Chair, will be 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 face-to-face meetings at regular intervals throughout the study and in regularly scheduled teleconferences.

Details of the activities and responsibilities of the SC are provided in a separate SC Charter.

6.4.2 Data Monitoring Committee

An independent DMC will meet on a regular basis to review accumulating clinical study safety data. The DMC will be responsible for:

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

Safety data to be reviewed will be unblinded and include events and outcomes described in Section 6.4.3 for adjudication, as well as any additional safety data considered relevant.

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.

Details of the DMC processes and procedures are outlined in a separate DMC Charter.

6.4.3 Clinical Endpoint Committee

An independent Clinical Endpoint Committee (CEC) will be 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 will review and adjudicate all events of death, major adverse cardiovascular events (MACE) and selected CV events (MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), selected renal events, and DKA in a treatment-blinded manner. The CEC will also independently adjudicate the events of bone fractures in a blinded manner.

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

6.4.4 Other independent safety assessments

An expert review committee will also review all potential cases of DILI in a treatment-blinded manner to evaluate causality.

Expert review of cases of amputation will also take place in a treatment blinded manner.

7 SELECTION OF PATIENTS

Note: A patient must 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. Patient with T2D currently managed with diet and exercise only or with a stable antidiabetes regimen in monotherapy or combination therapy (including oral antidiabetes medications, insulin, or GLP-1 agonists) for more than 12 weeks.

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 inclusion criteria in Section 7.1 will be screened for the following exclusion criteria.

7.2.1 Exclusion criteria related to study methodology

E 01. Age <55 years at Screening.

E 02. Body mass index (BMI) ≤20 or >45 kg/m² at Screening or BW that exceeds the weight limits of the DXA scanner.

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 Screening.

E 04. Use of weight loss medications within 12 weeks or weight change of 5 kg or more during the 12 weeks prior to 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. Patient who has previously been randomized in any clinical trial of sotagliflozin/LX4211.

E 07. Patients with severe anemia, severe CV disease (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.

E 09. Known presence of factors that interfere with the central laboratory 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 screening or randomization, whichever is longer.

7.2.2 Exclusion criteria related to the diabetes history and treatment

E 13. Type 1 diabetes.

E 14. Hemoglobin A1c <7.0% or >11.0% measured by the central laboratory at Screening (Visit 1).

E 15. Not on stable prior antidiabetes treatment in the last 12 weeks prior to the Screening Visit (for prior insulin treatment: change of total daily dose of basal insulin by more than 20% within 8 weeks prior to the Screening Visit).

E 16. Use of a selective SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) or thiazolidinedione (eg, pioglitazone, rosiglitazone) within 24 months prior to Screening.

E 17. History of DKA or nonketotic hyperosmolar coma within 12 weeks prior to Screening.

E 18. History of severe hypoglycemia resulting in unconsciousness, seizure, or hospitalization within 6 months prior to Screening.

7.2.3 Exclusion criteria related to bone health assessments

E 19. Women who have been postmenopausal (or had undergone bilateral oophorectomy) for less than 5 years. Estradiol and follicle-stimulating hormone (FSH) will be measured at Screening to confirm the menopausal status.

Note: A postmenopausal state is defined as no menses for >12 months without an alternative medical cause. The FSH level in the postmenopausal range (>40 IU/L) may be used to confirm a postmenopausal state in women not using hormonal replacement therapy. For hysterectomized women, determination of menopausal status will be based on history of vasomotor symptoms, or FSH >40 IU/L and estradiol levels on postmenopausal range (<20 pg/mL).

E 20. BMD T-score <-2.0 at any site (ie, lumbar spine, total hip, or femoral neck), measured by DXA during the Screening Period (determination of eligibility based on this test can be made until the time of randomization).

E 21. Serum 25-hydroxyvitamin D levels ≤20 ng/mL (≤50 nmol/L) at the Screening Visit by central laboratory (determination of eligibility based on this test can be made until the time of randomization).

E 22. Hypercalcemia based on total serum calcium level >10.5 mg/dL (2.63 mmol/L) at the Screening Visit by central laboratory.

E 23. Alkaline phosphatase levels >1.5 times the upper limit of the normal laboratory range (ULN) at the Screening Visit by central laboratory.

E 24. Conditions that can interfere with accurate measurement of BMD at the hip, femoral neck, and lumbar spine, including:

- Rheumatoid arthritis affecting the hip and lumbar vertebrae.
- Degenerative spine changes.
- Severe scoliosis.
- Anatomical changes that affect accurate BMD measurements.
- Spinal fusion or metal implants; or,
- Bilateral hip replacement or other surgery resulting in metal implants in both hips.

E 25. Bone disorders that may confound assessment of BMD or bone metabolism (eg, Paget disease, osteomalacia, osteopetrosis, and osteogenesis imperfecta).

E 26. Endocrine disorders that affect BMD and bone turnover (eg, hyperparathyroidism, uncontrolled hyperthyroidism, endogenous hypercortisolism).

E 27. Malabsorption diseases (eg, celiac disease, cystic fibrosis, or Crohn's disease).

E 28. History of fracture within 12 months prior to the Screening Visit (except for fractures of the hand/fingers, foot/toes, facial bones, and skull).

E 29. Treatment with medications known to affect bone mass or modify the risk of fractures within 36 months prior to Screening, including:

- Bisphosphonates, selective estrogen-receptor modulators, calcitonin, teriparatide, denosumab, strontium ranelate, growth hormone.
- Hormonal replacement that includes systemic or transdermal estrogen or testosterone (except if treatment is stable for at least 24 months prior to the Screening Visit).
- Androgen deprivation therapy.
- Aromatase inhibitors.
- Anticonvulsants (eg. carbamazepine, phenytoin, and phenobarbital).

7.2.4 Exclusion criteria related to the current knowledge of sotagliflozin

E 30. Mean of 3 separate BP measurements >180 mmHg (SBP) or >100 mmHg (DBP) at the Screening Visit.

E 31. History of hypertensive emergency within 12 weeks prior to Screening.

E 32. History of gastric surgery including history of gastric banding or surgery for inflammatory bowel disease within 3 years prior to Screening.

E 33. Difficulty swallowing such that the patient cannot take the IMP.

E 34. Known allergies, hypersensitivity, or intolerance to SGLT2 inhibitors or any inactive component of sotagliflozin or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicon dioxide, and magnesium stearate [nonbovine]), unless the reaction is deemed irrelevant to the study by the Investigator.

E 35. Renal disease as defined by eGFR <30 mL/min/1.73m^2 at the Screening Visit by the 4 variable Modification of Diet in Renal Disease (MDRD) equation.

E 36. Laboratory findings with the central laboratory tests at Visit 1:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the ULN.
- 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 37. 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).

7.2.5 Additional exclusion criteria during or at the end of the Run-in Phase before randomization

E 38. Patients unwilling or unable to perform SMBG and complete the patient diary, or comply with study visits and other study procedures as required per protocol.

E 39. Patient withdraws informed consent before randomization (patient who is not willing to continue) or fails to return.

E 40. Any clinically significant abnormality identified on physical examination, laboratory tests, 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 41. Patient insufficiently compliant during run-in phase based on tablet count (<80%) or in the opinion of the Investigator.

E 42. 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 PRODUCT(S)

8.1.1 Formulations

The IMPs are sotagliflozin (400 mg and 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). Treatment kits will be provided to the sites containing the appropriate number of IMP for the given Treatment Period, including visit windows. Each patient will be supplied with the appropriate number of kits, on a schedule according to the dispensing scheme indicated in the study flow chart (see Section 1.2).

Table 1 provides a summary of each IMP.

Table 1 - Summary of investigational medicinal products

Treatment group:	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Placebo (sotagliflozin-matching)
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 and sotagliflozin-matching placebo tablets.	Placebo will be supplied as sotagliflozin-matching placebo tablets.
Dose, timing, and route of administration	Two 200-mg sotagliflozin tablets taken orally once daily, before first meal of the day.	One 200-mg sotagliflozin tablet and one sotagliflozin-matching placebo tablet taken orally once daily, before first meal of the day.	Two sotagliflozin-matching placebo tablets taken orally once daily, before first meal of the day.
Duration of treatment	104 weeks following randomization.	104 weeks following randomization	106 weeks: 2 weeks during single-blind Run-in phase + 104 weeks following randomization.
Storage conditions	Store between +15°C and +30°C (59°F and 86°F)		

IMP = Investigational medicinal product

8.1.2 Starting dose and dose adjustment

All patients will receive treatment at a fixed dose of sotagliflozin (200 mg or 400 mg), or matching placebo as assigned at randomization throughout the 104-week study treatment period. No dose reductions are planned.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Background antidiabetes medications

Patients may be enrolled with or without a background therapy consisting of a stable antidiabetes regimen in monotherapy or combination therapy (including oral antidiabetes medications, insulin, or GLP-1 agonists) for more than 12 weeks.

Dose of background antidiabetes medication (if any) should be stable throughout the study, unless a change is required for safety reasons or if protocol defined hyperglycemia rescue criteria is satisfied. For patients on insulin therapy, the total daily dose of basal insulin should remain within 20% of the randomization dose, unless changes are needed for safety reasons or hyperglycemia rescue criteria are met.

8.2.2 Rescue therapy

The threshold values for rescue are defined as follows, depending on the study period:

- From Baseline visit (Visit 3, Day 1) to Visit 5 (Week 6), inclusive: FPG >270 mg/dL (15.0 mmol/L).
- From Visit 5 (Week 6) to Visit 6 (Week 12), inclusive: FPG >240 mg/dL (13.3 mmol/L).
- From Visit 6 (Week 12) up to Visit 8 (Week 26), inclusive: FPG >200 mg/dL (11.1 mmol/L) or HbA1c ≥8.5%.
  Note: The 8.5% criterion does not apply if the HbA1c decrease from Baseline was ≥1.0%.
- From Visit 8 (Week 26) up to Visit 10 (Week 52), inclusive: FPG >170 mg/dL (9.4 mmol/L) or HbA1c ≥8.0%.
  Note: The 8.0% criterion does not apply if the HbA1c decrease from Baseline was ≥1.0%.
- From Visit 10 (Week 52) up to the EOT Visit 13 (Week 104): FPG >160 mg/dL (8.9 mmol/L) or HbA1c ≥7.5%.

Routine fasting SMBG and central laboratory alerts on FPG (and HbA1c after 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 1 day, the patient will check it again during the 2 following days. If all the values in the 3 consecutive days exceed the specific limit, the patients should contact the Investigator and a central laboratory FPG measurement (and HbA1c after Week 12 and onwards) will be performed as soon as possible, preferably within 7 days to confirm the hyperglycemia.
- Upon receipt of a central laboratory rescue alert, a central laboratory re-test must be completed **and confirmed as exceeding the criteria** 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 values, 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 planned dose or matching placebo.
- 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.

