Official Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin Added to a Sulfonylurea alone or in combination with Metformin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on a Sulfonylurea Alone or with Metformin

NCT Number: NCT03066830

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AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: sotagliflozin/SAR439954

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin Added to a Sulfonylurea alone or in combination with Metformin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on a Sulfonylurea Alone or with Metformin

STUDY NUMBER: EFC14835

STUDY NAME: SOTA-SU (SOTAgliflozin added to SUlfonylurea)

VERSION DATE / STATUS: Approval date (20-Dec-2017) / Approved

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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.: EFC14835**
TITLE	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin Added to a Sulfonylurea alone or in combination with Metformin in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on a Sulfonylurea Alone or with Metformin
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objective:** The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo on hemoglobin A1c (HbA1c) reduction at Week 26 in patients with type 2 diabetes (T2D) who have inadequate glycemic control with a sulfonylurea alone or in combination with metformin. **Secondary objectives:** • To compare sotagliflozin 400 mg versus placebo for: - Change from Baseline in fasting plasma glucose (FPG) at Week 26 - Change from Baseline in body weight at Week 26 - Change from Baseline in systolic blood pressure (SBP) at Week 12 for patients with Baseline SBP ≥130 mmHg - Change from Baseline in SBP at Week 12 for all patients - Proportion of patients with HbA1c <6.5%, <7.0% at Week 26 • To evaluate the safety of sotagliflozin 400 mg versus placebo throughout the 79-week trial **Other:** • To compare sotagliflozin versus placebo based on other blood pressure (BP) endpoints • To compare sotagliflozin versus placebo with respect to change from Baseline in the following endpoints: - Estimated glomerular filtration rate (eGFR) - Reduction in body weight by ≥2%, ≥5%, and ≥10% • To compare sotagliflozin versus placebo for: - Change from Baseline in HbA1c at Week 79 - Change from Baseline in FPG at Week 79 - Change from Baseline in body weight at Week 79 • To compare the use of rescue medications for hyperglycemia in the sotagliflozin and placebo treatment groups • To assess plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite

STUDY DESIGN	This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Patients taking a sulfonylurea (≥half the maximum recommended dose as per local label or maximum tolerated dose [documented]) as monotherapy or in combination with metformin (≥1500 mg per day or maximum tolerated dose [documented]) each at a stable dose for at least 12 weeks before enrollment will be eligible for Screening. The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients. All patients will have a Screening Period comprised of an up to 2-week Screening phase and a 2-week, single-blind placebo Run-in phase prior to randomization. In order 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%) • Metformin use at Screening (Yes, No) • SBP at Screening (<130 mmHg, ≥130 mmHg) Following randomization, patients will have a 26-week, double-blind Core Treatment Period, a 53-week double-blind Extension Period, and a 2-week post-treatment Follow-up Visit. Patients will be randomly assigned 1:1 to 1 of the following 2 treatment groups: • Sotagliflozin 400 mg as two (2) 200 mg tablets, once daily • Placebo as two (2) placebo tablets (identical to sotagliflozin in appearance), once daily 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 investigational medicinal product (IMP) early during the double-blind Core Treatment Period or the 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 all patients return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit and Week 79 Visit emphasizing the collection of primary and main secondary endpoints. If a patient does not agree to site visits, he/she will be contacted by telephone to inquire about their safety status, particularly at the time of the initially scheduled Week 79 Visit. The study design is presented graphically at the end of the synopsis.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with T2D taking a sulfonylurea (≥half the maximum recommended dose as per local label or maximum tolerated dose [documented]) as monotherapy or in combination with metformin (≥1500 mg per day or maximum tolerated dose [documented]) each at a stable dose for at least 12 weeks without a dose adjustment before Screening **Note:** The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients. • Signed written informed consent **Major exclusion criteria:** • At the time of Screening age <18 years or < legal age of majority, whichever is greater • Type 1 diabetes mellitus • Body Mass Index (BMI) ≤20 or >45 kg/m^2 at Screening • HbA1c <7% or HbA1c >10% via central laboratory test at Screening • FPG >15 mmol/L (>270 mg/dL) measured by the central laboratory at Screening (Visit 1) and confirmed (>15 mmol/L [>270 mg/dL]) by a repeat test before randomization • Women of childbearing potential with no effective contraceptive method (see Appendix A) • Treated with an antidiabetic pharmacological regimen other than a sulfonylurea at a stable dose with or without metformin within 12 weeks preceding the Screening Visit • Previous insulin use >1 month (at any time, aside from treatment of gestational diabetes) • History of gastric surgery including history of gastric banding or inflammatory bowel disease within 3 years before the Screening Visit • History of diabetic ketoacidosis or nonketotic hyperosmolar coma within 12 weeks prior to the Screening Visit • History of severe hypoglycemia within 6 months prior to the Screening Visit • Mean blood pressure after 3 separate measurements >180 mmHg (SBP) or >100 mmHg (diastolic blood pressure [DBP]) • Patients with severe anemia, severe cardiovascular (including congestive heart failure New York Heart Association [NYHA] IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy making 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 ULN (except in case of Gilbert's syndrome) • Use of systemic glucocorticoids (excluding topical or ophthalmic application or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit

	• Patient who has taken other investigational drugs or prohibited therapy for this study within 3 months or 5 half-lives, whichever is longer, prior to Screening or randomization • Pregnancy, breastfeeding • Patient is unwilling to perform self-monitoring of blood glucose (SMBG), and complete the patient diary as required per protocol • Patient with contraindication to sulfonylurea as per local labeling • Patient with contraindication to metformin as per local labeling if the patient uses sulfonylurea in combination with metformin
Total expected number of patients	500 randomized patients.
STUDY TREATMENTS **Investigational medicinal products** **Noninvestigational medicinal products**	• Sotagliflozin 400 mg as two (2) 200 mg tablets, once daily, before the first meal of the day • Placebo as two (2) placebo tablets (identical to sotagliflozin 200 mg tablets in appearance), once daily, before the first meal of the day • Sulfonylurea tablets administered as per Principal Investigator • Metformin tablets, administered as per Principal Investigator • The doses of sulfonylurea and metformin should be maintained stable throughout the study unless down-titration is required for safety reasons • Rescue therapy (see Rescue therapy section, below)
	Rescue therapy The threshold values are defined as follows, depending on study period: • FPG >270 mg/dL (15.0 mmol/L) from Randomization up through the scheduled Week 8 visit • FPG >240 mg/dL (13.3 mmol/L) after the Week 8 visit up through the scheduled Week 12 visit • FPG >200 mg/dL (11.1 mmol/L) after the Week 12 visit through the end of the 26-week Core Treatment Period • FPG >170 mg/dL (9.4 mmol/L) or HbA1c ≥8.0% after the Week 26 Visit through the end of the treatment period (Week 79) Routine fasting SMBG and central laboratory alerts on FPG (and HbA1c at Week 26 and onward) are set up to ensure that glycemic parameter results remain under predefined thresholds. • If one fasting SMBG value exceeds the specific glycemic limit on one day, the patient checks it again during the two following days. If all the values in three consecutive days exceed the specific limit, the patient should contact the Investigator and a central laboratory FPG measurement (and HbA1c at Week 26 and onward) 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 threshold 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 exceeds the threshold, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that: • The increased FPG has been tested at a fasting status (ie, no food intake for ≥8 hours) • Investigational medicinal product is given at the planned dose • 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 the 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 e-CRF 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 to reinforce the absolute need to be compliant with 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, rescue medication may be introduced. Open-label rescue medication(s) to treat hyperglycemia will be at the discretion of the Investigator and in accordance with local standard of care and prescribing practice. Except for sodium-glucose co-transporter Type 2 (SGLT2) inhibitors, and additional metformin and sulfonylurea, any approved medication(s) including oral antidiabetic drugs, glucagon-like peptide 1 receptor agonists, or insulin can be prescribed to treat the hyperglycemia. Metformin will also be permitted for patients on sulfonylurea only at Screening. The patient continues the study treatment (blinded) and stays in the study in order to collect efficacy and safety information. The planned visits and assessments should occur until the last scheduled visit. For patients with renal impairment, contraindications to antihyperglycemic drugs should be taken into consideration.
ENDPOINTS	**Primary endpoint:** Change from Baseline to Week 26 in HbA1c **Secondary efficacy endpoints:** • Change from Baseline to Week 26 in FPG • Change from Baseline to Week 26 in body weight • Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg • Change from Baseline to Week 12 in SBP for all patients • Proportion of patients with HbA1c <6.5%, <7.0% at Week 26

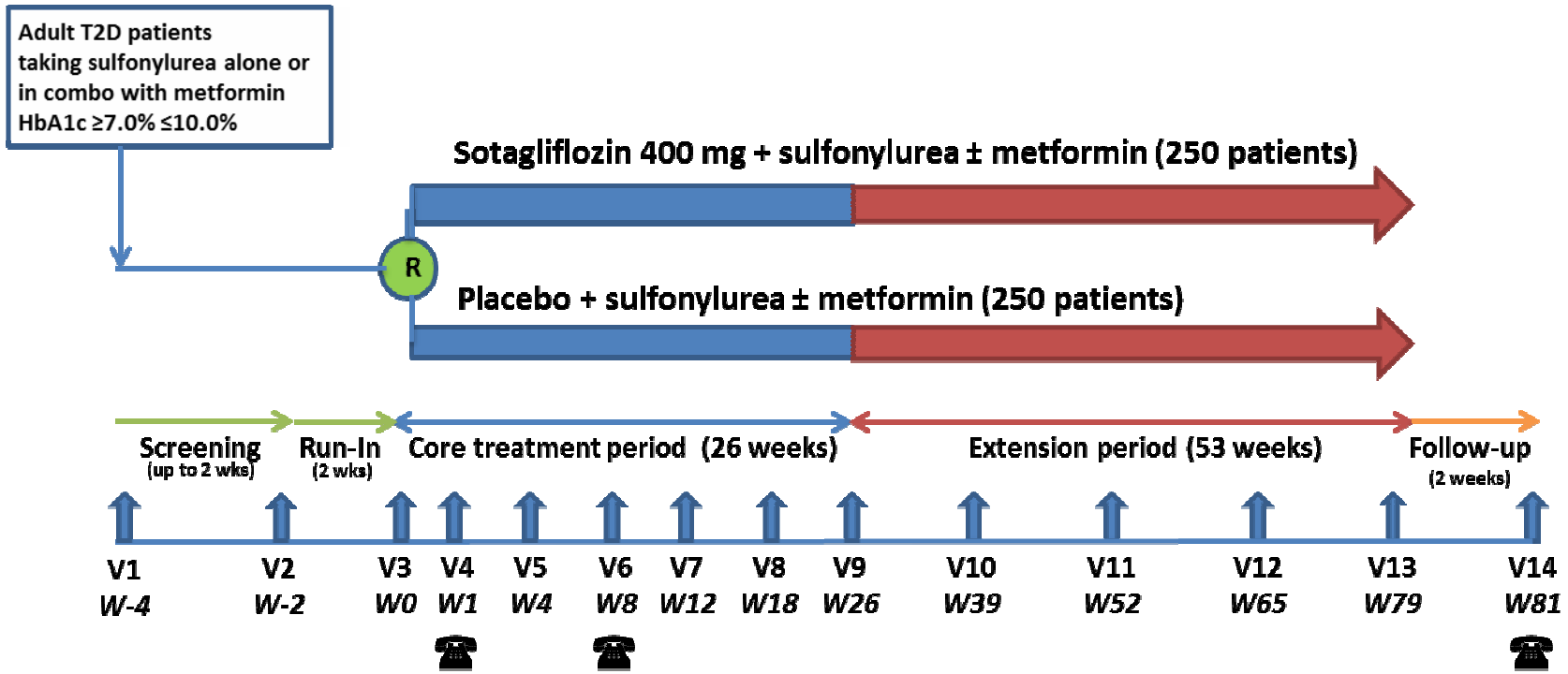
	Other efficacy endpoints: • Change from Baseline to Week 12 in SBP for patients with Baseline SBP <130 mmHg • Proportion of patients with reduction in body weight by ≥2%, ≥5%, and ≥10% from Baseline • Change from Baseline to Week 12 in DBP • Proportion of patients achieving SBP <130 mmHg for those with Baseline SBP ≥130 mmHg • Proportion of patients achieving DBP <80 mmHg for those with Baseline DBP ≥80 mmHg • Proportion of patients requiring rescue for hyperglycemia. • Change from Baseline in: - Serum creatinine - eGFR • Change from Baseline to Week 79 in HbA1c • Change from Baseline to Week 79 in FPG • Change from Baseline to Week 26 in SBP for all patients and for patients with Baseline SBP ≥130 mmHg • Change from Baseline to Week 79 in SBP for all patients and for patients with Baseline SBP ≥130 mmHg • Change from Baseline to Week 79 in body weight **Safety endpoints:** • 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 • Clinical laboratory results, including fasting lipids, vital signs, and electrocardiogram (ECG) results **Pharmacokinetic endpoints:** • Plasma concentrations of sotagliflozin and its metabolite pre-dose at Weeks 4, 18, 26, 52, 79 and 1 hour 30 minutes post-dose at Week 26 and 79
ASSESSMENT SCHEDULE	See Study Flowchart, Section 1.2.
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size/power calculation is based on the primary variable, 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, 250 patients per arm will have at least 99% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo. The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients. **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.

	Primary analysis: 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. The primary efficacy endpoint of change in HbA1c from Baseline to Week 26 will be analyzed with missing values imputed by control-based multiple imputation method under the missing not at random framework. • For placebo patients, missing data will be imputed based on the placebo group data • For patients in the sotagliflozin group, 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 in the imputation model Each of the complete datasets will be analyzed by an Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP (<130, ≥130 mmHg), and country as fixed effects, and Baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing sotagliflozin versus placebo) and the 95% confidence interval (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, 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 efficacy endpoints:** The secondary 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 with treatment groups (sotagliflozin, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed effects, and Baseline secondary endpoint value as a covariate. For the analysis of SBP in patients with Baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included in the ANCOVA model. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing sotagliflozin versus placebo) and the 95% CI for the difference. The categorical secondary efficacy variables of HbA1c <6.5%, <7% at Week 26 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), and randomization stratum of SBP (<130, ≥130 mmHg).

