Official Title: A 26-week Randomized, Double-blind, Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Empagliflozin, and Placebo in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Dipeptidyl Peptidase 4 Inhibitor (DPP4(i)) With or Without Metformin

NCT Number: NCT03351478

Document Date: Protocol Version 2: 12-April -2018

AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: sotagliflozin/SAR439954

A 26-week Randomized, Double-blind, Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Empagliflozin, and Placebo in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Dipeptidyl Peptidase 4 Inhibitor (DPP4(i)) With or Without Metformin

STUDY NUMBER: EFC14867

STUDY NAME: SOTA-EMPA

VERSION DATE / STATUS: Approval date (11-Apr-2018) / Approved

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NAMES AND ADDRESSES OF

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

CLINICAL TRIAL SUMMARY

COMPOUND: sotagliflozin/SAR439954	**STUDY No.: EFC14867** **STUDY NAME: SOTA-EMPA**
TITLE	A 26-week Randomized, Double-blind, Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Empagliflozin, and Placebo in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Dipeptidyl Peptidase 4 Inhibitor (DPP4(i)) With or Without Metformin
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary objective:** The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo on hemoglobin A1c (HbA1c) reduction at Week 26 in patients with Type 2 diabetes (T2D) who have inadequate glycemic control on a DPP4(i) with or without metformin. **Secondary objective:** The secondary objectives of this study are to demonstrate: • Noninferiority of sotagliflozin 400 mg versus empagliflozin on HbA1c reduction from Baseline at Week 26 • Superiority of sotagliflozin 400 mg versus placebo with respect to: - Change from Baseline in 2-hour postprandial glucose (PPG) reduction following a mixed meal tolerance test (MMTT) at Week 26 - Change from Baseline in Fasting plasma glucose (FPG) reduction at Week 26 - Change from Baseline in Body weight reduction at Week 26 - Proportion of patients with HbA1c <6.5% and <7.0% at Week 26 - Change from baseline in sitting systolic blood pressure (SBP) reduction at Week 12 in Patients with SBP ≥130 mmHg at Baseline - Change from baseline in sitting SBP reduction at Week 12 in all patients • Superiority of sotagliflozin 400 mg versus empagliflozin with respect to change from baseline in - HbA1c reduction at Week 26 - Sitting SBP reduction at Week 12 in patients with SBP ≥130 mmHg at Baseline - Sitting SBP reduction at Week 12 in all patients • To evaluate the safety of sotagliflozin 400 mg versus empagliflozin 25 mg, and placebo, throughout the 26-week trial.

	Other objectives: Other objectives of this study are: • To compare sotagliflozin versus empagliflozin and placebo with respect to change from Baseline in: - Estimated glomerular filtration rate (eGFR) - Serum creatinine - Urinary glucose excretion (UGE) and urine glucose to creatinine ratio (UGCR) - Urine albumin to creatinine (UACR) for all patients and patients with UACR >30 mg/g at Baseline - Sitting SBP for patients with Baseline SBP <130 mmHg at Weeks 12 and 26 - Sitting SBP for patients with Baseline SBP ≥130 mmHg at Week 26 - Sitting SBP for all patients at Week 26 - Sitting diastolic blood pressure (DBP) for patients with Baseline SBP ≥130 mmHg at Weeks 12 and 26 - Reduction in body weight by ≥2%, ≥5%, and ≥10%. • To compare sotagliflozin versus empagliflozin with respect to change from Baseline in: - 2-hour PPG reduction following an MMTT at Week 26 - FPG reduction at Week 26 - Body weight reduction at Week 26. • To compare the use of rescue medications for hyperglycemia in the sotagliflozin and empagliflozin treatment groups • To assess plasma levels of sotagliflozin and sotagliflozin-3-O-glucuronide in the sotagliflozin treatment arm • To compare hemodynamic markers (including plasma renin activity [PRA], aldosterone, angiotensinogen 1, angiotensinogen 2 and glucagon) in the sotagliflozin and empagliflozin treatment groups. **Ambulatory Blood Pressure Monitoring substudy** A substudy will be undertaken to monitor ambulatory blood pressure (BP) over 24 hours (in addition to all other study assessments) in a subset of the study population (approximately 180 patients). The objective of the ambulatory blood pressure monitoring (ABPM) substudy is to compare the effect of sotagliflozin, empagliflozin, and placebo in a subset of patients based on: • 24-hour average SBP and DBP • Average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy • Average adjusted sleeping time BP as measured by SBP and DBP with adjustment based on actigraphy.
STUDY DESIGN	This study is a Phase 3, multicenter and multinational, 2:2:1 randomized, double-blind (single-blind Run-in Phase), placebo- and active-controlled, double-dummy, parallel-group study that is anticipated to enroll approximately 700 subjects. Patients with T2D who have inadequate

	glycemic control on DPP4(i) with or without metformin for at least 12 weeks prior to Screening will be eligible for enrollment in this study. To ensure an approximately equal number of patients have Screening SBP <130 mmHg or SBP ≥130 mmHg, the number of patients enrolled in each category will be limited to 60% of all patients (≤420 patients). All patients will have an up to 4-week Screening Period (consisting of a Screening Phase up to 2-weeks and a 2-week, single-blind Run-in phase prior to randomization, followed by a 26-week Double-blind Treatment Phase and a 4-week post-treatment Follow-up visit. To qualify for randomization, patients must demonstrate compliance based upon tablet and capsule count (≥80%) during the Run-in Phase. Randomization will be stratified by: • HbA1c at Screening (≤8.5%, >8.5%) • SBP at Screening (<130 mmHg, ≥130 mmHg) • Metformin use at Screening (Yes, No) Patients will be randomly assigned 2:2:1 to the following 3 treatment groups on top of DPP4(i) with or without metformin: • Sotagliflozin 400 mg • Empagliflozin 25 mg • Placebo The patient's HbA1c, FPG, PPG, UGE, and UGCR will be masked to study centers and patients after randomization and until the end of the study. Additionally, urinalysis by dipstick will not include the measurement of urine glucose. Urine glucose, albumin, calcium, and creatinine will be measured separately at Visits 3, 6, and 8 by the central laboratory. To further evaluate the diurnal effect of sotagliflozin on SBP compared with the comparator arms (placebo and empagliflozin) and to avoid the white-coat effect, SBP will be evaluated by 24-hour ABPM in a subset of 180 patients. **Early termination** If a patient discontinues treatment with investigational medicinal product (IMP) early during the double-blind Treatment Period, the patient will have a Premature End of Treatment (EOT) Visit, and Follow-up Visit 4 weeks after the last dose of IMP. In addition, every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit. If the patient does not agree to site visits, they will be contacted by telephone to inquire about safety status and collect adverse event (AE) data.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with Type 2 Diabetes on DPP4(i) with or without metformin at a stable dose for at least 12 weeks prior to Screening Visit will be included. Metformin dose will be ≥1500 mg per day (or maximum tolerated dose [documented]). DPP4(i) dose must be the appropriate dose as per local label. • Signed written informed consent. **Exclusion criteria:** • At the time of Screening age <18 years or less than legal age of majority, whichever is greater • Type 1 diabetes mellitus

	• Body mass index (BMI) ≤20 kg/m² or >45 kg/m² at Screening • Use of any antidiabetic drug other than DPP4(i) and metformin within 12 weeks preceding the Screening Visit • 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 • Use of weight loss medications or weight change of 5 kg or more during the 12 weeks before Screening • Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol (eg, long-term systemic glucocorticoids) and refusing to or unable to take alternative treatment • Patients who have previously participated in any clinical trial of sotagliflozin/LX4211 • Use of a selective sodium-glucose cotransport type 2 (SGLT2) inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) within 3 months prior to Screening Visit. • Patients with severe anemia, severe CV (including congestive heart failure New York Heart Association IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy that, according to Investigator, will preclude their safe participation in this study, or will make implementation of the protocol or interpretation of the study results difficult • Current diagnosis of chronic hepatitis, and/or other clinically active liver disease requiring treatment • Known presence of factors that interfere with the central laboratory HbA1c measurement (eg, genetic Hb variants) compromising the reliability of HbA1c assessment or medical conditions that affect interpretation of HbA1c results (eg, blood transfusion or severe blood loss in the last 3 months prior to Randomization Visit, any condition that shortens erythrocyte survival) • Patient who has taken other investigational drugs or prohibited therapy for this study within 12 weeks or 5 half-lives from prior to Screening, whichever is longer • Patients with contraindication to empagliflozin as per local labeling • Patients with contraindication to metformin as per local labeling • Hemoglobin A1c <7.0% or >11.0% at Screening (central laboratory) • FPG >270 mg/dL (>15.0 mmol/L) measured by the central laboratory at Screening (Visit 1), and confirmed by a repeat test (>270 mg/dL [>15.0 mmol/L]) before Randomization • Previous use of any types of insulin for >1 month (except for treatment of gestational diabetes) • Pregnant (confirmed by serum pregnancy test at Screening) or breast-feeding women

	• Women of childbearing potential not willing to use highly effective method(s) of birth control during the study treatment period and the follow-up period, or who are unwilling or unable to be tested for pregnancy (see Appendix A), during the study • Mean of 3 separate BP measurements >180 mmHg (SBP) or >100 mmHg (DBP) • History of hypertensive crisis resulting in emergency medical care within 12 weeks prior to Screening • Known allergies, hypersensitivity, or intolerance to SGLT2 inhibitor or any inactive component or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), or intolerance of empagliflozin unless the reaction is deemed irrelevant to the study by the Investigator • Laboratory findings with the central laboratory tests at Visit 1: - Alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of the normal laboratory range (x ULN) - Total bilirubin >1.5 times the ULN (except in case of Gilbert's syndrome) - Neutrophils <1 500/mm^3 (or according to ethnic group) and/or platelets <100 000/mm^3 - Amylase and/or lipase >3 times the ULN - Patients with renal impairment as defined by the eGFR criterion that precludes initiation of empagliflozin as per the approved local label (eg, <45 mL/min/1.73 m^2 in the United States; <60 mL/min/1.73 m^2 in EU) • At the sites with participating ABPM patients, patient works a night (third) shift (defined as 11:00 PM [2300] to 7:00 AM [0700]) • Patient has an upper arm circumference <24 cm or >42 cm • Secondary hypertension of any etiology (eg, renovascular disease, pheochromocytoma, Cushing's syndrome) • If the patient is on hypertensive medications, the antihypertensive has been changed in the 8 weeks prior to Screening (new drug or new dose)
Total expected number of patients	Approximately 700 patients
STUDY TREATMENTS **Investigational medicinal products**	**Single-blind placebo Run-in Phase:** All patients will receive two (2) placebo tablets (identical to sotagliflozin in appearance) and one placebo capsule (identical to empagliflozin capsule in appearance). **26-week Randomized Double-blind Treatment Period:** Patients will receive sotagliflozin, empagliflozin, or placebo treatment. **Sotagliflozin arm**: sotagliflozin 400 mg, given as two (2) 200 mg tablets and one (1) placebo capsule (identical to empagliflozin capsule), once daily before the first meal of the day. **Empagliflozin arm**: placebo, given as two (2) placebo tablets (identical to sotagliflozin in appearance) and one capsule of empagliflozin 25 mg, once daily before the first meal of the day. **Placebo**: given as two (2) placebo tablets (identical to sotagliflozin) and one placebo capsule (identical to empagliflozin) once daily before the first meal of the day.

Formulation:	Tablet or capsule
Route(s) of administration:	Oral
Dose regimen:	Once daily before the first meal of the day
Noninvestigational medicinal products	Patients will continue on their existing DPP4(i) with or without metformin, if applicable. The doses should remain unchanged during the study period unless as needed for safety reason. **Rescue therapy (Glycemic Parameters)** The threshold values for rescue are defined as follows, depending on the study period: • From Baseline Visit (V3, Day 1) to Visit 5 (Week 8) (including value at Visit 5): FPG >270 mg/dL (>15.0 mmol/L) • From Visit 5 (Week 8) to Visit 6 (Week 12) (including value at Visit 6): FPG >240 mg/dL (>13.3 mmol/L) • From Visit 6 (Week 12) up to the end of the treatment period Visit 8 (Week 26): FPG >200 mg/dL (>11.1 mmol/L) or HbA1c ≥8.5% (the 8.5% criteria does not apply if the HbA1c decrease from Baseline was ≥1.0%) Routine fasting self-monitored blood glucose (SMBG) and central laboratory alerts on FPG (and HbA1c after Week 12 and onwards) are set up to ensure that glycemic parameter results remain within predefined thresholds. If a central laboratory FPG and/or HbA1c is above the threshold, the Investigator will receive an alert from the central laboratory. Upon receipt of a central laboratory rescue alert, a central laboratory retest must be completed and confirmed. Likewise, patients are instructed to contact the sites for a confirmatory FPG test via central laboratory in case of high fasting SMBG readings for 3 consecutive days. Hyperglycemia must be confirmed as exceeding the criterion for rescue before rescue therapy is initiated. The central laboratory FPG confirmation should be performed as soon as possible preferably within 7 days by unscheduled visit. If rescue thresholds are reached, it is recommended to use sulfonylurea (glimepiride, if available) first (unless there is a contraindication to sulfonylurea treatment per label). In case of contraindication to sulfonylurea, another antidiabetic medication, eg, insulin or oral antidiabetic drugs (except SGLT2 inhibitors) will be added according to the Investigator's clinical judgment and in accordance with the treatment guidelines. If a patient requires rescue, the IMP received at Randomization should continue and must remain blinded until the end of the study.
ENDPOINT(S)	**Primary efficacy endpoint:** • Change from Baseline to Week 26 in HbA1c. **Secondary efficacy endpoints:** • Change from Baseline to Week 26 in 2-hour PPG following an MMTT • Change from Baseline to Week 26 in FPG

	• Change from Baseline to Week 26 in body weight • Proportion of patients with HbA1c <6.5%, <7.0% at Week 26 (HbA1c responders) • Change from Baseline to Week 12 in sitting SBP in patients with SBP ≥130 mmHg at Baseline • Change from Baseline to Week 12 in sitting SBP in all patients. **Other efficacy endpoints:** • Change from Baseline in: - eGFR - Serum creatinine - UGE and UGCR - UACR for all patients and patients with UACR >30 mg/g - Sitting SBP for patients with Baseline SBP <130 mmHg at Weeks 12 and 26 - Sitting SBP for patients with Baseline SBP ≥130 mmHg at Week 26 - Sitting SBP for all patients at Week 26 - Sitting DBP for patients with Baseline SBP ≥130 mmHg at Weeks 12 and 26 - Reduction in body weight by ≥2%, ≥5%, and ≥10% • Use of rescue medications for hyperglycemia in the sotagliflozin and empagliflozin treatment groups. • Plasma concentration of sotagliflozin and sotagliflozin-3-O-glucuronide for patients receiving sotagliflozin • Hemodynamic markers (including plasma renin activity [PRA], aldosterone, angiotensinogen 1, angiotensinogen 2 and glucagon). **Safety endpoints:** To be collected throughout trial: • 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 • Acute renal failure • Clinical laboratory and vital signs results. **Other endpoints:** • Plasma levels of sotagliflozin and sotagliflozin-3-O-glucuronide in the sotagliflozin treatment arm • Hemodynamic markers (including PRA, aldosterone, angiotensinogen 1, angiotensinogen 2 and glucagon)

	ABPM substudy endpoints: The ABPM endpoints are changes from Baseline to Week 12 and Week 26 for all patients participating in the substudy, patients with baseline 24-hour average SBP ≥130 mmHg and patients with baseline 24-hour average SBP <130 mmHg in: • 24-hour average SBP and DBP • Average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy • Average adjusted sleeping time BP as measured by SBP and DBP with adjustment based on actigraphy.
ASSESSMENT SCHEDULE	See Study Flow Chart (Section 1.2)
STATISTICAL CONSIDERATIONS	**Sample size determination:** A sample size of 280 patients in the sotagliflozin group and 140 patients in the placebo group will provide more than 90% power to detect a difference of 0.6% for change from Baseline to Week 26 in HbA1c between sotagliflozin and placebo (standard deviation [SD]=1.1%; 5% significance level 2-sided). A sample size of 280 patients in the sotagliflozin group and 280 patients in the empagliflozin group will ensure that the upper bound of the 2-sided 95% confidence interval (CI) of the adjusted mean difference would not exceed 0.3% with more than 80% power to show noninferiority for intent-to-treat (ITT) analysis and for completer analysis considering 15% dropout. This calculation assumes a common SD of 1.1%, and the true difference between sotagliflozin and empagliflozin is zero for change from Baseline to Week 26 in HbA1c. The total sample size will be 700 patients to be randomized (sotagliflozin group: 280; empagliflozin group: 280; placebo group: 140). **Analysis population:** Efficacy analyses will be based on the ITT population, defined as all randomized patients, irrespective of compliance with the study protocol and procedures. **Analysis of the primary efficacy endpoint:** Analysis of the primary efficacy endpoints will be performed using the ITT population, using measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. The statistical test will be two-sided tests at a nominal 5% significance level. The primary efficacy endpoint of change from Baseline to Week 26 in HbA1c will be analyzed with missing post-baseline values imputed by placebo control-based copy reference 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 active arms (sotagliflozin and empagliflozin), missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model.