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 hours fast).
- Initiate an evaluation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the electronic case report form (eCRF) and the medical record).
- Stress the absolute need to be compliant with treatment.
- 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 a FPG/HbA1c assessment at the next visit.

If none of the above mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, open-label rescue medication may be introduced.

- Rescue medication can be added up to the Investigator's decision except for SGLT2 inhibitors and thiazolidinediones.
- The patient continues the study treatment (blinded) and stays in the study to collect efficacy and safety information. The planned visits and assessments should occur until the last scheduled visit.
- Rescue therapy is considered a (NIMP). Rescue therapy is to be reported in the eCRF. This information should include specific drug name, dose, route of administration, and frequency.
- The Investigators can provide rescue at any time if there is a medical rationale.

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

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

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

During the double-blind Treatment Periods, 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 will generate the patient randomization list from which is allocates treatment groups to the patients.

To prevent partial unblinding, results of laboratory assessments of 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 randomization code must 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 must 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.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

Patients will be randomized to receive either sotagliflozin 400 mg, sotagliflozin 200 mg, or matching placebo once daily during the randomized double-blind Treatment Periods. Randomization (ratio 1:1:1) will be stratified by HbA1c at Screening (≤8.5%, >8.5%) and sex (male, female).

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. At Visit 3 (Baseline), patient eligibility will be reviewed and baseline assessments completed; then the IRT will be contacted for randomization and allocation of corresponding treatment packages.

After Visit 3 (Baseline), the IRT is contacted again each time new treatment package(s) allocation is required by the protocol. For each randomized patient, the IRT will allocate treatment package number(s) corresponding to the treatment group assigned.

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

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

A patient may not be randomized in this study more than once. In case 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 rescreened patient in the IRT, assigned a new patient number (first Screening Visit is to be registered as a screen failure in the IRT), and complete the Screening Visit procedures and assessments again.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Packaging is 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 8.1). Storage conditions and use-by-end date are part of the label text.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

Control of IMP storage conditions, especially control of temperature 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 labels. The IMP should be stored between +15°C and +30°C (59°F and 86°F).

8.7 RESPONSIBILITIES

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

All IMP 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 issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.4.7).

A potential defect in the quality of an IMP 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, to recall the IMP and eliminate potential hazards.

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

8.7.1 Treatment accountability and compliance

Accounting and compliance for IMPs will be performed at Visit 3 (Treatment Day 1) and all subsequent visits, except for the follow-up visit (Visit 14).

The Investigator will check the compliance to the IMP dose schedule based on the patient diary and will complete the appropriate site treatment and patient treatment log forms. Returned IMP should be counted by site staff. In addition, the dosing information will be recorded on the appropriate pages of the eCRF.

For NIMP, the name, start and end date of treatment, total daily dose, etc, will be documented in the source documents. Compliance to background therapy medication will be checked by interviewing the patient and reviewing the patient diary at each visit, and documented in the source documents and eCRF.

Rescue therapy (see Section 8.2.2) is to be reported in the eCRF. This information should include specific drug name, dose, route of administration, and frequency.

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

8.7.2 Return and/or destruction of treatments

Patients are to return all IMP (unused, in-use, or empty wallet[s]) at each on-site visit (or at final assessment visit in case of permanent premature discontinuation), as described in Section 1.2.

All used, partially-used, or unused IMPs will be retrieved by the Sponsor, CRO, or Delegate. A detailed site log and patient treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

For NIMP not provided by the Sponsor (ie, rescue therapy), 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 the IMP. 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 trial, beginning at Visit 1.

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

8.8.1 Prohibited prior and concomitant medications

During the study, the following medications are prohibited:

- Initiation of any antidiabetes agents, including oral or injectable antihyperglycemic agents other than the IMP is not allowed before the rescue therapy. The existing background medication (NIMP) should not be modified before the rescue.

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

- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin) and thiazolidinediones (eg. pioglitazone, rosiglitazone) are not allowed for rescue.
- Systemic use of glucocorticoids for more than 10 consecutive days within 90 days prior to the Screening Visit (**Note**: topical, intra-articular, ophthalmic, nasal spray, or inhaled applications are allowed).

- Use of investigational medication in any other clinical study.
- Initiation of any weight loss drugs (eg, phentermine, orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, liraglutide).
- Initiation of medication known to affect bone mass or modify the risk of fractures:
  - Bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, teriparatide, denosumab, strontium ranelate, growth hormone.
  - Androgen deprivation therapy.
  - Aromatase inhibitors.
  - Anticonvulsants (eg. carbamazepine, phenytoin and phenobarbital).
  - Hormone replacement therapy (systemic or transdermal) that includes estrogens or androgens.

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 Sponsor recommends that the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments. Other medications which are unlikely to interfere with the pharmacokinetics or pharmacodynamics of the IMP or confound interpretation of the study endpoints are allowed as needed following discussion between the Investigator and the Sponsor/CRO.

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.

It is recommended that patients receiving calcium or vitamin D at the time of screening, or initiating supplementation during the study, should maintain as stable a dose as possible throughout the study. Patients receiving replacement therapy with estrogen or testosterone for more than 24 months at the time of screening should also be advised to maintain stable dose for the duration of the study, unless if required for safety reasons. Any changes to ongoing medications or initiation of new medications should be discussed with the Investigator and documented in the patient records and the respective eCRF page.

8.9 POSTSTUDY TREATMENT

Because sotagliflozin may reduce BP, adjustment 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 and in accordance with local standard of care and prescribing practices.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINT

9.1.1 Primary endpoint

The primary efficacy endpoint is the change from Baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg versus placebo.

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

9.1.2 Secondary endpoints

9.1.2.1 Key secondary safety endpoint

The key secondary safety endpoint is the percent change from Baseline to Week 26 in BMD (lumbar spine, total hip, and femoral neck).

The methods of assessment of safety endpoints are detailed in Section 9.2.1.

9.1.2.2 Secondary efficacy endpoints

- Change from Baseline to Week 26 in HbA1c (sotagliflozin 200 mg only).
- Change from Baseline to Week 26 in BW.
- Change from Baseline to Week 26 in FPG.
- Change from Baseline to Week 12 in SBP for all patients.
- Proportion of patients with HbA1c <7.0% at Week 26.

9.1.3 Other efficacy endpoints

- Change from Baseline to Weeks 52 and 104 in HbA1c.
- Change from Baseline to Weeks 52 and 104 in FPG.
- Change from Baseline to Weeks 52 and 104 in BW.
- Proportion of patients with HbA1c <7.0 % at Weeks 52 and 104.
- Proportion of patients starting rescue therapy during the 104 weeks of treatment.
- Change from Baseline to Weeks 26 and 104 in SBP for all patients.
- Change from Baseline to Weeks 12, 26, and 104 in SBP for the subsets of patients with Baseline SBP <130 mmHg and ≥130 mmHg, respectively.
- Change from Baseline to Weeks 12, 26, and 104 in DBP for all patients and the subsets of patients with Baseline DBP ≥80 mmHg and <80 mmHg, respectively.

- Change from Baseline to Weeks 26, 52, and 104 in total body fat mass and total lean mass measured by DXA.
- Change from Baseline to Weeks 26, 52, and 104 in serum estradiol (only for women).
- Change from Baseline to Weeks 26, 52, and 104 in UACR.
- Change from Baseline to Weeks 26, 52, and 104 in eGFR.

9.1.4 Assessment methods of efficacy endpoints

9.1.4.1 Hemoglobin A1c

Hemoglobin A1c will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 12 (Visit 6), and Week 26 (Visit 8), Week 52 (Visit 10), Week 86 (Visit 12), and Week 104 (Visit 13) and measured by a certified Level I "National Glycohemoglobin Standardization Program" Central Laboratory.

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

9.1.4.2 Blood pressure

Systolic BP and DBP will be assessed at all on-site visits. Blood pressure measurements will be taken as described in Section 9.2.1.6 with full details and directions for the measurement of BP and heart rate (HR) in Appendix C.

9.1.4.3 Fasting plasma glucose

Fasting plasma glucose will be assessed at Baseline (Visit 3), Week 3 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6), Week 26 (Visit 8), Week 52 (Visit 10), Week 86 (Visit 12), and Week 104 (Visit 13). Fasting is defined as no food intake for ≥8 hours. The FPG assessment is performed on the morning of the visit. For the efficacy assessments of the study, FPG is measured at a central laboratory.

9.1.4.4 Body weight

Body weight is measured at every study visit. 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 and calcium metabolism parameters

Serum creatinine, 24-hour home-collected urine albumin, calcium (adjusted for creatinine), creatinine, phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and creatinine) will be assessed at Baseline (Visit 3), Week 26 (Visit 8), Week 52 (Visit 10), and Week 104 (Visit 13) (see Section 1.2). Serum creatinine will also be measured at Screening (Visit 1). Patients will be instructed to initiate the 24-hour urine collection on the day before the planned visits. In exceptional situations, the 24-hour urine collection can be done up to 2 days maximum prior or after the visit, and the specimen should be sent to the study site as soon as possible. Patients will be instructed to keep the 24-hour urine specimens at home in a cool place at room temperature, or refrigerated at 2°C to 4°C before they are sent to the site. The patient will be advised to refrain from heavy exercise or sex during the day of the collection. Specific details about specimen collection, storage, packaging, and shipping will be provided in the laboratory operational manual. A central laboratory will analyze samples and calculate the eGFR and UACR to allow assessment of change from baseline in eGFR and UACR. Details of urine collection and analysis are provided in Section 9.1.4.5.

9.1.4.6 Body composition measurements

Body composition assessments, ie, change in total body fat mass and total lean mass, will be assessed in all patients using DXA. Baseline DXA scans for body composition assessments will be performed during Run-in (between Week -2 [Visit 2] and Baseline [Visit 3]). To assess change from Baseline in body composition, post-Baseline DXA scans will be performed within 2 weeks prior to the on-site visits at Week 26 (Visit 8), Week 52 (Visit 10), and Week 104 (Visit 13). In exceptional situations, if justified based on Investigator's assessment, the DXA scan can be performed up to a maximum of 7 days after the scheduled visit. All scans will be archived onto digital media at the site and forwarded to the central image review facility within 24 hours of acquiring the scan. The site is also required to maintain a copy of the data. All DXA scans will be retained as source data. Details of DXA measurement and data analyses are included in a separate protocol for DXA imaging provided by the central image review facility.

9.1.4.7 Use of rescue medications for hyperglycemia

The use of rescue medications for hyperglycemia will be assessed and reported throughout the 104 weeks of double-blind treatment. 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 8.2.2.

9.2 SAFETY ENDPOINTS

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

Adjudication of all deaths, MACE and other selected CV events, selected renal events, bone fracture, and DKA will be performed in a blinded manner by a CEC. Further details are available in Section 6.4.3 and in the CEC Charter.