	Analysis of other efficacy endpoints The analysis of other endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using observed cases will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time. **Analyses of safety data** All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. These analyses will be based on the Safety Population, which is defined as all randomized patients who receive at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Patients will be analyzed for safety analyses according to the treatment actually received. The safety analyses will be provided for the 26-week Core Treatment Period and for the entire treatment period.
DURATION OF STUDY PERIOD (per patient)	Up to 85 weeks, including a Screening Period consisting of a Screening phase of up to 2 weeks and a 2-week single-blind Run-in phase, a 26-week double blind Core Treatment Period, a 53 week double blind Extension Period, a 2-week post treatment Follow-up period to collect safety information.
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; R: randomization; T2D: type 2 diabetes; V: visit; W: week; ☎: telephone visit.

1.2 STUDY FLOW CHART

	Screening Period		Double-Blind Core Treatment Period[a]							Double-Blind Extension Period[b]				Follow-up
	Screening	Run-In												
VISIT	**1**	**2**	**3 Baseline**	**4** ☎	**5**	**6[c]** ☎	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14** ☎
Week	**-4**	**-2**	**0**	**1**	**4**	**8**	**12**	**18**	**26**	**39**	**52**	**65**	**79**	**81**
Day (window [days])		**-14 (±3)**	**1 (-)**	**7 (±3)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**455 (±7)**	**551 (-3 to +4)**	**565 (±3)**
Informed consent	X													
Inclusion criteria	X													
Exclusion criteria	X	X	X											
Demographics	X													
Medical/Surgical History	X													
Medication History	X													
Body weight, height[d]	X	X	X		X		X	X	X	X	X	X	X	
Vital signs[e]	X	X	X		X		X	X	X	X	X	X	X	
Physical Examination:														
Complete	X								X				X	
Abbreviated[f]		X	X		X		X	X		X	X	X		
Diet & exercise instruction		X	X						X		X		X	
Instruction on basic GU hygiene & hydration		X	X	X	X	X	X	X	X	X	X	X	X	
Interactive response technology (IRT) contact	X	X	X		X		X	X	X	X	X	X	X	X
Randomization			X											
Dispense glucose meter		X												

	Screening Period		Double-Blind Core Treatment Period[a]							Double-Blind Extension Period[b]				Follow-up
	Screening	Run-In												
VISIT	1	2	3 Baseline	4 ☎	5	6[c] ☎	7	8	9	10	11	12	13	14 ☎
Week	-4	-2	0	1	4	8	12	18	26	39	52	65	79	81
Day (window [days])		-14 (±3)	1 (-)	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	455 (±7)	551 (-3 to +4)	565 (±3)
Dispense diary	X	X	X		X		X	X	X	X	X	X		
Collect/review diary		X	X		X		X	X	X	X	X	X	X	
Instruction on diabetic ketoacidosis symptoms, glucose testing			X	X	X	X	X	X	X	X	X	X	X	
Dispense IMP		X	X		X		X	X	X	X	X	X		
IMP accounting & compliance			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[g]		X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X								X				X	
Laboratory testing[i]														
Hepatitis serology	X													
FPG	X		X		X		X	X	X	X	X	X	X	
HbA1c	X		X		X		X		X	X	X	X	X	
Clinical chemistry, hematology[j]	X		X				X		X	X	X	X	X	
Fasting lipids	X								X		X		X	
Pregnancy test (WOCBP)[k]	X		X		X		X	X	X	X	X	X	X	
FSH and/or estradiol as needed[k]	X													
Plasma concentration[l]					X			X	X		X		X	

	Screening Period		Double-Blind Core Treatment Period[a]							Double-Blind Extension Period[b]				Follow-up
	Screening	Run-In												
VISIT	1	2	3 Baseline	4 ☎	5	6[c] ☎	7	8	9	10	11	12	13	14 ☎
Week	-4	-2	0	1	4	8	12	18	26	39	52	65	79	81
Day (window [days])		-14 (±3)	1 (-)	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	455 (±7)	551 (-3 to +4)	565 (±3)
Urinalysis (dipstick and microscopy)[m]	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													
AEs/SAEs/AESIs/EOSIs	To be assessed and reported throughout the study[p]													

a If a patient discontinues treatment with investigational medicinal product (IMP) early during the 26-Week Core Treatment Period, the patient will have a Premature End-of-Treatment (EOT) Visit and a Follow-up Visit 2 weeks after the last dose of IMP. In addition, every effort will be made to have all patients return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit and Week 79 Visit. If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status. If a patient discontinues (or completes) treatment and study at the same time, a single visit will be performed using the procedure normally planned for the EOT visit.

b If a patient completes the Core Treatment, but discontinues IMP during the Extension Period, the patient will have a Premature EOT Visit, and a Follow-up Visit 2 weeks after the last dose of IMP. Every effort will be made to have all patients return to the site at the time corresponding to their quarterly visits (ie, every 13 weeks) during the Extension Period, particularly the Week 79 Visit. If the patient does not agree to a site visit, at the time corresponding to their Week 79 Visit, all attempts will be made to contact the patient to inquire about safety status. If a patient discontinues (or completes) treatment and study at the same time, a single visit will be performed using the procedure normally planned for the EOT visit.

c At Visits 4 (Week 1), 6 (Week 8) and 14 (2 weeks after the last dose of IMP) patients will be contacted by telephone, and not seen on-site.

d Height to be measured only at screening.

e Vital sign measurements (sitting BP and heart rate): 3 separate seated BP and heart rate measurements should be taken with at least 1 minute between readings, following a 5-minute rest period and prior to phlebotomy (see Section 9.2.1.4 and detailed instructions in Appendix C).

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

g See Section 9.2.1.6 for details of SMBG measurements. Glucose meters used for SMBG display results as plasma glucose concentration. Patients should measure their fasting plasma glucose at least 3 times per week (including on day of each on-site study visit). After Visit 9 (Week 26), if fasting SMBG values are <120 mg/dL, over a 2-week period, the Investigator can instruct patients to self-monitor blood glucose once a week (on day of on-site study visit for weeks with on-site study visits).

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

i All laboratory assessments occur prior to IMP administration on the day of the visit.

j Clinical chemistry, hematology: please see list in Table 2.

k Serum pregnancy testing only at screening; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to the Run-In phase for all women of childbearing potential (WOCBP) unless there is documented history of menopause (based on documented follicle-stimulating hormone [FSH] and estradiol levels – if results not documented then FSH and estradiol will be tested at Screening visit) or they are surgically sterile. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

l Pre-dose plasma concentration samples (ie, of sotagliflozin and sotagliflozin-3-O-glucuronide) should be drawn with the other laboratory assessments at Week 4, Week 18, Week, 26, Week 52, and Week 79. Post-dose plasma concentration samples should be drawn 1 hour 30 minutes after sotagliflozin administration at Week 26 and Week 79. The date and time of the last intake of study drug prior to visits where pharmacokinetic (PK) samples are taken should be recorded by the patient in the patient diary. Patients should be reminded of this at visits preceding PK time points to ensure these details are captured. In the case of premature IMP discontinuation, PK samples should not be drawn at the premature EOT visit, nor at any subsequent visits.

m Urinalysis performed by the central laboratory 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 suspicious of urinary tract infection, urine culture should be performed. Positive urine culture determination will be based upon the criteria of the reporting laboratory.

[redacted]

p All serious adverse events (SAEs), adverse events (AEs), AEs of special interest (AESIs), and Events of Special Interest (EOSIs) will be collected starting with signing informed consent and continue until the end of the study. All AEs that occur during treatment should be followed until study completion (or until patients leave the study) or until the event has resolved, the condition has stabilized, or the patient is lost to follow-up. All patients will have a follow-up visit 2 weeks after the last dose of IMP to collect safety information.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	Analysis of Covariance
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
CEC:	Clinical Endpoint Committee
CI:	confidence interval
CRF:	case report form
CRO:	contract research organization
CSR:	clinical study report
CV:	cardiovascular
DBP:	diastolic blood pressure
DILI:	drug-induced liver injury
DKA:	diabetic ketoacidosis
DMC:	Data Monitoring Committee
DRF:	discrepancy resolution form
ECG:	electrocardiogram
e-CRF:	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
GI:	gastrointestinal
GLP-1:	glucagon-like peptide-1
HbA1c:	hemoglobin A1c
HLGT:	high-level group term
HLT:	high level term
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council on Harmonisation
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology

ITT:	intention-to-treat
MACE:	major adverse cardiovascular events
MI:	myocardial infarction
NIMP:	noninvestigational medicinal product
OC:	observed cases
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
P-gp:	p-glycoprotein
PI:	principal investigator
PK:	pharmacokinetic
PPG:	postprandial glucose
PT:	preferred term
PYY:	peptide YY
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	Steering Committee
SD:	standard deviation
SE:	standard error
SGLT:	sodium-glucose co-transporter
SGLT1:	sodium-glucose contransporter type 1
SGLT2:	sodium-glucose cotransporter type 2
SMBG:	self-monitoring of blood glucose
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T1D:	type 1 diabetes mellitus
T2D:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
TG:	triglyceride
UGE:	urinary glucose excretion
ULN:	upper limit of the normal laboratory range
US:	United States
WOCBP:	women of child-bearing potential

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: SOTAGLIFLOZIN AND DISEASE

Sotagliflozin is a dual inhibitor of the sodium-glucose cotransporters type 1 and 2 (SGLT1 and SGLT2) being developed for use in type 2 diabetes (T2D), a metabolic disorder characterized by hyperglycemia that results from a combination of increased insulin resistance and beta cell dysfunction. The microvascular complications of diabetes are well known and can result in impaired renal function, retinopathy and neuropathy. Other comorbidities that are frequently associated with diabetes are hypertension, obesity, and cardiovascular (CV) disease. Recently, the Centers for Disease Control and Prevention released a report stating that if current trends continue, 1 in 3 Americans will have diabetes by the year 2050. According to the most recent International Diabetes Federation Diabetes Atlas, the estimates in 2015 were that 1 in 11 adults have diabetes, which means 415 million people; estimated to rise to 642 million by 2040 (1).

According to the World Health Organization, there are about 60 million people with diabetes in the European Region, or about 10.3% of men and 9.6% of women aged 25 years and over (2). While these numbers include both people with T2D and type 1 diabetes (T1D), over 90% of adults with diabetes have T2D. Diabetes is among the leading causes of death by disease and is a leading cause of heart disease, stroke, blindness, kidney disease, and amputation (1, 2). Despite the fact that the population of people with diabetes is growing, none of the current therapies is curative and the results of treatment are variable.

Although lifestyle changes, including diet, exercise, and education, are valuable components of diabetes treatment, the vast majority of people with T2D require pharmacological therapy to control the disease. In the United States (US) and Europe, metformin is the standard first-line therapy in the absence of any contraindications or tolerability issues, as per guidance from the American Diabetes Association (ADA; 3).

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

In patients with diabetes, it is desirable to maintain blood glucose in the normal range without exhausting the ability of the pancreatic beta-cells to produce insulin. Glucose is transported across the cell membrane by 2 different types of glucose transporters: glucose-facilitated transporters and SGLT proteins (4). In the kidney, after blood is filtered by the glomerulus, glucose passes into the urine, but 99% is reabsorbed, primarily via SGLT2, which is responsible for 90% of glucose reabsorption, while 10% is reabsorbed by SGLT1. When functional SGLT2 is lacking in humans, a significant amount of glucose remains in the urine and is removed from the body (5). This way of reducing blood glucose is not an insulin-dependent mechanism and therefore hyperglycemia may be reduced while the pancreas is spared from an increased demand for insulin production that

is caused by hyperglycemia. Since obesity is a significant comorbidity in T2D, and insulin resistance is increased in obesity, the caloric loss from glucose in the urine may represent an additional benefit resulting in decreased weight, which should result in decreased insulin resistance (5).

The SGLT1 is expressed predominantly in the gastrointestinal (GI) tract; SGLT1 is responsible for the majority of glucose absorption by the small intestine (6). Inhibition of SGLT1 in the GI tract prevents glucose from being absorbed. 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 (7), pharmacologic inhibition of SGLT1 by sotagliflozin has not produced these effects in preclinical models or patients with T2D. Selective inhibitors of the SGLT1 transporter are in early stages of development.

Extensive clinical studies conducted for selective SGLT2 inhibitors have established this class as effective agents for the treatment of T2D (3, 8) and have led to approvals by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Studies with sotagliflozin, a potent, dual inhibitor of SGLT2 and SGLT1, 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 subjects has resulted in dose-dependent increases in glucosuria. Multiple-dose (28-day) administration in patients with diabetes produced improvements in several metabolic parameters, including urinary glucose excretion (UGE), fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), GLP-1, and PYY. These data suggest that sotagliflozin should be of therapeutic benefit to patients with T2D.

4.2 CLINICAL TRIALS OF SOTAGLIFLOZIN IN HUMANS

Approximately 780 subjects (639 assigned to sotagliflozin and 141 assigned to placebo) have participated in completed clinical studies of sotagliflozin. No significant safety concerns have been identified in the sotagliflozin drug program, and sotagliflozin has been well-tolerated in all studies to date. Serious adverse events (SAEs) and discontinuations due to adverse events (AEs) have been infrequent and have been balanced between treatment and comparator groups. Reports of treatment-emergent adverse events (TEAE) 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, and dizziness, all of which were reported at a frequency greater than placebo. However, the majority were described as mild to moderate, and most resolved spontaneously.