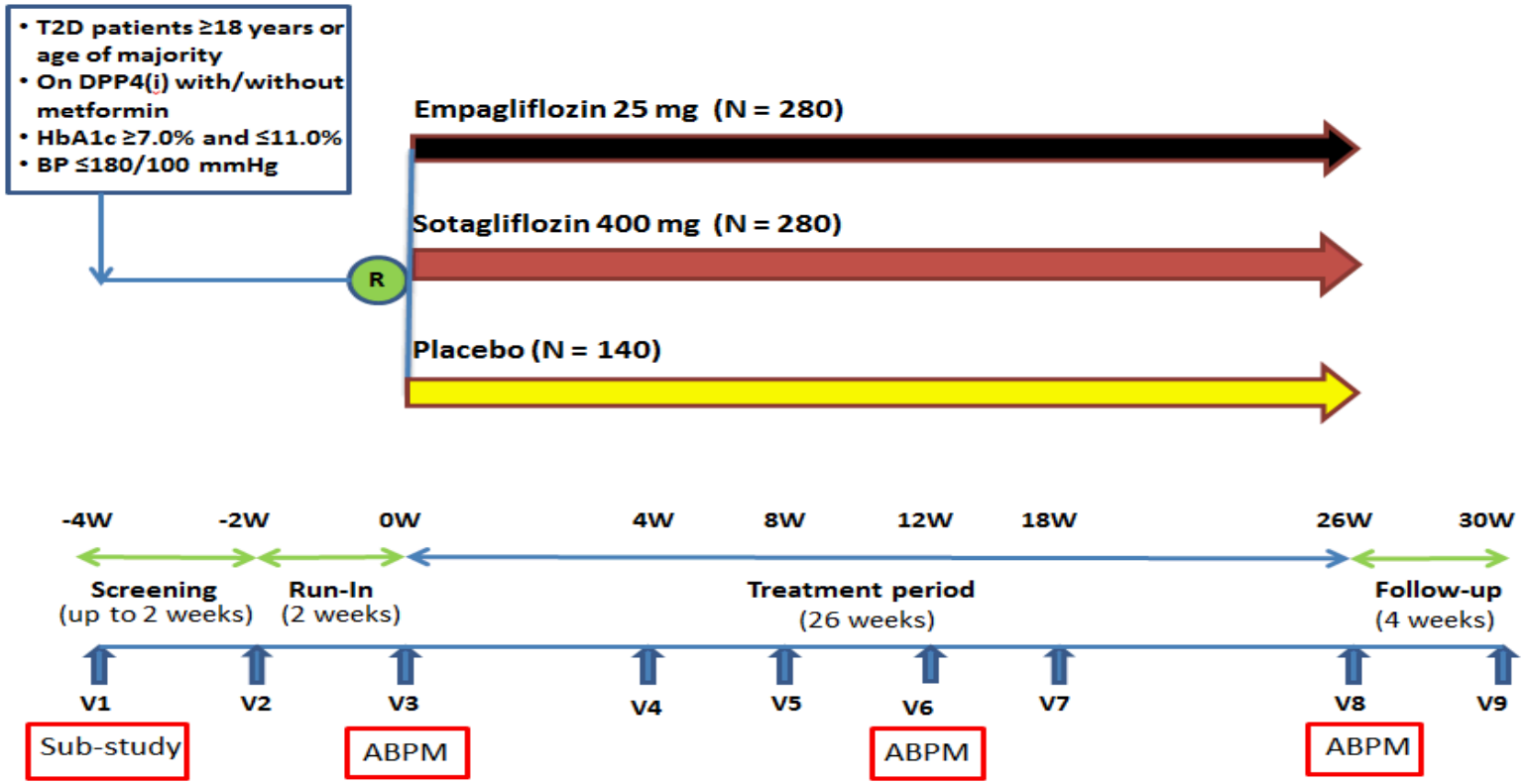
	Each of the complete datasets will be analyzed by the analysis of covariance (ANCOVA) model with treatment groups (sotagliflozin, empagliflozin, placebo), randomization strata of Screening HbA1c (≤8.5%, >8.5%), randomization strata of Screening SBP (<130 mmHg, ≥130 mmHg) and metformin use at Screening (Yes, No), and country as fixed effects, and Baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 26 in HbA1c for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg versus placebo) and the 95% CI for the between-group 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:** For each of the continuous secondary endpoints, a similar approach to the primary efficacy endpoint will be used, with missing values imputed by placebo control-based copy reference 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 active arms (sotagliflozin and empagliflozin) missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model. Each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin, empagliflozin, placebo), randomization strata of Screening HbA1c (≤8.5%, >8.5%), randomization strata of Screening SBP (<130 mmHg, ≥130 mmHg) and metformin use at Screening (Yes, No) and country as fixed effects, and Baseline value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 12/Week 26 for each treatment group, as well as the between-group differences and the 95% CIs for the differences. Categorical secondary endpoints such as HbA1c responders (<6.5%, <7.0%) at Week 26 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization strata of Screening HbA1c (≤8.5%, >8.5%), Screening SBP (<130 mmHg, ≥130 mmHg), and metformin use at Screening (Yes, No). 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, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 26 will be treated as nonresponders. A sensitivity analysis to noninferiority test will be conducted with the 26-week treatment completers (ie, all patients who complete the 26-week

	Treatment Period and do not start rescue therapy) using the Week 26 values and the same ANCOVA model described above. **Multiplicity considerations:** To control for the family-wise Type I error, a fixed-sequence testing procedure will be applied. Once the primary hypothesis (superiority of the change from Baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg versus placebo) is established statistically significant for the primary efficacy endpoint, the following secondary hypotheses will be tested in the following prioritized order: 1. The noninferiority of sotagliflozin versus empagliflozin on HbA1c reduction at Week 26 2. The superiority of sotagliflozin versus placebo on 2-hour PPG reduction at Week 26 3. The superiority of sotagliflozin versus placebo on FPG reduction at Week 26 4. The superiority of sotagliflozin versus placebo on body weight reduction at Week 26 5. The superiority of sotagliflozin versus placebo on HbA1c responder analysis (HbA1c<7.0% at Week 26) 6. The superiority of sotagliflozin versus placebo on sitting SBP reduction at Week 12 in patients with Baseline SBP ≥130 mmHg 7. The superiority of sotagliflozin versus placebo on sitting SBP reduction at Week 12 8. The superiority of sotagliflozin versus empagliflozin on HbA1c reduction at Week 26 9. The superiority of sotagliflozin versus empagliflozin on sitting SBP reduction at Week 12 in patients with Baseline SBP ≥130 mmHg 10. The superiority of sotagliflozin versus empagliflozin on sitting SBP reduction at Week 12. If any hypothesis is found to be not statistically significant, the testing procedure will be stopped and the following hypotheses will not be tested. The noninferiority hypothesis will be declared statistically significant if the upper bound of the 2-sided 95% CI for the adjusted mean difference is <0.3. The superiority hypothesis will be declared statistically significant at $\alpha = 0.05$ (2-sided). **Analysis of other efficacy endpoints:** The analysis of other endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using OC will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time. **Analysis of safety data:** All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. These analyses will be based on the Safety Population, which is defined as all randomized patients who receive at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Patients will be analyzed for safety analyses according to the treatment actually received.

	Analysis of ABPM endpoints: The analysis of ABPM endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using OC of sufficient quality will be provided by each treatment group.
DURATION OF STUDY PERIOD (per patient)	Up to 34 weeks, including a Screening Phase of up to 2 weeks, a 2-week Run-In Phase, a 26-week double-blind Treatment Period and a 4-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: ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DPP4(i) = dipeptidyl peptidase 4 inhibitor; HbA1c = hemoglobin A1c; R = randomization; T2D = Type 2 Diabetes; V = visit; W = week.

1.2 STUDY FLOW CHART

	Screening Period			Double-blind Treatment Period[a]								Follow-up[b]
	Screening	Run-in										
Visit	**1**	**2**	**3A ABPM**	**3 Rando-mization**	**4**	**5**	**6A ABPM**	**6**	**7**	**8A ABPM**	**8**	**9**
Week	**Up to -4**	**-2**	**-1**	**0 Baseline**	**4**	**8**	**12**	**12**	**18**	**26**	**26**	**30**
Day (window [days])		**-14 (±3)**	**-7**	**1**	**28 (±3)**	**56 (±3)**	**83 (±3)**	**84 (±3)**	**126 (±5)**	**181 (±5)**	**182 (±5)**	**210 (±5)**
Informed consent	X											
Interactive Response Technology (IRT) contact	X	X		X	X	X		X	X		X	X
Inclusion criteria	X											
Exclusion criteria	X			X								
Demographics	X											
Medical and surgical history	X											
Medication history	X											
Concomitant medication	X	X		X	X	X		X	X		X	X
Body weight, height[c]	X	X		X	X	X		X	X		X	X
Vital signs[d]	X	X		X	X	X		X	X		X	X
Physical examination:												
Complete	X										X	
Abbreviated[e]		X		X	X	X		X	X			X
Diet and exercise instruction		X		X							X	
Instruction on basic genitourinary (GU) hygiene and hydration		X		X	X	X		X	X		X	

	Screening Period			Double-blind Treatment Period[a]								Follow-up[b]
	Screening	Run-in										
Visit	**1**	**2**	**3A ABPM**	**3 Rando-mization**	**4**	**5**	**6A ABPM**	**6**	**7**	**8A ABPM**	**8**	**9**
Week	**Up to -4**	**-2**	**-1**	**0 Baseline**	**4**	**8**	**12**	**12**	**18**	**26**	**26**	**30**
Day (window [days])		**-14 (±3)**	**-7**	**1**	**28 (±3)**	**56 (±3)**	**83 (±3)**	**84 (±3)**	**126 (±5)**	**181 (±5)**	**182 (±5)**	**210 (±5)**
Randomization				X								
Dispense glucose meter		X										
Collect glucose meter												X
Dispense diary		X		X	X	X		X	X		X	
Collect/review diary				X	X	X		X	X		X	X
Instruction on diabetic ketoacidosis symptoms and glucose testing		X		X	X	X		X	X		X	
Dispense investigational medicinal product (IMP)		X		X	X	X		X	X			
IMP accounting and compliance				X	X	X		X	X		X	
SMBG[f]		X		X	X	X		X	X		X	
12-lead electrocardiogram[g]		X									X	
MMTT/Postprandial glucose[h]				X							X	
Ambulatory blood pressure monitoring (ABPM)[i]			X				X			X		
Central Laboratory testing[j]												
Fasting plasma glucose (FPG)[k]	X			X	X	X		X	X		X	
HbA1c	X			X		X		X			X	
Chemistry	X			X	X			X			X	X

	Screening Period			Double-blind Treatment Period[a]								Follow-up[b]
	Screening	Run-in										
Visit	**1**	**2**	**3A ABPM**	**3 Rando-mization**	**4**	**5**	**6A ABPM**	**6**	**7**	**8A ABPM**	**8**	**9**
Week	**Up to -4**	**-2**	**-1**	**0 Baseline**	**4**	**8**	**12**	**12**	**18**	**26**	**26**	**30**
Day (window [days])		**-14 (±3)**	**-7**	**1**	**28 (±3)**	**56 (±3)**	**83 (±3)**	**84 (±3)**	**126 (±5)**	**181 (±5)**	**182 (±5)**	**210 (±5)**
Hematology	X			X	X			X			X	
Fasting lipids				X							X	
Pregnancy test (WOCBP)[l]	X			X	X	X		X	X		X	
FSH and/or estradiol as needed[l]	X											
Sotagliflozin plasma concentration[m]					X				X		X	
Hemodynamic markers[n]				X				X			X	
Urinalysis with microscopy[o]	X			X							X	
Collection of home overnight urine for albumin, total protein, creatinine, calcium, phosphorus, magnesium, and glucose[p]				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[s]											
AEs/SAEs/AESI/EOSI[s]	To be assessed and reported throughout the study[s]											

a If a patient discontinues treatment with IMP early during the Double-blind Treatment Period, the patient will have a Premature EOT Visit (similar to Visit 8) and a Follow-up Visit 4 weeks ± 5 days after the last dose of IMP. In addition, every effort will be made to have the patient return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit. If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status.

b The Follow-up Visit will take place 4 weeks ± 5 days after the last dose of IMP. All attempts will be made to contact the patient to inquire about safety status.

c Height will be measured only at Screening Visit.

d Vital sign measurements (sitting blood pressure [BP] and heart rate): At the Screening Visit, BP will be measured on both arms to identify and select the appropriate arm for future measurements. Three 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. Assessment for volume contraction and correct volume status, if indicated, will be done before randomization.

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

f The SMBG is to be performed fasting (before first meal of the day) for at least 3 days in the week prior to each study visit. The SMBG should be performed in case of hypoglycemia symptoms; any SMBG values ≤70 mg/dL (≤3.9 mmol/L) should be documented in the diary and collected in the hypoglycemia event case report form (CRF). The SMBG will be presented as equivalent SMPG.

g The 12-lead ECG should be performed after the patient has spent at least 10 minutes in supine position and prior to IMP administration. The ECG results will be evaluated as “normal” or “abnormal”.

h Plasma postprandial glucose will be assessed at Baseline Week 0 and Week 26, 2 hours after consuming a standard mixed liquid breakfast meal via an MMTT.

i Visit for ABPM for a subset of patients (180 patients) will occur 1 week before the Randomization Visit; patients will return the ABPM device by mail after 24-hour monitoring is complete. Patients will also have additional in-person visits for placement of the ABPM device on the day before Week 12 and 26 visits. At least 70% recording of the expected BP recording is needed in each 24-hour period. The measurement will be done on the nondominant upper arm. Patients who discontinue the IMP before the visit for ABPM will not continue in the ABPM substudy post-IMP discontinuation. Patients who receive rescue therapy but remain on IMP will continue on the ABPM substudy as planned.

j With the exception of PPG, all laboratory assessments will occur prior to IMP administration on the day of the visit. All visit dates will be scheduled based on the date of randomization with a ±3-day visit window allowed during the core treatment period, except for Visits 7, 8A, 8, and 9, when a ±5 days visit window will apply. Laboratory tests are outlined in Table 2.

k The FPG collection will be performed on the morning of visit.

l Serum pregnancy testing will be performed only at Screening and urine pregnancy testing is performed at subsequent visits. Serum pregnancy test results must be reviewed prior to beginning the Run-in Phase for all women of childbearing potential (WOCBP, Appendix A). Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations. For women of nonreproductive potential (Appendix A), follicle-stimulating hormone (FSH) and/or estradiol levels should be tested if the definition of postmenopausal or premenopausal cannot be satisfied, eg, no medical document of hysterectomy or cessation of menses <12 months without an alternative medical cause.

m Plasma concentration samples (ie, of sotagliflozin and sotagliflozin-3-O-glucuronide) should be drawn with the other laboratory assessments. However, timing should be carefully recorded; previous dose should be captured in the eCRF. Samples will be collected at predose and for Week 26 an additional sample will be collected 3 hours postdose.

n Hemodynamic markers including PRA, aldosterone, angiotensinogen 1, angiotensinogen 2, and glucagon will be checked to provide better characterization of hemodynamic markers in relation to sotagliflozin treatment.

o Urinalysis will include urine dipstick and microscopy. Dipstick will include assessment of specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. Microscopy will include, but not be limited to, detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment. In the event of abnormal urinalysis findings suspicious of urinary tract infection (UTI), urine culture should be performed. Positive urine culture determination will be based upon the criteria of the reporting laboratory. Additionally, urine culture should be performed if at any point the Investigator suspects the presence of a UTI.

p Patients will collect overnight urine on Week 0, 12, and 26 (Visits 3, 6 and 8). In the night prior to the visits, the urine before sleep will be discarded and the urine during sleep and the first morning urine (after getting up) will be collected. The visits should be rescheduled to allow for urine collection in case a patient missed it. Urinary albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose will be assessed.

[redacted]

s All SAEs, AEs, AESI, and EOSI will be collected starting from signing informed consent and continue until the end of the study. All AEs that occur during treatment should be followed until study completion (or until patients leave the study) or until the event has resolved, the condition has stabilized or the patient is lost to follow-up. All patients will have a Follow-up visit 4 weeks ±5 days after the last dose of IMP to collect safety information.

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3 LIST OF ABBREVIATIONS

ABPM: ambulatory blood pressure monitoring
AE: adverse event(s)
AESI: adverse event(s) 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
CRO: contract research organization
CSR: clinical study report
CV: cardiovascular
DBP: diastolic blood pressure
DILI: drug-induced liver injury
DKA: diabetic ketoacidosis
DMC: Data Monitoring Committee
DNA: deoxyribonucleic acid
DPP4(i): dipeptidyl peptidase 4 inhibitor
ECG: electrocardiogram
eCRF: electronic case report form
eGFR: estimated glomerular filtration rate
EOSI: event(s) of special interest
EOT: End of Treatment
FDA: Food and Drug Administration
FPG: fasting plasma glucose
FSH: follicle-stimulating hormone
GCP: Good Clinical Practice
GI: gastrointestinal
GLP-1: glucagon-like peptide-1
GU: genitourinary
HbA1c: hemoglobin A1C
HLGT: high level group term
HLT: high level term
HR: heart rate
HRT: hormone replacement therapy
IB: Investigator's Brochure
ICF: informed consent form
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID: identification

IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
MACE:	major adverse cardiovascular event(s)
MI:	myocardial infarction
NIMP:	noninvestigational medicinal product
OC:	observed cases
PCSA:	potentially clinically significant abnormality
P-gp:	P-glycoprotein
PK:	pharmacokinetic
PPG:	postprandial glucose
PRA:	plasma renin activity
PT:	preferred term
PYY:	peptide YY
SAE:	serious adverse event(s)
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	Steering Committee
SD:	standard deviation
SE:	standard error
SGLT1:	sodium-glucose cotransporter type 1
SGLT2:	sodium-glucose cotransporter type 2
SMBG:	self-monitoring of blood glucose
SOC:	system organ class
T1D:	type 1 diabetes
T2D:	type 2 diabetes
TEAE:	treatment-emergent adverse event(s)
UACR:	urine albumin to creatinine ratio
UGCR:	urine glucose to creatinine ratio
UGE:	urinary glucose excretion
ULN:	upper limit of normal
US:	United States
UTI:	urinary tract infection
WOCBP:	women of childbearing potential

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: SOTAGLIFLOZIN AND DISEASE

Sotagliflozin is a dual inhibitor of the sodium-glucose cotransporters Type 1 and 2 (SGLT-1 and 2) being developed for use in Type 2 diabetes (T2D), a metabolic disorder characterized by hyperglycemia that results from a combination of increased insulin resistance and beta-cell dysfunction (1). The microvascular complications of diabetes are well known and can result in impaired renal function, retinopathy, and neuropathy. Other comorbidities that are frequently associated with diabetes are hypertension, obesity, and cardiovascular (CV) disease (2).
The Centers for Disease Control and Prevention released a report in 2010 stating that if current trends continue, 1 in 3 Americans will have diabetes by the year 2050 (3). 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 and is estimated to be 642 million by 2040 (4).

