Official Title: A 52-week Randomized, Double-blind, Double-dummy, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Glimepiride or Placebo Added to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycemic Control with Metformin Monotherapy

NCT Number: NCT03332771

Document Date: Protocol Version 2: 11-April-2018

SANOFI

AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: sotagliflozin/SAR439954

A 52-week Randomized, Double-blind, Double-dummy, Active and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Glimepiride or Placebo Added to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycemic Control with Metformin Monotherapy

STUDY NUMBER: EFC14838

STUDY NAME: SOTA GLIM (SOTAgliflozin compared to GLIMepiride)

VERSION DATE / STATUS: Approval date (09-Apr-2018) / Approved

Protocol Amendment 02		Version number: 1 (electronic 1.0)	Date: 09-Apr-2018
Amended Clinical Trial Protocol 01		Version number: 1 (electronic 3.0)	Date: 07-Sep-2017
Protocol Amendment 01		Version number: 1 (electronic 3.0)	Date : 07-Sep-2017
Clinical Trial Protocol		Version number: 1 (electronic 1.0)	Date : 09-May-2017
Version Number:	1	EudraCT IND Number(s) WHO universal trial number	2016-001801-17 [redacted] U1111-1190-7596
Date:	09-Apr-2018	Total number of pages:	120

NAMES AND ADDRESSES OF

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MONITORING TEAM'S REPRESENTATIVE

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Company:
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OTHER EMERGENCY TELEPHONE NUMBERS

CLINICAL TRIAL SUMMARY

COMPOUND: sotagliflozin/SAR439954	STUDY No.: EFC14838
TITLE	A 52-week Randomized, Double-blind, Double-dummy, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Glimepiride or Placebo Added to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycemic Control with Metformin monotherapy.
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objectives:** The primary objective of this study is to demonstrate the non-inferiority of sotagliflozin 400 mg compared to glimepiride on hemoglobin A1c (HbA1c) reduction at Week 52 in patients with Type 2 diabetes (T2D) who have inadequate glycemic control with metformin. **Secondary objectives:** • To demonstrate the superiority of sotagliflozin 400 mg compared to glimepiride on: - Change in body weight from Baseline to Week 52. - Change in systolic blood pressure (SBP) from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg. - Change in SBP from Baseline to Week 12 in all patients. - The proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period. • To demonstrate the superiority of sotagliflozin 400 mg compared to placebo on change in HbA1c from Baseline to Week 26. • To demonstrate the superiority of sotagliflozin 200 mg compared to placebo on change in HbA1c from Baseline to Week 26. • To demonstrate the superiority of sotagliflozin 400 mg compared to placebo on: - Change in body weight from Baseline to Week 26. - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg. - Change in SBP from Baseline to Week 12 in all patients. • To demonstrate the non-inferiority of sotagliflozin 200 mg compared to glimepiride on change in HbA1c from Baseline to Week 52. • To demonstrate the superiority of sotagliflozin 400 mg compared to glimepiride on change in HbA1c from Baseline to Week 52. • To evaluate the safety of sotagliflozin compared to glimepiride and placebo over 52 weeks of treatment.