An expert committee will review all potential cases of DILIs in a treatment-blinded manner to evaluate causality.

The following safety endpoints will be assessed throughout the 104 weeks of double-blind treatment:

- Adverse events, hypoglycemia (all, severe, and/or documented symptomatic hypoglycemia), EOSI, adverse events of special interest (AESI), AEs leading to discontinuation of IMP, SAEs, and deaths.
- Percent change from Baseline to Weeks 26, 52 and 104 in BMD (lumbar spine, total hip, and femoral neck).
- Proportion of patients with adjudicated bone fractures over 104 weeks.
- Proportion of patients with ≥3% decline in BMD at Week 104.
- Changes from Baseline in bone turnover markers to Week 26, 52, and 104 (serum bone resorption markers: N-terminal telopeptide of Type 1 collagen [NTX] and β-CTX-1; serum bone formation markers: P1NP and osteocalcin).
- Changes from Baseline in markers of calcium metabolism to Week 26, 52, and 104 (serum: calcium, phosphorus, magnesium, parathyroid hormone [iPTH], 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D; urinary: calcium, phosphorus and magnesium).

Clinical laboratory results (see Section 9.2.1.4), vital signs results, and 12-lead ECG.

Observation period of safety endpoints

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

- The pretreatment period is defined as the time between the date of the informed consent and the first dose of double-blind IMP.
- The treatment-emergent 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 treatment-emergent period).

The Baseline value for safety endpoints in the safety population is the last available value prior to the first administration of the double-blind IMP.

9.2.1 Assessment methods of safety endpoints

9.2.1.1 Bone mineral density

Change in BMD at lumbar spine, total hip, and femoral neck will be assessed in all patients using DXA. Baseline DXA scans for BMD assessment will be performed during Run-in (between Week -2 [Visit 2] and Baseline [Visit 3]) and centrally reviewed to confirm eligibility. To assess percent change from Baseline in BMD, post-Baseline DXA scans will be performed within 2 weeks prior to the on-site visits at Week 26 (Visit 8), Week 52 (Visit 10), and Week 104 (Visit 13). In exceptional situations, if justified based on Investigator's assessment, the DXA scan can be performed up to a maximum of 7 days after the scheduled visit. All BMD assessments will be performed locally with central review. The DXA scanners will be calibrated and monitored using phantoms provided by the central image review facility. Detailed guidance on acceptable DXA scanners and scanning procedures will be provided by the central review facility to the DXA operating sites. Sites will forward scans to the central image review facility on an ongoing basis for quality control, data validation, and imaging review. All scans will be archived onto digital media at the site and forwarded to the central image review facility within 24 hours of acquiring the scan. The site is also required to maintain a copy of the data. All DXA scans will be retained as source data. Details of DXA measurement and data analyses will be included in a separate protocol for DXA imaging provided by the central image review facility.

9.2.1.2 Adverse events

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

9.2.1.2.1 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.

9.2.1.2.2 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 10.4.1.3 and Section 10.4.4, respectively.

9.2.1.3 Hypoglycemia

Hypoglycemia events (all, severe and/or documented symptomatic hypoglycemia) will be assessed starting with signing of the ICF until 2 weeks after the last dose of IMP (**Note:** for patients who discontinue treatment before Week 104, safety data will be collected until scheduled study end). Patients will also complete the patient diary, which will be regularly reviewed by Investigators. See Section 10.6.1 for further details.

9.2.1.4 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including clinical chemistry, hematology amylase lipase, fasting lipid profile, and additional evaluations) and urinalysis, according to the schedule presented in Section 1.2. Clinical laboratory values will be evaluated after conversion into standard international units. International units will be used in all listings and tables. Table 2 lists the blood analysis parameters to be assessed by the central laboratory. Urinalysis parameters are presented in Section 9.2.1.5.

Serum FSH and estradiol will be measured in women at Screening (Visit 1, Week -4) to confirm menopausal status as needed. A postmenopausal state is defined as no menses for >12 months without an alternative medical cause. An FSH level in the postmenopausal range (>40 IU/L) may be used to confirm a postmenopausal state in women not using hormonal replacement therapy. For hysterectomized women, determination of menopausal status will be based on history of vasomotor symptoms, or FSH >40 IU/L and estradiol levels on postmenopausal range (<20 pg/mL).

Table 2 - Blood safety parameters

Clinical chemistry	Hematology	Other parameters
Sodium	Complete blood count (CBC)	**Fasting lipid profile**
Potassium	Differential white blood count (WBC)	Total cholesterol (TC)
Chloride	Platelet count	High-density lipoprotein cholesterol (HDL-C)
Carbon dioxide (bicarbonate)	Hemoglobin	Low-density lipoprotein cholesterol (LDL-C)[b]
Blood urea nitrogen (BUN)	Hematocrit	Non–HDL-C[c]
Creatinine (for eGFR calculation[a])	Erythrocyte count	Triglycerides (TG)
Glucose (serum)		
Alanine aminotransferase (ALT)		**Other tests**
Aspartate aminotransferase (AST)		Amylase
Total bilirubin (TB)		Lipase
Alkaline phosphatase (ALP)		
Uric acid		**Markers of bone and calcium metabolism**
Phosphorus[d]		25-hydroxyvitamin D
Calcium[d]		1,25-dihydroxyvitamin D
Magnesium[d]		Parathyroid hormone (iPTH)
Total protein		Markers of bone resorption: NTX, β-CTX-1
Albumin		Marker of bone formation: P1NP, osteocalcin
Creatine phosphokinase (CPK)		
Lactic acid dehydrogenase (LDH)		

Clinical chemistry	Hematology	Other parameters

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CBC = complete blood count, CPK = creatine phosphokinase, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, IDMS = isotope dilution mass spectrometry, iPTH = parathyroid hormone, LDH = lactic acid dehydrogenase, LDL-C = low-density lipoprotein cholesterol, MDRD = Modification of Diet in Renal Disease, NTX = N-terminal telopeptide of Type 1 collagen, P1NP = Type 1 procollagen N-terminal propeptide, SI = Standardized International, TB = total blood, TC = total cholesterol, TG = triglycerides, US = United States, WBC = white blood count, β-CTX-1 = beta C-terminal telopeptide of Type 1 collagen.

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

a The eGFR will be calculated. The recommended equation for estimating eGFR from serum creatinine is the 4-variable MDRD (32) Study equation. The IDMS-traceable version of the MDRD Study equation will be used. Either equation below may be used based on whether the laboratory reports conventional units or SI units.

Conventional Units (for use predominantly in the US): http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-conventional-unit.asp.

SI Units (for use predominately outside the US): http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units.asp.

b LDL-C will be calculated by Friedwald equation.

c Non–HDL-C will be calculated as the difference between TC and HDL-C.

d Serum calcium, phosphorus, and magnesium are also part of the panel of markers of bone and calcium metabolism.

9.2.1.5 Urinalysis

Urinalysis (urine dipstick with microscopy) will be performed by central laboratory at Screening (Visit 1), Baseline (Visit 3), Week 26 (Visit 8), and Week 52 (Visit 10) and Week 104 (Visit 13). The central laboratory 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.

To prevent partial unblinding, the central laboratory urinalysis dipstick will not include the measurement of urine glucose.

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 cultures should be performed if at any point the Investigator suspects the presence of a UTI.

In addition, urine albumin, calcium, phosphorus, magnesium, and creatinine will be assessed by 24-hour urine collection at Baseline (Visit 3), Week 26 (Visit 8), Week 52 (Visit 10), and Week 104 (Visit 13). See Section 9.1.4.5 for information on 24-hour urine collection.

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).

9.2.1.6 Vital signs and physical examination

Vital signs, including sitting BP and HR, will be assessed at all study visits for safety and efficacy endpoints. Full details and directions for the measurement of BP and HR are presented in Appendix C. Physical examinations will be performed at every study visit.

A complete physical examination will be performed at Screening (Visit 1), Week 26 (Visit 8), and Week 104 (Visit 13). An abbreviated physical examination will be performed at all the other visits, including the Follow-up Visit/Week 106 (Visit 14). The abbreviated physical examination should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs, if necessary. The complete physical examination will also include recording of BW and vital signs. Body weight measurements are discussed in Section 9.1.4.4. Height will be measured only at Screening Visit, Week 52, Week 104, and Premature EOT Visit.

9.2.1.7 Electrocardiogram variables

Twelve-lead ECG recording will be performed locally at the Run-in Visit (Visit 2), and at Week 26 (Visit 8), and Visit 13 (Week 104).

The 12-lead ECG should be performed after the patient has spent at least 10 minutes in supine position and prior to IMP administration. The Investigator should review the ECG trace and document the interpretation, sign and date the ECG print out, and report the interpretation in the eCRF. Each subsequent ECG trace will be analyzed in comparison to the Run-in Phase (Visit 2) Screening ECG trace. All original ECG traces are retained as source data.

The ECG results will be evaluated as “normal” or “abnormal”.

Note: Any new ECG abnormality should be re-reviewed for confirmation and reported as appropriate for that finding.

9.2.1.8 Self-monitored blood glucose

A meter for the self-assessment of blood glucose will be dispensed at the Run-in Visit (Visit 2). Patients will receive a patient diary at each visit except for Screening Visit (Visit 1) and Follow-up Visit (Visit 14, Week 106). The patient will enter SMBG levels into this diary. The diary will be collected and reviewed at all visits starting from the Baseline Visit (Visit 3).

Patients will be requested to self-assess blood glucose levels in the fasted state and whenever they experience any illnesses (eg, cold, flu), or symptoms of hyperglycemia or hypoglycemia. Symptoms of hypoglycemia may include shakiness, dizziness, sweating, hunger, headache, pale skin color, sudden moodiness or behavior changes (such as crying for no apparent reason), clumsy or jerky movements, seizure, difficulty paying attention or confusion, or tingling sensations around the mouth. Patients will be instructed to record the presence or absence of hypoglycemic episodes or hypoglycemic symptoms in the patient diary provided.

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

Patients should be instructed to contact the site in case 3 consecutive fasting SMBG values are:

- >270 mg/dL (15.0 mmol/L) from Baseline visit (Visit 3, Day 1) to Visit 5 (Week 6), inclusive.
- >240 mg/dL (13.3 mmol/L) from Visit 5 (Week 6) to Visit 6 (Week 12), inclusive.
- >200 mg/dL (11.1 mmol/L) from Visit 6 (Week 12) up to Visit 8 (Week 26), inclusive.
- >170 mg/dL (9.4 mmol/L) from Visit 8 (Week 26) up to Visit 10 (Week 52), inclusive.
- >160 mg/dL (8.9 mmol/L) from Visit 10 (Week 52) up to the EOT Visit 13 (Week 104).