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 (5). 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 (4, 5).

The sodium-glucose cotransporter Type 1 (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 delays 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 that are 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 in patients with T2D. Selective inhibitors of the SGLT1 transporter are in early stages of development.

Extensive clinical studies conducted for selective sodium-glucose cotransporter type 2 (SGLT2) inhibitors have established this class as effective agents for the treatment of T2D (8, 9, 10, 11, 12, 13) and have led to approvals by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency. 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 patients has resulted in dose-dependent increases in glucosuria. Multiple-dose (28-day) administration in diabetic patients produced improvements in several metabolic parameters, including urinary glucose excretion (UGE), fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), GLP-1, and PYY (14). These data suggest that sotagliflozin should be of therapeutic benefit to patients with T2D.

In Study LX4211.1-202-DM, patients with systolic blood pressure (SBP) ≥130 mmHg at Baseline had reduction in SBP after 12 weeks of treatment with sotagliflozin (15). The reduction noted in patients with Baseline SBP ≥130 mmHg (a target based on guidelines for management of blood pressure (BP) in diabetic patients and used by several SGLT2 inhibitors) was 1, 3, 10, 16, and 17 mmHg, respectively, in placebo, 75 mg once daily, 200 mg once daily, 400 mg once daily, and 200 mg twice daily of sotagliflozin. Similar to other parameters, the sotagliflozin 400-mg daily dose has optimal effect on the SBP reduction.

Empagliflozin is shown to reduce BP and HbA1c. Patients (N = 825) with T2D and mean seated SBP of 130 to 159 mmHg and diastolic blood pressure (DBP) of 80 to 99 mmHg were randomized (double-blind) to 10 mg or 25 mg empagliflozin or placebo once daily for 12 weeks. At Week 12, adjusted mean difference versus placebo in change from Baseline in mean 24-hour SBP (ambulatory blood pressure monitoring [ABPM]) was -3.44 mmHg (95% confidence interval [CI]: -4.78, -2.09) with 10 mg empagliflozin and -4.16 mmHg (95% CI: -5.50, -2.83) with 25 mg empagliflozin (both p <0.001). At Week 12, adjusted mean difference versus placebo in change from Baseline in mean 24-hour DBP (ABPM) was -1.36 mmHg (95% CI: -2.15, -0.56) with 10 mg empagliflozin and -1.72 mmHg (95% CI -2.51, -0.93) with 25 mg empagliflozin (both p <0.001). Changes in office BP were consistent with ABPM. Adjusted mean difference versus placebo in change from Baseline to Week 12 in HbA1c was -0.62% (95% CI: -0.72, -0.52) (-6.8 mmol/mol [95% CI: -7.9, -5.7]) with 10 mg empagliflozin and -0.65% (95% CI: -0.75, -0.55) (-7.1 mmol/mol [95% CI: -8.2, -6.0]) with 25 mg empagliflozin (both p <0.001) (13).

Based on the glucose-lowering and BP-lowering effects of sotagliflozin and empagliflozin, the purpose of this trial is to evaluate the effects of sotagliflozin (a SGLT1/2 inhibitor) compared with empagliflozin (a SGLT2 inhibitor) and placebo. In addition, patients in this study will be taking concomitant dipeptidyl peptidase 4 inhibitor (DPP4[i]), which will enable the investigation of the increase in medium chain fatty acid and sodium excretion in patients treated with sotagliflozin compared with patients treated with empagliflozin.

4.2 CLINICAL TRIALS OF SOTAGLIFLOZIN IN HUMANS

Approximately 840 subjects (698 assigned to sotagliflozin and 229 assigned to placebo) have participated in completed clinical studies of sotagliflozin. No significant safety concerns have been identified in the sotagliflozin drug program, and sotagliflozin has been well-tolerated in all studies to date. Serious adverse events (SAEs) and discontinuations due to adverse events (AEs) have been infrequent and have been balanced between treatment and comparator groups. Reports of treatment-emergent AEs (TEAEs) across all sotagliflozin studies for which data are available were generally balanced between treatment and comparator groups. The most frequently reported TEAEs (≥2.0%) were headache, nausea, diarrhea, constipation, dizziness, and upper respiratory tract infection, all of which were reported at a greater frequency with sotagliflozin than with placebo. However, most were described as mild to moderate, and most resolved spontaneously and without discontinuation of the study drug.

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

Cumulatively, across the completed studies 8 SAEs were reported in 6 patients (4 patients with T2D and 2 patients with T1D), all of which were assessed as unrelated to study drug; those reported in 4 patients with T2D who received sotagliflozin included pulmonary embolism, deep vein thrombosis, bile duct stone, cholangitis and lower limb fracture, while a myocardial infarction (MI) was experienced by a patient receiving placebo. Two SAEs of diabetic ketoacidosis (DKA) were reported in 2 patients with T1D receiving 400 mg once daily sotagliflozin in the Phase 2 T1D study LX4211.1-203-TIDM (16); both SAEs were assessed as due to failure of insulin delivery via insulin pump.

Study LX4211.1-114-NRM, a drug interaction study with digoxin, a sensitive P-glycoprotein (P-gp) substrate, indicated that sotagliflozin acts as a weak P-gp inhibitor. Thus, sotagliflozin increases systemic exposure of digoxin and other substrates of P-gp (17).

The efficacy of sotagliflozin has been shown in other studies in T2D patients. Study LX4211.1-202-DM, which was also described in Section 4.1, was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the safety and efficacy of sotagliflozin in combination with metformin in patients with T2D who had inadequate glycemic control on metformin monotherapy (N = 299) (15). The primary objective of this dose-ranging study was to evaluate the change from Baseline to Week 12 in HbA1c of 4 different dosing regimens of sotagliflozin (75 mg once daily, 200 mg once daily, 400 mg once daily, and 200 mg twice daily given as tablets) versus placebo in combination with metformin. Prespecified secondary efficacy endpoints were proportion of subjects achieving an HbA1c value of <7.0% at Week 12, change from Baseline in FPG and 3-hour oral glucose tolerance test, and changes from Baseline in body weight, BP, and triglycerides. Sotagliflozin reduced mean HbA1c from Baseline to Week 12 to a statistically and clinically significant degree for all four dose regimens compared to placebo ($p = 0.025$, $p = 0.018$, $p < 0.001$, and $p < 0.001$), respectively. The arithmetic mean change from Baseline in HbA1c was greatest for the 400 mg once daily group (-0.92%), followed by the 200 mg twice daily group (-0.80%). The least squares (LS) mean difference from placebo was also greatest for the 400 mg once daily group (-0.79%; $p < 0.001$), followed by the 200 mg twice daily group (-0.61%; $p < 0.001$). The LS mean differences from placebo were similar for the 200 mg once daily group (-0.34%) and the 75 mg once daily group (-0.33%).

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 400 mg once daily dosage is based on the results of the Phase 2b study LX4211.1-202-DM (15). In this study, dosages of 75 mg once daily, 200 mg once daily, 200 mg twice daily, and 400 mg once daily sotagliflozin were tested over a 12-week, double-blind period. The 400 mg once daily dosage 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 400 mg once daily dosage lowered HbA1c by a mean of 0.92%, while placebo lowered HbA1c by a mean of 0.09%. Lower doses were less effective than the 400-mg dose and did not have any advantages in safety or tolerability. The overall incidence of AEs at the 400 mg once daily dosage was similar to placebo. In addition for this active controlled trial, it is appropriate to compare the projected maximum dose for sotagliflozin versus the approved maximum dose for the comparator (empagliflozin) (12).

In Study LX4211.202, patients with SBP ≥130 mmHg at Baseline had a reduction in SBP after 12 weeks of treatment with sotagliflozin (15). The reduction noted in patients with Baseline SBP ≥130 mmHg was 1, 3, 10, 16, and 17 mmHg, respectively, in placebo, sotagliflozin 75 mg once daily, sotagliflozin 200 mg once daily, sotagliflozin 400 mg once daily, and sotagliflozin 200 mg twice daily. Similar to other parameters, the sotagliflozin 400 mg daily dose has optimal effect on the SBP reduction.

From a safety perspective, sotagliflozin was well tolerated across studies. In healthy subjects, sotagliflozin was well tolerated following single doses up to 2 000 mg, and in multiple doses up to 800 mg over 10 days. Furthermore, in a thorough QT study, single doses of sotagliflozin (800 mg and 2000 mg) were well tolerated and did not prolong the QT interval. Additionally, evaluation of metabolites in urine and plasma of healthy subjects resulted in no safety concerns following single doses of 400 mg sotagliflozin. In patients with T2D, single doses of 400 mg in combination with sitagliptin, and multiple doses up to 400 mg in combination with metformin over 12 weeks were also well tolerated. Additional details on these studies are available in the IB.

4.4 RATIONALE FOR STUDY DESIGN AND CONTROL GROUPS

This study is designed to demonstrate the efficacy in lowering HbA1c, lowering BP and safety of sotagliflozin when used as add-on therapy in patients with T2D who have inadequate glycemic control. 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 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.

The study will be a double-blind design. There will be 3 arms in this study: placebo, empagliflozin, and sotagliflozin. The control group will be treated with the maximum tolerated dose of empagliflozin (SGLT2 inhibitor) or placebo, and the double-blind design will 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. A placebo arm was included to support the primary objective of demonstrating benefit of sotagliflozin as add-on therapy to patients inadequately controlled on a DPP4(i) with or without metformin.

A parallel-group, randomized, controlled design was selected because trial participants are exposed to a single treatment and assignment to that treatment is based solely on chance. This design is free of the limitations of competing designs such as crossover in which there may be a carryover 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 program will also provide efficacy and safety data for sotagliflozin in combination with other antidiabetic medications. The use of sotagliflozin in the treatment of T1D is also being studied in a separate development program.

Sotagliflozin may benefit a wide variety of diabetic patients based on multiple potential beneficial effects of dual 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, BP, and triglycerides observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

Overall, sotagliflozin has been well tolerated in all studies to date, with the majority of events assessed as mild to moderate; most of which resolved spontaneously. Serious AEs and discontinuations due to AEs have been limited and balanced between treatment and comparator groups. Based on an evaluation of the cumulative safety data for the sotagliflozin clinical program, genital infections are monitored closely as an important identified risk. However, reports of these events have been infrequent and have responded to standard treatment.

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 hemoglobin A1c (HbA1c) reduction at Week 26 in patients with T2D who have inadequate glycemic control on a DPP4(i) with or without metformin.

5.2 SECONDARY

The secondary objectives of this study are to demonstrate:

- Noninferiority of sotagliflozin 400 mg versus empagliflozin on HbA1c reduction from Baseline at Week 26
- Superiority of sotagliflozin 400 mg versus placebo with respect to:
  - Change from Baseline in 2-hour PPG reduction following a mixed meal tolerance test (MMTT) at Week 26
  - Change from Baseline in FPG reduction at Week 26
  - Change from Baseline in Body weight reduction at Week 26
  - Proportion of patients with HbA1c <6.5% and <7.0% at Week 26
  - Change from baseline in sitting SBP reduction at Week 12 in Patients with SBP ≥130 mmHg at Baseline
  - Change from baseline in sitting SBP reduction at Week 12 in all patients
- Superiority of sotagliflozin 400 mg versus empagliflozin with respect to change from baseline in:
  - HbA1c reduction at Week 26
  - Sitting SBP reduction at Week 12 in patients with SBP ≥130 mmHg at Baseline
  - Sitting SBP reduction at Week 12 in all patients
- To evaluate the safety of sotagliflozin 400 mg versus empagliflozin 25 mg, and placebo, throughout the 26-week trial.

5.3 OTHER

Other objectives of this study are:

- To compare sotagliflozin versus empagliflozin and placebo with respect to change from Baseline in:
  - Estimated glomerular filtration rate (eGFR)

- Serum creatinine
- Urinary glucose excretion and urine glucose to creatinine ratio (UGCR)
- Urine albumin to creatinine (UACR) for all patients and patients with UACR >30 mg/g at Baseline
- Sitting SBP for patients with Baseline SBP <130 mmHg at Weeks 12 and 26
- Sitting SBP for patients with Baseline SBP ≥130 mmHg at Week 26
- Sitting SBP for all patients at Week 26
- Sitting DBP for patients with Baseline SBP ≥130 mmHg at Weeks 12 and 26
- Reduction in body weight by ≥2%, ≥5%, and ≥10%

- To compare sotagliflozin versus empagliflozin with respect to change from Baseline in:
  - 2-hour PPG reduction following an MMTT at Week 26
  - FPG reduction at Week 26
  - Body weight reduction at Week 26
- To compare the use of rescue medications for hyperglycemia in the sotagliflozin and empagliflozin treatment groups
- To assess plasma levels of sotagliflozin and sotagliflozin-3-O-glucuronide in the sotagliflozin treatment arm
- To compare hemodynamic markers (including plasma renin activity [PRA], aldosterone, angiotensinogen 1, angiotensinogen 2 and glucagon) in the sotagliflozin and empagliflozin treatment groups.

5.4 AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDY

The objective of the ABPM substudy is to compare the effect of sotagliflozin, empagliflozin, and placebo in a subset of patients based on:

- 24-hour average SBP and DBP
- Average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy
- Average adjusted sleeping time BP as measured by SBP and DBP with adjustment based on actigraphy.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multicenter and multinational, 2:2:1 randomized, double-blind (single-blind Run-in Phase), placebo- and active-controlled, double-dummy, parallel-group study that is anticipated to enroll approximately 700 patients.

The study comprises an up to 4-week Screening Period (consisting of a Screening Phase of up to 2 weeks and a 2-week single-blind placebo Run-in Phase), a 26-week Double-blind Treatment Phase, and a 4-week post-treatment Follow-up visit. To qualify for randomization, patients must demonstrate compliance based upon tablet and capsule count (≥80%) during the Run-in Phase.

The study design is presented graphically in Section 1.1.

6.1.1 Screening Period

6.1.1.1 Screening Phase

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

Patients with T2D who have inadequate glycemic control on DPP4(i) with or without metformin for at least 12 weeks prior to Screening are eligible for enrollment in this study. To ensure an approximately equal number of patients have Screening SBP <130 mmHg or SBP ≥130 mmHg, the number of patients enrolled in each category will be limited to 60% of all patients (≤420 patients).

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

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

6.1.1.2 Single-blind Placebo Run-in Phase

The Run-in Phase will last 2 weeks. Patients will be treated in a single-blind manner with placebo (identical to sotagliflozin 200 mg and empagliflozin 25 mg in appearance) administered once daily during the Run-in Phase, starting from Visit 2, to assess patients' compliance to the study medication.

During the Run-in Phase, patients will receive a glucose meter and study diary. Patients will be trained to perform blood glucose measurements and complete the study diary correctly.

6.1.2 Double-blind Treatment Period

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

Randomization will be stratified by:

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

Following randomization, patients will be treated in a double-blind manner for 26 weeks. Approximately 700 patients will be randomly assigned 2:2:1 to the following 3 treatment groups on top of DPP4(i) with or without metformin:

- Sotagliflozin arm (estimated N = 280): sotagliflozin 400 mg, given as two (2) 200 mg tablets and one (1) placebo capsule (identical to empagliflozin capsule), once daily before the first meal of the day
- Empagliflozin arm (estimated N = 280): placebo, given as two (2) placebo tablets (identical to sotagliflozin in appearance) and one capsule of empagliflozin 25 mg, once daily before the first meal of the day
- Placebo arm (estimated N = 140): placebo, given as two (2) placebo tablets (identical to sotagliflozin) and one placebo capsule (identical to empagliflozin), once daily before the first meal of the day.

The doses of the OADs (DPP4[i]) and/or metformin should be held constant throughout the entire 26-week double-blind Treatment Period (ie, not changed except for safety reasons), and the dose of all antihypertensive medications should be held constant for the first 12 weeks except for safety reasons.

6.1.3 Ambulatory blood pressure monitoring substudy

In several preselected study sites, approximately 180 patients will participate in a substudy of ABPM to further assess BP changes over time. In sites participating in the ABPM substudy, patients must consent to conducting ABPM to participate in this study until the planned number of subset patients has been reached (sites will be informed).

Baseline ABPM will be measured starting at an additional study visit 1 week before Randomization (Visit 3A). Postrandomization ABPM will take place at 2 additional in-person study visits 1 day prior to the Week 12 (Visit 6A) and Week 26 (Visit 8A) visits. The details of the ABPM substudy procedures are provided in Appendix B.

6.1.4 Follow-up period

Following the last dose of the investigational medicinal product (IMP; either as scheduled or prematurely), a post-treatment Follow-up Visit should be scheduled for all patients 28 days (4 weeks) ±5 days after permanent IMP discontinuation to collect safety information.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The total duration of the study for each patient will be up to 34 weeks and will include a Screening Phase of up to 2 weeks, a 2 week Run-in Phase, a 26-week double-blind Treatment Period, and a 4-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 the Follow-up Visit.