	Other: • To evaluate sotagliflozin compared to glimepiride and placebo with respect to: - Change in fasting plasma glucose (FPG) - The number of hospital visits due to hypoglycemia - Change in estimated glomerular filtration rate (eGFR) - Change in SBP for all patients, the subset with baseline SBP <130 mmHg, and the subset with baseline SBP ≥130 mmHg - Change in diastolic blood pressure (DBP) for all patients and the subset of patients with baseline DBP ≥80 mmHg - The proportion of patients requiring rescue medication for hyperglycemia - The proportion of patients with HbA1c <6.5%, <7.0% - The proportion of patients with HbA1c <6.5%, <7.0% and no documented symptomatic hypoglycemic event (≤70 mg/dL) - Patient Qualitative Assessment of Treatment (PQAT)
STUDY DESIGN	This is a Phase 3, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, double-dummy study. All patients with T2D treated with metformin at a stable dose ≥1500 mg/day or maximum tolerated dose (documented) for at least 12 weeks will have a Screening phase of up to 2 weeks and a 2-week single-blind Run-in phase prior to randomization. In order to qualify for randomization, patients must demonstrate compliance based upon tablet and capsule count (≥80%) and as assessed at the discretion of the Investigator. Patients will be randomly assigned at a 2:1:2:1 ratio to receive one of the following 4 treatments, on top of open-label metformin at Visit 3 (Week 0, Day 1): • **Sotagliflozin 400 mg group:** sotagliflozin (2 tablets of sotagliflozin 200 mg) and glimepiride-matching placebo (2 over-encapsulated tablets [referred to as capsules]) (N = 310 patients). • **Sotagliflozin 200 mg group:** sotagliflozin (1 tablet of sotagliflozin 200 mg), sotagliflozin-matching placebo (1 tablet, identical in appearance to sotagliflozin 200 mg), and glimepiride-matching placebo (2 capsules) (N = 155 patients). • **Glimepiride group:** sotagliflozin-matching placebo (2 tablets), combination of 2 glimepiride (or matching placebo) capsules with adequate dose strengths per dose titration (titrated up to 6 mg, see Table 2) (N = 310 patients) • **Placebo group:** sotagliflozin-matching placebo (2 tablets) and glimepiride-matching placebo (2 capsules) (N = 155 patients).

	Randomization will be stratified by: • HbA1c at Screening (≤8.5%, >8.5%) • SBP at Screening (<130 mmHg, ≥130 mmHg) Please see section on study treatments/Investigational Medicinal Products (IMP) for a detailed description of the IMP. Following randomization, patients will have a 52-week, double-blind and double-dummy Treatment Period, followed by a 2-week post-treatment Follow-up Visit to collect safety information. Fasting glucose (plasma or serum) and HbA1c will be masked to study sites and patients after randomization until study end. Additionally, urinalysis by dipstick will not include the measurement of urine glucose. **Titration of glimepiride (and mock titration of glimepiride placebo):** After randomization patients will start with 1 mg of glimepiride (or matching placebo) and may be titrated at 1 to 2 mg increments up to a maximum dose of 6 mg (or maximum tolerated dose). Titration will be possible at 5 dose levels (1, 2, 3, 4, and 6 mg). Best efforts should be made to complete the titration within the first 18 weeks. After then, no further titration of glimepiride (or matching placebo) will be allowed. During the titration phase, patients will measure their fasting glucose values via self-monitoring of blood glucose (SMBG) before first meal at least 3 times in the week before on-site or phone visits (using a study glucose meter that displays results converted to plasma glucose concentration). Patients will review SMBG values with site staff at on-site, phone visits or unscheduled safety phone contacts to decide if/when dose adjustments are warranted. • Dose may be increased by 1 to 2 mg after at least 2 weeks of treatment on the same dose, without occurrence of hypoglycemia in the previous 2 weeks. • Dose increase will be considered if the average of 3 most recent (not necessarily consecutive days) fasting SMBG values in the week prior to the visit is >108 mg/dL (>6 mmol/L). • The Investigator may decide to withhold titration if considered that it could put the patient at risk of hypoglycemia and upon a documented safety rationale. • Dose may be down titrated at any time, if necessary, based on occurrence of one episode of severe hypoglycemia, or 2 or more episodes of documented hypoglycemia within 2 weeks (symptomatic hypoglycemia with glucose measurement ≤70 mg/dL [3.9 mmol/L]). In this situation, the dose can be decreased by 1 to 2 mg, while necessary actions are taken to manage the hypoglycemia risk. The dose can subsequently be re-increased up to Week 18 inclusive. **Note:** Increase to a higher glimepiride dose level will be possible only at on-site visits. Temporary decreases due to severe or recurrent hypoglycemia are allowed if instructed by the Investigator during safety unscheduled phone visits. An on-site visit should follow as soon as possible within 7 days.