In completed and ongoing clinical trials, no safety issues in addition to those already described in the current Investigator's Brochure (IB) were observed. In general, no significant imbalances of SAE/AEs between sotagliflozin and comparators were observed in completed studies. Cumulatively, during the clinical trial program 8 SAEs were reported by 6 patients (4 T2D and

2 T1D), all of which were assessed as unrelated to study drug; those reported by 4 T2D patients 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 by 2 T1D patients receiving 400 mg once daily sotagliflozin in the Phase 2 T1D study LX4211.1-203-TIDM; both SAEs were assessed as due to failure of insulin delivery via insulin pump.

Inhibition of SGLT2 and SGLT1 is expected to improve glycemic control, but may also potentially increase the risk of hypoglycemia when given with insulin or insulin secretagogues like sulfonylurea. Other medicines in the SGLT2 class have had a low incidence of hypoglycemia in general, but when used in combination with insulin or insulin secretagogues, an increase in hypoglycemia has been observed.

A drug interaction study with digoxin, a sensitive P-glycoprotein (P-gp) substrate, indicated that sotagliflozin acts as a weak P-gp inhibitor. Thus, sotagliflozin increases systemic exposure of digoxin and other substrates of P-gp (9).

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

The proposed sotagliflozin 400 mg once-daily dose is based on the results of the Phase 2b study LX4211.1-202-DM. In this study, sotagliflozin doses of 75 mg once daily, 200 mg once daily, 200 mg twice daily, and 400 mg once daily sotagliflozin were tested over a 12-week, double-blind period. The sotagliflozin 400 mg once daily dose was chosen for further evaluation based on its HbA1c lowering effect and the overall safety and tolerability observed at this dose. At 12 weeks, the sotagliflozin 400 mg dose lowered HbA1c by a mean of 0.93%, while placebo lowered HbA1c by a mean of 0.14%. Lower sotagliflozin doses were less effective than the 400 mg dose and did not have any advantages in safety or tolerability. The overall incidence of AEs on sotagliflozin 400 mg once daily was similar to that seen with placebo.

From a safety perspective, sotagliflozin was well-tolerated across studies. In healthy subjects sotagliflozin was well-tolerated following single doses up to 2000 mg, and in multiple doses up to 800 mg over 10 days. Furthermore, in a thorough QT study, single doses of sotagliflozin (800 mg and 2000 mg) were well tolerated and did not prolong the QT interval. Additionally, evaluation of metabolites in urine and plasma of healthy subjects resulted in no safety concerns following single doses of sotagliflozin 400 mg. In patients with T2D, single doses of sotagliflozin 400 mg in combination with sitagliptin, and multiple doses up to sotagliflozin 400 mg in combination with metformin over 12 weeks were also well-tolerated.

4.4 RATIONALE FOR STUDY DESIGN AND CONTROL GROUPS

This study is designed to demonstrate the efficacy and safety of sotagliflozin when used as add-on therapy to a sulfonylurea (alone or in combination with metformin) in patients with T2D who

have inadequate glycemic control. Sotagliflozin plus a sulfonylurea (alone or in combination with metformin) will be compared to placebo plus a sulfonylurea (alone or in combination with metformin). Based on the study design, the protocol stipulates that patients be provided antidiabetic agent rescue therapy according to a predefined algorithm. Safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of sotagliflozin are supported by Phase 1 and Phase 2 studies and animal toxicology data in rats up to 26 weeks and dogs up to 39 weeks as well as 2 year carcinogenicity data in rats.

To achieve balanced randomization for assessment of the primary endpoint, randomization will be stratified based on preexisting metabolic control (Screening HbA1c ≤8.5% versus >8.5%) as well as metformin use at Screening (Yes, No). Another stratification factor (systolic blood pressure [SBP] <130 mmHg versus ≥130 mmHg) has been added to ensure balance in randomization for a secondary endpoint (change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg).

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, the Sponsor, and the service provider to the treatment allocations, and by adjudicating the endpoints in a blinded fashion.

The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients.

A parallel-group, randomized placebo 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 of effect from one treatment to the second treatment. Although this carryover effect can be minimized with a washout period, it is possible that some longer term effects may persist. While the sample size of the parallel group design is larger to account for more variability when participants cannot serve as their own control, the above mentioned limitations of the crossover design have led the randomized controlled trial design to be the standard for therapeutic confirmatory trials for regulatory approval such as this trial.

4.5 BENEFIT/RISK OF SOTAGLIFLOZIN

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

Sotagliflozin may benefit a wide variety of patients with diabetes based on multiple potential beneficial effects of dual SGLT2/SGLT1 inhibition, and its insulin-independent mechanism of action. Improvements in HbA1c, FPG, and postprandial glucose (PPG) were observed with sotagliflozin in multiple studies. As anticipated from the mechanism of action, treatment with

sotagliflozin resulted in increased UGE (from inhibition of SGLT2) as well as increased incretin levels (from inhibition of SGLT1). In addition, the improvements in body weight, blood pressure (BP), and triglycerides (TG) observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

Phase 2 data indicated that sotagliflozin may reduce SBP by 10 to 15 mmHg in patients with SBP ≥130 mmHg at Baseline, while having little effect in patients with SBP <130 mmHg, and did not induce hypotension. Since this could be of benefit to patients with T2D, this finding is being followed up as a secondary objective in this trial.

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. SAEs and discontinuations due to AEs have been limited and balanced between treatment and comparator groups.

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

The improvement in glycemic control, the reductions in weight and BP, and the tolerability and safety profile of sotagliflozin to date, demonstrate a favorable benefit-risk assessment for sotagliflozin.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo on HbA1c reduction at Week 26 in patients with T2D who have inadequate glycemic control with a sulfonylurea alone or in combination with metformin.

5.2 SECONDARY

- To compare sotagliflozin 400 mg versus placebo for:
  - Change from Baseline in FPG at Week 26
  - Change from Baseline in body weight at Week 26
  - Change from Baseline in SBP at Week 12 for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline in SBP at Week 12 for all patients
  - Proportion of patients with HbA1c <6.5%, <7.0% at Week 26
- To evaluate the safety of sotagliflozin 400 mg versus placebo throughout the 79-week trial

5.3 OTHER

- To compare sotagliflozin versus placebo based on other BP endpoints
- To compare sotagliflozin versus placebo with respect to change from Baseline in the following endpoints:
  - Estimated glomerular filtration rate (eGFR)
  - Reduction in body weight by ≥2%, ≥5%, and ≥10%
- To compare sotagliflozin versus placebo for:
  - Change from Baseline in HbA1c at Week 79
  - Change from Baseline in FPG at Week 79
  - Change from Baseline in body weight at Week 79
- To compare the use of rescue medications for hyperglycemia in the sotagliflozin and placebo treatment groups
- To assess plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multicenter and multinational, 1:1 randomized, double-blind, placebo-controlled, parallel group study that is anticipated to enroll approximately 500 patients.

The study will comprise a Screening Period consisting of a Screening phase of up to 2 weeks and a 2-week single blind Run-in phase, a double-blind Core Treatment Period, a double-blind Extension Period, and a Follow-up Period.

The study design is presented graphically at the end of the synopsis.

6.1.1 Screening Period

6.1.1.1 Screening phase (Visit 1)

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

Patients taking a sulfonylurea (≥half the maximum recommended dose as per local label or maximum tolerated dose [documented]) as monotherapy or in combination with metformin (≥1500 mg per day or maximum tolerated dose [documented]) each at a stable dose for at least 12 weeks before enrollment will be eligible for Screening. The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients.

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

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

6.1.1.2 Run-in phase (Visit 2)

The Run-in phase will last 2 weeks. Patients will be treated in a single-blind manner with placebo (2 tablets) once daily during the Run-in phase, starting from Visit 2.

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

Eligible patients will be randomized on Day 1 (Visit 3). In order to qualify for randomization, patients must demonstrate compliance during the single-blind placebo Run-in phase based upon tablet count (≥80%), and as assessed at the Investigator's discretion.

Randomization will be stratified by:

- HbA1c at Screening (≤8.5%, >8.5%)
- Metformin use at Screening (Yes, No)
- SBP at Screening (<130 mmHg, ≥130 mmHg)

Following randomization, patients will be treated in a double-blind manner for 26 weeks. Approximately 500 patients ≥18 years of age (or ≥ legal age of majority if greater) will be randomly assigned 1:1 to 1 of the following 2 treatment groups:

- Sotagliflozin 400 mg as two 200 mg tablets, once daily
- Placebo as two placebo tablets (identical to sotagliflozin 200 mg tablets in appearance), once daily

Fasting glucose (plasma or serum) and HbA1c (both measured at central laboratory) will be masked to study sites after randomization until study end. To prevent partial unblinding, the central laboratory urine dipstick will not include the measurement of urine glucose.

All Visits will be on-site with the exception of Visit 4 (Week 1) and Visit 6 (Week 8), which will be telephone visits.

If a patient discontinues treatment with investigational medicinal product (IMP) early during the 26-week Core Treatment Period, the patient will have a Premature End-of-Treatment (EOT) Visit and a Follow-up Visit 2 weeks after the last dose of IMP. In addition, every effort will be made to have all patients return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit and Week 79 Visit. If the patient does not agree to site visits, they will be contacted by telephone to inquire about their safety status at the time of initially scheduled Week 79 Visit.

6.1.3 Double-blind Extension Period (Week 27 to Week 79)

From Week 27 to 79, patients will be in a 53-week double-blind Extension Period. Patients will continue to receive the blinded medication (sotagliflozin or placebo) to which they were randomized on Day 1. Patients who received rescue medication during the 26-week 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).

If a patient completes the Core Treatment Period, but discontinues IMP during the Extension 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 all patients (including those who discontinue treatment early, prior to the Week 26 Visit) return to the site at the time corresponding to their quarterly visits (ie, every 13 weeks) during the Extension Period, particularly the Week 79 Visit. If the patient does not agree to site visits, at the time corresponding to their Week 79 Visit, all attempts will be made to contact the patients to inquire about their safety status.

6.1.4 Follow-up period

Following the last dose of IMP (either as scheduled or prematurely), a post-treatment follow-up should be scheduled for all patients 14 days (±3 days) after permanent IMP discontinuation. This will be a telephone visit.

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 85 weeks and includes a Screening phase of up to 2 weeks, a 2-week single-blind Run-in phase, a 26-week double-blind core treatment period followed by a 53-week double-blind treatment extension, and a 2-week Follow-up Period after completion of study treatment.

6.2.2 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 follow-up visit.

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

6.3 INTERIM ANALYSIS

No interim analysis is planned.

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.

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

Among its responsibilities, the SC will receive blinded study status reports from 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.

Detailed activities and responsibilities of the SC are provided in the SC charter.

6.4.2 Data Monitoring Committee

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

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

Safety data to be reviewed will be unblinded and include events and outcomes described below for adjudication, as well as any additional safety data considered relevant. Details describing the DMC processes and procedures are outlined in a separate DMC Charter. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data.

6.4.3 Clinical Endpoint Committee(s)

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

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

6.4.4 Safety adjudication of events requiring ongoing monitoring

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

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

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

7 SELECTION OF PATIENTS

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

7.1 INCLUSION CRITERIA

I 01. Patients with T2D currently treated with diet and exercise and on a sulfonylurea (≥half the maximum recommended dose as per local label or the maximum tolerated dose [documented]) for ≥12 weeks with or without metformin (≥1500 mg per day or the maximum tolerated dose [documented]) each at a stable dose for at least 12 weeks before Screening

Note: The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients.

I 02. Signed written informed consent

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Age <18 years at Screening or < legal age of majority, whichever is greater

E 02. Type 1 diabetes

E 03. Body Mass Index (BMI) ≤20 or >45 kg/m² at Screening

E 04. Previous use of any antidiabetic drug other than a sulfonylurea or metformin unless the other antidiabetic drug has been discontinued for a period of at least 12 weeks before the Screening Visit

E 05. Use of systemic glucocorticoids (excluding topical or ophthalmic application, nasal spray or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit

E 06. Use of weight loss medications or medications known to lead to weight gain within 12 weeks or weight change of 5 kg or more during the 12 weeks before Screening

E 07. 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 08. Patients who have previously participated in any clinical trial of sotagliflozin/LX4211

E 09. Patients with severe anemia, severe cardiovascular (including congestive heart failure New York Heart Association IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy making implementation of the protocol or interpretation of the study results difficult

E 10. History of chronic hepatitis or serologic evidence by known history of current infectious liver disease (hepatitis B or C) including hepatitis B surface antigen or antihepatitis C virus (patients with isolated positive hepatitis B Surface antibody may be included)

E 11. Hemoglobinopathy or hemolytic anemia, transfusion of blood or plasma products, or blood donation within 12 weeks prior to Screening

E 12. History of drug or alcohol abuse within 6 months prior to screening

E 13. 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 14. Patient who has taken other investigational drugs or prohibited therapy for this study within 12 weeks or 5 half-lives, whichever is longer, prior to Screening

E 15. Current enrollment in any other clinical study involving an investigational study treatment or any other type of medical research

E 16. Patient is unwilling to perform self-monitoring of blood glucose (SMBG) and complete the patient diary as required per protocol

E 17. Patient insufficiently compliant during Run-in phase based upon tablet count (<80%) or in the opinion of the Investigator

E 18. Patient with contraindication to sulfonylurea as per local labeling

E 19. Patient with contraindication to metformin as per local labeling if the patient is taking sulfonylurea in combination with metformin

E 20. Any country-related specific regulation that would prevent the patient from entering the study

7.2.2 Exclusion criteria related to the diabetes history and treatment

E 21. Hemoglobin A1c <7% or >10% measured by the central laboratory at Screening

E 22. Fasting plasma glucose >15 mmol/L (>270 mg/dL) measured by the central laboratory at Screening (Visit 1), and confirmed by a repeat test (>15 mmol/L [>270 mg/dL]) before randomization

E 23. Previous use of any types of insulin for >1 month (at any time, except for treatment of gestational diabetes)

E 24. History of DKA or nonketotic hyperosmolar coma within 12 weeks prior to the Screening Visit