The Sponsor can terminate the trial prematurely based on the advice of the independent data monitoring committee (DMC) (Section 6.4.2) 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) will be composed of experts in diabetes and scientists with clinical and methodological expertise.

This Committee, led by a Chair, will be responsible for producing and conducting a scientifically sound study and for ensuring accurate reporting of the study. In that capacity, the SC will need to 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.

Details of the activities and responsibilities of the SC are provided in a separate 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 study safety data by treatment
- Make 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 in Section 6.4.3 for adjudication, as well as any additional safety data considered relevant. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician and measures will be taken to ensure the validity of the data.

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

6.4.3 Clinical Endpoint Committee

The Clinical Endpoint Committees (CECs) 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, major adverse cardiovascular events (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 injury (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 separate Charters.

7 SELECTION OF PATIENTS

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

For study sites participating in the ABPM substudy, patients must also consent to the ABPM to participate in this study until the planned the number of participants has been reached.

7.1 INCLUSION CRITERIA

I 01. Patients with Type 2 Diabetes on DPP4(i) with or without metformin at a stable dose for at least 12 weeks prior to Screening Visit. Metformin dose will be ≥1500 mg per day (or maximum tolerated dose [documented]). DPP4(i) dose must be the appropriate dose per local label.

I 02. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in Section 7.1 will be screened for exclusion criteria.

7.2.1 Exclusion criteria related to study methodology

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

E 02. Body mass index (BMI) ≤20 kg/m^2 or >45 kg/m^2 at Screening

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

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

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

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

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

E 08. Known presence of factors that interfere with the central laboratory HbA1c measurement (eg, genetic Hb variants), compromising the reliability of HbA1c assessment, or medical conditions that affect interpretation of HbA1c results (eg, blood transfusion or severe blood loss in the last 3 months prior to Randomization Visit, any condition that shortens erythrocyte survival)

E 09. History of drug or alcohol abuse within 6 months prior to Screening

E 10. 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 11. At the sites with participating ABPM patients, patients work night (third) shift (defined as 11:00 PM [23:00] to 7:00 AM [07:00])

E 12. Patient has an upper arm circumference <24 cm or >42 cm

E 13. Patients unwilling or unable to perform self-monitoring of blood glucose (SMBG), complete the patient diary, or comply with study visits and other study procedures as required per protocol.

7.2.2 Exclusion criteria related to mandatory background therapies

E 14. Type 1 diabetes mellitus

E 15. HbA1c <7.0% or >11.0% at Screening Visit (central laboratory)

E 16. FPG >270 mg/dL (>15.0 mmol/L) measured by the central laboratory at Screening (Visit 1), and confirmed by a repeat test (>270 mg/dL [>15.0 mmol/L]) before Randomization Visit

E 17. Use of any antidiabetic drug other than DPP4(i) and metformin within 12 weeks preceding the Screening Visit

E 18. Previous use of any types of insulin for >1 month (except for treatment of gestational diabetes)

E 19. History of DKA or nonketotic hyperosmolar coma within 12 weeks prior to the Screening Visit

E 20. Use of a selective SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) within 3 months prior to Screening Visit

E 21. Patient who has taken other investigational drugs or prohibited therapy for this study within 12 weeks or 5 half-lives from prior to Screening, whichever is longer

E 22. Patients with contraindication to metformin as per local labeling.

7.2.3 Exclusion criteria related to the current knowledge of sotagliflozin and empagliflozin

E 23. Patients with contraindication to empagliflozin as per local labeling.

E 24. Pregnant (confirmed by serum pregnancy test at Screening) or breast-feeding women.

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

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

E 27. History of hypertensive crisis resulting in emergency medical care within 12 weeks prior to Screening Visit.

E 28. History of gastric surgery including history of gastric banding or inflammatory bowel disease within 3 years prior to the Screening Visit.

E 29. Known allergies, hypersensitivity, or intolerance to SGLT2 inhibitor or any inactive component or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), or intolerance of empagliflozin unless the reaction is deemed irrelevant to the study by the Investigator.

E 30. Laboratory findings with the central laboratory tests at Visit 1

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of the normal laboratory range (x ULN)
- Total bilirubin >1.5 x ULN (except in case of Gilbert's syndrome)
- Neutrophils <1500/mm^3 (or according to ethnic group) and/or platelets <100 000/mm^3
- Amylase and/or lipase >3 x ULN
- Patients with renal impairment as defined by the eGFR criterion that precludes initiation of empagliflozin as per the approved local label (eg, <45 mL/min/1.73 m^2 in US; <60 mL/min/1.73 m^2 in EU).

E 31. Secondary hypertension of any etiology (eg, renovascular disease, pheochromocytoma, Cushing's syndrome)

E 32. For patients on hypertensive medications, the antihypertensive has changed in the 8 weeks prior to Screening (new drug or new dose).

E 33. Current diagnosis of chronic hepatitis, and/or other clinically active liver disease requiring treatment.

E 34. Any country-related specific regulation that would prevent the patient from entering the study (eg, individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities).

7.2.4 Additional exclusion criteria during or at the end of screening before randomization

E 35. Patients insufficiently compliant during Run-in Phase. Noncompliance will be based on tablet and capsule count (<80%) or based on the opinion of the Investigator

E 36. Patient withdraws informed consent before randomization (patient who is not willing to continue) or patient fails to return

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

E 38. Lower extremity complications (such as skin ulcers, infection, osteomyelitis and gangrene) identified during the Screening period, and still requiring treatment at Randomization.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

The IMPs are sotagliflozin 400 mg, empagliflozin 25 mg, and matching placebo. Patients will be provided with kits containing wallets of sotagliflozin or empagliflozin, or their sotagliflozin-matching placebo (supplied as tablets identical to sotagliflozin 200 mg tablets in appearance) or empagliflozin-matched placebo (supplied as capsules identical to empagliflozin 25 mg capsules in appearance). Each patient will be supplied with the appropriate number of kits, on a schedule according to the dispensing scheme indicated in the study flow chart (See Section 1.2).

Table 1 provides a summary of the IMP (dose and timing).

Table 1 - Summary of investigational medicinal products during Treatment Period

Treatment group	Sotagliflozin 400 mg group	Empagliflozin 25 mg group	Placebo group
Name of IMP	Sotagliflozin (SAR439954)	Empagliflozin	Placebo
Pharmaceutical form	Sotagliflozin (SAR439954) will be supplied as 200 mg tablets	Empagliflozin will be supplied as 25 mg capsules	Placebo will be supplied as tablets (identical to sotagliflozin in appearance) and capsules (identical to empagliflozin in appearance)
Dose, timing, and route of administration	Two 200-mg tablets, taken orally once daily, before first meal of the day One placebo capsule	One 25 mg capsule, taken orally once daily, before first meal of the day Two placebo tablets	Two placebo tablets and one placebo capsule, taken orally once daily, before first meal of the day
Duration of treatment	26-week double-blind Treatment Period following randomization	26-week double-blind Treatment Period following randomization	2 weeks Run-in and 26 weeks following randomization
Storage conditions	Store between +15°C and +30°C (59°F and 86°F)		

IMP = investigational medicinal product

No dose reductions are planned.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Noninvestigational medicinal product (NIMP) treatment is defined as the rescue medication(s) that will be used to treat hyperglycemia when a patient's hyperglycemia reaches the rescue threshold. It also includes the background medications DPP4(i) and metformin.

8.2.1 Background medications

Patients will be enrolled with a background therapy consisting of their existing DPP4(i) treatment and metformin treatment (for patients on metformin at Screening). Background metformin and DPP4(i) are considered to be NIMPs.

Metformin (commercial formulation) will be administered orally according to the Investigator's recommendation and the locally approved label. The metformin dose must be ≥1500 mg per day (or maximum tolerated dose [documented]). The dose of metformin must be stable for at least 12 weeks before Screening. The metformin dose should remain unchanged during the 26-week treatment period unless down-titration or discontinuation is required for safety reasons, or the patient's requirement for rescue medication.

The DPP4(i) will be administered orally at the appropriate dose per local label. The dose of DPP4(i) must be stable for at least 12 weeks before the Screening Visit and should remain unchanged during the 26-week treatment period unless as needed for safety reasons, or the patient's requirement for rescue medication.

Metformin and DPP4(i) treatment will be reported in the electronic case report form (eCRF). This information should include specific drug name, dose, route of administration, and frequency.

The cost of the background treatment metformin and DPP4(i) not covered by health insurance will be reimbursed where permitted by local regulations.

Rescue therapies (see Section 8.2.2) will also be considered as NIMPs.

8.2.2 Rescue therapy

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

- From Baseline Visit (Visit 3, Day 1) to Visit 5 (Week 8) (including value at Visit 5): FPG >270 mg/dL (>15.0 mmol/L)
- From Visit 5 (Week 8) to Visit 6 (Week 12) (including value at Visit 6): FPG >240 mg/dL (>13.3 mmol/L)
- From Visit 6 (Week 12) up to the end of the treatment period Visit 8 (Week 26): FPG >200 mg/dL (>11.1 mmol/L) or HbA1c ≥8.5%.

  Note: The 8.5% criterion does not apply if the HbA1c decrease from Baseline was ≥1.0%).

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

- If one fasting SMBG value exceeds the specific glycemic limit on 1 day, the patient will check it again during the 2 following days. If all the values in 3 consecutive days exceed the specific limit, the patient should contact the Investigator and a central laboratory FPG measurement (and HbA1c after Week 12 and onwards) will be performed as soon as possible, preferably within 7 days to confirm the hyperglycemia.

- Upon receipt of a central laboratory rescue alert a central laboratory retest must be completed **and confirmed as exceeding the criterion** for rescue before rescue therapy is initiated. The retest confirmation should be performed as soon as possible, but within 7 days of receipt by unscheduled visit.

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

- The increased FPG has been tested at a fasting status (ie, no food and drink [with the exception of water] intake for ≥8 hours)
- IMP 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 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 eCRF and the medical record)
- Stress the absolute need to be compliant with treatment
- Organize a specific interview with the patient and a Registered Dietician or other qualified nutrition professional and to reinforce on the absolute need to be compliant to diet and lifestyle recommendations, and schedule a FPG/HbA1c assessment at the next visit (in case the next visit is a phone call, it should be replaced by an on-site visit).

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

- Sulfonylurea (eg, glimepiride) should be added first, unless there is a contraindication to sulfonylurea treatment per label. In case of contraindication to sulfonylurea, another rescue medication (oral or injectable) can be added at the Investigator's decision except for SGLT2 inhibitors
- The patient continues the study treatment (blinded) and stays in the study to collect efficacy and safety information. The planned visits and assessments should occur until the last scheduled visit
- Rescue therapy is considered a NIMP. Rescue therapy is to be reported in the eCRF. This information should include specific drug name, dose, route of administration, and frequency.

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

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

To maintain blinding sotagliflozin, empagliflozin, and their matching placebo tablets (including 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.

To prevent partial unblinding, results of laboratory assessments of HbA1c, FPG, PPG, UGE, and UGCR will be masked to study centers and patients after randomization and until study end. Additionally urinalysis by dipstick will not include the measurement of urine glucose. Urine glucose, albumin, calcium, and creatinine will be measured separately at Visit 3, 6, and 8 by the central laboratory.

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 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 database lock.

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 sotagliflozin 400 mg, empagliflozin 25 mg, or matching placebo once daily during the randomized double-blind Treatment Period. Randomization (ratio 2:2:1) will be stratified by HbA1c at Screening (≤8.5%, >8.5%), SBP at Screening (<130 mmHg, ≥130 mmHg), and metformin use at Screening (Yes, No).

The randomization and the treatment package allocation are performed centrally by an IRT. At the Screening Visit, the Investigator or designee will contact the IRT to receive the patient number. [redacted] At Visit 2 (Run-in), the IRT will be contacted for dispensing single-blinded placebo Run-in kit. At Visit 3 (Baseline), patient eligibility will be reviewed; the IRT will be contacted and corresponding treatment packages will be allocated.

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.

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 rescreened in the IRT and assigned a new patient number in IRT (first Screening Visit is to be registered as a screen failure in the IRT), and complete the Screening Visit procedures and assessments again.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

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

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

Control of IMP storage conditions, especially control of temperature and instructions for handling the compounds should be managed according to the rules provided by the Sponsor.

The expiry date and storage conditions are written on the IMP labels. The IMPs should be stored between +15ºC and +30ºC (59ºF and 86ºF).

8.7 RESPONSIBILITIES

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

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

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

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, to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party 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 (Treatment Day 1) and all subsequent on-treatment visits.

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

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

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

8.7.2 Return and/or destruction of treatments

Patients are to return all IMP (unused, in-use, or empty wallet[s]) at each on-site visit, or at on-site visits after premature treatment discontinuation, as described in Section 1.2.

Patients are to return all the used, in-use and unused IMP at Visit 8 (or final assessment on-treatment visit in case of permanent premature discontinuation).

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

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

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP. The IMP includes sotagliflozin 400 mg, empagliflozin 25 mg, and placebo.

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

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

8.8.1 Prohibited prior and concomitant medications

During the study treatment period, the following medications are prohibited:

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

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

- Systemic use of glucocorticoids is not allowed for more than 10 consecutive days within 90 days prior to the Screening Visit.

Note: Topical, ophthalmic, nasal spray, or inhaled applications are allowed.

- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin) are not allowed for rescue or post-IMP treatment until the planned end of the study (Visit 9, Week 30)
- Modification of antihypertensive medication before Week 12 is not allowed unless for safety reasons
- Use of investigational medication in any other clinical study
- Initiation of any weight loss drugs (eg, phentermine, orlistat)
- Patients taking sotagliflozin with concomitant digoxin should have digoxin concentrations monitored and doses reduced as needed. In addition, other P-gp substrates may be affected and the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments.

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

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

8.9 POSTSTUDY TREATMENT

Because sotagliflozin may reduce BP, adjustment of antihypertensive medication may be needed during the study in patients with hypertension. Conversely, monitoring for an increase in BP should be performed after withdrawal of study medication. If the BP is elevated after withdrawal of study treatment, the Investigator should consider adding or adjusting antihypertensive medication.

Sotagliflozin will not be provided after End of Treatment (EOT). Patient's further treatment, for diabetes and other pathologies, will be at the Investigator's discretion based on his/her clinical judgment.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINT

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

9.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the change from Baseline to Week 26 in HbA1c.

9.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Change from Baseline to Week 26 in 2-hour PPG following an MMTT
- Change from Baseline to Week 26 in FPG
- Change from Baseline to Week 26 in body weight
- Proportion of patients with HbA1c <6.5%, <7.0% at Week 26 (HbA1c responders)
- Change from Baseline to Week 12 in sitting SBP in patients with SBP ≥130 mmHg at Baseline
- Change from Baseline to Week 12 in sitting SBP in all patients.

9.1.3 Other efficacy endpoints

Other efficacy endpoints include:

- Change from Baseline in:
  - eGFR
  - Serum creatinine
  - UGE and UGCR
  - UACR for all patients and patients with UACR >30 mg/g
  - Sitting SBP for patients with Baseline SBP <130 mmHg at Weeks 12 and 26
  - Sitting SBP for patients with Baseline SBP ≥130 mmHg at Week 26
  - Sitting SBP for all patients at Week 26
  - Sitting DBP for patients with Baseline SBP ≥130 mmHg at Weeks 12 and 26
  - Reduction in body weight ≥2%, ≥5%, and ≥10%.
- Use of rescue medications for hyperglycemia in the sotagliflozin and empagliflozin treatment groups

- Plasma concentration of sotagliflozin and sotagliflozin-3-O-glucuronide for patients receiving sotagliflozin
- Hemodynamic markers (including plasma renin activity [PRA], aldosterone, angiotensinogen 1, angiotensinogen 2 and glucagon).

9.1.4 Assessment methods of efficacy endpoints

9.1.4.1 Hemoglobin A1c

Hemoglobin A1c will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 8 (Visit 5), Week 12 (Visit 6), and Week 26 (Visit 8), measured by a certified Level I "National Glycohemoglobin Standardization Program" central laboratory.

9.1.4.2 Blood pressure

Blood pressure is measured as part of the vital signs assessment that is performed at all study visits, except for ABPM substudy visits, for both safety and efficacy endpoints. At Screening, BP will be measured on both arms to identify and select the appropriate arm for future measurements. Full details and directions for the measurement of BP and heart rate (HR) are presented in Appendix E. The investigator will assess for volume contraction and correct volume status if indicated before randomization.

9.1.4.3 Postprandial glucose via MMTT

Postprandial glucose will be assessed at Baseline (Visit 3, Week 0) and at Visit 8 (Week 26) via MMTT to allow estimation of change from Baseline to Week 26 in 2-hour PPG following a mixed meal. For the efficacy assessments of the study, PPG will be measured at a central laboratory. Full details of the MMTT procedure at Baseline and Week 26 are presented in Appendix C. At Baseline (Visit 3) and Visit 8 (Week 26), PPG will be assessed by MMTT at Baseline (fasting) and 2 hours after consuming a standard mixed liquid breakfast meal.

The first dose of double-blind IMP (and dosing with DPP4[i] and metformin, if applicable) on Day 1 (Visit 3) will be given **after** collection of the 2-hour PPG sample is completed.

For the Week 26 (Visit 8) standardized MMTT, the patient should take the dose of double-blind IMP immediately after the fasting blood samples are obtained, and approximately 30 minutes **before** ingestion of the standardized mixed meal begins. At Week 26, DPP4(i) and metformin (if applicable) dosing will occur **after** collection of the 2-hour PPG sample and 3-hour PK sample is completed.