Patients will be recommended to self-assess fasting blood glucose levels at least once a week during the study.

9.3 OTHER ENDPOINTS

9.4 APPROPRIATENESS OF MEASUREMENTS

Sotagliflozin therapy in patients with T2D who have inadequate glycemic control with a stable antidiabetic therapy is expected to lower HbA1c over 26 weeks of treatment (primary efficacy analysis). Sotagliflozin treatment for 26 weeks is likely to be of sufficient duration to observe effects on reduction of HbA1c, and is, therefore, selected as the time point for assessment of the primary endpoint HbA1c. The length of the study is considered appropriate for detection of the primary endpoint given the power estimates. The double-blind controlled extension up to 104 weeks will provide additional long-term data on efficacy and safety, including long-term assessment of bone safety with sotagliflozin treatment.

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 known to reduce the risk of long-term microvascular complications. Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. The duration of study treatment (26 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.

Improvements in FPG have 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 efficacy of an antidiabetic agent.

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. Treatment with sotagliflozin is expected to result in weight loss based on the mechanism of action. Therefore, in this study, assessing change in BW from Baseline to Week 26 is a secondary endpoint.

Potential therapeutic effect of sotagliflozin on BP reduction will be assessed in all trial patients. To avoid confounding factors, modification of antihypertensive medications is not allowed during the first 12 weeks of the Treatment Period. The beneficial effect of sotagliflozin to patients with inadequately controlled hypertension (patients with Baseline SBP ≥130 mmHg or Baseline DBP ≥80 mmHg) will be assessed, but also the impact of sotagliflozin in the BP of normotensive patients (patients with Baseline SBP <130 mmHg or Baseline DBP <80 mmHg) will also be assessed. Given the mechanism of action of sotagliflozin on renal tubular absorption of glucose and sodium, it is appropriate to assess the impact on calcium metabolism. For this reason, specific biomarkers for calcium metabolism and bone turnover will be assessed at several time points.

Decreases in bone mass measured by BMD have been reported with canagliflozin treatment and assessment of BMD changes will be a key safety endpoint for this study. The assessment of impact of treatment on bone mass will be performed by evaluation of BMD T-scores initially after 26 weeks of treatment to enable early detection of a bone safety signal and followed out yearly after the beginning of treatment. This duration of follow-up is appropriate to detect longitudinal trends in changes in bone mass in this population that is vulnerable to development of age-related bone loss.

Alterations in calcium homeostasis have been noted in nonclinical studies with selective SGLT2 inhibitors. Changes in calcium and bone biomarkers were evaluated in diabetic patients in Study LX4211.202, and no clinically significant changes on these parameters were observed. However, as changes in bone biomarkers have been observed in clinical studies of other selective SGLT2 inhibitors, the Sponsor will continue to evaluate bone biomarkers and events of fractures in the sotagliflozin clinical program.

It is recognized that weight loss is associated with reduction in bone mass and also reduction of estradiol levels in postmenopausal women. This study will include assessment of body composition to allow evaluation of differential changes in total body fat mass versus lean mass during the treatment. The change in levels of estradiol in women will be also assessed as adipose tissue is a major source of estradiol in postmenopausal women and decrease in these levels can be implicated in changes in bone turnover.

The other efficacy and safety assessments in this study are standard and well-established measurements for a Phase 3 study evaluating the treatment of T2D in adult patients.

Safety analyses focusing on the TEAE include occurrences with SAE, AESI, EOSI, AE leading to IMP discontinuation, and hypoglycemic events. Other standard safety parameters such as vital signs, ECG and laboratory measurements will also be evaluated. 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 participants.

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 14 on-site visits. Additional on-site visits or telephone contacts can be scheduled at any time during the study whenever considered necessary by the Investigator.

The patients need to arrive at the study site in a fasting state for Visit 1, Visit 3, Visit 4, Visit 5, Visit 6, Visit 8, Visit 10, Visit 12, Visit 13, and Visit 14 unless instructed otherwise by the investigator. Throughout the study, “fasting” is defined as at least 8 hours without food (no food or liquid intake, other than 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. All laboratory assessments will occur prior to IMP and NIMP administration on the day of the visit.

The Run-in Visit (Visit 2) can be performed up to 2 weeks (± 3) days after the Screening Visit and once the results of all Screening tests are available and the patient is confirmed to be eligible for participation in the study. The visit windows for the Double-blind Treatment Period visits will be as follows: Visit 3 through Visit 8 should occur at the schedule ±3 days; Visit 9 through Visit 12 should occur at the schedule ±7 days. Visit 13 should occur at the schedule ±3 days and Follow-up Visit (Visit 14) should occur within 2 weeks after last dose of IMP ±3 days.

If one visit date is changed, the next visit should occur according to the original schedule, ie, calculated from the date of Baseline visit (Visit 3, Week 0).

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 study visits are reviewed by the Investigator and Sub-investigators who are qualified in treatment of T2D and are trained on the study.

10.1.1 Screening Period

The Screening Period is up to 4 weeks and includes a Screening phase and a Run-in phase.

10.1.1.1 Screening Phase

The Screening Phase will be up to 2 weeks in duration and includes Visit 1 (Week -4) only. The Screening Phase 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 -4) following signing of the ICF. Patients who meet the inclusion criteria as noted in Section 7.1 and meet no exclusion criteria as noted in Section 7.2 will be randomized at Visit 3 (Day 1).

The IRT will be contacted at Visit 1 for notification of 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 the Run-in Phase of this study. In these cases, a patient will need to sign a new ICF, be registered as a rescreened in IRT, and assigned a new patient number in IRT (first Screening Visit is to be registered as screen failure in IRT), and complete Screening Visit procedures and assessments again.

10.1.1.1.1 Screening Visit, Visit 1 (Week -4)

The following procedures/assessments will be performed at Visit 1 (Week -4):

- Obtain 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 signed by the patient and Investigator prior to any investigations.
  - [redacted]
- IRT notification (allocation of ID, registration of Screening).
- Assessment of inclusion/exclusion criteria.
- Collection of demographic data (age, gender, race, and ethnic origin).
- Assessment of the patient's medical and surgical history, including history, treatment and complications (eye, kidney, history of smoking/tobacco use, history of alcohol, and history of amputation events, etc) of T2D.
- Concomitant medication and medication history, including any prior medications for T2D.
- Measurement of BW and height.
- Complete physical examination including vital signs (SBP and DBP, HR, temperature, and respiratory rate) (see Appendix C for details).
- The following laboratory testing (by the central laboratory):
  - Serum 25-hydroxyvitamin D.

- HbA1c.
- Serum FSH and estradiol (for documentation of menopausal status).
- Clinical chemistry (including amylase, lipase) and hematology.

- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Urinalysis (dipstick and microscopy).
- Patients will be instructed to return to the site in the fasting state for Visit 3 (Week 0).

10.1.1.2 Run-in Phase

The Run-in Phase is 2 weeks in duration and includes Visit 2 (Week -2). As an exception, if justified according to the Investigator's assessment, the Run-in period can be extended up to a maximum of 14 additional days to complete all the eligibility assessments prior to the randomization.

10.1.1.2.1 Run-in Visit, Visit 2 (Week -2)

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

- Exclusion criteria are to be reviewed.
- Changes in concomitant medication are reviewed.
- Measurement of BW.
- Abbreviated physical examination.
  - The abbreviated physical examination should focus on cardiac and respiratory systems, (as well as any areas important for assessment of AEs, if necessary), and vital signs (SBP and DBP, and HR) (see Appendix C for details).
  - Diet and exercise instruction will be provided.
- Blood glucose meter is dispensed and instructions/training are provided.
- Patient diary is dispensed and instructions/training are provided.
- Instruction on glucose testing, basic genito-urinary (GU) hygiene and hydration, and recognizing DKA symptoms (see Appendix B) is provided.
- The IRT is notified for registration of Run-in Visit and allocation of single-blind Run-in kit.
- Run-in kit/placebo is dispensed.
- 12-lead ECG is conducted.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Patients are instructed to return to the site in the fasting state with used, partially used, or not used single-blind Run-in kit for Visit 3 (Randomization).

- Patients will be referred to DXA scan facility to perform DXA scan prior to Visit 3 (Randomization).
- Patients are provided with a urine container and instructed on how to collect 24-hour urine at home to be brought to the site at Visit 3 (Randomization).

10.1.2 Randomized Double-blind Core Treatment Period (Day 1 to Week 26)

Upon successful completion of the Run-in Phase, patients will be randomly allocated to either sotagliflozin 400 mg, sotagliflozin 200 mg, or sotagliflozin-matching placebo for the entire duration of the 104 weeks of Double-blind treatment. The first 26 weeks after the randomization correspond to the Core Treatment Period. All randomized patients will be followed at regular on-site visits for the duration of the treatment period.

In addition to routine laboratory testing, the following will be performed at specified time points: [redacted]; collection of home 24-hour urine for assessment of albumin, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine).

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 Investigator suspects the presence of a UTI.

10.1.2.1 Randomization (Baseline Day 1/Visit 3/Week 0)

The following procedures will be performed at this visit:

- Exclusion criteria are to be reviewed, including review of DXA results for eligibility, and assessment of compliance with single-blind IMP treatment during Run-in Phase.
- Concomitant medications are reviewed.
- Measurement of BW.
- Abbreviated physical examination and vital signs (see Appendix C).
- IRT to be notified and randomization to occur.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Diet and exercise instruction.
- Patient diary collected and reviewed and a new one is dispensed. Instructions/training are provided as needed.
- Instructions on glucose testing, basic GU hygiene, hydration, and DKA symptoms are provided.
- SMBG records will be reviewed.

- The following laboratory testing (by the central laboratory):
  - FPG.
  - HbA1c.
  - Clinical chemistry (including amylase, lipase) and fasting lipids.
  - Hematology.
  - Serum estradiol (only for women).
  - Bone turnover markers.
  - Markers of calcium metabolism.
  - Urinalysis (dipstick and microscopy).
  - Albumin, creatinine, calcium, phosphorus, and magnesium concentration in 24-hour urine.
- Collection of samples for additional laboratory testing:
  - [redacted]
- IRT will be notified IMP for resupply.
- Double-blind IMP is dispensed.
- Patients are instructed to return to the site in the fasting state for their next visit.
- For accountability and compliance purposes, patients are instructed to return to the site at the next visit bringing their used, partially used, or not used medication kit(s).

10.1.2.2 On-site visits from Visit 4 to Visit 7 (Week 3 to Week 18)

The following procedures will be performed at study visits from Week 3 to Week 18:

- Concomitant medications will be assessed.
- Measurement of BW.
- Abbreviated physical examination and vital signs (see Appendix C).
- IMP accountability and compliance with double-blind IMP treatment.
- IRT will be notified for IMP resupply.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) occurring since the previous visit will be reported.
- Patient diary will be collected and reviewed and a new one will be dispensed. Instructions/training will be provided as needed.
- SMBG records will be reviewed.
- Patients will be evaluated for glycemic rescue.