	Early Termination: If a patient discontinues treatment with IMP early during the Treatment Period, the patient will have a Premature End of Treatment (EOT) Visit and a Follow-up Visit, 2 weeks after the last dose of IMP. In addition, every effort will be made to have all patients return to the site at the time corresponding to their scheduled visits, particularly at Week 26 and Week 52. If a patient does not agree to site visits, he/she will be contacted by telephone to inquire about their safety status, particularly at the time of the initially scheduled end of study. The study design is presented graphically in Section 1.1.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with Type 2 Diabetes treated with metformin at a stable dose ≥1500 mg/day or maximum tolerated dose (documented) for at least 12 weeks prior to Screening Visit; in case of documented lack of tolerance, metformin dose <1500 mg/day is acceptable, and the dose should be stable for at least 12 weeks prior to Screening Visit. • Patient has given written informed consent to participate in the study in accordance with local regulations. **Major exclusion criteria:** • Age <18 years at the Screening Visit or <legal age of majority, whichever is greater. • Type 1 diabetes mellitus. • HbA1c <7.0% or HbA1c >10% at Screening (central laboratory). • FPG >15 mmol/L (>270 mg/dL) measured by the central laboratory at Screening (Visit 1) and confirmed by a repeat test (>15 mmol/L [>270 mg/dL]) before randomization. • Body mass index ≤20 or >45 kg/m² at Screening. • Pregnant (confirmed by pregnancy test at the Screening) or breast-feeding women. • Women of childbearing potential (WOCBP) 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. • Previous use of any antidiabetic drug other than metformin within 12 weeks preceding the Screening Visit. • Use of a selective SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) within 3 months prior to the Screening visit. • Use of systemic glucocorticoids (excluding topical, or ophthalmic application, intra-articular, nasal spray or inhaled forms) for more than 10 consecutive days within 90 days prior to the Screening Visit. • Previous insulin use >1 month (at any time, except for treatment of gestational diabetes). • History of prior gastric surgical procedure, including gastric banding, or inflammatory bowel disease within 3 years prior

	to the Screening Visit. • Difficulty swallowing such that the patient cannot take the IMP. • History of diabetic ketoacidosis or nonketotic hyperosmolar coma within 12 weeks prior to the Screening Visit. • Mean of 3 separate blood pressure measurements >180 mmHg (SBP) or >100 mmHg (DBP). • History of hypertensive emergency within 12 weeks prior to Screening. • Patients who have previously been randomized in any clinical trial of sotagliflozin/LX4211. • Patients with severe renal disease as defined by an eGFR of <30 mL/min/1.73 m² at Screening, based on the 4 variable Modification of Diet in Renal Disease (MDRD) equation (or according to the renal function restrictions of metformin use defined in the local approved label). • Patients with severe anemia, severe cardiovascular (including congestive heart failure New York Heart Association IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy that, according to Investigator, will preclude their safe participation in this study, or will make implementation of the protocol or interpretation of the study results difficult. • Aspartate aminotransferase and/or alanine aminotransferase: >3 times the upper limit of the normal laboratory range (ULN). • Total bilirubin: >1.5 times ULN (except in case of Gilbert's syndrome). • Patients who have taken other investigational drugs within 12 weeks or 5 half-lives from Screening whichever is longer • Patients unwilling or unable to perform SMBG, complete the patient diary, or comply with study visits and other study procedures as required per protocol. • Patients with contraindication to glimepiride as per local labeling. • Patients with contraindication to metformin as per local labeling.
Total expected number of patients **Expected number of sites**	Approximately 930 randomized patients Approximately 142 sites
STUDY TREATMENTS	
Investigational medicinal products	Tested drug: Sotagliflozin 400 and 200 mg, given as 200 mg tablets Control drug: Glimepiride 1 mg (starting dose) titrated up to 6 mg (glimepiride capsules: 1, 2, and 4 mg dose strengths) Placebo: Sotagliflozin-matching placebo (200 mg) and glimepiride-matching placebo: • During the single-blind placebo Run-in period all patients will receive 2 placebo tablets (identical to sotagliflozin 200 mg in appearance) and 2 placebo capsules (identical to glimepiride capsules in appearance). • At the beginning of the 52-week randomized double-blind and double-dummy period patients will receive either