Plasma concentration samples at Week 26 (Visit 8) should be taken at the same time as the fasting blood sample and 3 hours postdose (30 minutes after the 2-hour PPG sample collection; see Section 9.3.1.1).

The composition and the quantity of the standard mixed liquid breakfast meal must be identical throughout the study; see Appendix C for further details. In some study sites, for which the

standard meal supplies are not approved by the local regulatory agency, the patients will not participate in the MMTT. Any patient who requires the addition of rescue medication prior to Week 26 should still have the standardized MMTT performed as scheduled.

In case of permanent discontinuation of the treatment with IMP before Week 26, every effort will be made to have the patient return to the site at the time of their Week 26 visit; however, the MMTT should not be performed at these or any other visit following a Premature EOT visit.

On the days of the MMTT, patients will come to the investigational site in the morning, in fasted conditions for at least 8 hours and must not eat any food or drink, except water, before the scheduled standardized meal test.

The exact times of the IMP administration, standard mixed liquid breakfast meal intake, and the blood draws are to be documented.

9.1.4.4 Fasting plasma glucose

Fasting plasma glucose will be assessed at all study visits except at the Run-in Phase Visit (Week -2, Visit 2), the Follow-up Visit (Week 30, Visit 9), and ABPM substudy visits. Fasting is defined as no food and drink (with the exception of water) intake for ≥8 hours. The FPG assessment is performed on the morning of the visit. For the efficacy assessments of the study, FPG is measured at a central laboratory.

9.1.4.5 Body weight

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

9.1.4.6 Kidney function parameters

Serum creatinine will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 4 (Visit 4), Week 12 (Visit 6), Week 26 (Visit 8), and the Follow-up Visit (Visit 9). Home-collected urine albumin, total protein, creatinine, calcium, phosphorus, magnesium, and glucose will be assessed at Baseline (Visit 3), Week 12 (Visit 6), Week 26 (Visit 8), and the Follow-up Visit (Visit 9) (Section 1.2). Details of urine collection and analysis are provided in Section 9.2.1.4.

9.1.4.7 Use of rescue medications for hyperglycemia

The use of rescue medications for hyperglycemia will be assessed and reported throughout the double-blind Treatment Period. Routine alerts on FPG and/or HbA1c will be sent to the Investigator from the central laboratory to ensure that glycemic parameter results remain within predefined thresholds. For details and further actions should FPG values fall above thresholds, refer to Section 8.2.2.

9.2 SAFETY ENDPOINTS

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

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

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

The following safety endpoints will be assessed throughout the 26-week double-blind Treatment Period:

- Adverse events, 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, SAEs, and deaths
- Acute renal failure (see Section 9.1.4.6)
- 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 pretreatment 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 the double-blind IMP.

9.2.1 Assessment methods of safety endpoints

9.2.1.1 Adverse events

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

9.2.1.1.1 Adverse events of special interest

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

9.2.1.1.2 Events of special interest

Events of special interest are a separate category from AESI. For a list of events defined as EOSI and their reporting requirements see Section 10.4.1.4 and Section 10.4.4, respectively.

9.2.1.2 Hypoglycemia

Hypoglycemia events (all, severe, and/or documented symptomatic hypoglycemia) will be assessed starting with signing of the ICF until 4 weeks after the last dose of IMP (**Note:** For patients who discontinue treatment before Week 26, safety data will be collected until scheduled study end). Patients will also complete the patient diary, which will be regularly reviewed by Investigators. See Section 10.6.1 for further details.

9.2.1.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including clinical chemistry, hematology amylase, lipase, fasting lipid profile, and additional evaluations) and urinalysis, according to the schedule presented in Section 1.2. Clinical laboratory values will be evaluated after conversion into standard international units. International units will be used in all listings and tables. Table 2 lists the blood safety parameters to be assessed by the central laboratory. Urinalysis parameters are presented in Section 9.2.1.4.

In addition, for WOCBP, a serum pregnancy test is performed at Screening (Visit 1, Week -4) and urine pregnancy tests are taken at all visits during the double-blind Treatment Period (there is no pregnancy testing at the Run-in Phase Visit (Visit 2, Week -2). Any positive urine test result must be confirmed by a serum pregnancy test. The Investigator may perform additional pregnancy tests at their discretion or as required by local regulations.

For women of nonreproductive potential (Appendix A), follicle-stimulating hormone (FSH) and/or estradiol levels should be tested if the definition of postmenopausal or premenopausal cannot be satisfied, eg, no medical documentation of hysterectomy or cessation of menses <12 months without an alternative medical cause.

Table 2 - Blood safety parameters

Clinical chemistry	Hematology	Other parameters
Sodium	Complete blood count (CBC)	**Fasting lipid profile**
Potassium	Differential WBC	Total cholesterol (TC)
Chloride	Platelet count	High-density lipoprotein cholesterol (HDL-C)
Carbon dioxide (bicarbonate)	Hemoglobin	Low-density lipoprotein cholesterol (LDL-C)[b]
Blood urea nitrogen (BUN)	Hematocrit	Non–HDL-C[c]
Creatinine (for eGFR calculation[a])	Erythrocyte count	Triglycerides (TG)
Glucose (serum)		
Alanine aminotransferase (ALT)		**Other tests**
Aspartate aminotransferase (AST)		Amylase
Total bilirubin (TB)		Lipase
Alkaline phosphatase (ALP)		
Uric acid		
Phosphorus		
Total protein		
Albumin		
Magnesium		
Creatine phosphokinase (CPK)		
Lactic acid dehydrogenase (LDH)		

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

a The eGFR will be calculated. The recommended equation for estimating eGFR from serum creatinine is the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation (18, 19). The IDMS-traceable version of the MDRD Study equation will be used. Either equation below may be used based on whether the laboratory reports conventional units or Standardized International (SI) units.
Conventional Units (for use predominantly in the US): http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-conventional-unit.asp
SI Units (for use predominantly outside the US): http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units.asp.

b LDL-C will be calculated by Friedwald equation.

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

9.2.1.4 Urinalysis

Urinalysis (urine dipstick with microscopy) will be performed at the Screening Visit (Visit 1), Baseline Visit (Visit 3), and at the end of the Double-Blind Treatment Period (Visit 8, Week 26). Central laboratory urinalysis includes:

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

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

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

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

Serum creatinine will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 4 (Visit 4), Week 12 (Visit 6), Week 26 (Visit 8), and the Follow-up Visit (Visit 9). Home-collected urine albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose will be assessed at Baseline (Visit 3), Week 12 (Visit 6), and Week 26 (Visit 8) (Section 1.2).

Patients will collect home overnight urine samples during the night prior to Visits 3 (Week 0), 6 (Week 12) and 8 (Week 26). The urine sample before the sleep will be discarded and all urine during sleep and the first urine after getting up the next morning will be collected.

A central laboratory will analyze samples and estimate change from Baseline in UACR, UGE, UGCR, serum creatinine, and eGFR. To prevent partial unblinding, results of laboratory assessments of HbA1c, FPG, PPG, UGE, and UGCR will be masked to study centers and patients after randomization and until study end.

9.2.1.5 Vital signs and physical examination

Vital signs, including sitting BP and HR, will be assessed at all study visits, except for ABPM substudy visits, for safety and efficacy endpoints. Full details and directions for the measurement of BP and HR are presented in Appendix E.

Physical examinations will be performed at every study visit.

A complete physical examination will be performed at Visit 1 (Screening) and Visit 8 (Week 26). Body weight measurements are discussed in Section 9.1.4.5. The complete physical examination will include recording height, body weight, and vital signs. Height will be measured only at Screening Visit, for BMI calculations.

An abbreviated physical examination will be performed at the Run-in Phase Visit (Visit 2, Week -2), at every visit during the Double-blind Treatment Period except for Visit 8, and at the Follow-up or Premature EOT Visit (within 4 weeks of the last dose of IMP or after patient withdraws early from treatment). The abbreviated physical examination should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs, if necessary.

9.2.1.6 Electrocardiogram variables

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

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

The ECG results will be evaluated as "normal" or "abnormal".

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

9.2.1.7 Self-monitored blood glucose

A meter for the self-assessment of blood glucose will be dispensed at the start of Run-in (Visit 2). Patients will receive a patient diary at each visit except for the Follow-up Visit (Week 30) and ABPM substudy visits. The patient will enter SMBG levels into this diary. The diary will be collected and reviewed by investigators and study staff at each visit (except ABPM substudy visits).

Patients will be asked to self-assess blood glucose levels 3 times a week (at least 3 times in the week prior to a study visit) from the Run-in Visit (Visit 2) through the end of the study (Visit 9).

Patients will be requested to self-assess blood glucose levels in the fasted state and whenever they experience any illnesses (eg, cold, flu), or symptoms of hyperglycemia or hypoglycemia. Symptoms of hypoglycemia may include shakiness, dizziness, sweating, hunger, headache, pale skin color, sudden moodiness or behavior changes (such as crying for no apparent reason), clumsy or jerky movements, seizure, difficulty paying attention or confusion, or tingling sensations around the mouth. Patients will be instructed to record the presence or absence of hypoglycemic episodes or hypoglycemic symptoms in the patient diary provided. Patients will also be instructed to record SMBG values that are ≤70 mg/dL (≤3.9 mmol/L) in the patient diary.

SMBG for hyperglycemia: 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 Baseline Visit (Visit 3, Day 1) to Visit 5 (Week 8) (including value at Visit 5)
- >240 mg/dL (13.3 mmol/L) from Visit 5 (Week 8) to Visit 6 (Week 12) (including value at Visit 6)
- >200 mg/dL (11.1 mmol/L) from Visit 6 (Week 12) to Visit 8 (Week 26) (including value at Visit 8).

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics of sotagliflozin

The PK endpoint for sotagliflozin is the plasma levels of sotagliflozin and sotagliflozin-3-O-glucuronide in the sotagliflozin treatment arms.

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

9.3.1.1 Sampling time

At Weeks 4, 18, and 26 (Visits 4, 7, and 8, respectively), blood samples for PK assessment are to be drawn with the other laboratory assessments, prior to administration of IMP. An additional blood sample will be drawn at Week 26 (Visit 8), 3 hours after administering the dose of IMP (30 minutes after the 2-hour PPG sample collection). The time of the last intake of study drug prior to visits PK samples were taken should be recorded by the patient in the patient diary. Patients should be reminded of this at visits preceding PK time points to ensure these details are captured. In the case of premature IMP discontinuation, PK samples should not be drawn at the Premature EOT Visit, or at subsequent visits. See Table 3 for identification of samples.

Table 3 - Sotagliflozin samples identification

Visit	Week	Relative to dosing	PK
Visit 4	Week 4	Predose	P00
Visit 7	Week 18	Predose	P01
Visit 8	Week 26	Predose	P02
Visit 8	Week 26	3 hours postdose	P03

PK: pharmacokinetic

9.3.1.2 Pharmacokinetics handling procedure

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

9.3.1.3 Bioanalytical method

Concentration of sotagliflozin and its 3-O-glucuronide metabolite

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

[redacted]

9.3.3 Hemodynamic markers

Hemodynamic markers including PRA, aldosterone, angiotensinogen 1, angiotensinogen 2, and glucagon will be assessed.

9.3.4 Ambulatory blood pressure monitoring substudy

A 24-hour ABPM substudy will be conducted in a subset of 180 patients, with ABPM assessed at Baseline (Visit 3A, Week -1), Visit 6A (Week 12), and Visit 8A (Week 26) (see Section 6.1.3).

The ABPM endpoints are changes from Baseline to Week 12 and Week 26 for all patients participating in the substudy, patients with baseline 24-hour average SBP ≥130 mmHg and patients with baseline 24-hour average SBP <130 mmHg in:

- 24-hour average SBP and DBP
- Average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy
- Average adjusted sleeping time BP as measured by SBP and DBP with adjustment based on actigraphy.

Exclusion criteria for ABPM analyses due to nonevaluable data will be defined in the statistical analysis plan (SAP). The procedure for the ABPM substudy and required quality of the BP data are specified in Appendix B.

[redacted]

9.5 APPROPRIATENESS OF MEASUREMENTS

Sotagliflozin therapy in patients with T2D who have inadequate glycemic control with DPP4(i) with or without metformin is expected to lower HbA1c over 26 weeks of treatment (primary efficacy analysis). Sotagliflozin treatment for 26 weeks is likely to be of sufficient duration to observe effects on reduction of HbA1c, and is, therefore, selected as the time point for assessment of the primary endpoint HbA1c.

The concentration of HbA1c reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2 to 3 months. Hemoglobin A1c has also been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is known to reduce the risk of long-term microvascular complications. Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. The duration of study treatment (26 weeks for the primary HbA1c endpoint) is considered to be sufficient for achieving stable conditions with IMP and for enabling an adequate assessment of time-dependent changes in HbA1c.

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.

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

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

To further evaluate the diurnal effect of sotagliflozin on SBP compared with the comparator arms (placebo and empagliflozin) and to avoid the white-coat effect, a subset of patients (180 patients) similar to the full study population in BP levels (ie, equal distribution in SBP <130 mmHg or ≥130 mmHg) will be evaluated by ABPM.

Safety analyses focus on the TEAEs include occurrences with SAE, AESI, EOSI, AE leading to IMP discontinuation, and hypoglycemic events. Other standard safety parameters such as vital signs, ECG and laboratory measurements will also be evaluated. The other efficacy and safety assessments in this study are standard, well-established measurements for a Phase 3 study evaluating the treatment of T2D in adult participants.

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 and 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 and assessments should be performed.

This is an out-patient study and consists of 9 on-site visits (a total of 12 on-site visits for patients participating in the ABPM substudy).

The patients need to arrive at the study site in a fasting state for Visit 1 through Visit 8 (Week -4/Screening through Week 26/end of double-blind Treatment Period), 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. With the exception of PPG, all laboratory assessments will occur prior to IMP administration on the day of the visit.

The Run-in Visit (Visit 2) can be performed up to 2 weeks after the Screening Visit and once the results of all Screening tests are available and the patient is confirmed to be eligible for participation in the study. The visit windows for the Double-blind Treatment Period visits will be as follows: Visit 4 through Visit 6 should occur at the schedule ±3 days; Visit 7 through Visit 8 should occur at the schedule ±5 days. For the Follow-up Visit (Visit 9), the visit window should occur within ±5 days, 4 weeks after 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 Flow Chart (Section 1.2), which details the procedures to be performed.

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

10.1.1 Screening Period

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

10.1.1.1 Screening phase

The Screening Phase will be up to 2 weeks in duration and includes Visit 1 (Week -4) only. The Screening Phase must be long enough to collect the data to establish whether the patient satisfies the inclusion/exclusion criteria.

Patients will undergo Screening assessments at Visit 1 (Week -4) following signing of the ICF. Patients who meet the inclusion criteria as noted in Section 7.1 and 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 the Run-in Phase of this study. In these cases, a patient will need to sign a new ICF, be registered as a rescreened in IRT and assigned a new patient number in IRT (first Screening Visit is to be registered as screen failure in IRT), and complete Screening Visit procedures and assessments again.

10.1.1.1.1 Screening Visit, Visit 1 (Week -4)

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

- Obtain informed consent:
  - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration. Written information will be provided to the patient. Written informed consent must be signed by the patient and Investigator prior to any investigations
  - [redacted]
  - [redacted]
  - For the ABPM substudy, written informed consent must be obtained prior to involvement (at Screening Visit).
- IRT notification (allocation of ID, registration of Screening)
- Assessment of inclusion/exclusion criteria
- Collection of demographic data (age, gender, race, and ethnic origin)
- Assessment of the patient's medical and surgical history, including history, treatment and complications (eye, kidney, history of smoking/tobacco use, history of alcohol, and history of amputation events, etc) of T2D
- Concomitant medication and medication history, including any prior medications for T2D
- Complete physical examination including height, body weight, and vital signs (SBP and DBP, HR, temperature, and respiratory rate). After 5 minutes resting, seated SBP, DBP, and HR will be assessed 3 times with at least 1 minute between each measurement (see Appendix E for details).

- The following laboratory testing (by the central laboratory):
  - FPG
  - HbA1c
  - Serum pregnancy testing for WOCBP or serum FSH and/or estradiol (for women of nonreproductive potential if definition of postmenopausal or premenopausal cannot be satisfied; see Appendix A)
  - Clinical chemistry (including amylase, lipase, and uric acid) and hematology.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Urinalysis (dipstick and microscopy).
- Patients will be instructed to return to the site in the fasting state for Visit 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 Run-in Visit, Visit 2 (Week -2)

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

- Measurement of body weight
- Abbreviated physical examination:
  - The abbreviated physical examination should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs, if necessary) and vital signs (SBP and DBP, and HR). After 5 minutes of rest, seated SBP, DBP, and HR will be assessed 3 times with at least 1 minute between each measurement (see Appendix E for details on BP and HR measurement).
- Diet and exercise instruction will be provided
- Instructions on basic GU hygiene and hydration is provided
- Patient diary is dispensed and instructions/training are provided
- Blood glucose meter is dispensed and instructions/training are provided
- Fasting SMBG is assessed.
- Instructions on DKA symptoms, glucose testing, basic genitourinary (GU) hygiene, and hydration (see Appendix D)
- The IRT is notified for registration of Run-in Visit and allocation of single-blind Run-in kit
- The 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
- 12-lead ECG is conducted

- Patients are instructed to return to the site in the fasting state with used/not-used single-blind Run-in kit for Visit 3 (Randomization).

10.1.1.2.2 Ambulatory Blood Pressure Monitoring visit (Week -1)

A subset of patients (180 patients) will complete ABPM. The first ABPM visit will occur 1 week before Randomization (Visit 3A, Week -1). Patients will return the ABPM device by mail after 24-hour monitoring is complete. At least 70% recording of the expected BP recording is needed in each 24-hour period. The measurement will be done on the nondominant arm. Additional details on ABPM procedures are provided in Appendix B.