E 25. History of severe hypoglycemia (requiring assistance of another person) within 6 months prior to the Screening Visit

7.2.3 Exclusion criteria related to the current knowledge of sotagliflozin

E 26. Pregnant (confirmed by serum pregnancy test at Screening) or breast-feeding women

E 27. Women of childbearing potential not protected by highly effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy (see Appendix A)

E 28. Mean BP after 3 separate measurements >180 mmHg (SBP) or >100 mmHg (diastolic blood pressure [DBP])

E 29. History of hypertensive urgency or emergency within 12 weeks prior to randomization unless patient is being aggressively treated for hypertension according to local guidelines Examples of guidelines current at the time of protocol writing include those from the ADA (10) and the European Society of Cardiology (11)

E 30. History of gastric surgery including history of gastric banding or inflammatory bowel disease within 3 years before the Screening Visit

E 31. Difficulty swallowing such that the patient cannot take the IMP

E 32. Known allergies, hypersensitivity, or intolerance to sotagliflozin or any inactive component of sotagliflozin or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), unless the reaction is deemed irrelevant to the study by the Investigator

E 33. Intolerance to any SGLT2 inhibitor

E 34. Laboratory findings with the central laboratory tests at Visit 1:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of the normal laboratory range (ULN)
- Total bilirubin >1.5 × ULN (except in case of Gilbert's syndrome)
- Neutrophils <1,500/mm^3 (or according to ethnic group; see Appendix D for details) and/or platelets <100,000/mm^3
- Amylase and/or lipase >3 × ULN
- Fasting triglycerides >600 mg/dL (>6.77 mmol/L) unless value determined to be due to nonfasting status in which case it may be repeated once

E 35. Severe renal disease as defined by eGFR of <30 mL/min/1.73m^2 at screening by the 4 variable Modification of Diet in Renal Disease equation

E 36. Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant or initiation of chronic dialysis within 4 weeks prior to the Screening Visit or expected to occur within 180 days after the Screening Visit

E 37. History of hereditary glucose-galactose malabsorption or primary renal glucosuria

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The IMPs are sotagliflozin 200 mg and matching placebo. Patients will be provided with 70 tablet bottle(s) of sotagliflozin 200 mg or matching placebo. Table 1 provides a summary of each IMP.

Table 1 - Summary of investigational medicinal products

IMP:	Sotagliflozin	Placebo
Name of the IMPs	Sotagliflozin (SAR439954)	Placebo
Pharmaceutical form	Sotagliflozin (SAR439954) will be supplied as 200 mg tablets	Placebo will be supplied as tablets (identical to sotagliflozin 200 mg tablets in appearance)
Dose, timing and route of administration	Two 200 mg tablets, taken orally once daily, before first meal of the day	Two tablets, taken orally once daily, before first meal of the day
Duration of treatment	79 weeks following randomization including a 26-week double-blind Core Treatment Period and a 53-week double-blind Extension	2 weeks during single-blind Run-in phase 79 weeks following randomization including a 26-week double-blind Core Treatment Period and a 53-week double-blind Extension
Storage conditions	Store between +15°C and +30°C (59°F and 86°F)	Store between +15°C and +30°C (59°F and 86°F)

IMP: Investigational medicinal product

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

8.2.1 Sulfonylurea and metformin

Patients are enrolled with a background therapy consisting of a sulfonylurea alone or in combination with metformin. Background sulfonylurea and metformin are considered as noninvestigational medicinal products (NIMP). Sulfonylurea and metformin (commercial formulations) will be administered orally according to the locally approved label.

The dose of sulfonylurea must be ≥half the maximum recommended dose as per local label or maximum tolerated dose (maximum tolerate dose needs to be documented). If applicable, the dose of metformin must be ≥1500 mg/day or maximum tolerated dose (maximum tolerate dose needs to be documented). Sulfonylurea and metformin doses must be stable for at least 12 weeks before Screening.

The doses of sulfonylurea and, if applicable, metformin, should be stable throughout the study unless down-titration is required for safety reasons.

Sulfonylurea and metformin treatment are to be reported in the electronic case report form (e-CRF). This information should include specific drug name, dose, route of administration, and frequency.

The cost of the background treatment sulfonylurea or metformin not covered by health insurance will be reimbursed where permitted by local regulations.

8.2.2 Rescue therapy

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

- FPG >270 mg/dL (15.0 mmol/L) from Randomization up through the scheduled Week 8 Visit
- FPG >240 mg/dL (13.3 mmol/L) after the Week 8 visit up through the scheduled Week 12 Visit
- FPG >200 mg/dL (11.1 mmol/L) after the Week 12 Visit through the end of the 26-week Core Treatment Period
- FPG >170 mg/dL (9.4 mmol/L) or HbA1c ≥8.0% after the Week 26 Visit through the end of the treatment period (Week 79)

Routine fasting SMBG (see Section 9.2.1.6) and central laboratory alerts on FPG (and HbA1c at Week 26 and onward) are set up to ensure that glycemic parameter results remain under predefined thresholds.

- If one fasting SMBG value exceeds the specific glycemic limit on one day, the patient checks it again during the two following days. If all the values in three consecutive days exceed the specific limit, the patient should contact the Investigator and a central laboratory FPG measurement (and HbA1c at Week 26 and onward) 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 threshold 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 exceeds the threshold, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- The increased FPG has been tested at a fasting status (ie, no food intake for ≥8 hours)
- Investigational medicinal product is given at the planned dose
- 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 the 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 e-CRF 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 to reinforce the absolute need to be compliant with 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, rescue medication may be introduced.

Open-label rescue medication(s) to treat hyperglycemia will be at the discretion of the Investigator and in accordance with local standard of care and prescribing practice. Except for SGLT2 inhibitors, and additional metformin and sulfonylurea, any approved medication(s) including oral antidiabetic drugs, GLP-1 receptor agonists, or insulin can be prescribed to treat the hyperglycemia. Metformin will also be permitted for patients on sulfonylurea only at Screening. The patient continues the study treatment (blinded) and stays in the study in order to collect efficacy and safety information. The planned visits and assessments should occur until the last scheduled visit. For patients with renal impairment, contraindications to antihyperglycemic drugs should be taken into consideration.

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

If not covered by health insurance, the cost of the 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 placebo tablets and packaging will be blinded and indistinguishable.

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

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

Fasting glucose (plasma or serum) and HbA1c will be masked to study sites and patients after randomization and until study end. To prevent partial unblinding, the central laboratory urine 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 should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

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

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

Refer to Section 10.5 for suspected unexpected serious adverse drug reaction 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 or placebo once daily during the randomized double- blind treatment period. Randomization (ratio 1:1) will be stratified by HbA1c at Screening (≤8.5, >8.5%), metformin use at Screening (Yes, No) and SBP at Screening (<130 mmHg, ≥130 mmHg). The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients.

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]

[redacted] At Visit 3 (Baseline), assessment results are reviewed and Baseline assessments are completed, the IRT is contacted for randomization and allocation of the treatment package(s).

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 number(s).

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

8.5 PACKAGING AND LABELING

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

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

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

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 IMPs 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) should be promptly notified to the Sponsor or Delegate. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of 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 or Delegate, in order 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 IMP in any other manner.

8.7.1 Treatment accountability and compliance

Accounting and compliance for IMPs will be performed at Visit 3 and all subsequent on-treatment, on-site visits.

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

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

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

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

8.7.2 Return and/or destruction of treatments

Patients are to return all IMP (unused, in use or empty bottle[s]) at each on-site visit (or final assessment on-treatment 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 or Delegate. A detailed site 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, sulfonylurea, metformin, and rescue therapy), tracking is to be undertaken by the Investigator (or pharmacist if appropriate) according to the system proposed by the Sponsor/CRO.

8.8 CONCOMITANT MEDICATION

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

All concomitant medications should be documented on the Medications page of the e-CRF. 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 treatment period, the following medications are prohibited:

- Initiation of any antidiabetic agents, including oral or injectable antihyperglycemic agents other than the IMP before the rescue therapy

  Note: short-term use (<10 consecutive days) of the prohibited medication, eg, short-acting insulin for treatment of acute illness or surgery is allowed.
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, ophthalmic, nasal spray or inhaled applications are allowed)
- Initiation of any weight loss drugs (eg, phentermine, orlistat)
- Investigational medicinal products in any other clinical study

SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin), additional sulfonylurea and metformin are not allowed for rescue or post IMP therapy until the end of study.

Reduction of digoxin dose should be considered because sotagliflozin acts as a weak P-gp inhibitor and increases systemic exposure to digoxin. Patients taking sotagliflozin with concomitant digoxin should have digoxin concentrations monitored and doses reduced as needed.

In addition, other P-gp substrates may be affected and the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments.

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

After premature permanent discontinuation of the IMP, any treatments (other than SGLT2 inhibitors, and additional sulfonylurea and metformin) are permitted, as deemed necessary by the Investigator.

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.

8.8.2 Concomitant diabetes therapy

For patients in both groups, background sulfonylurea and (if applicable) metformin should be stable throughout the study unless down-titration is required for safety reasons.

The rescue medication(s) that will be used to treat hyperglycemia when a patient's hyperglycemia reaches the rescue threshold are also defined as NIMPs. Except for SGLT2 inhibitors, additional metformin and sulfonylurea, any approved medication(s) including oral antidiabetic drugs, GLP-1 receptor agonists, or insulin can be prescribed at the Investigator's discretion to treat the hyperglycemia. Metformin will also be permitted for patients on sulfonylurea only at Screening. The regimen of the rescue medications will be in accordance with local standard of care and prescribing practice.

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.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

9.1.1 Primary efficacy endpoint

- Change from Baseline to Week 26 in HbA1c (%)

9.1.2 Secondary efficacy endpoints

The continuous secondary efficacy endpoints are:

- Change from Baseline to Week 26 in FPG
- Change from Baseline to Week 26 in body weight
- Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Week 12 in SBP for all patients
- Proportion of patients with HbA1c <6.5%, <7.0% at Week 26

9.1.3 Other efficacy endpoints

- Change from Baseline to Week 12 in SBP for patients with Baseline SBP <130 mmHg
- Proportion of patients with reduction in body weight by ≥2%, ≥5%, and ≥10% from Baseline
- Change from Baseline to Week 12 in DBP
- Proportion of patients achieving SBP <130 mmHg for those with Baseline SBP ≥130 mmHg
- Proportion of patients achieving DBP <80 mmHg for those with Baseline DBP ≥80 mmHg
- Proportion of patients requiring rescue for hyperglycemia
- Change from Baseline in:
  - Serum creatinine
  - eGFR
- Change from Baseline to Week 79 in HbA1c
- Change from Baseline to Week 79 in FPG
- Change from Baseline to Week 26 in SBP for all patients and for patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Week 79 in SBP for all patients and for patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Week 79 in body weight

9.1.4 Assessment methods of efficacy endpoints

9.1.4.1 Hemoglobin A1c

Hemoglobin A1c will be assessed at Screening (Visit 1) and all on-site visits during the double-blind treatment period with the exception of Week 18 (Visit 8).

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I "National Glycohemoglobin Standardization Program" central laboratory to allow estimation of the change from Baseline to Week 26 in HbA1c and the proportion of patients with HbA1c <6.5%, <7.0% at Week 26.

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

9.1.4.2 Fasting plasma glucose measurement

Plasma glucose is measured in the fasting state at Screening (Visit 1) and all on-site visits during the treatment period. For the eligibility and efficacy assessments of the study, FPG is measured at a central laboratory to allow estimation of change from Baseline to Week 26 in FPG.

9.1.4.3 Body weight measurement

Body weight is measured at all on-site Visits. Body weight will be measured to allow the estimation of change from Baseline to Week 26 in body weight and reduction in body weight by ≥2%, ≥5%, and ≥10% from Baseline.

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 documents should be filed in the study file.

The use of balance scales is recommended. 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 e-CRF and Source Data. Self-reported weights are not acceptable; patients must not read the scales themselves.

9.1.4.4 Blood pressure endpoint measurements

Systolic BP and DBP will be assessed at all on-site visits. Blood pressure measurements must be taken as described in Section 9.2.1.4 with details provided in Appendix C.

9.1.4.5 Kidney function parameter measurement

Serum creatinine will be assessed at Baseline (Visit 3) and selected on-site visits (see Study Flowchart in Section 1.2). A central laboratory will analyze samples and estimate change from Baseline in serum creatinine and eGFR.

9.1.4.6 Proportion of patients requiring rescue for hyperglycemia

The use of rescue medications for hyperglycemia will be assessed and reported throughout the treatment period. Routine alerts on FPG and/or HbA1c will be sent to the Investigator from the central laboratory to ensure that glycemic parameter results remain within predefined thresholds. For details and further actions should FPG and/or HbA1c 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, electrocardiogram (ECG), weight, and vital signs. An independent DMC will meet on a regular basis to review accumulating clinical trial safety data.

Adjudication of all deaths, MACE/other selected CV events (MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), selected renal events, bone fracture, and DKA will be performed in a blinded manner by a CEC(s) comprised of experts. Details will be provided in the charter of the CEC(s). Further details are available in Section 6.4.

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

The following safety endpoints will be assessed:

- Adverse events, AEs leading to discontinuation from the IMP, adverse events of special interest (AESIs), events of special interest (EOSIs), SAEs and deaths
- Hypoglycemia (all, severe, and/or documented symptomatic hypoglycemia)
- Clinical laboratory results (including fasting lipids; see Section 9.2.1.3)
- Vital signs and ECG results.