- Instructions on glucose testing, basic GU hygiene, hydration, and recognizing DKA symptoms will be provided (see Appendix B).
- Central laboratory testing:
  - FPG: Visit 4 (Week 3), Visit 5 (Week 6), and Visit 6 (Week 12).
  - HbA1c: Visit 6 (Week 12) only.
  - Clinical chemistry: Visit 4 (Week 3), Visit 5 (Week 6), and Visit 6 (Week 12).
  - Hematology: Visit 6 (Week 12) only.
  - Urinalysis (dipstick and microscopy): Visit 6 (Week 12) only.
  - [redacted]
- IMP is dispensed.
- Patients are instructed to return to the site in the fasting state for the next visit, except for Visit 7 (Week 18) when fasting is not required.
- For accountability and compliance purposes, patients are instructed to return to the site at the next visit bringing their used, partially used, or not used medication kit(s).
- At Visit 7 (Week 18) patients will be referred to DXA scan facility to perform DXA scan within 2 weeks prior to Visit 8 (Week 26).
- At Visit 7 (Week 18) patients will be provided with a urine container and instructed on how to collect 24-hour urine at home to be brought to the site at the next visit.

10.1.2.3 On-site Visit 8 (Week 26) - End of Randomized Double-blind Core Treatment Period

The following procedures will be performed at this visit:

- Concomitant medications will be reviewed.
- Measurement of BW.
- Complete physical examination and vital signs (see Appendix C).
- IMP accountability and compliance with double-blind IMP treatment.
- IRT will be notified for IMP resupply.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) occurring since the previous visit will be reported.
- Diet and exercise instruction will be provided.
- Patient diary will be collected and reviewed and a new one will be dispensed. Instructions/training will be provided as needed.
- SMBG records will be reviewed.
- Patients will be evaluated for glycemic rescue.

- Instructions on glucose testing, basic GU hygiene, hydration, and recognizing DKA symptoms will be provided (see Appendix B).
- 12-lead ECG.
- Central laboratory testing:
  - FPG.
  - HbA1c.
  - Clinical chemistry.
  - Hematology.
  - Fasting lipids.
  - Serum estradiol (only for women).
  - Bone turnover markers.
  - Markers of calcium metabolism.
  - Urinalysis (dipstick and microscopy).
  - Albumin, creatinine, calcium, phosphorus, and magnesium concentration in 24-hour urine.
- [redacted]
- Double-blind IMP is dispensed.
- Confirm with the central review facility that the DXA procedures for Visit 8 (Week 26) were performed successfully. In case the DXA scan needs to repeated, or has not been done yet, instruct the patients to perform the DXA scan within the next 7 days.
- For accountability and compliance purposes, patients are instructed to return to the site at the next visit bringing their used, partially used, or not used medication kit(s).

10.1.3 Double-blind, Randomized Extension Period (Week 27 to Week 104)

10.1.3.1 On-site visits from Visit 9 to Visit 12 (Week 27 to Week 86)

The following procedures will be performed at each Visit, except as specified:

- Concomitant medications will be assessed.
- Measurement of BW.
- Measurement of height only at Visit 10 (Week 52).
- Abbreviated physical examination and vital signs (see Appendix C).
- IMP accountability and compliance with double-blind IMP treatment.
- IRT will be notified for IMP resupply.

- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) occurring since the previous visit will be reported.
- Diet and exercise instruction will be provided, except at Visit 9 (Week 39).
- Patient diary will be collected and reviewed and a new one will be dispensed. Instructions/training will be provided as needed.
- SMBG records will be reviewed.
- Patients will be evaluated for glycemic rescue.
- Instructions on glucose testing, basic GU hygiene, hydration, and recognizing DKA symptoms will be provided.
- Central laboratory testing:
  - FPG: Visit 10 (Week 52) and Visit 12 (Week 86).
  - HbA1c: Visit 10 (Week 52) and Visit 12 (Week 86).
  - Clinical chemistry, including amylase and lipase: Visit 10 (Week 52) and Visit 12 (Week 86).
  - Hematology: Visit 10 (Week 52) and Visit 12 (Week 86).
  - Serum estradiol (only for women): Visit 10 (Week 52).
  - Bone turnover markers: Visit 10 (Week 52).
  - Markers of calcium metabolism: Visit 10 (Week 52).
  - Urinalysis (dipstick and microscopy): Visit 10 (Week 52) and Visit 12 (Week 86).
  - Albumin, creatinine, calcium, phosphorus, and magnesium concentration in 24-hour urine will be done at Visit 10 (Week 52).
- Double-blind IMP is dispensed.
- At Visit 10 (Week 52) confirm with the central review facility that the DXA procedures for Visit 8 were performed successfully. In case the DXA scan needs to repeated, or has not been done yet, instruct the patients to perform the DXA scan within the next 7 days.
- Patients are instructed to return to the site in the fasting state for the next visit, except for Visit 9 (Wek 39) and Visit 11 (Week 68) when fasting is not required.
- For accountability and compliance purposes, patients are instructed to return to the site at the next visit bringing their used, partially used, or not used medication kit(s).
- At Visit 9 (Week 39) and at Visit 12 (Week 86), patients will be referred to DXA scan facility to perform DXA scan within 2 weeks prior to the next visit.
- At Visit 9 (Week 39) and at Visit 12 (Week 86) patients will be provided with a urine container and instructed on how to collect 24-hour urine at home to be brought to the site at the next visit.

10.1.3.2 On-site Visit 13 (Week 104) - End of treatment (EOT)

The following procedures will be performed at this Visit:

- Concomitant medications will be reviewed.
- Measurement of BW and height.
- Complete physical examination will be done and vital signs (see Appendix C).
- IMP accountability and compliance with double-blind IMP treatment.
- IRT will be notified for end of treatment.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) occurring since the previous visit will be reported.
- Patient diary will be collected and reviewed and a new one will be dispensed.
- SMBG records will be reviewed.
- 12-lead ECG.
- Central laboratory testing:
  - FPG.
  - HbA1c.
  - Clinical chemistry, including amylase, lipase, and fasting lipids.
  - Hematology.
  - Serum estradiol (only for women).
  - Bone turnover markers.
  - Markers of calcium metabolism.
  - Urinalysis (dipstick and microscopy).
  - Albumin, creatinine, calcium, phosphorus, and magnesium concentration in 24-hour urine.
- Confirm with the central review facility that the DXA procedures for Visit 13 (Week 104) were performed successfully. In case the DXA scan needs to repeated, or has not been done yet, instruct the patients to perform the DXA scan within the next 7 days.
- Patients are instructed to return to the site in 2 weeks for the follow-up visit.
- Patients are instructed to return to the site in the fasting state for the next visit.

10.1.4 Post-treatment follow-up period

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

10.1.4.1 Follow-up Visit (Week 106/Visit 14)

The following procedures will be performed at this visit:

- Concomitant medications will be reviewed.
- Measurement of BW.
- Abbreviated physical examination including vital signs (see Appendix C).
- IRT to be notified of End of Study.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) since the previous visit will be reported.
- Collect glucose meter.
- Patient diary is collected and reviewed.
- The patient is instructed to schedule future follow-up with their health care provider.
- SMBG records will be reviewed.
- Central laboratory testing.
  - Hematology.
  - Clinical chemistry (including amylase and lipase).

10.2 DEFINITION OF SOURCE DATA

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.
  - 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 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.
- Patient's diary.

10.2.1 Source data verification requirements for screen failures

For screen failure patients, the following source data must be verified: patient's identification 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 temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible 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(s)

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

Since the IMP received is blinded, patients must return to the site and IRT will be contacted for IMP reinitiation.

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 9.2.1.8).

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

Temporary treatment discontinuation 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) will be recorded as concomitant medication with the name and dose recorded in the eCRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the patient to the IMP at any time during the study, or from the patient not to be re-exposed to the IMP whatever the reason.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. Patients should discuss stopping study medication with the site before doing so, to allow for questions to be addressed, glycemic therapy to be adjusted, and a follow-up assessment to be arranged. All efforts should be made to document the reason(s) 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 casual relationship of the concerned event and the IMP is possible (according to the Investigator's best medical judgment).
- BMD decrease of >7% from Baseline.
- Specific request of the Sponsor.

Any abnormal laboratory value or ECG parameter will be immediately rechecked to confirm the result before making a decision of permanent discontinuation of the IMP for the concerned patient.

For patients who prematurely discontinue the IMP, the assessments planned at EOT visit (Section 1.2) 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), and a Follow-up Visit 2 weeks (±3 days) after the last dose of IMP. In addition, every effort will be made to have the patient return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit and Week 104 Visit. If the patient does not agree to site visits, he or she will be contacted by telephone to inquire about safety status and collect AE data. The reason(s) for IMP discontinuation will be clearly specified. This Premature EOT assessment may occur at a regularly scheduled or at an unscheduled visit.

10.3.4 Handling of patients after permanent treatment discontinuation

Every effort should be made to maintain patients in the study. Patients will 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 10.1.3.2) should be scheduled prior to treatment discontinuation, if possible. If not possible, the Premature EOT Visit should be scheduled as soon as possible after the permanent treatment discontinuation and the patients will be assessed using the procedure normally planned for the last dosing day with the IMP. For patients that discontinue treatment but remain in the study, remaining study visits should occur as scheduled, as possible. The IRT should be notified of the EOT.

All cases of permanent treatment discontinuation must 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 Week 104 (EOT) visit.

The Investigators should discuss with them key visits to attend. 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.

Patients who withdraw from the study treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must 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 study withdrawals must 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.

In addition, a patient may withdraw his/her consent to stop participating in the study. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonpatient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must 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

A 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.
- Alanine aminotransferase >3 times the ULN + total bilirubin >2 times the ULN or asymptomatic ALT increase >10 times the 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 nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

The AESIs for this study are:

- Pregnancy of a female partner of a male patient entered in a study with IMP/NIMP:
  - Pregnancy occurring 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).
  - Follow-up of the pregnancy in female partner of a male patient 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.

Note: An asymptomatic overdose with the IMP/NIMP, accidental or intentional, is defined as 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 AE "Asymptomatic OVERDOSE, accidental or intentional".

- ALT increase >3 times the ULN (refer to related flowchart [Appendix D]).

10.4.1.4 Events of special Interest

An EOSI is a serious or nonserious 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 to characterize and understand them. These events should be reported on the specific eCRF page (where applicable) and will only qualify for expedited reporting when serious (fulfilling SAE criteria).