10.1.2 Double-blind Randomized 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, empagliflozin 25 mg, or matching placebo for the 26-week Double-Blind Treatment Period. All randomized patients will be followed at regular on-site visits for the duration of the Treatment Period.

In addition to routine laboratory testing, the following will be performed at specified time points: PK samples for sotagliflozin and sotagliflozin metabolite plasma concentration; collection of home overnight urine for assessment of albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose.

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

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

10.1.2.1 Visit 3, Randomization, Day 1 (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 and vital signs
- IMP accountability and compliance with single-blind placebo Run-in treatment
- IRT to be notified and randomization to occur

- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported
- Diet and exercise instruction
- Patient diary collected and reviewed and a new one is dispensed. Instructions/training are provided as needed
- Instructions on DKA symptoms, glucose testing, basic GU hygiene, and hydration is provided
- Fasting SMBG is assessed
- Patients are evaluated for glycemic rescue (see Section 9.1.4.7)
- The following laboratory testing (by the central laboratory):
  - FPG
  - HbA1c
  - Urine pregnancy testing for WOCBP
  - Clinical chemistry (including amylase, lipase, and fasting lipids)
  - Hematology
  - Hemodynamic markers
  - Urinalysis (dipstick and microscopy)
  - Collection of home overnight urine for albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose.
- Collection of samples for additional laboratory testing:
  - [redacted]
  - [redacted]
- PPG assessment via MMTT 2 hours after consuming a standard mixed liquid breakfast meal
- IMP is dispensed
- Patients are instructed to return to the site in the fasting state for their next visit (Visit 4; Week 4)
- Patients should be reminded to record the time of study drug intake on the day before their next visit
- For accountability and compliance purposes, patients are instructed to return to the site with their used, in-use and not-used wallet(s) dispensed during Visit 3.

10.1.2.2 Week 4 to Week 18 (Visit 4 to Visit 7)

The following procedures will be performed at Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12), and Visit 7 (Week 18), except as specified:

- Concomitant medications will be assessed
- Measurement of body weight
- Abbreviated physical examination and vital signs
- IMP accountability and compliance for double-blind IMP
- IRT will be notified IMP for resupply
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) occurring since the previous visit will be reported
- Patients will be evaluated for glycemic rescue
- Patient diary will be collected and reviewed and a new one will be dispensed. Instructions/training will be provided as needed
- Instructions on DKA symptoms, glucose testing, basic GU hygiene, and hydration will be provided
- Fasting SMBG will be assessed
- Central laboratory testing:
  - FPG: all visits
  - HbA1c: Visit 5 (Week 8) and Visit 6 (Week 12)
  - Clinical chemistry, including amylase and lipase: Visit 4 (Week 4) and Visit 6 (Week 12)
  - Hematology: Visit 4 (Week 4) and Visit 6 (Week 12)
  - Pregnancy test (WOCBP): all visits
  - FSH and/or estradiol: as needed
  - Predose PK (plasma concentration samples for sotagliflozin and sotagliflozin-3-O-glucuronide): Visit 4 (Week 4), Visit 7 (Week 18)
  - Hemodynamic markers: Visit 6 (Week 12)
  - Collection of home overnight urine for albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose will be done prior to Visit 6 (Week 12)
  - [redacted]
  - [redacted]

- Patients participating in the ABPM assessments will have an additional visit 1 day before the Week 12 visit (Visit 6A) for placement of the ABPM device. The ABPM device will be returned at the Week 12 visit (Visit 6) the following day
- IMP is dispensed
- Patients are instructed to return to the site in the fasting state for each subsequent visit
- Patients should be reminded to record the time of study drug intake on the day before their next visit
- For accountability and compliance purposes, patients are instructed to return to the site with their kit(s) dispensed during the previous visit.

10.1.2.3 Week 26 (Visit 8) - End of Treatment

The following procedures will be performed at this visit:

- Concomitant medications are assessed
- Measurement of body weight
- Complete physical examination including vital signs
- IMP accountability and compliance
- Diet and exercise instruction
- Instructions on DKA symptoms, glucose testing, basic GU hygiene, and hydration
- IRT will be notified
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) occurring since the previous visit will be reported
- Patients evaluated for glycemic rescue
- Patient diary will be collected and reviewed and a new one will be dispensed. Instructions/training will be provided as needed
- 12-lead ECG
- Fasting SMBG will be assessed.
- The following laboratory testing (by the central laboratory):
  - FPG
  - HbA1c
  - Clinical chemistry (including amylase, lipase, and fasting lipids)
  - Hematology
  - Hemodynamic markers
  - Urine pregnancy testing for WOCBP
  - Urinalysis sample collection (dipstick and microscopy)

- Collection of home overnight urine for albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose.
- [redacted]
- Predose PK (plasma concentration sample for sotagliflozin and sotagliflozin-3-O-glucuronide) and postdose PK (collected 3 hours after IMP administration.

- PPG assessment via MMTT 2 hours after consuming a standard mixed liquid breakfast meal
- Patients participating in the ABPM assessments will have an additional visit 1 day before the Week 26 visit (Visit 8A) for placement of the ABPM device. The ABPM device will be returned at the Week 26 visit (Visit 8) the following day
- Patients are to return all the used, in-use, and unused IMP at Visit 8 (or final assessment on-treatment visit in case of permanent premature discontinuation).

10.1.3 Post-treatment Follow-up Period

The post-treatment Follow-up Period will include an on-site visit, 4 weeks ± 5 days after the last dose of IMP.

The following procedures will be performed at this visit:

- Concomitant medications will be assessed.
- Measurement of body weight.
- Abbreviated physical examination including vital signs.
- IRT to be notified.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) since the previous visit will be reported.
- Collect glucose meter.
- Patient diary is collected and reviewed.
- Central laboratory testing:
  - Clinical chemistry (including amylase and lipase).

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient's file

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

- Agreement and signature of ICF with the study ID

- Study ID (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)
- AEs 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 ID details, the informed consent signed by the patient, the study ID (name), dates of study visits, and the main reasons for screen failure.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the patient should remain in the study and followed for the remainder of the study to collect vital safety status and endpoint data.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

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

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

It is in the interest of the patient to monitor their blood glucose during the temporary discontinuation period, therefore regular determination of SMBG is to be performed and documented (see Section 9.2.1.7).

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

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

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is 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 if they decide to do so, at any time, and irrespective of the reason, or this may be the Investigator’s decision. Patients should discuss stopping study medication with the site before doing so, to allow for questions to be addressed, glycemic therapy to be adjusted, and a follow-up assessment to be arranged. All efforts should be made to document the reasons for treatment discontinuation; this reason should be documented in the eCRF.

The following reasons can lead to permanent discontinuation:

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

- Intercurrent condition that requires permanent discontinuation of the study treatment as long as the abnormality persists and if the casual relationship of the concerned event and the IMP is possible (according to the Investigator's best medical judgment)
- Pregnancy (in female patients)
- Specific request of the Sponsor
- Renal dysfunction as defined as eGFR <45 mL/min/1.73 m^2 which is confirmed with a repeat test (by a local or central laboratory) as soon as possible, preferably within a week.

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

For patients who prematurely discontinue the IMP, the assessments planned at EOT visit (Section 1.2) will be performed at the Premature EOT Visit scheduled preferably prior to treatment discontinuation or as soon as possible after the time of discontinuation (at the latest at the next scheduled on-site visit), and a Follow-up Visit 4 weeks (±5 days) after the last dose of IMP. In addition, every effort will be made to have the patient return to the site at the time corresponding to their scheduled visits, particularly the Week 26 Visit. If the patient does not agree to site visits, they will be contacted by telephone to inquire about safety status and collect AE data. In the case of premature IMP discontinuation, no PK samples should be taken at the Premature EOT Visit or at any subsequent visit. The reason(s) for IMP discontinuation will be clearly specified. This Premature EOT assessment may occur at a regularly scheduled or at an unscheduled visit.

10.3.4 Handling of patients after permanent treatment discontinuation

Every effort should be made to maintain patients in the study. Patients should be followed up according to the study procedures as 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 (Section 1.2) 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, or at any subsequent visits. For patients who discontinue treatment but remain in the study, the remaining study visits should occur as scheduled where possible. The IRT should be notified of EOT.

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

10.3.5 Procedure and consequence for patient withdrawal from study

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

If possible, the patients are assessed using the procedure normally planned for the Week 26 (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.

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

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact 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 rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

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

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

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

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

10.4.1.3 Adverse event of special interest

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

The AESI for this study are:

- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP:
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2)
  - In the event of pregnancy in a female participant, IMP should be discontinued
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix A).
- Symptomatic overdose with IMP/NIMP:
  - A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and resulting in clinical symptoms and/or signs accompanied by administration of more than twice the intended daily dose within a 24-hour period. It will be recorded in the eCRF as an AESI with immediate notification "Symptomatic OVERDOSE (accidental or intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.

Note: An asymptomatic overdose with the IMP/NIMP, accidental or intentional, is defined as administration of more than twice the intended daily dose within a 24-hour period, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient, not based on accountability assessment. It will be recorded as an AE "Asymptomatic OVERDOSE, accidental or intentional".

- ALT increase >3 x ULN (refer to related flowchart, Appendix F).

10.4.1.4 Events of special Interest

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

The EOSI for this study are:

- MACE (CV death, MI, or stroke) and other specific CV events (eg, heart failure leading to hospitalization)
- Severe hypoglycemia (see Section 10.6.1)
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candidal balanitis in males)
- UTIs
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Diarrhea
- Pancreatitis
- Bone fractures
- Venous thrombotic events, to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- DKA
- Renal events, to include 50% decline in eGFR, end-stage kidney disease, renal death
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid cancer)
- AEs 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 pages of the eCRF
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s)
- In this study, the use of concomitant medications including antidiabetic medications, as well as metformin and DPP4(i), may make it difficult to assess the causal relationship, particularly for hypoglycemia. The Global Safety Officer with input from other appropriate study team members will determine the causal relationship when it is not clearly provided by the Investigator
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, 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 sign, or ECG abnormalities are to be recorded as AEs if they are medically relevant based on the investigator's medical judgment, eg,:
  - Symptomatic, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI or EOSI.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team and pharmacovigilance after approval of the Investigator within the eCRF
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification
- A back-up plan (using a paper CRF process) must be available and should be used when the eCRF system does not work.

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

10.4.4 Guidelines for reporting adverse events of special interest

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

10.4.5 Guidelines for reporting events of special interest

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

10.4.6 Guidelines for management of specific laboratory abnormalities

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

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

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

10.4.7 Guidelines for reporting product complaints (IMP/NIMP)

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

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

10.5 OBLIGATIONS OF THE SPONSOR

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

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

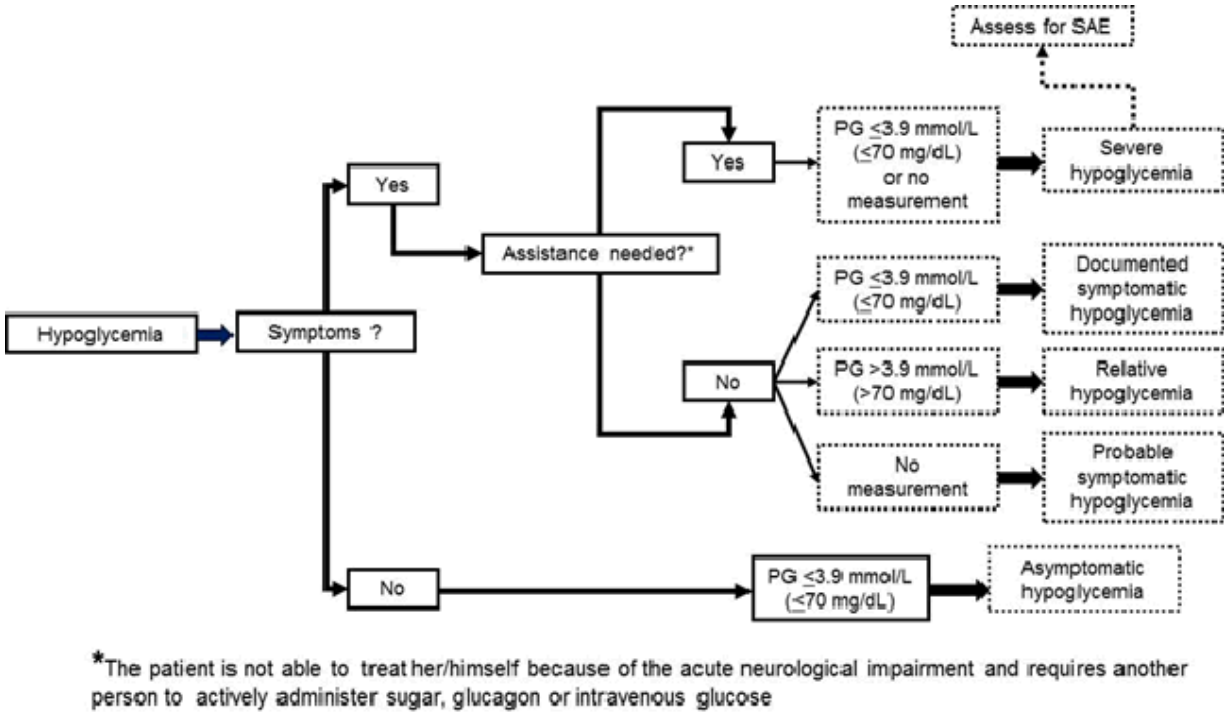
10.6.1 Hypoglycemia

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

Hypoglycemia is categorized according to the American Diabetes Association workgroup on hypoglycemia classification (20, 21) and summarized in Figure 1.

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

Figure 1 - Hypoglycemia classification in Study EFC14867



*The patient is not able to treat her/himself because of the acute neurological impairment and requires another person to actively administer sugar, glucagon or intravenous glucose

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 blood glucose values may not be available, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

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

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

Documented symptomatic hypoglycemia

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

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

Asymptomatic hypoglycemia

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

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

Probable symptomatic hypoglycemia

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

Relative hypoglycemia

Relative hypoglycemia, recently termed "pseudo-hypoglycemia" (22), is an event during which the patient reports typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L).

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations were performed based on the primary endpoint.

A sample size of 280 patients in the sotagliflozin group and 140 patients in the placebo group will provide more than 90% power to detect a difference of 0.6% for change from Baseline to Week 26 in HbA1c between sotagliflozin and placebo (standard deviation [SD]=1.1%; 5% significance level 2-sided).

A sample size of 280 patients in the sotagliflozin group and 280 patients in the empagliflozin group will ensure that the upper bound of the 2-sided 95% CI of the adjusted mean difference would not exceed 0.3% with more than 80% power to show noninferiority for intent-to-treat (ITT) analysis and for completer analysis considering 15% dropout. This calculation assumes a common SD of 1.1%, and the true difference between sotagliflozin and empagliflozin is zero for change from Baseline to Week 26 in HbA1c.

The total sample size will be approximately 700 patients to be randomized (sotagliflozin group: 280; empagliflozin group: 280; placebo group: 140).

11.2 DISPOSITION OF PATIENTS

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

- Screened patients: patients who have signed the ICF
- Run-in patients
- Randomized patients: patients with a treatment kit number allocated and recorded in IRT database, regardless of whether the treatment kit was used or not
- The safety population (ie, randomized and treated patients)
- The ITT population
- The randomization strata (HbA1c at Screening [≤8.5%, >8.5%], SBP at Screening [<130 mmHg, ≥130 mmHg], and metformin use at Screening [Yes, No]). Any discrepancy between the strata assigned by IRT and the information reported on eCRF will be listed for all randomized patients.
- Patients who have completed the 26-week Double-Blind Treatment Period
- Patients who discontinued the IMP during the 26-week Double-Blind Treatment Period, and the reasons for treatment discontinuation
- Patients who have completed the study
- Patients who discontinued the study, and the reasons for study discontinuation.

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

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

Patients treated 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 included 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.

11.3.2 Intent–to-treat population

Efficacy analyses (with the exception of MMTT 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.

For some sites for which the standard meal supplies are not approved by the local regulatory agency, the patients will not participate in the MMTT. Those patients in the specific region will not be included in the efficacy population for MMTT analyses (change from Baseline to Week 26 in 2-hour PPG following an MMTT).

11.3.3 Safety population

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

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

In addition:

- 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 active treatment group and placebo, the patient will be analyzed in the corresponding active treatment group
- When a patient is exposed to both sotagliflozin and empagliflozin, 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 at least 1 dose of double-blind IMP.

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 (OCs), ie, inclusion of only patients having nonmissing assessments at a specific visit.

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

For serum creatinine and eGFR, the Baseline value is defined as 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 SAP.

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

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

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

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

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

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

11.4.1.2 Compliance

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

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

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).

11.4.2.1 Analysis of primary efficacy endpoint

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

Analysis of the primary efficacy endpoint (change from Baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg versus placebo) 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 from Baseline to Week 26 in HbA1c will be analyzed with missing post-baseline values imputed by placebo control-based copy reference 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 active arms (sotagliflozin and empagliflozin), missing data will be imputed as if the patients were on placebo throughout the study, where all patients'

measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model.

Each of the complete datasets will be analyzed by the analysis of covariance (ANCOVA) model with treatment groups (sotagliflozin, empagliflozin, placebo), randomization strata of Screening HbA1c (≤8.5%, >8.5%), randomization strata of Screening SBP (<130 mmHg, ≥130 mmHg) and metformin use at Screening (Yes, No) and country as fixed effects, and Baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg vs placebo) and the 95% CI for the between-group 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 OCs).