Observation period of safety endpoints

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

- The pre-treatment period is defined as the time between the date of the informed consent and the first dose of double-blind IMP
- The on-treatment period (TEAE period) is defined as the time from the first dose of double-blind IMP up to 10 days (1 day for hypoglycemia) after the last dose of double-blind IMP, regardless of the introduction of rescue therapy. The 10-day interval is

chosen based on the half-life of the IMP (approximately 5 times the half-life of sotagliflozin in patients with moderate renal dysfunction)

- The post-treatment period is defined as the time starting 11 days after the last dose of double-blind IMP (after the on-treatment period)

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

9.2.1 Assessment methods of safety endpoints

9.2.1.1 Adverse events

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

9.2.1.1.1 Adverse events of special interest

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

9.2.1.1.2 Events of special interest

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

9.2.1.2 Hypoglycemia

Hypoglycemia will be assessed from the signing of the ICF until 2 weeks after the last dose of IMP (note: for patients who discontinue treatment before Week 79, safety data will be collected until scheduled study end). Patients will also complete the hypoglycemia specific page (as part of the patient diary) from Visit 1 onwards, which will be regularly reviewed by Investigators. See Section 10.6.1 for further details.

9.2.1.3 Laboratory safety variables

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

In addition, for WOCBP a serum pregnancy test is performed at Screening, and urine pregnancy tests are taken at all on-site visits during the double-blind treatment period excluding Visit 4 (Week 1). Any positive urine test results must be confirmed by a serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

Serum follicle-stimulating hormone (FSH) and estradiol will be measured in menopausal women at Screening (Visit 1, Week -4) (see Appendix A for definition of menopausal women).

Table 2 - Blood safety parameters

Clinical chemistry	Hematology	Other blood parameters
Sodium	Complete blood count (CBC)	**Lipid profile**
Potassium	Differential	Total cholesterol (TC)
Chloride	Platelet count	High-density lipoprotein cholesterol (HDL-C)
Carbon dioxide (bicarbonate)	Hemoglobin	Low-density lipoprotein cholesterol (LDL-C) will be calculated by Friedwald equation
Blood urea nitrogen (BUN)	Hematocrit	Non-HDLC will be calculated as the difference between TC and HDLC
Creatinine (eGFR will be calculated)		Triglycerides (TG)
Glucose (serum)		**Other chemistry tests**
Alanine aminotransferase (ALT)		
Aspartate aminotransferase (AST)		
Total bilirubin (TB)		
Alkaline phosphatase (ALP)		
Uric acid		
Calcium		
Phosphorus		
Total protein		
Albumin		
Magnesium		
Creatine phosphokinase (CPK)		
Lactic acid dehydrogenase (LDH)		
Amylase		
Lipase		

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

9.2.1.3.1 Urinalysis

Urinalysis (urine dipstick with microscopy) will be performed by central laboratory at Screening (Visit 1), Baseline (Visit 3), Week 26 (Visit 9), and Week 79 (Visit 13). To prevent partial unblinding, the central laboratory urinalysis dipstick will not include the measurement of urine glucose. Central urinalysis includes:

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

In the event of abnormal urinalysis findings, suspicious of urinary tract infection, urine culture should be performed. Additionally, urine culture should be performed if at any point the PI suspects the presence of a urinary tract infection. 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).

9.2.1.4 Vital signs and physical exam

A complete physical exam (including sitting BP and heart rate, temperature and respiratory rate) will be performed at Visit 1 (Screening), Visit 9 (Week 26), and Visit 13 (Week 79). Abbreviated physical exams (including sitting BP and heart rate) will be performed at all other on-site visits. The abbreviated physical exam should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs if necessary.

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

9.2.1.5 Electrocardiogram variables

The ECG assessment of "normal" or "abnormal" will be analyzed.

A 12-lead ECG record is performed locally at Screening (Visit 1), Week 26 (Visit 9), and Week 79 (Visit 13).

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

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

9.2.1.6 Self-monitoring of blood glucose

A meter for self-assessment of blood glucose will be dispensed at the Run-in visit (Visit 2). In addition to home measurements of self-monitored blood glucose, self-monitoring of blood glucose will be performed at the Run-in Visit (Visit 2), Baseline (Visit 3) and all subsequent on-site visits. Glucose meters used for SMBG display results as plasma glucose concentration.

Patients will also receive a patient diary at all on-site visits with the exception of Visit 13 (End of Treatment visit). The diary will be reviewed at all on-site visits from Visit 2 to Visit 13. Self-assessed blood glucose levels will be entered in the patient diary.

Patients will be asked to self-assess fasting blood glucose levels at least 3 times a week from the Run-in Visit (Visit 2) to the end of the Treatment Period including on day of each on-site study visit. After Visit 9 (Week 26), if SMBG values are <120 mg/dL over a two-week period, the Investigator can (at their own discretion) instruct patients to self-monitor blood glucose once a week (on day of on-site study visit for weeks with on-site study visits).

Patients will also be requested to self-assess blood glucose levels 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 if fasting SMBG values over 3 consecutive days are:

- >270 mg/dL (15.0 mmol/L) from Randomization up through the scheduled Week 8 Visit
- >240 mg/dL (13.3 mmol/L) after the Week 8 visit up through the scheduled Week 12 Visit
- >200 mg/dL (11.1 mmol/L) after the Week 12 Visit and through the end of the 26-week double-blind Core Treatment Period
- >170 mg/dL (9.4 mmol/L) after the Week 26 Visit through the end of the Extension treatment period

9.2.1.7 Diabetic ketoacidosis

Patients will be provided with instructions on how to recognize the symptoms of DKA and instructed to contact the site (or seek emergency medical services if after business hours) if these symptoms develop. Patients should have a full clinical evaluation with laboratory testing for possible DKA by the Investigator or emergency medical services physician. If such evaluation and laboratory testing confirm the presence of metabolic acidosis, then appropriate treatment should be implemented and the "Possible DKA" e-CRF should be completed. See Appendix B for further details.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

The PK endpoint is:

- Plasma concentrations of sotagliflozin and its metabolite pre-dose at Week 4, 18, 26, 52, 79, and 1 hour 30 minutes post-dose at Week 26 and 79

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

9.3.1.1 Sampling time

Pre-dose PK samples at Weeks 4, 18, 26, 52, and 79 (Visits 5, 8, 9, 11, and 13, respectively) are to be drawn with the other laboratory assessments immediately before IMP administration. Post-dose PK samples at Weeks 26 and 79 (Visits 9 and 13, respectively) should be drawn 1 hour 30 minutes after administration of IMP. See Table 3 for the identification of samples.

Table 3 - Samples identification

Visit	Week	Relative to dosing	PK
Visit 5	Week 4	Pre-dose	P00
Visit 8	Week 18	Pre-dose	P01
Visit 9	Week 26	Pre-dose	P02
Visit 9	Week 26	Post-dose 1 h 30 min	P03
Visit 11	Week 52	Pre-dose	P04
Visit 13	Week 79	Pre-dose	P05
Visit 13	Week 79	Post-dose 1 h 30 min	P06

PK: pharmacokinetic.

9.3.1.2 Pharmacokinetics handling procedure

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

9.3.1.3 Bioanalytical method

Concentration of sotagliflozin and its 3-O-glucuronide

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

[redacted]

[redacted]

9.6 APPROPRIATENESS OF MEASUREMENTS

The addition of sotagliflozin to background therapy consisting of sulfonylurea treatment with or without metformin is expected to lower HbA1c over 26 weeks of treatment (primary efficacy analysis).

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 12 weeks. 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.

The problem of weight gain in T2D is widely recognized. More than 80% of individuals with T2D are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. Therefore, in this study assessing change in body weight from Baseline to Week 26 is a secondary endpoint.

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

Phase 2 data indicated that sotagliflozin may reduce SBP by 10 to 15 mmHg in patients with SBP ≥130 mmHg at Baseline, while having no significant effect in patients with SBP <130 mmHg, and did not induce hypotension. Since this could be of benefit to patients with T2D, this finding is being followed up as a secondary objective in this trial, as well as the potential in patients with DBP >80 mmHg. Although effects on BP in Phase 2 data were observed with the 400 mg dose at 12 weeks, the effects will be examined at Weeks 12, 26, and 79.

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

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

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 11 on-site visits and 3 telephone visits, although optional on-site and/or telephone visits can be scheduled at any time for any reason during the study whenever considered necessary by the Investigator.

The patients need to be fasting for on-site visits Visit 1 through Visit 13 (Week -4 through Week 79), unless instructed otherwise by the Investigator. Throughout the study, "fasting" is defined as 8 hours without food.

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 administration on the day of the visit.

The Run-in visit (Visit 2) can be performed as soon as the results of all Screening tests are available and the patient is confirmed to be eligible for participation in the study. The visit window for Visit 4 through Visit 9 is ±3 days. Visits 10, 11, and 12 should occur at the scheduled timepoint ±7 days. Visit 13 (EOT) should occur from Day 548 to Day 555. For the Follow-up (Visit 14), the visit should occur within a window of ± 3 days, 2 weeks after the last dose of IMP.

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 flowchart (Section 1.2), which details the procedures to be performed.

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

10.1.1 Screening Period

The Screening Period is up to 4 weeks and includes the Screening phase and the 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. It must be long enough to collect the data to establish whether the patient satisfies the inclusion/exclusion criteria.

Patients will undergo screening assessments at Visit 1 (Week -4) following signing of the ICF. Patients who meet the inclusion criteria as noted in Section 7.1 and have no exclusion criteria as noted in Section 7.2, will be randomized at Visit 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 Run-in for this study. In these cases, a patient will need to sign a new ICF, be registered as a new patient in the IRT and assigned a new patient number (first Screening Visit is to be registered as screen failure in the IRT), and again complete the Screening Visit procedures/assessments.

10.1.1.1.1 On-site Visit 1 (Week -4) Screening Visit

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

[redacted]

- Concomitant medication and medication history, including any prior medications for T2D
- Complete physical examination including height, weight, and vital signs (SBP and DBP, temperature, heart rate, and respiratory rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- IRT to be notified (allocation of ID, registration of screening)
- Assessment of all inclusion/exclusion criteria
- Collection of demographic data (age, gender, race, and ethnic origin)

- Assessment of the patient's medical and surgical history: to include history of T2D, treatment and complications (eye, kidney, amputations, etc); history of smoking/tobacco use; history of alcohol and drug abuse
- Patient diary is dispensed and instructions/training are provided
- 12-lead ECG
- The following laboratory testing (by the central laboratory):
  - Fasting plasma glucose
  - HbA1c
  - Hepatitis serology
  - Serum pregnancy testing for WOCBP or serum FSH and estradiol for postmenopausal women
  - Hematology
  - Clinical chemistry to include amylase and lipase
  - Fasting lipids
  - Urinalysis (dipstick and microscopy)
- Patients are instructed to return to the site for Visit 2 (Week -2)

10.1.1.2 Run-in phase

The Run-in phase is 2 weeks and includes Visit 2 (Week -2).

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

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

- Measurement of body weight
- Abbreviated physical examination including vital signs (SBP and DBP, and heart rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- Diet and exercise instruction
- Blood glucose meter is dispensed and instructions/training are provided
- Instruction on basic GU hygiene and hydration (see Appendix B)
- IRT to be notified (registration of run-in, allocation of single-blind run-in kit)
- Patient diary is collected/reviewed and a new diary dispensed. Instruction/training is provided as needed
- AEs/SAEs/AESI/EOSI and hypoglycemia occurring since Visit 1 (if any) are reported.
- Run-in kit/placebo is dispensed
- Changes in concomitant medication are reported
- Fasting SMBG is assessed
- Patients are instructed to return to the site in the fasting state for Visit 3 (Randomization)

10.1.2 Double-blind randomized 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 or placebo for the double-blind treatment period. All randomized patients will be followed at regular on-site visits for the duration of the treatment period. Visit 4 (Week 1) and Visit 6 (Week 8) are telephone visits.

In addition to routine laboratory testing, the following will be performed at specified time points: plasma concentration.

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

In the event of abnormal urinalysis findings, urine cultures should be performed (microbial testing). Additionally, urine cultures should be performed if at any point the PI suspects the presence of a urinary tract infection.

10.1.2.1 On-site Randomization Visit on Day 1 (Visit 3; Baseline; Week 0)

The following procedures will be performed at this visit:

- Exclusion criteria are to be reviewed, including assessment of compliance during Run-in phase
- Concomitant medications are assessed
- Measurement of body weight
- Abbreviated physical examination including vital signs (SBP and DBP, and heart rate). After 5 minutes resting, seated SBP, DBP and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- IMP accounting and compliance for single-blind placebo Run-in phase
- IRT to be notified and randomization will occur
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Diet and exercise instruction
- Patient diary is collected/reviewed and a new diary dispensed. Instruction/training is provided as needed
- Instruction on DKA symptoms and basic GU hygiene and hydration (see Appendix B) is provided
- Fasting SMBG is assessed
- The following laboratory testing (by the central laboratory):
  - Fasting plasma glucose
  - HbA1c

- Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
- Hematology
- Clinical chemistry to include amylase and lipase
- Urinalysis (dipstick and microscopy)

- Additional laboratory testing at this visit:

- IMP is dispensed
- Patients are instructed to return to the site in the fasting state for Visit 5 (Week 4) and a telephone call is scheduled in 1 week (Visit 4)
- For accountability and compliance purposes, patients are instructed to return to the site with their used, in-use, and unused bottle(s) dispensed during Visit 3

10.1.2.2 On-site visits at Weeks 4, 12, and 18 (Visits 5, 7, and 8)

The following will be performed at these visits:

- IRT to be notified
- IMP re-supply
- IMP accountability and compliance
- Patient diary is collected/reviewed and a new diary dispensed. Instructions/training are provided as needed
- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are evaluated for glycemic rescue (see Section 9.1.4.6)
- Measurement of body weight
- Abbreviated physical examination including vital signs (SBP and DBP, and heart rate). After 5 minutes resting, seated SBP, DBP and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- Instruction on DKA symptoms and basic GU hygiene and hydration (see Appendix B) is provided
- Fasting SMBG is assessed
- The following laboratory testing (by the central laboratory):
  - Fasting plasma glucose (all visits)
  - HbA1c (all visits except Visit 8)