The EOSIs for this study are:

- MACE (CV death, MI, or stroke) and other specific CV events (eg, hospitalization for heart failure).
- Severe hypoglycemia (see Section 10.6.1).
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candida 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).
- TEAEs leading to 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).

- 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, 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.

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 after approval of the Investigator within the eCRF or after a standard delay.
- 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 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 AESIs, 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.

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 D.

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

- Neutropenia.
- Thrombocytopenia.
- ALT increase.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

10.4.7 Guidelines for reporting product complaints (IMP/NIMP)

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels, or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

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 (SUSAR), to the regulatory authorities, independent ethics committees (IECs)/institutional review boards (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 AESIs to those regulatory authorities who require such reporting:
  - Pregnancy in a male participant's female partner.
  - Symptomatic overdose.
  - ALT increase >3 times the 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

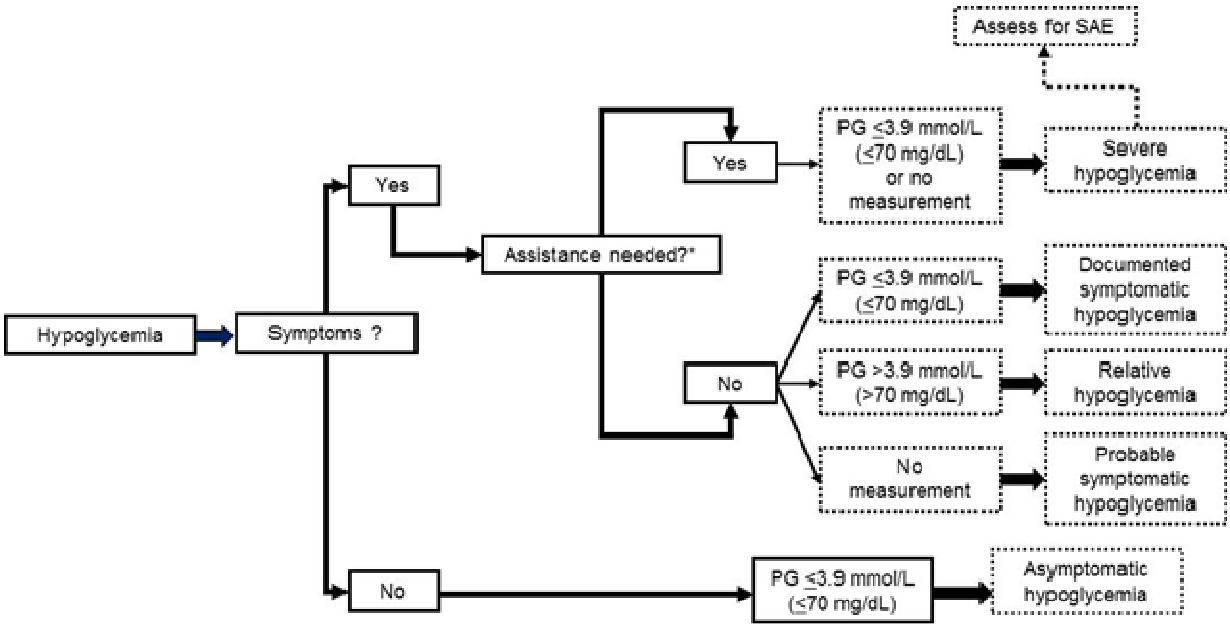
10.6.1 Hypoglycemia

During the study, patients will be instructed to document any hypoglycemic episodes 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 (33, 34) and summarized in Figure 1.

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

Figure 1 - Hypoglycemia classification in Study EFC15294



PG = plasma glucose; SAE = serious adverse event

Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, 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 ≤70 mg/dL (≤3.9 mmol/L).

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 ≤70 mg/dL (≤3.9 mmol/L).

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 ≤70 mg/dL [≤3.9 mmol/L]), 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 >70 mg/dL (>3.9 mmol/L).

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 variable of change from Baseline to Week 26 in HbA1c (%).

Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 360 patients (120 patients per arm) will have 97% power to detect a treatment difference of -0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

This sample size will also allow to exclude a decline in BMD from Baseline of >2% with a 95% power, assuming a missing rate of 30% and an SD of 3.5%.

The total sample size will be approximately 360 patients to be randomized (120 in sotagliflozin 200 mg group, 120 in sotagliflozin 400 group, and 120 in placebo group).

Calculations were made using East 6.4 software.

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 at randomization 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 11.3.1.1.
- The randomization strata (HbA1c at Screening [≤8.5%, >8.5%]) and sex (female, male). Any 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 26-week Double-blind Core Treatment Period.
- Patients who discontinued the IMP during the 26-week Double-blind Core Treatment Period, and the reasons for treatment discontinuation.
- Patients who have completed the 104-week Double-blind Treatment Period.
- Patients who discontinued the IMP during the 104-week entire 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 listing of patients prematurely discontinued from the treatment, along with reasons for discontinuation, will be provided. Similarly, a listing of patients prematurely discontinued from the study, along with reasons for discontinuation, will be provided.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be included in the safety population.

Patients randomized but not treated and patients randomized but not treated as randomized will be identified and described in separate listings.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy population

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

11.3.1.1 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.

11.3.2 Safety population

The safety analysis will be conducted on the safety population, defined as all randomized patients who did actually receive at least one dose of study treatment during the treatment period (regardless of the amount of treatment administered). Patients will be analyzed according to the treatment actually received.

In addition:

- Nonrandomized 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 and sotagliflozin 200 mg, 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 nonmissing 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 randomized and exposed or before randomization for patients who were randomized but never exposed to IMP.

Analysis of demographics and Baseline characteristics and prior and concomitant medications will be provided in detail in the Statistical Analysis Plan (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 within 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, minimum, and maximum). 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 and secondary endpoints at Week 26 (or Week 12 for SBP).

The superiority tests will be tested at two-sided 5% significance level.

All efficacy endpoints, other than primary and secondary efficacy endpoints, will only be summarized by descriptive statistics without formal statistical testing.

11.4.2.1 Analysis of primary efficacy endpoints

- Analysis of the primary efficacy endpoint (change from Baseline to Week 26 in HbA1c) will be performed on the ITT population, using HbA1c measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy (de facto estimand). The primary efficacy endpoint of change in HbA1c from Baseline to Week 26 will be analyzed with missing values imputed by control-based copy reference multiple imputation method under the missing not at random framework for the active treatment group. The imputation model parameters will be first derived under missing at random. Then the mean of the placebo group will be used in the imputation model for imputing values for missing data for patients in the placebo group and also the active treatment groups.
- 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 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 stratum of HbA1c (≤8.5%, >8.5%) at Screening, randomization stratum of sex (male, female) and country as fixed effects, and Baseline HbA1c value as a covariate.

Results from each complete dataset will be combined using Rubin's formula to provide the adjusted LS mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg vs placebo), with the corresponding standard error (SE) and the 95% confidence intervals (CI) for the difference.

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, 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 (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander).
- Ethnicity (Hispanic, Not Hispanic).
- Age group (<65 years, ≥65 years).
- Sex (male, female).
- Baseline BMI level (<30, ≥30 kg/m^2).
- Baseline HbA1c (≤8.5%, >8.5%).
- Baseline SBP (<130 mmHg, ≥130 mmHg).
- Country.

The treatment effects across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 26 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 (comparing sotagliflozin 400 mg versus placebo) with SE and 95% CIs will be provided as appropriate across the subgroups using contrast statements.

In the event that the subgroup factor is identical or similar to a randomization strata factor (eg, Baseline HbA1c category or sex), only the subgroup factor (as a single factor and/or an interaction term) will be included in the model to avoid the issue of collinearity in the analysis. The corresponding strata factor will not be included in the model.

11.4.2.2 Analysis of secondary efficacy endpoints

The continuous secondary efficacy endpoints (see Section 9.1.2) 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.

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 HbA1c (≤8.5%, >8.5%) at screening and sex (male, female), 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 LS mean change from Baseline to Week 26 (respectively, Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing each sotagliflozin group vs placebo group) with the corresponding (SE) and the 95% CI.

The categorical secondary endpoint such as HbA1c responders (<7.0%) at Week 26 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization stratum of Screening HbA1c (≤8.5%, >8.5%) and randomization stratum of sex (male, female).
The proportion in each treatment group will be provided, as well as the difference of proportions between each sotagliflozin group and placebo with associated 2-sided 95% CI.
For HbA1c responders at Week 26, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 26 will be treated as nonresponders.

For all secondary endpoints, summary statistics 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

The analysis of other efficacy 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

11.4.2.4 Multiplicity considerations

To control the family-wise Type I error, a fixed sequence testing approach will be used to test primary and secondary endpoints. Only if the difference in mean change from Baseline to Week 26 in HbA1c of sotagliflozin 400 mg versus placebo is statistically significant at $\alpha = 0.05$ (2-sided), a hierarchical testing procedure will be performed to test the secondary endpoints in the following prioritized order:

- Superiority of sotagliflozin 400 mg versus placebo with respect to:
  - Change from Baseline to Week 26 in BW.

  - Change from Baseline to Week 26 in FPG.
  - Change from Baseline to Week 12 in SBP for all patients.
- Superiority of sotagliflozin 200 mg versus placebo with respect to:
  - Change from Baseline to Week 26 in HbA1c.
  - Change from Baseline to Week 26 in BW.
  - Change from Baseline to Week 26 in FPG.
  - Change from Baseline to Week 12 in SBP for all patients.

Superiority tests will be tested at 2-sided 5% significant level. If any of the endpoints is found to be not statistically significant, the testing procedure will be stopped and the following endpoints will not be tested. Multiplicity adjustment will not be performed on other secondary endpoints not mentioned above.

11.4.3 Analysis of safety endpoints

No formal statistical tests will be performed on safety endpoints analysis.

Safety endpoints are presented in Section 9.2. These analyses will be based on the Safety Population as defined in Section 11.3.2. Patients will be analyzed for safety analyses according to the treatment actually received. All safety analyses will be performed on the safety population using the following common rules:

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

- Potentially clinically significant abnormality (PCSA) values for clinical laboratory tests and vital signs will be 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 TEAE Period, taking into account all evaluations performed during the TEAE Period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment-emergent PCSA percentage.

The "observation periods" defined in Section 9.2 are applicable for classification of AEs and determination of PCSA values on the TEAE period.

11.4.3.1 Analysis of the key and other safety endpoints for BMD

Analysis of percent change from Baseline in BMD to Week 26, Week 52, and Week 104 will be performed on the safety population, using BMD measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. No statistical significance tests will be performed.

Analysis of the key secondary safety endpoint of percent change from Baseline to Week 26 in BMD will be performed using an ANCOVA model. To compare sotagliflozin 400 mg and 200 mg versus placebo, the model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of HbA1c (≤8.5%, >8.5%), sex (male, female), and country as fixed effects, and Baseline BMD value as a covariate, providing the adjusted LS mean percent change from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing each sotagliflozin group vs placebo group) and the 95% CI for the difference.