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 kg/m^2, ≥30 kg/m^2)
- Baseline HbA1c (≤8.5%, >8.5%)
- Baseline SBP (<130 mmHg, ≥130 mmHg)
- Country
- Metformin use at Screening (Yes, No)
- Baseline eGFR (≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73m^2 [Normal])
- Duration of diabetes (<10, ≥10 years).

The treatment effects across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 26 in HbA1c in the ITT population, and using a similar approach to the analysis for the primary efficacy endpoint. The adjusted estimates of treatment mean differences (comparing sotagliflozin 400 mg versus empagliflozin and placebo) with SE and 95% CIs will be provided as appropriate across the subgroups using contrast statements.

In the event that the subgroup factor is identical or similar to a randomization strata factor (eg, Baseline HbA1c category); only the subgroup factor (as a single factor and/or an interaction

term) will be included in the model to avoid the issue of co-linearity in the analysis. The corresponding strata factor will not be included in the model.

11.4.2.2 Analyses of secondary efficacy endpoints

For each of the continuous secondary endpoints, a similar approach to the primary efficacy endpoints will be used, with missing values imputed by placebo control-based copy reference multiple imputation method under the missing not at random framework:

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

Each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin, empagliflozin, placebo), randomization strata of Screening HbA1c (≤8.5%, >8.5%), randomization strata of Screening SBP (<130 mmHg, ≥130 mmHg) and metformin use at Screening (Yes, No) and country as fixed effects, and Baseline value as a covariate. For analysis 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 12/Week 26 for each treatment group, as well as the between-group differences and the 95% CIs for the differences.

Categorical secondary endpoints such as HbA1c responders (<6.5%, <7.0%) at Week 26 will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization strata of Screening HbA1c (≤8.5%, >8.5%), Screening SBP (<130 mmHg, ≥130 mmHg) and metformin use at Screening (Yes, No). 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, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 26 will be treated as nonresponders.

A sensitivity analysis to noninferiority test will be conducted with the 26-week treatment completers using the Week 26 values and the same ANCOVA model described above.

11.4.2.3 Analysis of other efficacy endpoints

The analysis of other endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using OCs 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 for the family-wise Type I error, a fixed-sequence testing procedure will be applied.

Once the primary hypothesis (superiority of the change from Baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg versus placebo) is established statistically significant for the primary efficacy endpoint, the following secondary hypotheses will be tested in the following prioritized order:

1. The noninferiority of sotagliflozin versus empagliflozin on HbA1c reduction at Week 26
2. The superiority of sotagliflozin versus placebo on 2-hour PPG reduction at Week 26
3. The superiority of sotagliflozin versus placebo on FPG reduction at Week 26
4. The superiority of sotagliflozin versus placebo on body weight reduction at Week 26
5. The superiority of sotagliflozin versus placebo on HbA1c responder analysis (HbA1c<7.0% at Week 26)
6. The superiority of sotagliflozin versus placebo on sitting SBP reduction at Week 12 in patients with Baseline SBP ≥130 mmHg
7. The superiority of sotagliflozin versus placebo on sitting SBP reduction at Week 12
8. The superiority of sotagliflozin versus empagliflozin on HbA1c reduction at Week 26
9. The superiority of sotagliflozin versus empagliflozin on sitting SBP reduction at Week 12 in patients with Baseline SBP ≥130 mmHg
10. The superiority of sotagliflozin versus empagliflozin on sitting SBP reduction at Week 12.

If any hypothesis is found to be not statistically significant, the testing procedure will be stopped and the following hypotheses will not be tested. The noninferiority hypothesis will be declared statistically significant if the upper bound of the 2-sided 95% CI for the adjusted mean difference is <0.3. The superiority hypothesis will be declared statistically significant at $\alpha = 0.05$ (2-sided).

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

11.4.3 Analyses of safety data

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

Safety endpoints are presented in Section 9.1.2. These analyses will be based on the Safety Population as defined in Section 11.3.3. Patients will be analyzed for safety analyses according to the treatment actually received. All safety analyses will be performed on the safety population as defined in Section 11.3.3 using the following common rules:

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

- Potentially clinically significant abnormality (PCSA) values for clinical laboratory tests and vital signs will be defined as abnormal values considered medically important by the

Sponsor's Global Pharmacovigilance and Epidemiology department and in effect at the time of the final SAP approval. The PCSA criteria for parameters not cited in the protocol as safety parameters will not be analyzed

- The PCSA criteria will determine which patients had at least 1 PCSA during the Double-blind Treatment Period, taking into account all evaluations performed during the Double-blind Treatment Period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

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

11.4.3.1 Analysis of adverse events

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

Treatment-emergent AEs are AEs that developed or worsened (according to the Investigator's opinion) or became serious during the 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 (n) and percentage (%) of patients who died by study period (on-study, on-treatment, poststudy) summarized on the safety population by treatment received
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (n) and percentage (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adverse events leading to permanent treatment discontinuation

Treatment-emergent AEs leading to permanent treatment discontinuation will be summarized and presented as number (n) and percentage (%) of patients in each treatment group.

11.4.3.2 Analyses of hypoglycemia

The number (n) and percentage (%) of patients and rate in patient-years (2 types: the number of patients with events or the total number of events per 100 patient-years) of all hypoglycemia, severe hypoglycemia, and documented symptomatic hypoglycemia will be summarized by treatment group, respectively. In addition, documented hypoglycemia will also be analyzed by using a threshold of plasma glucose of <54 mg/dL (<3.0 mmol/L) if applicable. 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. Any ALT increase of >3 x ULN will be included in laboratory PCSA summary.

11.4.3.4 Analyses of events of special interest

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

11.4.3.5 Analyses of laboratory variables

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

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

11.4.3.6 Analyses of vital sign variables

The number (n) and percentage (%) of patients with PCSA at any evaluation during the 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 Analysis of 12-lead electrocardiogram status

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

11.4.4 Analyses of other endpoints

11.4.4.1 Pharmacokinetic

The PK endpoints are presented in Section 9.3.1. Pharmacokinetic sotagliflozin data may be subjected to a population PK analysis, which will be reported separately.

Individual plasma concentrations of sotagliflozin and of sotagliflozin-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 (predose, 3 hours postdose), 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.

11.4.4.2 Hemodynamic markers

The hemodynamic marker endpoints are presented in Section 9.3.3.

Hemodynamic markers including PRA, aldosterone, angiotensinogen 1, angiotensinogen 2, and glucagon will be checked to provide better characterization of hemodynamic markers in relation to sotagliflozin treatment.

11.4.4.3 Ambulatory blood pressure monitoring substudy

The analysis of ABPM endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using OC of sufficient quality will be provided by each treatment group.

11.5 INTERIM ANALYSIS

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

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

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

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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.

Separate informed consent will be sought for participation in the ABPM substudy.

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

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

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

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, IB with any addenda or labeling documents, summary of product characteristics, package insert, Investigator’s curriculum vitae, 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

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR 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 regarding ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

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

13.3 SOURCE DOCUMENT REQUIREMENTS

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

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

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

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

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

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

The computerized handling of the data by the Sponsor or 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 eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidentiality for 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 eCRF, the IB, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Patient race and ethnicity (race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, unknown; ethnicity: Hispanic, Not Hispanic) will be collected in this study because these data are required by several regulatory authorities (eg, on African American population for US FDA, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on Chinese population for the Chinese Food and Drug Association 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). The data may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel 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 will inform the Sponsor and authorize the Sponsor to participate in this inspection.

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

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

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

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

14.8.1 By the Sponsor

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

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and providing 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 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 Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal 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.

CONTRACEPTION GUIDANCE

Female participants

Women of reproductive potential (WOCBP) must use a highly effective method of contraception during the treatment period and the post-treatment follow up period (28 ±5 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).

Table 4 - Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods that are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• 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[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation: - Intrauterine device - Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
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 treatment. 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 participant.*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

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

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information 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

  Any pregnancy complication or elective termination of a pregnancy will be reported as an adverse event (AE) or serious adverse event (SAE). A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 10.4.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting

- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Appendix B Ambulatory blood pressure monitoring substudy

Background

A Phase 2 trial of sotagliflozin (LX4211.1-202) provided evidence that sotagliflozin reduced both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with elevated SBP and DBP at Baseline, but not in normotensive patients. In this substudy of approximately 180 patients, patients with similar Baseline BP distribution as the full study population (ie, equal numbers of patients with SBP <130 mmHg or ≥130 mmHg) will have ambulatory blood pressure monitoring (ABPM) assessed for 24 hours via ambulatory blood pressure (BP) monitoring technology. The ABPM substudy includes 3 sets of assessments, at 1 week before the Randomization Visit, and the days before the Week 12 and 26 visits, respectively, to provide a more systematic assessment of the SBP and DBP lowering efficacy of sotagliflozin.

Ambulatory blood pressure monitoring will be performed with a validated device provided by the Sponsor or Sponsor representative. The ABPM data process will be facilitated by a vendor, [redacted] ([redacted], USA).

Substudy procedures

At the preselected study sites participating in the ABPM substudy, patients must consent to be a part of the substudy to participate in the main study until the planned number of patients for substudy has been achieved.

At Visit 1, patients will be provided with information on the ABPM substudy and separate written consent will be taken before ABPM substudy-specific procedures are performed. Patients who work a night (third) shift (defined as 11:00 PM [23:00] to 7:00 AM [07:00]) will be excluded from the ABPM substudy.

Patients in the ABPM substudy will have 3 additional visits to the site for placement of the ABPM device. These will be Visits 3A, 6A, and 8A. Visit 3A will occur at Week -1, 1 week before the Randomization Visit. Visit 6A, and Visit 8A will occur the day before Visit 6 (Week 12) and Visit 8 (Week 26). Patients do not need to be fasting at these 3 visits.

Patients who discontinued the Investigational Medicinal Product (IMP) during the study before the visit for ABPM will not continue in the ABPM substudy post-IMP discontinuation. Patients who receive rescue therapy but remain on IMP will continue on the ABPM substudy as planned.

On the 3 visit days (Visits 3A, 6A, and 8A) each recording will start in the morning, preferably between 08:00 and 10:00 immediately after the administration of study medication, and will end after at least 24 hours of recording on the following day.

- Investigator and/or designee will help patients wear the ambulant BP monitor and the appropriate BP cuff (depending on the patient's arm size) on the nondominant upper arm

- Patients should be aware that the device will automatically inflate the cuff and measure the BP every 20 minutes during the day-time (08:00 and 21:59) and every 30 minutes during the sleeping time (22:00 and 07:59) over a 24-hour period
- During the ABPM period, patients should continue their daily activities and concomitant medications, but avoid activities that may interfere with functioning of the device such as vigorous exercise, bathing, or taking a shower
- When the cuff starts to inflate, the patient should remain still and avoid arm movement.
- Patients will record the time of sleep and any unusual events or poor sleep quality during the ABPM recording period in their study diary
- Patients will be instructed to remove the BP device after 24-hour wearing the ABPM device:
  - Once the ABPM device has been placed at Visit 3A, patients will be instructed to remove it 24 hours later and return it to the site by mail in appropriate packaging provided by the site
  - Twenty-four hours after Visits 6A and 8A, patients will return to the site in a fasting state at Visits 6 and 8, respectively, and the device will be removed at the site.

All ABPM data will be reviewed following return of the device to ensure quality of the recording. The quality of a visit recording will be considered insufficient if the visit recording does not meet the criteria below:

1. Visit recording does not contain ≥17 nonconsecutive hours of data where each hour has at least one valid BP measurement
2. Visit recording has <44 total measurements.

Patients with ABPM data not of sufficient quality will be asked to repeat the process as soon as possible. Patients with ABPM data not of sufficient quality at Visit 3A should not be randomized until the Baseline ABPM recording has been repeated, and the Randomization Visit (Visit 3) will be postponed correspondingly.

Patients must be well trained to understand the importance of the ABPM performance and compliance of the instruction. Technique support via a 24/7 help-line service for troubleshooting will be provided by [redacted]. The patients should immediately contact the sites if they encounter any device-related events (malfunction) or any questions about the ABPM. The investigator or site staff will help patients contact the [redacted] service line for problem solving.

Appendix C Two-hour standardized mixed meal

A 2-hour postprandial glucose (PPG) will be obtained after a standardized mixed meal in all patients at Baseline (Day 1, Visit 3) and at Week 26 (Visit 8). Patients requiring rescue therapy prior to Week 26 (see Section 9.1.4.3) should still have the standardized mixed meal tolerance test (MMTT) performed at Week 26. Patients who permanently discontinued the Investigational Medicinal Product (IMP) before Week 26 will not perform the MMTT at the planned Visit 8 (Week 26).

The standardized MMTT must not be performed while patients are temporarily off IMP; the Medical Monitor will address any episodes on a case-by-case basis and the standardized MMTT will be rescheduled when the patient can resume IMP, if applicable.

The first dose of double-blind investigational medicinal product (IMP; and dosing with dipeptidyl peptidase 4 inhibitor [DPP4(i)] and metformin, if applicable) on Day 1 (Visit 3) will be given after completion of the 2-hour PPG collection. For the Week 26 standardized MMTT, the patient should take the dose of double-blind IMP immediately after the fasting blood samples are obtained, and approximately 30 minutes before ingestion of the standardized mixed meal begins. At Week 26, DPP4(i) and metformin (if applicable) dosing will occur after collection of the 2-hour PPG sample and 3 hour PK sample are completed.

Standard Meal for the Standardized Mixed Meal:

The standard (breakfast) meal will be provided by the Sponsor as a liquid nutrition drink (Boost®, Ensure®, or similar), with approximately 40 g carbohydrate and approximately 240 calories per bottle (approximately 8 ounces). The caloric composition of the meal is approximately 65% carbohydrate, approximately 15% protein, and approximately 20% fat. The amount given is 6 mL/kg body weight up to a maximum of 360 mL. Therefore, for patients ≥60 kg, the standard meal consists of approximately 60 g carbohydrate and 360 calories.

Patients are instructed to completely consume the meal within 15 minutes, and every effort should be made to complete the meal within 20 minutes after it is started. Water or noncaffeinated, zero calorie beverages may be consumed ad libitum. No other food may be consumed until the 2-hour PPG plasma sample has been collected. If the patient is unable to consume at least 50% of the standard mixed meal, the MMTT should not be completed and the subsequent standardized MMTT should not be performed. If the patient is able to consume >50% of the standardized mixed meal, the approximate amount should be recorded, and an equivalent amount should be consumed at the subsequent standardized mixed meal.

Baseline Visit (Day 1, Visit 3) Standardized MMTT:

1. Record in the source documents the amount and brand name of the standard meal liquid nutrition drink the patient is instructed to consume
2. Fasting blood samples are obtained, including Time 0 fasting FPG
3. Record the time of blood sample collection in the source documents

4. Immediately after the fasting blood samples are collected, the patient starts consuming the standard meal
5. Record the time the meal ingestion starts in the source documents
6. The 2-hour countdown for the 2-hour plasma PPG starts immediately after the patient begins ingestion of the standard meal
7. The patient is instructed to ingest the prescribed amount within 15 to 20 minutes.
8. Record the time ingestion is completed, measure the portion of the meal not ingested (if any), and record the assessed percent of prescribed amount ingested in the source documents
9. No blood samples for PK are collected at this visit
10. Two hours after the meal ingestion starts, the 2-hour plasma PPG is collected
11. Record the time the 2-hour plasma PPG is collected in source documents
12. Double-blind IMP (and DPP4[i] and metformin, if applicable) are administered after the blood sample is drawn at 120 minutes
13. Record the time the double-blind IMP is administered in the source documents.

Week 26 Visit (Visit 8) Standardized MMTT:

1. Record in the source documents the amount and brand name of the standard meal liquid nutrition drink the patient is instructed to consume
2. Fasting blood samples are obtained, including Time 0 FPG and predose PK samples
3. Record the time of blood sample collection in the source documents
4. Double-blind IMP is administered after the fasting blood samples are obtained
5. Record the time the double-blind IMP is administered in the source documents
6. Thirty minutes after the double-blind IMP is administered, the patient starts consuming the standard meal
7. Record the time the meal ingestion starts in the source documents
8. The 2-hour countdown for the 2-hour PPG starts immediately after the patient begins ingestion of the standard meal
9. The patient is instructed to ingest the prescribed amount within 15 to 20 minutes
10. Record the time ingestion is completed, measure the portion of the meal not ingested (if any), and record the assessed percent of prescribed amount ingested in the source documents
11. Two hours after the meal ingestion starts, the 2-hour PPG sample is collected
12. Two hours and 30 minutes after the meal ingestion starts, the 3-hour PK sample is collected
13. DPP4(i) and metformin (if applicable) are administered after the PK blood sample is drawn
14. Record in the source documents the time the 2-hour postprandial blood samples are collected.

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

Basic genitourinary hygiene

Patients with Type 2 diabetes are at risk for developing genitourinary (GU) infections. The following guidelines should be communicated to females and uncircumcised males regarding GU infections. Patient communication cards will be printed with the following:

For females:

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

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

For uncircumcised males:

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

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

Maintaining hydration:

Sodium-glucose cotransporter Type 2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. Before initiating study drug (at Screening, Run-in and Randomization) and during all on-site study visits thereafter, assess volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, 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 Type 2 diabetes:

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

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

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

Recognizing diabetic ketoacidosis

Potential gastrointestinal (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 data are 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 will be completed.

Appendix E Measurement of blood pressure and heart rate

Equipment

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

Patient factors

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

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

Determination of the arm with the highest blood pressure

At the Screening Visit (Visit 1, Week -4), BP will be measured on both arms to identify and select the appropriate arm for future measurements. Seated BP should be measured in both arms after 5-minute rest period, and then again after 1 minute in both arms in seated position. The arm with the highest SBP will be determined at this visit, and BP should be measured in this arm throughout the study.