- Urine pregnancy testing for WOCBP (all visits, any positive urine test results must be confirmed by a serum pregnancy test)
- Clinical chemistry (including amylase and lipase) and hematology (Visit 7 only)

- Additional laboratory testing at these visits:
  - Pre-dose plasma concentration samples are collected and sent to the appropriate laboratory (Visits 5 and 8 only)
- IMP is dispensed
- Patients are instructed to return to the site in the fasting state for their next on-site visit and next telephone visit is scheduled (if appropriate)
- Patients should be reminded to record in the diary the date and time of IMP intake on the day before their next visit (reminders at Visits 7 and 8)
- For accountability and compliance purposes, patients are instructed to return to the site with all used, unused, and in-use bottle(s) at the next visit

10.1.2.3 Telephone visit at Week 1 (Visit 4) and Week 8 (Visit 6)

The following will be performed at this visit:

- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are evaluated for glycemic rescue (see Section 9.1.4.6)
- Instruction on DKA symptoms and basic GU hygiene and hydration (see Appendix B) is provided
- Fasting SMBG is assessed
- Patients are instructed to return to the site in the fasting state for Visit 5 and Visit 7, respectively. They should be reminded to record in the diary the date and time of IMP intake on the day before their next visit (reminder at Visit 4 only)

10.1.2.4 On-site Visit 9 at Week 26 (End of core treatment period)

The following will be performed at this visit:

- IRT to be notified
- IMP accountability and compliance
- Patient diary is collected/reviewed and a new diary dispensed. Instructions/training are provided as needed
- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are evaluated for glycemic rescue (see Section 9.1.4.6)

- Measurement of body weight
- Complete physical examination including vital signs (SBP and DBP, temperature, heart rate, and respiratory rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- Diet and exercise instruction is provided
- Instruction on DKA symptoms and basic GU hygiene and hydration (see Appendix B) is provided
- 12-lead ECG, prior to IMP administration
- Fasting SMBG is assessed
- The following laboratory testing (by the central laboratory):
  - Fasting plasma glucose
  - HbA1c
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Clinical chemistry (including amylase, lipase, lipid profile) and hematology
  - Urinalysis (dipstick and microscopy)
- Additional laboratory testing at this visit:
  - [redacted]
  - Pre-dose and 1 hour 30 minute post-dose plasma concentration samples are collected and sent to the appropriate laboratory
- IMP is dispensed
- Patients are instructed to return to the site in fasting state in 13 weeks for Visit 10
- For accountability and compliance purposes, patients are instructed to return to the site with all used, unused, and in-use bottle(s) at Visit 10

10.1.3 Double-blind Extension Period

Upon completion of the double-blind core treatment period, patients will remain on the same blinded treatment throughout a 53-week double-blind Extension Period for a total treatment duration of 79 weeks.

The double-blind Extension Period will consist of 4 visits, occurring at Week 39 (Visit 10), Week 52 (Visit 11), Week 65 (Visit 12), and EOT visit at Week 79 (Visit 13).

10.1.3.1 On-site visits at Weeks 39, 52, and 65 (Visits 10 to 12)

The following will be performed at these visits:

- IRT to be notified
- IMP accounting and compliance
- Patient diary is collected/reviewed and a new diary dispensed. Instruction/training is provided as needed
- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are evaluated for glycemic rescue (see Section 9.1.4.6)
- Measurement of body weight
- Abbreviated physical examination including vital signs (SBP and DBP, and heart rate). After 5 minutes resting, seated SBP, DBP and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- Diet and exercise instruction is provided (Visit 11 only)
- Instruction on DKA symptoms and basic GU hygiene and hydration (see Appendix B) is provided
- Fasting SMBG is assessed
- The following laboratory testing (by the central laboratory):
  - Fasting plasma glucose
  - HbA1c
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Clinical chemistry (including amylase and lipase) and hematology
  - Lipid profile (Visit 11 only)
- Additional laboratory testing at these visits:
  - Pre-dose plasma concentration samples are collected and sent to the appropriate laboratory (Visit 11 only)
- IMP is dispensed
- Patients are instructed to return to the site in the fasting state for their next visit. They should be reminded to record in the diary the date and time of IMP intake on the day before their next visit (reminders at Visit 10 and Visit 12)
- For accountability and compliance purposes, patients are instructed to return to the site with all used, unused, and in-use bottle(s) at the next visit

10.1.3.2 On-site Visit 13 at Week 79 – End of treatment

The following will be performed at this visit:

- IRT to be notified
- IMP accountability and compliance
- Patient diary is collected/reviewed
- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Patients are evaluated for glycemic rescue (see Section 9.1.4.6)
- Measurement of body weight
- Complete physical examination including vital signs (SBP and DBP, temperature, heart rate, and respiratory rate). After 5 minutes resting, seated SBP, DBP, and heart rate will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details)
- Diet and exercise instruction is provided
- Instruction on DKA symptoms and basic GU hygiene and hydration (see Appendix B) is provided
- 12-lead ECG, prior to IMP administration
- Fasting SMBG is assessed
- The following laboratory testing (by the central laboratory):
  - Fasting plasma glucose
  - HbA1c
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Clinical chemistry (including amylase, lipase, and lipid profile) and hematology
  - Urinalysis (dipstick and microscopy)
- Additional laboratory testing at this visit:
  - [redacted]
  - Pre-dose and 1 hour 30 minute post-dose plasma concentration samples are collected and sent to the appropriate laboratory (this is not necessary if the patient discontinued study treatment early)
- A telephone call for last study visit (Visit 14) is scheduled in 2 weeks

10.1.4 Post-treatment Follow-up period

The post-treatment follow-up period will include a telephone visit 2 weeks after the last dose of IMP.

10.1.4.1 Telephone visit at Week 81 (Visit 14)

The following will be performed at this visit:

- IRT notified for end of study
- Concomitant medications are assessed
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Screening and last BP readings are reviewed, and post-treatment antihypertensive medication is added or adjusted as per instructions given in Section 8.9
- The patient is instructed to schedule future follow-up with their own personal physician

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient's file

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

- Agreement and signature of ICF with the study identification
- Study identification (name)
- Patient number, confirmation of randomization, treatment batch number, dates and doses of study medication administration
- Medical, surgical, diabetes history, including information on:
  - Demography, inclusion and exclusion criteria
  - Last participation in a clinical trial
  - Contraception method for WOCBP
  - Previous and concomitant medication
- Dates and times of visits and assessments including examination results
- Vital signs, height, body weight, 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

10.2.2 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 should be fully documented in the e-CRF. In any case, the patient should remain in the study and followed for the remainder of the study duration to collect vital safety status and endpoint data.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

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

It is in the interest of the patient to monitor their blood glucose during the temporary discontinuation period, therefore regular determination of SMBG is to be performed and documented (see Section 9.2.1.6).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF 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 different anti-hyperglycemic medication during the time of temporary treatment discontinuation (ie, insulin during a hospitalization) is recorded as concomitant medication with the name and doses recorded in the e-CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

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

10.3.3 List of criteria for permanent treatment discontinuation

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

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
- Inter-current 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)
- Pregnancy (in female patients)
- Specific request of the Sponsor

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

For patients who prematurely discontinue the IMP, the assessments planned at the EOT visit (see Section 10.1.3.2) will be performed at the Premature EOT Visit, scheduled preferably prior to treatment discontinuation or as soon as possible after the time of discontinuation (the latest at the next scheduled on-site visit). The reason(s) for IMP discontinuation will be clearly specified. This Premature EOT assessment may occur at a regularly scheduled visit 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 should be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If a patient decides to discontinue study treatment early, a Premature EOT visit (see Section 10.1.3.2) should be scheduled prior to treatment discontinuation, if possible. If not possible, the Premature EOT visit should be scheduled as soon as possible after treatment discontinuation. In the case of early discontinuation, no sample for measuring plasma concentration should be taken at the Premature EOT visit, nor at any subsequent visits. For patients that discontinue treatment but remain in the study, remaining study visits should occur as scheduled where possible. The IRT should be notified of EOT.

[redacted]

[redacted]

After premature permanent discontinuation of the IMPs, any treatments (other than SGLT2 inhibitors, and additional sulfonylurea and metformin) are permitted, as deemed necessary by the Investigator.

All confirmed cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF.

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 and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients will be told that they are free to withdraw from the study at any time without any adverse effect on their care. However, if they no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining study visits. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

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

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

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

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

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** 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 the study treatment.

10.4.1.2 Serious adverse event

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

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

10.4.1.3 Adverse event of special interest

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

The AESI for this study are:

- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP:
  - Pregnancy occurring in a female patient included in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2)
  - In the event of pregnancy in a female patient, IMP should be discontinued
  - Follow-up of the pregnancy in a female patient or in a female partner of a male patient is mandatory until the outcome has been determined
- 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 e-CRF as an AESI with immediate notification "Symptomatic OVERDOSE (accidental or intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria
  - (Please note that an Asymptomatic overdose with the IMP/NIMP, accidental or intentional, defined administration of more than twice the intended daily dose within a 24-hour period, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient, not based on accountability assessment. It will be recorded as an AE "Asymptomatic OVERDOSE, accidental or intentional")
- ALT increase >3 × ULN (refer to related flowchart, Appendix D)

10.4.1.4 Events of special interest

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

The EOSI for this study are:

- Major adverse cardiovascular events (MACE [cardiovascular death, MI, or stroke]) and other specific CV events (eg, heart failure leading to hospitalization)
- Severe hypoglycemia (see Section 10.6.1)
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candidal balanitis in males)
- Urinary tract infections
- 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)
- Diabetic ketoacidosis
- Renal events to include 50% decline in eGFR, end stage kidney disease, renal death
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid carcinoma)
- Adverse event leading to an amputation

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the ICF until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s)

- In this study, the use of concomitant medications including antidiabetic medications may make it difficult to assess the causal relationship, particularly for hypoglycemia. Global Safety Officer with input from other appropriate study team members will determine the causal relationship when it is not clearly provided by the Investigator
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs if they are medically relevant based on the Investigator's medical judgment, eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI or EOSI

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the Monitoring team and Pharmacovigilance after approval of the Investigator within the e-CRF
- 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 email 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 e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification
- A back-up plan (using a paper case report form [CRF] process) is available and should be used when the e-CRF 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/CRO 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 e-CRF.

10.4.5 Guidelines for reporting events of special interest

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

10.4.6 Guidelines for management of specific laboratory abnormalities

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

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

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

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction [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
  - Symptomatic overdose
  - ALT increase >3 × ULN

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

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

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

10.6 SAFETY INSTRUCTIONS

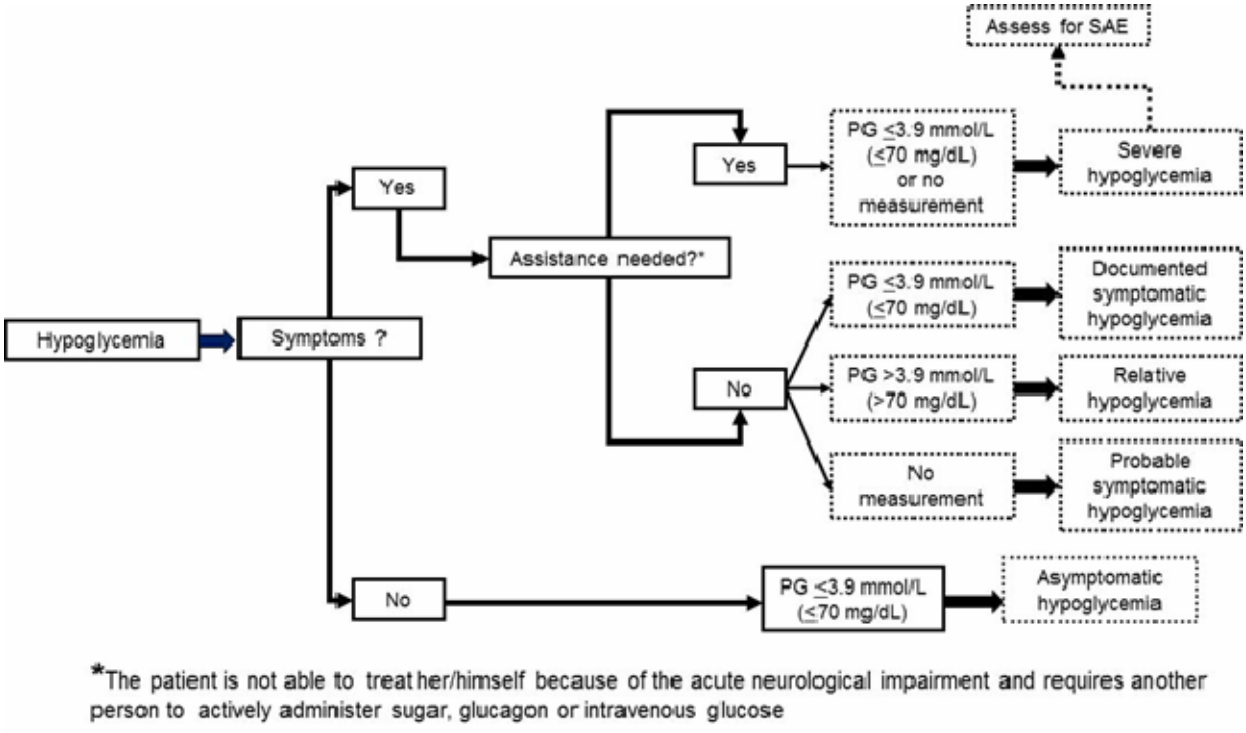
10.6.1 Hypoglycemia

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

Hypoglycemia is categorized according to the ADA workgroup on hypoglycemia classification (12)(13) and summarized in Figure 1.

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

Figure 1 - Hypoglycemia classification in Study EFC14835



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 ≤3.9 mmol/L (≤70 mg/dL).

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

Asymptomatic hypoglycemia

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

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

Probable symptomatic hypoglycemia

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

Relative hypoglycemia

Relative hypoglycemia, recently termed “pseudo-hypoglycemia” (14), is an event during which the patient reports typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >3.9 mmol/L (>70 mg/dL).