<table>
<tr><td></td><td>sotagliflozin and/or placebo tablets and glimepiride and/or placebo capsules, or 2 placebos as follows:
Sotagliflozin 400 mg group: Sotagliflozin 400 mg, given as two 200 mg tablets and 2 glimepiride placebo capsules, taken orally once daily before the first meal of the day.
Sotagliflozin 200 mg group: Sotagliflozin 200 mg, given as one 200 mg tablet and 1 sotagliflozin-matching placebo tablet, and 2 glimepiride placebo capsules, taken orally once daily before the first meal of the day.
Glimepiride group: 2 sotagliflozin-matching placebo tablets, and combination of 2 glimepiride (or matching placebo) capsules with adequate dose strengths per dose titration (titrated up to 6 mg, see Table 2), taken orally once daily before the first meal of the day.
Placebo group: 2 sotagliflozin-matching placebo tablets and 2 glimepiride placebo capsules, taken orally once daily before the first meal of the day.
Glimepiride (or glimepiride placebo) will be titrated (or mock-titrated) up to 6 mg (or maximum tolerated dose) as per instructions above. Titration will be possible at 5 dose levels (1, 2, 3, 4, and 6 mg) through a combination of glimepiride (or matching placebo) capsules with different dose strengths:
<table>
<tr><th>Dose level</th><th>Number of glimepiride/matching placebo capsules dispensed (dose strengths)</th></tr>
<tr><td>1 mg</td><td>1 (glimepiride placebo) + 1 (1 mg)</td></tr>
<tr><td>2 mg</td><td>1 (glimepiride placebo) + 1 (2 mg)</td></tr>
<tr><td>3 mg</td><td>1 (1 mg) + 1 (2 mg)</td></tr>
<tr><td>4 mg</td><td>2 (2 mg)</td></tr>
<tr><td>6 mg</td><td>1 (2 mg) +1 (4 mg)</td></tr>
</table>
In case of recurrent hypoglycemia, down-titration of glimepiride (or matching placebo) can be performed at any time during the study for the patients taking a daily dose higher than 2 mg of glimepiride. In the glimepiride blister delivered to the patient, the first column will correspond to the lower dose strength. If an unscheduled phone visit is prompted due to recurrent hypoglycemia, the Investigator may use discretion to advise patients to temporarily (<7 days) decrease glimepiride/matching placebo dose by omitting the capsule of lower dose until they are able to return to the site to be evaluated and receive a new treatment kit as needed. In this case an on-site visit should occur as soon as possible within 7 days.</td></tr>
<tr><td>Noninvestigational medicinal product</td><td>The dose of metformin (≥1500 mg/day or maximum tolerated dose as documented) should be stable throughout the study; a dose decrease is allowed only if required for safety reasons.</td></tr>
<tr><td></td><td>Rescue therapy
The threshold values are defined as follows, depending on study period:
• From Baseline Visit (Visit 3, Day 1) to Visit 6 (Week 8) (including value at Visit 6): FPG>270 mg/dL (>15.0 mmol/L)
• From Visit 6 (Week 8) to Visit 7 (Week 12) (including value at Visit 7): FPG>240 mg/dL (>13.3 mmol/L).</td></tr>
</table>