The last-observation-carried-forward (LOCF) approach will be applied for the missing data imputation of the key safety endpoint of percent change in BMD from Baseline to Week 26. As the Week 26 Visit is the first post-Baseline scheduled visit for BMD measurement, if a patient withdraws early from the study before Week 26, the BMD measurement collected at the withdrawal visit will be used carrying forward to Week 26 in analysis.

The percent change from Baseline to Week 52 (or Week 104) in BMD will be analyzed using a mixed-effect model with repeated measures (MMRM). The MMRM model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of HbA1c (≤8.5%, >8.5%), sex (male, female), visit, treatment-by-visit interaction, and country as fixed effects, and Baseline BMD value-by-visit interaction as covariate, providing the adjusted LS mean percent change from Baseline to Week 52 (or Week 104) for each treatment group, as well as the between-group difference (comparing each sotagliflozin group vs placebo group) and the 95% CI for the difference.

Descriptive analyses will be performed on safety endpoints of BMD change to summarize the treatment effects across subgroups defined by the following Baseline or Screening factors:

- Age group (<65 years, ≥65 years).
- Duration of T2D (<10 years, ≥10 years).
- Sex (male, female).
- Baseline BMI level (<25; 25 to <35; ≥35 kg/m^2).
- Baseline eGFR (<45; 45 to <60; ≥60 mL/min/1.73 m^2).

Summary statistics (observed values, observed percent change from Baseline) 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), mean changes from baseline (±SE), and mean percent change from baseline at each of the scheduled visits (using OC).

Sensitivity analyses might be performed to assess the impact of missing data if needed.

11.4.3.2 Analysis of adverse events

Pretreatment AEs are AEs that developed or worsened or became serious during the pretreatment period.

Treatment-emergent AEs are AEs that developed or worsened (according to the Investigator's opinion) or became serious during the TEAE 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 number (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 number (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 (n) and percentage (%) of patients who died by study period (on-study, TEAE period, poststudy) summarized on the safety population by treatment received.
- Death in nonrandomized 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 (n) and percentage (%) 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 (n) and percentage (%) of patients in each treatment group.

11.4.3.3 Analyses of hypoglycemia

The number (n) and percentage (%) of patients and rate in patient-years (2 types: the number of patients with events or the total number of events per 100 patient-years) of all hypoglycemia, severe hypoglycemia, 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.

11.4.3.4 Analyses of events of special interest

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

11.4.3.5 Analyses of laboratory variables

The number (n) and percentage (%) of patients with PCSA or by the predefined categories (if no PCSA criterion is defined) at any evaluation during the TEAE 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 TEAE 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 on-treatment 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 out of laboratory range values and PCSA values.

The liver function tests, namely ALT, AST, alkaline phosphatase (ALP), and total bilirubin, are used to assess possible DILI 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 (n) and percentage (%) of patients with PCSA at any evaluation during the TEAE 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 TEAE period. Descriptive statistics will be used to summarize the results and the changes from Baseline by visit on-treatment 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 Analysis of 12-lead electrocardiogram status

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

11.4.3.8 Analyses of body composition measurements

Change from Baseline in total body fat mass and total lean mass measured by DXA will be analyzed on the safety population using descriptive statistics 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), mean changes from baseline (±SE) and mean percent change from baseline at each of the scheduled visits (using OC).

[redacted]

[redacted]

11.5 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned since analysis of primary and key secondary endpoints will be considered final at the time of first step analyses described below. The study analyses will be conducted in 2 steps:

- First step: Efficacy analyses up to Week 26, and interim safety analyses.

The first step analyses will be conducted when all patients have been randomized and have all their data, at the minimum up to Week 26 (Visit 8), collected and validated. The first step analyses will include:

- Efficacy analyses up to Week 26, which are considered as the final analyses for primary and secondary endpoints.
- Safety analysis of the key secondary safety endpoint of BMD at Week 26.
- Interim safety analyses which will be performed on all safety data collected and validated at the time of the first step analyses.

The first step analyses will not be used to change the conduct of the ongoing study in any aspect. Since the primary efficacy and secondary analyses would have been concluded at the time of the first step analyses, the significance level for the study remains at 0.05 (see Section 11.4.2.4). The first step analyses will be included in the submission dossier to health authorities.

- Second step: Final analyses.

The second step analyses will be conducted at the end of the study. The second step analyses will include the final analyses of efficacy endpoints at Week 52 and Week 104 and safety endpoints, which will be descriptive only.

Individuals who are involved in the unblinding of the first step analysis will not be involved in the conduct of the study afterwards.

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, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP), and 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.

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc), the method should be specified following the ICH requirements. The first part of the section should be adapted, keeping the point as appropriate.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

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), 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(s).

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 INVESTIGATOR

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 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 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 preidentified 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 ELECTRONIC CASE REPORT FORMS (eCRFS) 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 are 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 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 trial master file.

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 CRFs, 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 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 African American population for FDA, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on Chinese population for the China Food and Drug Administration).

[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.

14.6 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.

14.7 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 or 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, with the understanding 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 Collection of pregnancy information

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants 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. The female 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, the 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.

Appendix B Recommendations on basic genito-urinary hygiene, maintaining hydration and recognizing diabetic ketoacidosis

Patients with Type 2 diabetes are at risk for developing genito-urinary (GU) infections.
The following guidelines should be communicated to females and uncircumcised males regarding genito-urinary 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. 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 Type 2 diabetes:

"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 gastrointestinal adverse events occurring with sotagliflozin may mask presenting symptoms of diabetic ketoacidosis (DKA). Patient communication cards will be printed with the following:

"If you have any of these symptoms on the list, 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 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 adverse event data are collected or the patient reports DKA or intercurrent illness (including infections), generalized weakness, increased weight loss, gastrointestinal symptoms including nausea, vomiting, or abdominal pain or other symptoms or signs that the Investigator believes may be consistent with DKA, then the site will determine if an assessment for DKA is appropriate. If laboratory testing confirms presence of metabolic acidosis, then the "Possible DKA" electronic case report form will be completed.

Appendix C Measurement of blood pressure and pulse rate

Equipment

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

Patient factors

Extraneous variables associated with the measurement of 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 arm. The proper sized cuff should fit snugly with the lower edge 2 to 3 cm above the antecubital fossa.
5. The patient should be allowed to sit quietly in a comfortably warm place (temperature around 25°C or 77°F) for 5 minutes with the arm supported at heart level, preferably with the cuff in place and with no restrictive clothing on the arm. The patient should be encouraged not to tense his or her muscles.

Determination of the reference arm

At Visit 1 (Week -4), seated BP should be measured in both arms after a 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 the BP should always be measured in this same arm throughout the study period.

Measurement technique

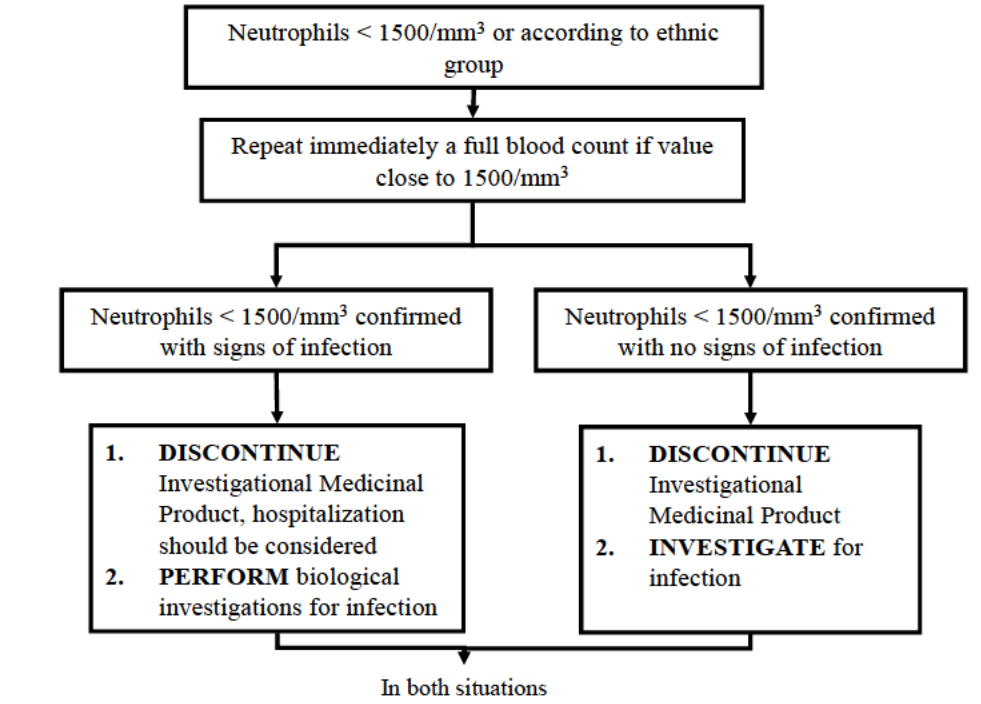
Following the 5-minute rest period, 3 separate seated BPs should be measured with at least 1 minute between BP measurements and with the cuff fully deflated between measurements.