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations are based on the primary variable, 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, 250 patients per arm will have at least 99% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

The number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients.

11.2 DISPOSITION OF PATIENTS

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

- Screened patients: patients who have signed the ICF
- Run-in patients
- Randomized patients: patients with a treatment kit number allocated and recorded in IRT database, and 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 and analyzed as randomized)
- The randomization strata (HbA1c at Screening [≤8.5%, >8.5%], metformin use at Screening (Yes, No), and SBP [<130, ≥130 mmHg]). The discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients
- Patients who have completed the 26-week main treatment period
- Patients who discontinued the IMP during the 26-week main treatment period, and the reasons for treatment discontinuation
- Patients who have completed the entire treatment period
- Patients who discontinued the IMP during the entire treatment period, and the reasons for treatment discontinuation
- Patients who have completed the study
- Patients who discontinued the study, and the reasons for study discontinuation

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

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

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

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 populations

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 Intention–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

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

Patients will be analyzed for safety analyses according to the treatment actually received.

In addition:

- 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

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

11.4 STATISTICAL METHODS

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

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

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

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

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

11.4.1.1 Extent of investigational medicinal product exposure

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

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

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

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

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

11.4.1.2 Compliance

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

Treatment compliance, above-planned and under-planned dosing percentages, will be summarized descriptively (N, mean, SD, median, 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). All efficacy variables after Week 26 will only be summarized by descriptive statistics without formal statistical testing.

11.4.2.1 Analysis of primary efficacy endpoint

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

Analysis of the primary efficacy endpoint (change from Baseline to Week 26 in HbA1c; see Section 9.1.1) will be performed on the ITT population, using HbA1c measurements obtained from visits during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

The primary efficacy endpoint of change in HbA1c from Baseline to Week 26 will be analyzed with missing values imputed by control-based multiple imputation method under the missing not at random framework.

- For placebo patients, missing data will be imputed based on the placebo group data
- For patients in the sotagliflozin group, 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 in the imputation model

Each of the complete datasets will be analyzed by an Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP (<130, ≥130 mmHg), and country as fixed effects, and Baseline HbA1c value as a covariate.

Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing sotagliflozin versus placebo) and the 95% confidence interval (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, standard error (SE), minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (± SE) and mean changes from Baseline (± SE) at each of the scheduled visits (using OC).

Assessment of treatment effect by subgroup

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

- Race
- Ethnicity (Hispanic, Not Hispanic)
- Age group (<50 years, ≥50 to <65 years, ≥65 years)
- Gender
- Baseline BMI level (<30, ≥30 kg/m^2)
- Baseline HbA1c (≤8.5%, >8.5%)
- Metformin use at Screening (Yes, No)
- 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 (sotagliflozin versus placebo) with SE and 95% CIs will be provided as appropriate across the subgroups.

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

11.4.2.2 Analyses of secondary efficacy endpoints

The secondary 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 placebo patients, missing data will be imputed based on the placebo group data

- For patients in the sotagliflozin group, missing data will be imputed as if the patients were on placebo group throughout the study

For each of the continuous secondary endpoints, each of the complete datasets will be analyzed by an ANCOVA model with treatment groups (sotagliflozin, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed effects, and Baseline secondary endpoint value as a covariate. For the analysis of SBP in patients with Baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included in the ANCOVA model. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 26 (or Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing sotagliflozin versus placebo) and the 95% CI for the difference.

The categorical secondary efficacy variables of HbA1c <6.5%, <7% at Week 26 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), and randomization stratum of SBP (<130 mmHg, ≥130 mmHg). The proportion in each treatment group will be provided, as well as the difference of proportions between sotagliflozin and placebo with associated 2-sided 95% CI. For HbA1c responders at Week 26 (<6.5%, <7% respectively), 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 non-responders.

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 Analyses of other efficacy endpoints

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

11.4.2.4 Multiplicity considerations

To control the family-wise type I error, a fixed-sequence testing procedure will be applied.

Once the main study primary variable (change from Baseline to Week 26 in HbA1c) is statistically significant at $\alpha = 0.05$ (2-sided), a hierarchical testing procedure will be performed to test the following main study secondary efficacy variables by the following prioritized order. The testing will stop as soon as an endpoint is found to be not statistically significant at $\alpha = 0.05$ (2-sided):

- Change from Baseline to Week 26 in FPG

- Change from Baseline to Week 26 in body weight
- Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
- Change from Baseline to Week 12 in SBP for all patients
- Proportion of patients with HbA1c <7.0% at Week 26

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

11.4.3 Analyses of safety data

Safety endpoints are presented in Section 9.2. The summary of safety results will be presented by treatment group. The safety data will be summarized for the 26-week Core Treatment Period and the entire treatment period separately, unless specified otherwise. All safety analyses will be performed on the Safety population as defined in Section 11.3.2 using the following common rules:

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

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

The "observation periods" defined in Section 9.2.1 are applicable for classification of AEs, determination of on-treatment PCSA values and the last on-treatment value for the laboratory, vital sign and ECG parameters.

11.4.3.1 Analysis of adverse events

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

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

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

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

All adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the 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 (%) of patients who died by study period (on-study, on-treatment, post-study) 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 e-CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

Adverse events leading to permanent treatment discontinuation

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

11.4.3.2 Analyses of hypoglycemia

The number (%) of patients and rate in patient years (2 types: the number of patients with events or the total number of events per 100 patient-year) of all hypoglycemia, severe hypoglycemia, and documented symptomatic hypoglycemia will be summarized by treatment group respectively. Their pattern of occurrence over time will also be assessed, as appropriate.

11.4.3.3 Analyses of adverse events of special interest

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

11.4.3.4 Analyses of events of special interest

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

11.4.3.5 Analyses of laboratory variables

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

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

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

11.4.3.6 Analyses of vital sign variables

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

11.4.3.7 Analyses of 12 lead ECG status

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

11.4.4 Analyses of pharmacokinetic variables

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

Concentration data will be summarized by visit and, if appropriate, within visit by nominal sampling times (pre-dose, 1 hour 30 minute post-dose), using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum, and maximum at each visit/nominal sampling time point for sotagliflozin-treated patients.

11.5 INTERIM ANALYSIS

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

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

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

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

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

[redacted]

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

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

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

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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 CRF, Discrepancy Resolution Form [DRF] 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 OR SERVICE PROVIDER

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. 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 CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor/service provider to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs 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 e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor/CRO as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor/service provider may generate additional requests (DRF) 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 e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

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

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor/service provider 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 INSURANCE COMPENSATION

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

14.6 DATA PROTECTION

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

Patient race and ethnicity (race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, unknown; ethnicity: Hispanic, Not Hispanic) will be collected in this study because these data are required by several regulatory authorities (eg, on 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 in China).

[redacted]

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory

- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator or Sub-Investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients are included earlier than expected

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

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

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

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

Reproductive potential (WOCBP)

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

CONTRACEPTIVE GUIDANCE

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

Female patients:

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

COLLECTION OF PREGNANCY INFORMATION

Male patients with partners of reproductive potential who become pregnant

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

Female patients who become pregnant

- The Investigator will collect pregnancy information on any female patient, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor/CRO within 24 hours of learning of a participant's pregnancy
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE
- A spontaneous abortion is always considered to be an SAE and will be reported as such
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.1.2. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting

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

Patients with T2D are at risk for developing genitourinary (GU) infections. The following guidelines should be communicated to females and uncircumcised males regarding GU infections. Patient communication cards will be printed with the following:

For females:

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

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

For uncircumcised males:

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

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

Maintaining Hydration:

Sodium-glucose co-transporter type 2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. Before initiating study drug (at Screening, Run-in and Randomization) and during all on-site study visits thereafter, assess volume status in patients with renal impairment, the elderly, in patients with low SBP, or if receiving diuretics, angiotensin-converting-enzyme inhibitors, or angiotensin receptor blockers. All patients will be advised to maintain proper fluid intake and to consider increasing it if they sense greater thirst, more urine production, or if they feel dizzy or faint.

Patient communication cards will be printed with the following for patients with T2D:

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

- Dehydration is when your body loses too much fluid, frequently due to diarrhea or increased urination

- Consider increasing the amount of fluids you drink if:
  - You sense greater thirst than usual
  - You have a dry mouth or cracked lips
  - You have a fever
  - You have diarrhea or vomiting
  - You urinate more frequently or in larger amounts than usual
  - You get up in the middle of the night to urinate (more than usual)
  - You feel dizzy or light-headed
  - You exercise, or when it is hot outside"

Recognizing Diabetic Ketoacidosis

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

Appendix C Measurement of Blood Pressure and Pulse Rate

Equipment

1. Blood pressure measurements will be taken by an automated BP monitor or a manual sphygmomanometer. The same equipment should be used throughout the study and should be calibrated as per manufacturer recommendation
2. Bladder Length – Should nearly or completely encircle the patient's arm. For many adults, the standard "adult" size bladder is not long enough and the "large" size bladder is recommended
3. Bladder Width – Should be at least 40% of the bladder length

Patient Factors

Extraneous variables associated with the measurement of BP should be minimized. These include:

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

Nondominant Arm

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

Measurement Technique

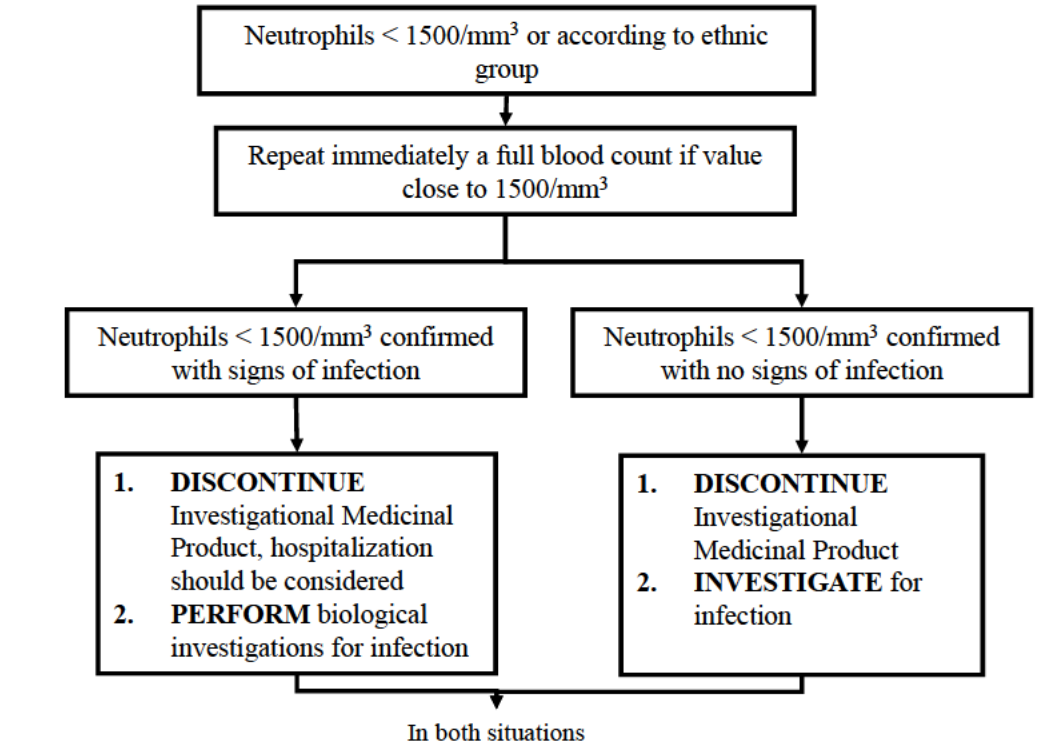
At all other on-site visits, following the 5-minute rest period, 3 separate seated BPs should be measured in the arm selected at Visit 1, with at least 1 minute between BP measurements and with the cuff fully deflated between measurements.