Measurement Technique (23)

At the Screening Visit (Visit 1, Week -4), immediately following arm selection, with the patient in the same position, an additional seated BP should be measured in the selected arm (at least 1 minute after last measurement).

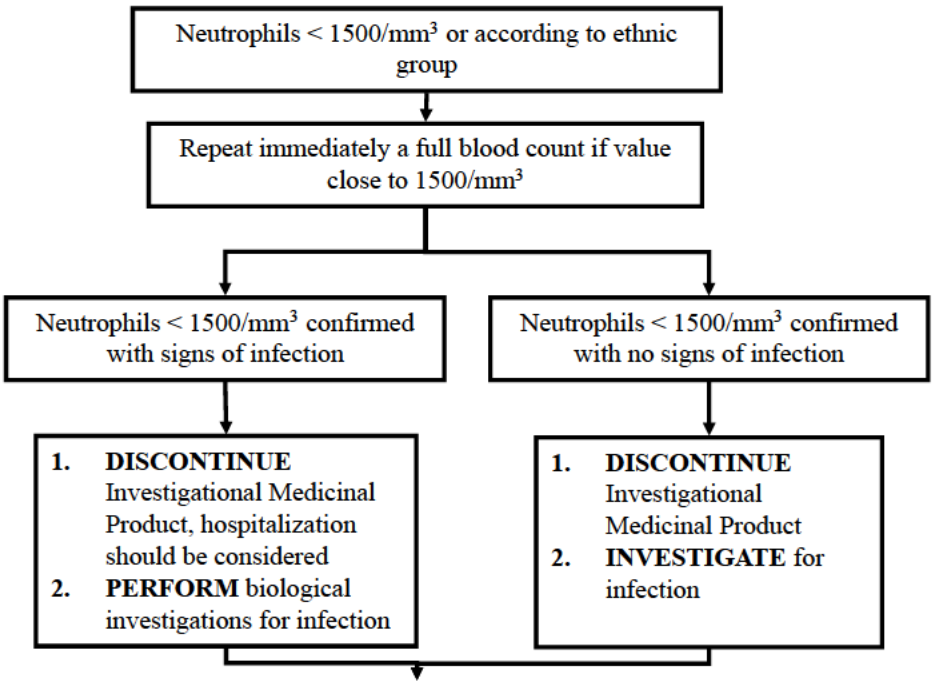
At all other visits, following the 5-minute rest period, 3 separate seated BPs should be measured in the arm selected at Visit 1, with at least 1 minute between BP measurements and with the cuff fully deflated between measurements.

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

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

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

NEUTROPENIA

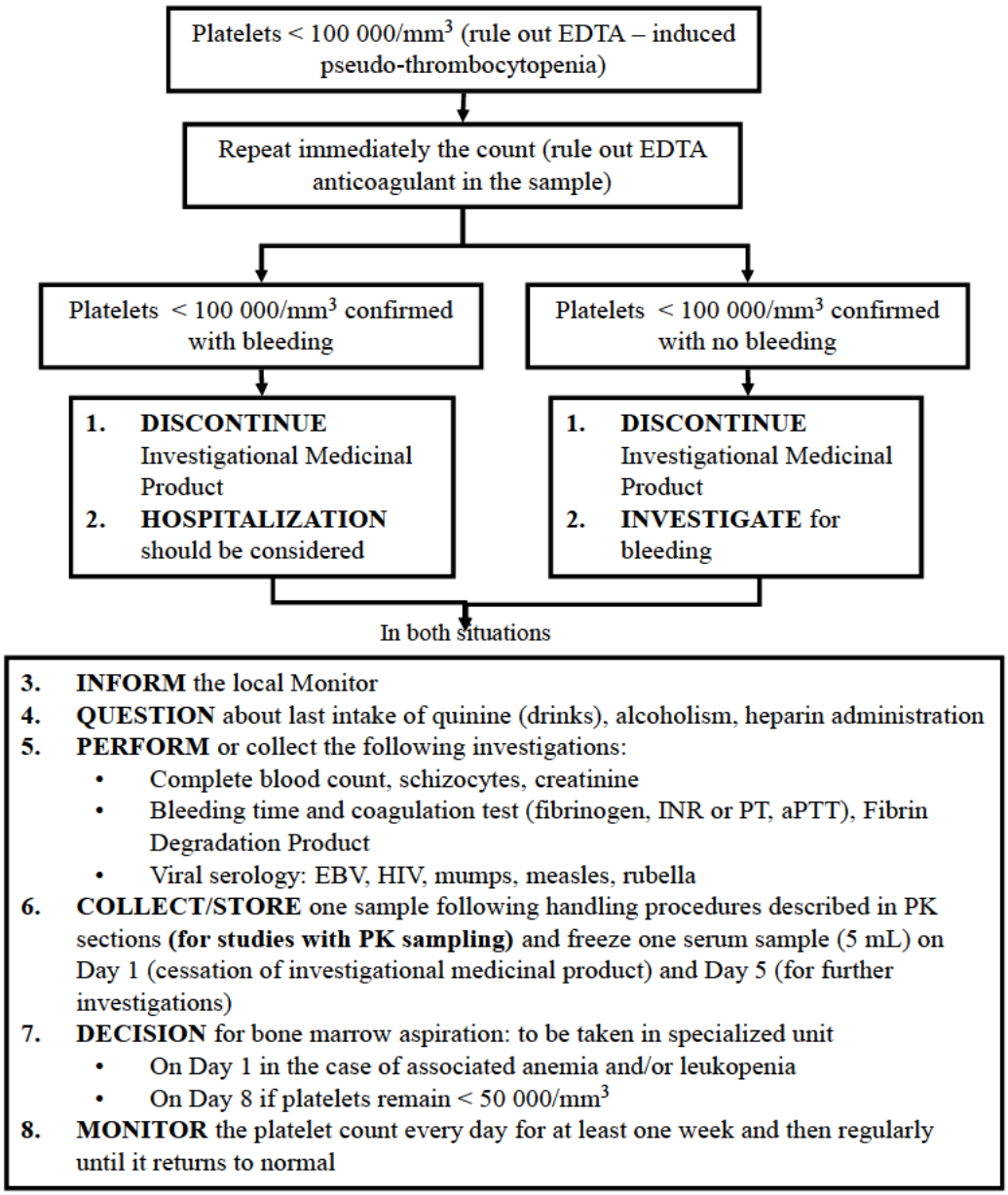


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps,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

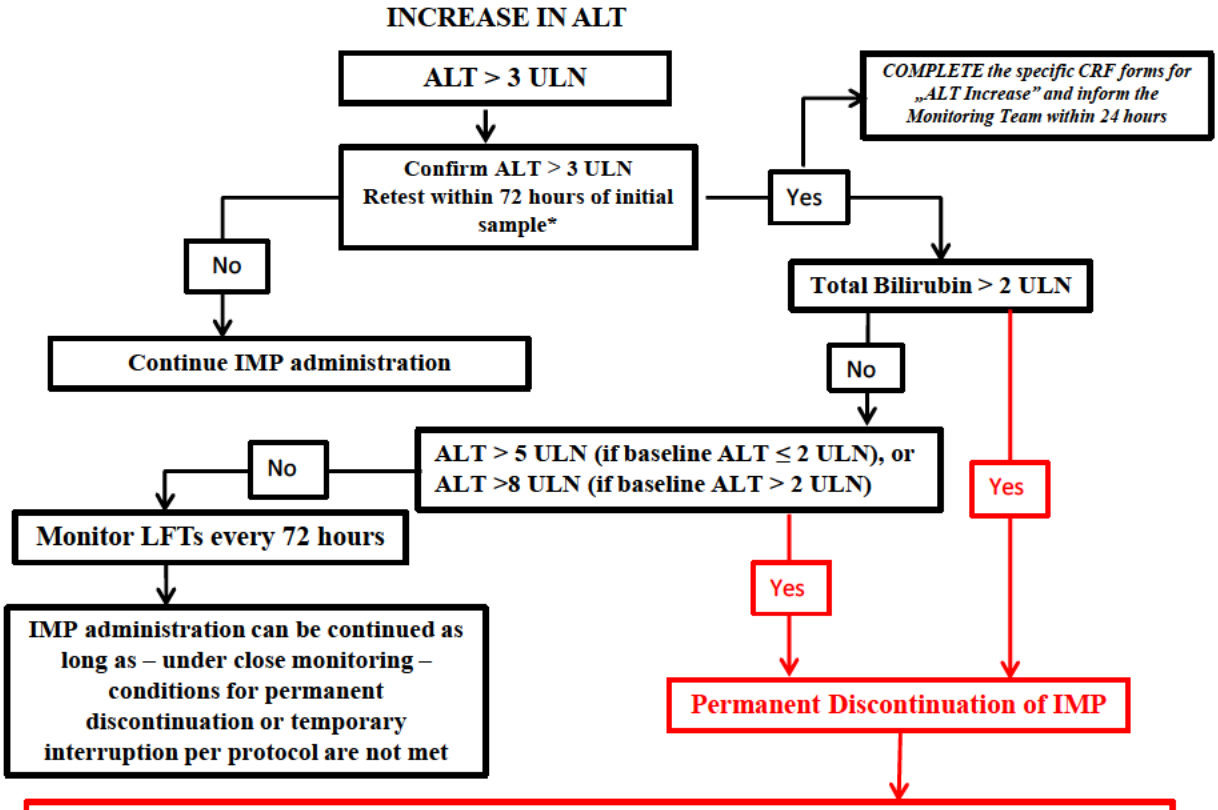
Neutropenia is to be recorded as an adverse event (AE) only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.4.2 is met.

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.



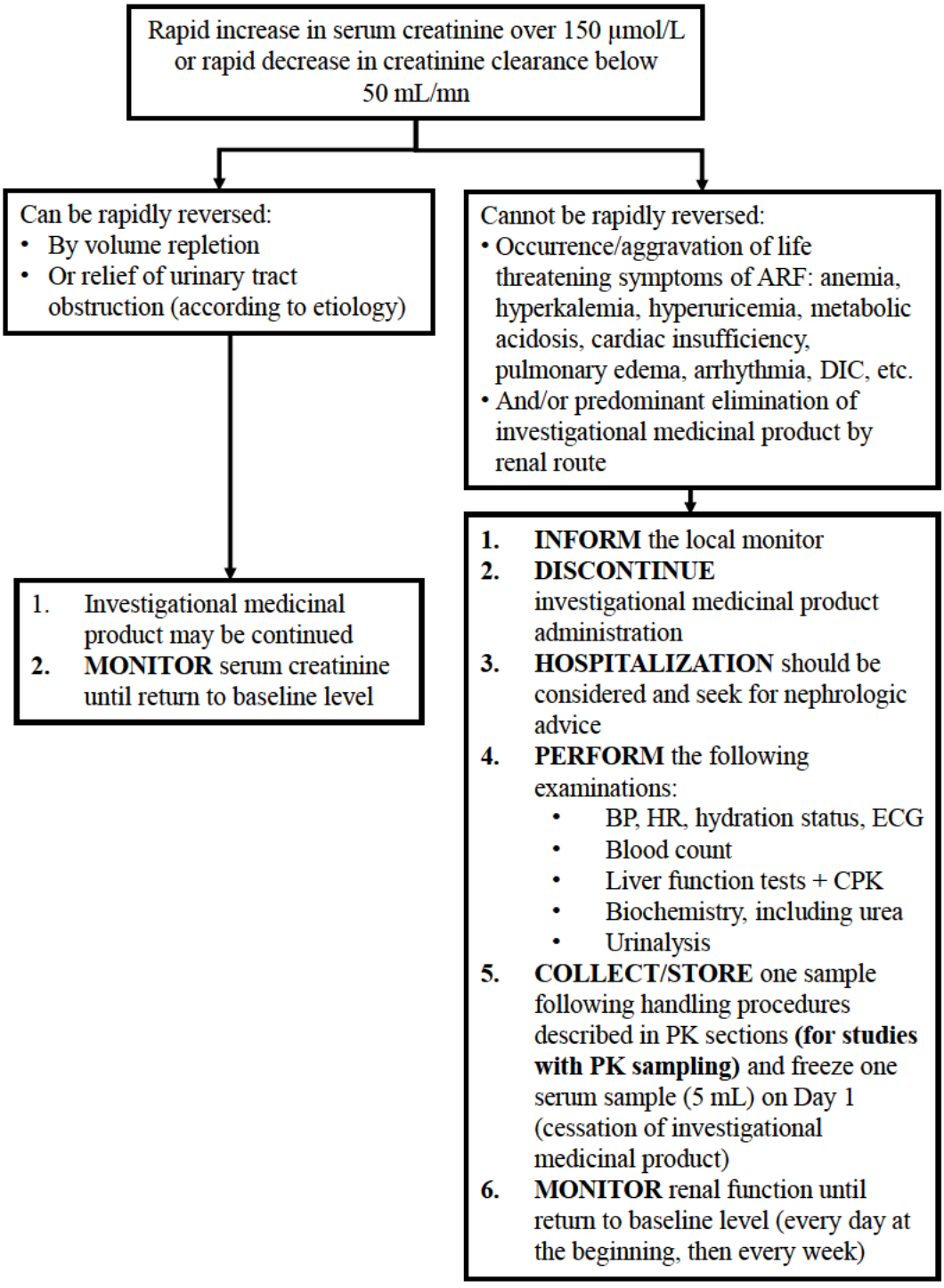
In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours**) until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)

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

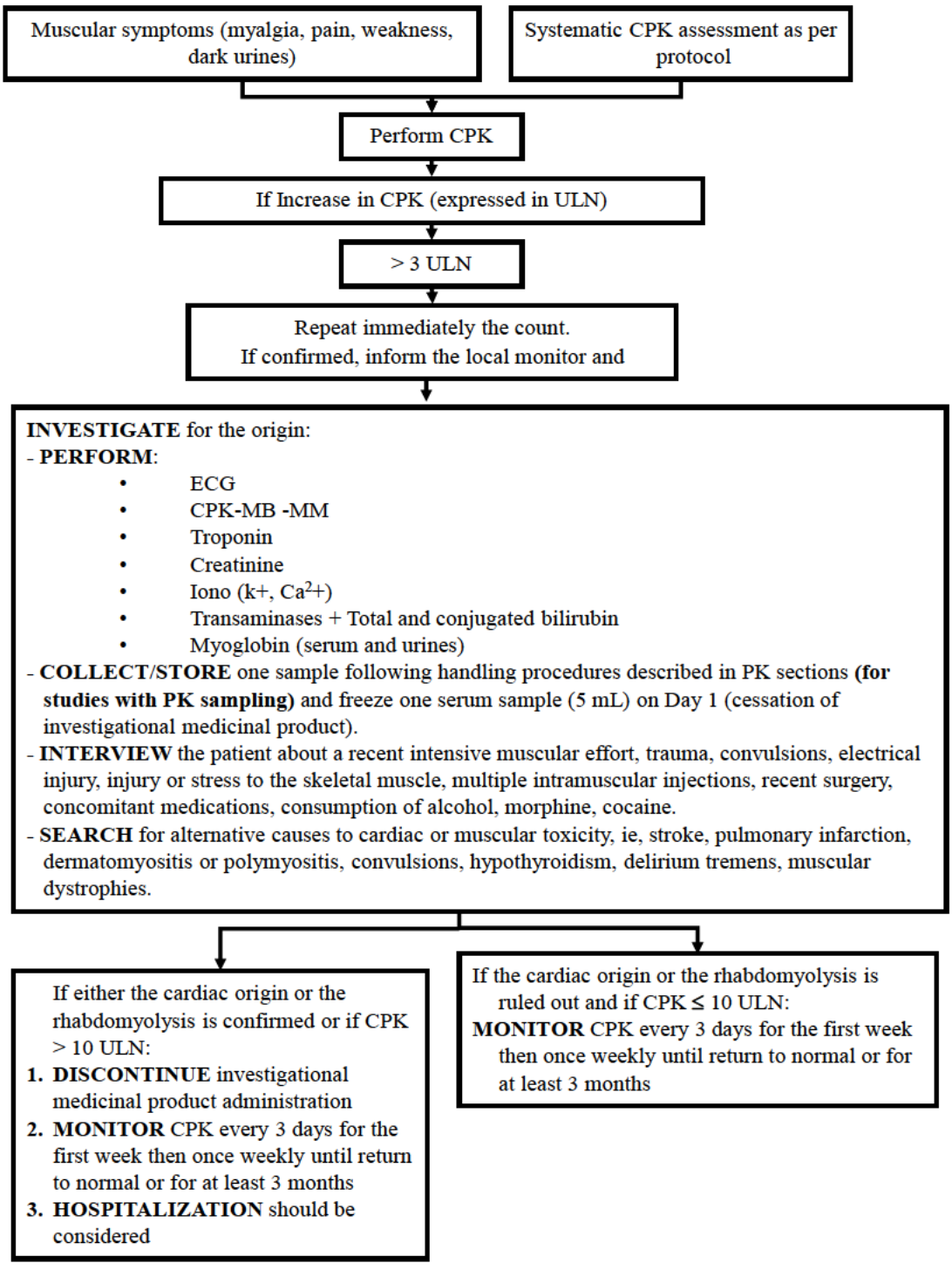
- "Baseline" refers to ALT sampled at Baseline visit; or if Baseline value unavailable, to the latest ALT sampled before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during Screening Period.
- See Section 10.4 for guidance on safety reporting.
- Normalization is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

INCREASE IN SERUM CREATININE



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

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



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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	11-Apr-2018 16:45 GMT+0200
[redacted]	Clinical Approval	11-Apr-2018 17:37 GMT+0200
[redacted]	Clinical Approval	12-Apr-2018 17:40 GMT+0200