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

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

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

NEUTROPENIA

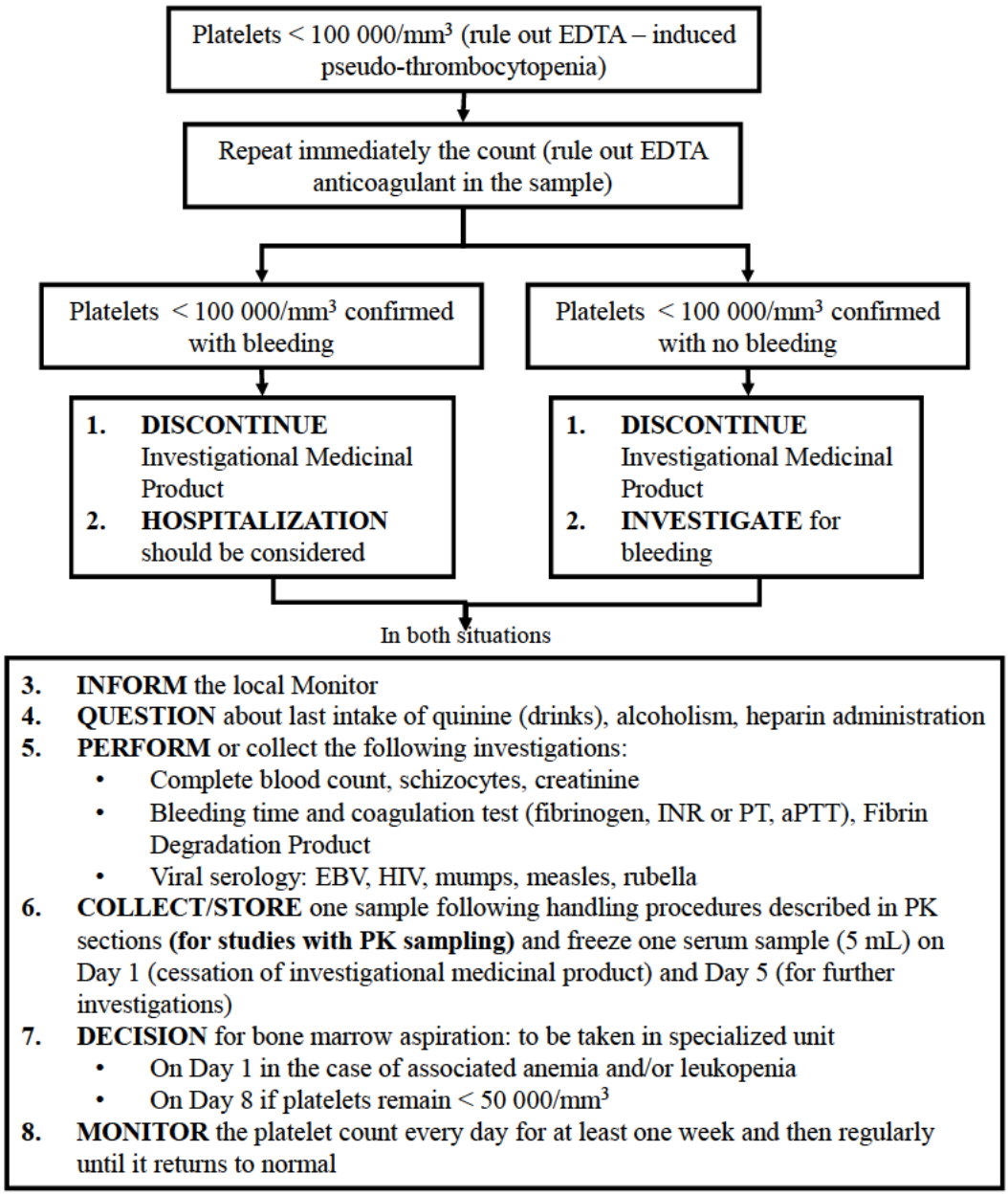


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **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)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

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

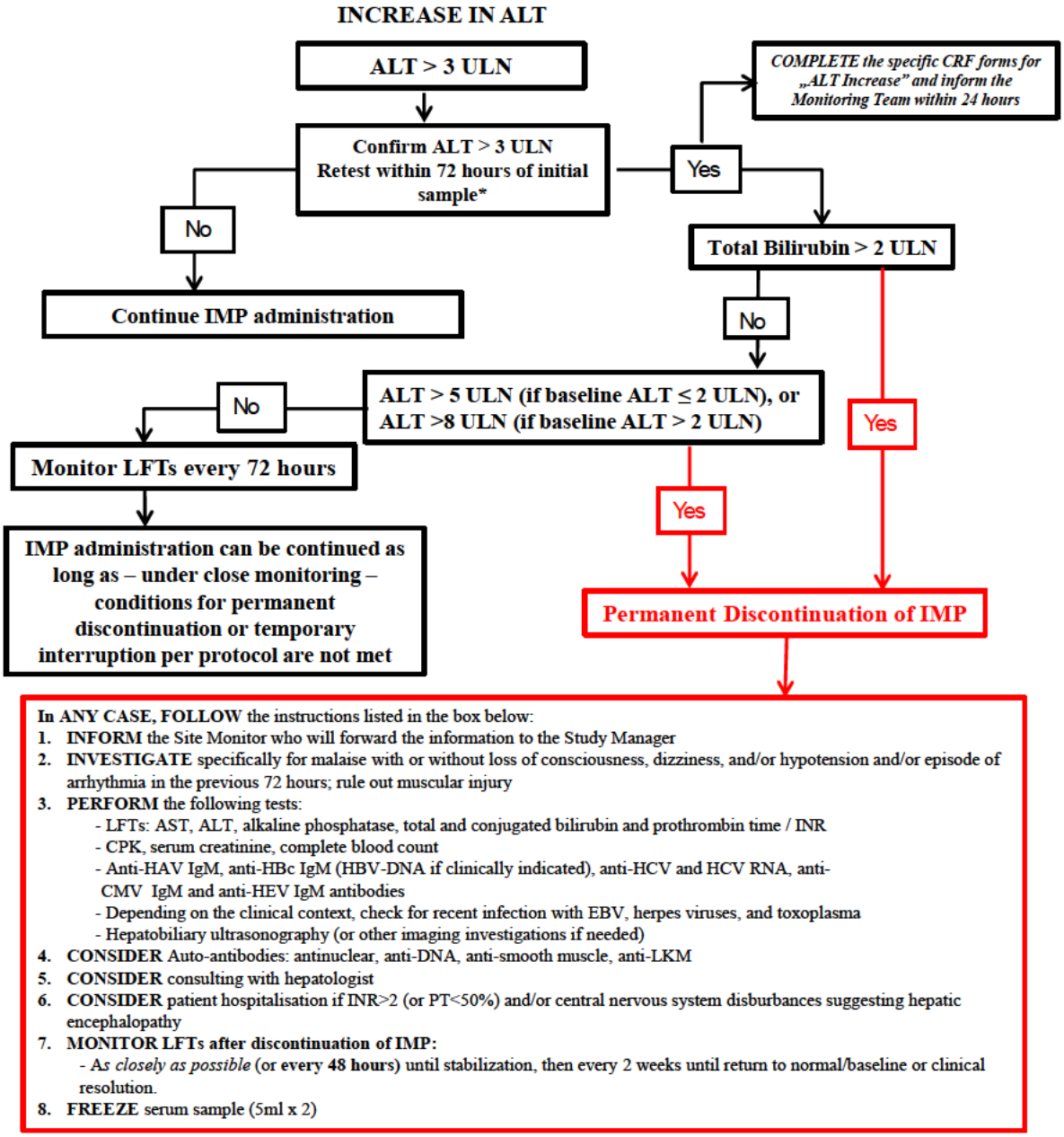
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

THROMBOCYTOPENIA



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.

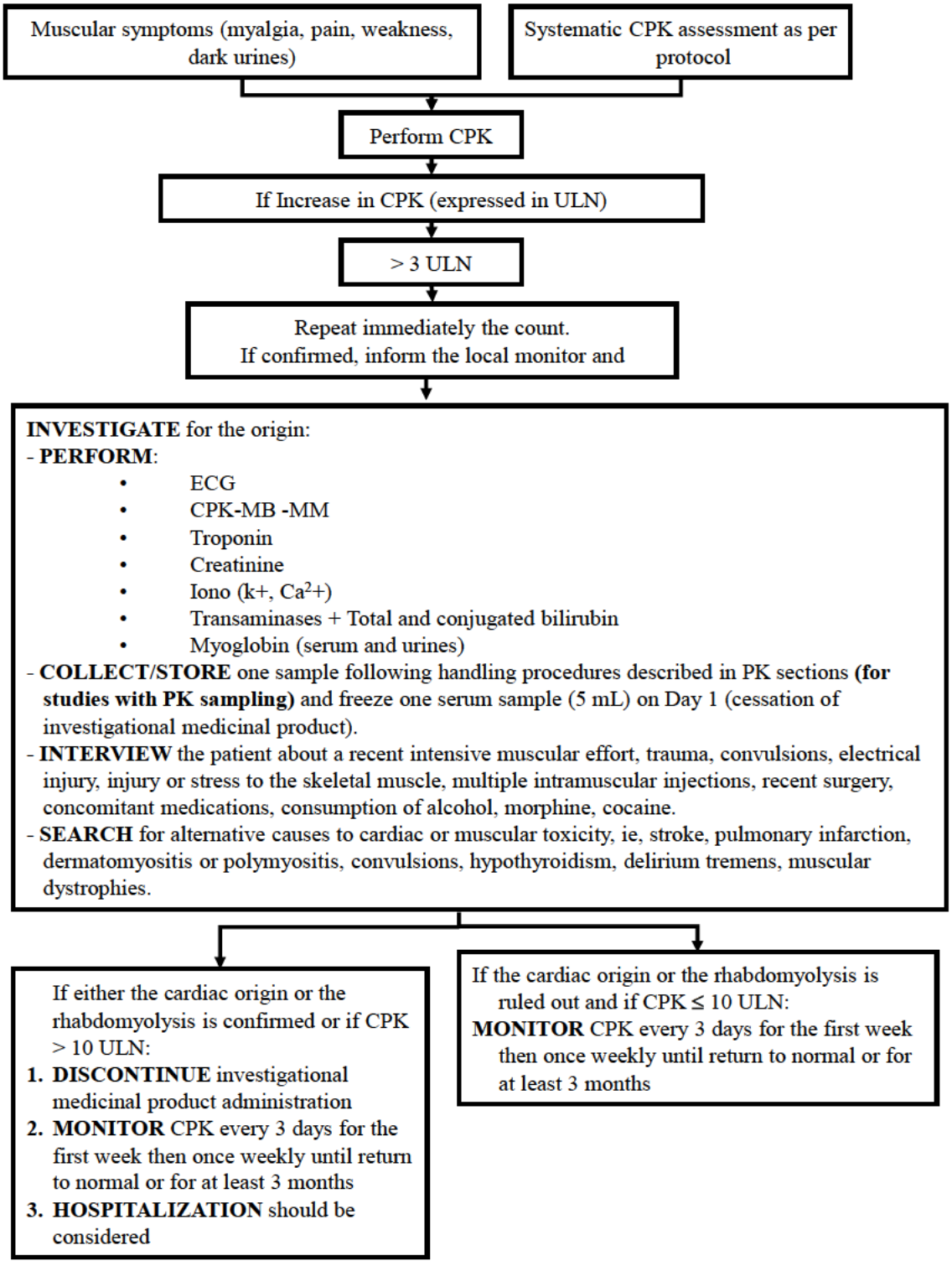


Baseline" refers to ALT sampled at Baseline visit; or if baseline value unavailable, to the latest ALT sample before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.
- "Baseline" refers to ALT sampled at Baseline visit; or if baseline value unavailable, to the latest ALT sample before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- If unable to re-test in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Increase in serum creatinine 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.

INCREASE IN CPK SUSPECTED TO BE OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in creatine phosphokinase (CPK) 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.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	10-Nov-2017 17:35 GMT+0100
[redacted]	Clinical Approval	13-Nov-2017 01:34 GMT+0100
[redacted]	Regulatory Approval	14-Nov-2017 17:35 GMT+0100