All 3 BPs will be recorded in the patient's electronic case report form (e-CRF). 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

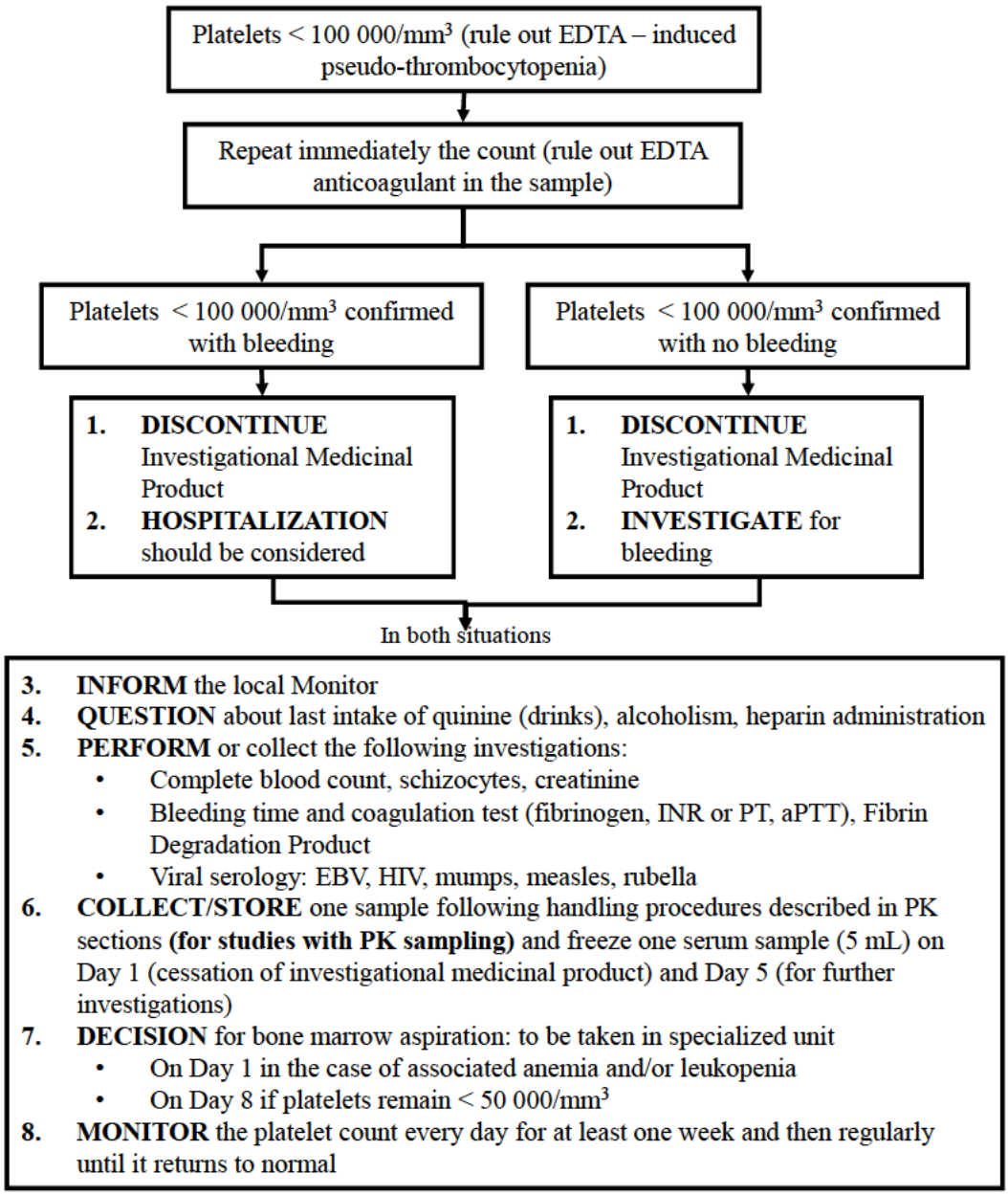


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, 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

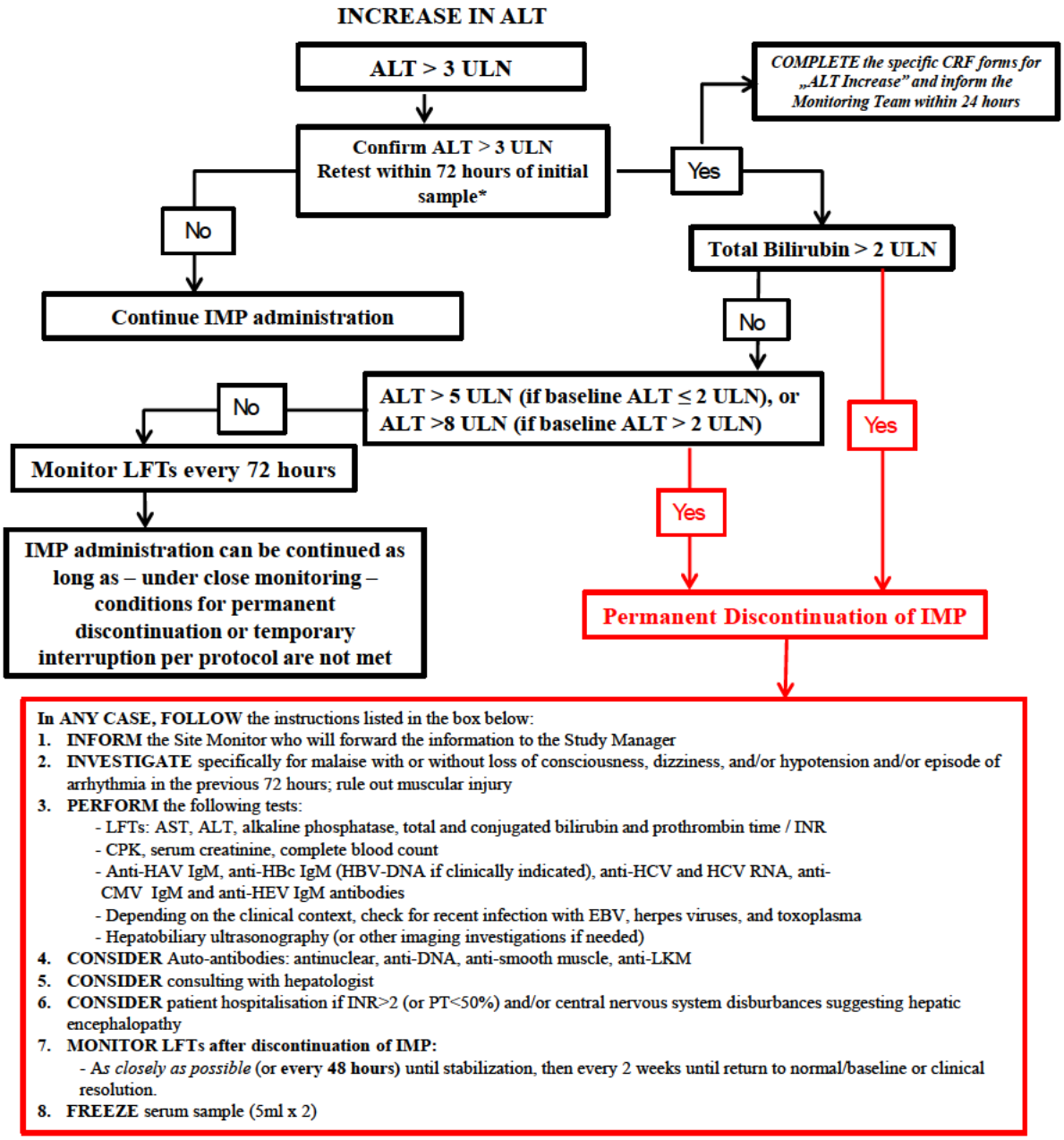
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.4.2 is met.

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 adverse events in Section 10.4.2 is met.

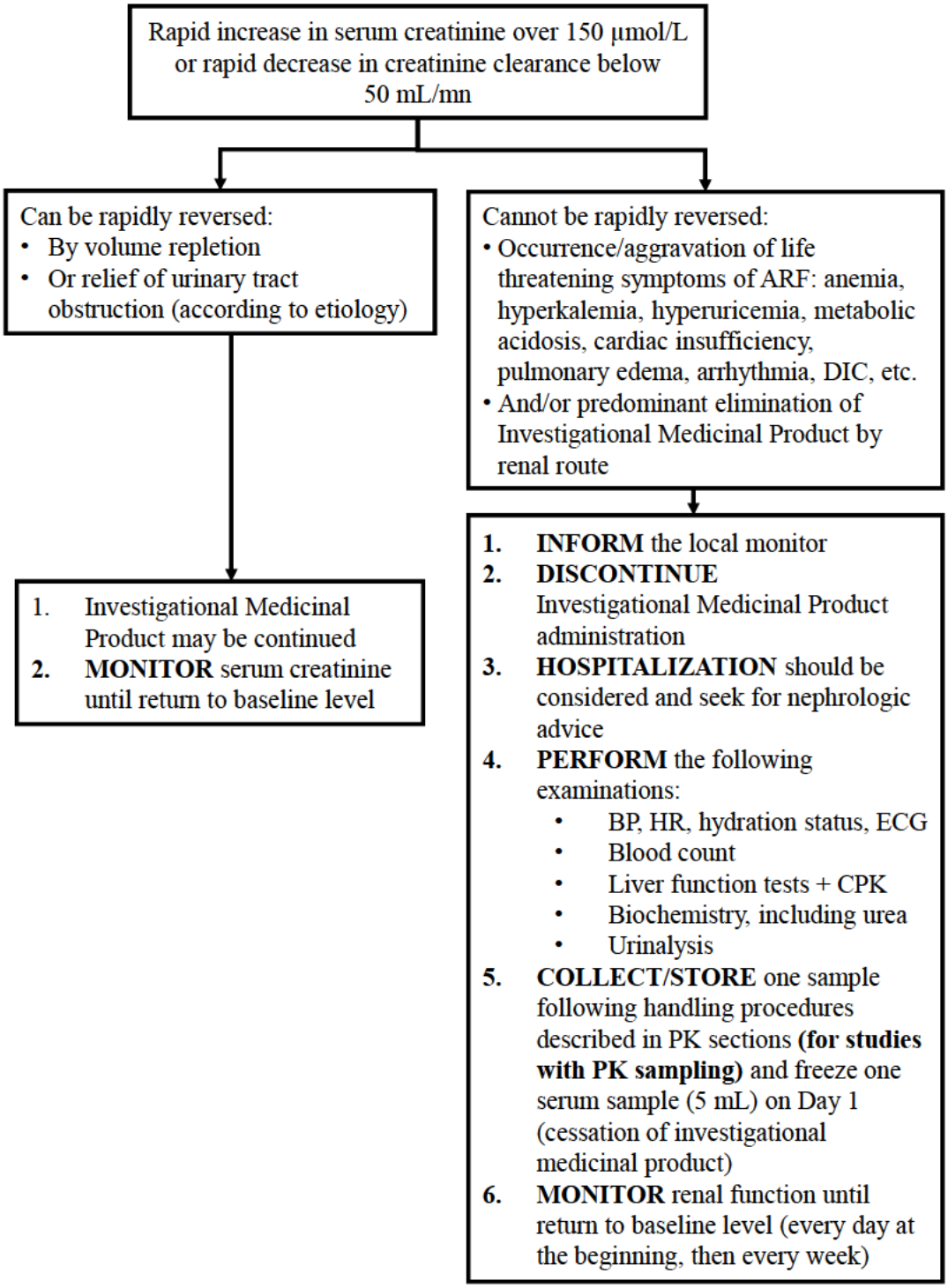


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

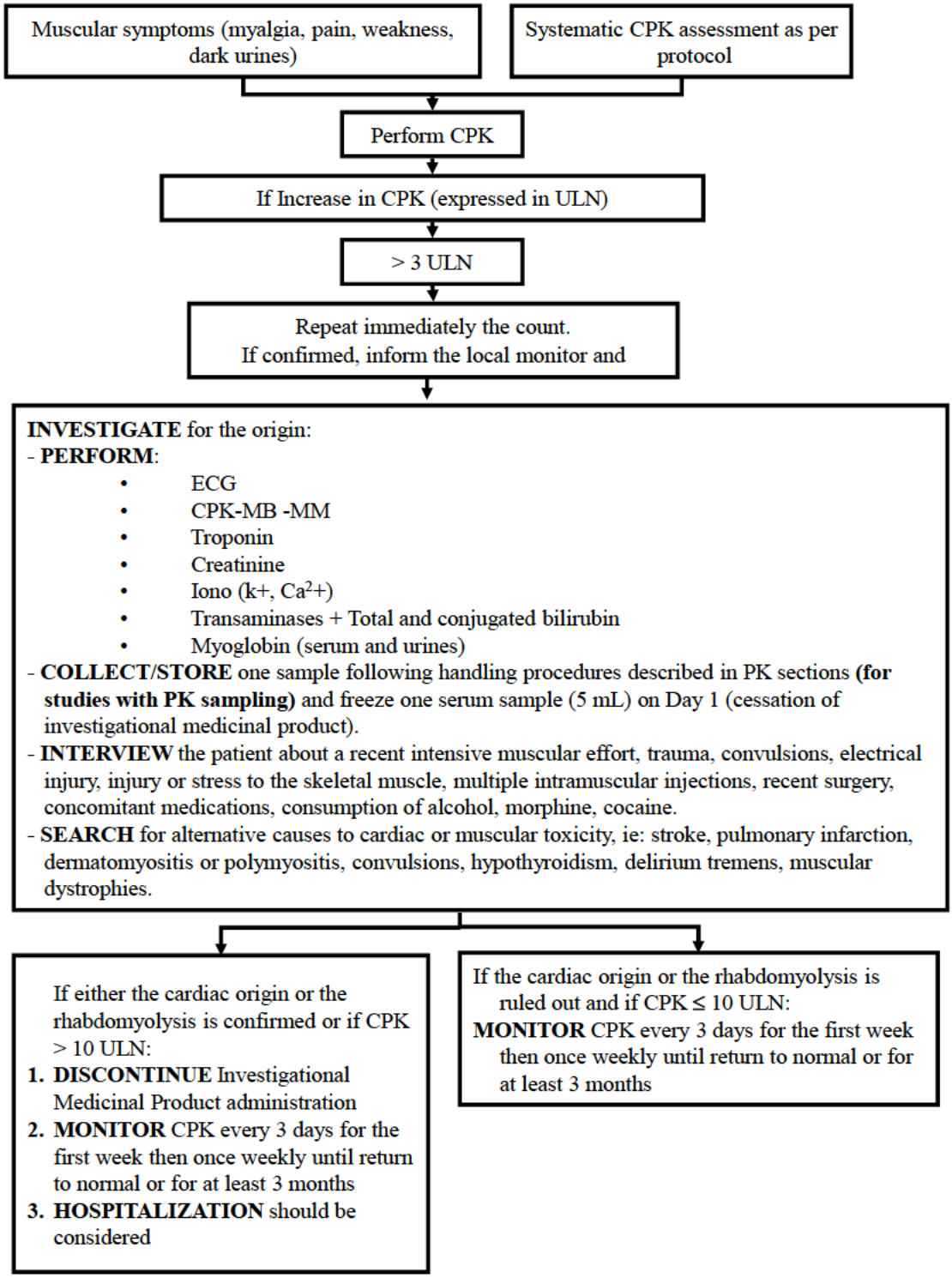
- "Baseline" refers to ALT sampled at Baseline visit; or if Baseline value unavailable, to the latest ALT sampled before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined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

ACUTE RENAL FAILURE



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

SUSPICION OF RHABDOMYOLYSIS



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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	20-Dec-2017 17:23 GMT+0100
[redacted]	Clinical Approval	20-Dec-2017 17:34 GMT+0100
[redacted]	Clinical Approval	21-Dec-2017 17:43 GMT+0100