	• From Visit 7 (Week 12) up to the EOT Period Visit 12 (Week 52): 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 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 1 fasting SMBG value exceeds the specific glycemic limit on 1 day, the patient checks it again during the following 2 days. If all the values in the 3 consecutive days exceed the specific limit, the patients should contact the Investigator and a central laboratory FPG measurement (and HbA1c after Week 12 and onwards) should be performed as soon as possible, preferably within 7 days to confirm the hyperglycemia. • Upon receipt of a central laboratory rescue alert, a central laboratory re-test must be completed and confirmed as exceeding the criterion for rescue before rescue therapy is initiated. The re-test confirmation should be performed as soon as possible, but within 7 days of receipt by unscheduled visit. In the event that a confirmatory FPG and/or HbA1c exceed the threshold, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that: • The increased FPG has been tested at a fasting status (ie, no food intake for ≥8 hours). • IMP is given at the planned dose and glimepiride (or matching placebo) is already at the maximum titrated dose (6 mg or maximum tolerated dose) or no longer possible to be titrated. • There is no intercurrent disease, which may jeopardize glycemic control (eg, infectious disease). • Compliance to treatment is appropriate. • Compliance to diet and lifestyle is appropriate. If any of the above can reasonably explain insufficient glycemic control, the Investigator should consider not initiating rescue medication and should undertake appropriate action, ie: • Assess plasma glucose in fasting condition (ie, after at least 8 hours fast). • Initiate an evaluation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the electronic case report form [e-CRF] and the medical record). • Stress on 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. • Rescue medication can be added up to the Investigator's decision except for SGLT2 inhibitors and sulfonylurea. • The patient continues the IMP (blinded) and stays in the study in order to collect efficacy and safety information. The planned visits and assessments should occur until the last scheduled visit. • Rescue therapy is considered a NIMP. Rescue therapy is to be reported in the e-CRF. This information should include specific drug name, dose, route of administration, and frequency.
ENDPOINTS	**Primary efficacy endpoint (sotagliflozin 400 mg dose):** Change from Baseline to Week 52 in HbA1c (%) **Secondary endpoints (sotagliflozin 400 mg dose):** • Change from Baseline to Week 26 in HbA1c • Change from Baseline to Weeks 26 and 52 in body weight • Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg • Change from Baseline to Week 12 in SBP for all patients • Proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period **Secondary endpoints (sotagliflozin 200 mg dose):** • Change from Baseline to Weeks 26 and 52 in HbA1c **Other efficacy endpoints (sotagliflozin 400 mg and 200 mg doses):** • Change from Baseline to Weeks 26 and 52 in FPG • Number of hospital visits due to hypoglycemia during the 52-week Treatment Period • Change from Baseline in eGFR • Change from Baseline to Week 26 and 52 in SBP for all patients and the subset with baseline SBP ≥130 mmHg • Change from Baseline to Weeks 12, 26, and 52 in SBP for patients with baseline SBP <130 mmHg • Change from Baseline to Weeks 12, 26, and 52 in DBP for all patients and the subset with baseline DBP ≥80 mmHg • Proportion of patients requiring rescue treatment for hyperglycemia during the 52-week Treatment Period • The proportion of patients with HbA1c <6.5%, <7.0% at Week 52 • The proportion of patients with HbA1c <6.5%, <7.0% at Week 52 and no documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period • PQAT at Weeks 26 and 52 **Safety endpoints:** • Adverse events (AEs), hypoglycemia, (all, severe, and/or documented symptomatic hypoglycemia), events of special interest (EOSIs), AEs of special interest (AESIs), AEs leading to discontinuation from the IMP, serious adverse

	events (SAEs), and deaths • Clinical laboratory results (including fasting lipids) • Vital signs and electrocardiogram (ECG) results
ASSESSMENT SCHEDULE	See Study Flowchart Section 1.2
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size/power calculations were performed based on the primary endpoint of the change of HbA1c from baseline to Week 52 in the intent-to-treat (ITT) population. Assuming a common standard deviation of 1.1%, and the true difference between sotagliflozin 400 mg and glimepiride is zero, 310 patients in each group of sotagliflozin 400 mg and glimepiride will ensure that the upper bound of the 2-sided 95% confidence interval (CI) of the adjusted mean difference is below 0.3% with 90% power. This sample size will have 80% power to test the non-inferiority of the change of HbA1c from Baseline to Week 52 in completers, with 30% dropout rate. A sample size of 310 patients in sotagliflozin 400 mg group and 155 patients in placebo group will have >99% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo (standard deviation [SD] 1.2%; 2-sided 5% significance level). A sample size of 155 patients in sotagliflozin 200 mg group and 155 patients in placebo group will have 95% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 200 mg and placebo (SD 1.2%; 2-sided 5% significance level). The total sample size will be 930 patients to be randomized (sotagliflozin 400 mg: 310 patients; sotagliflozin 200 mg: 155 patients; glimepiride: 310 patients; and placebo: 155 patients). **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. Patients will be analyzed for efficacy analyses according to the treatment group to which they are randomized. **Analysis of the primary endpoint:** For the primary efficacy endpoint, the following null and alternative hypotheses will be tested: • H_0: $\mu_T - \mu_C \geq 0.3\%$ • H_1: $\mu_T - \mu_C < 0.3\%$ Where μ_T and μ_C are the mean changes from Baseline in HbA1c at Week 52 for sotagliflozin and glimepiride groups, respectively. The null hypothesis will be tested at a 1-sided alpha level of 0.025 using a non-inferiority margin of 0.3% of HbA1c change. Analysis of the primary efficacy endpoint will be performed using the ITT population, using HbA1c measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. The primary efficacy endpoint of change in HbA1c from baseline to Week 52 will be analyzed with missing values imputed by

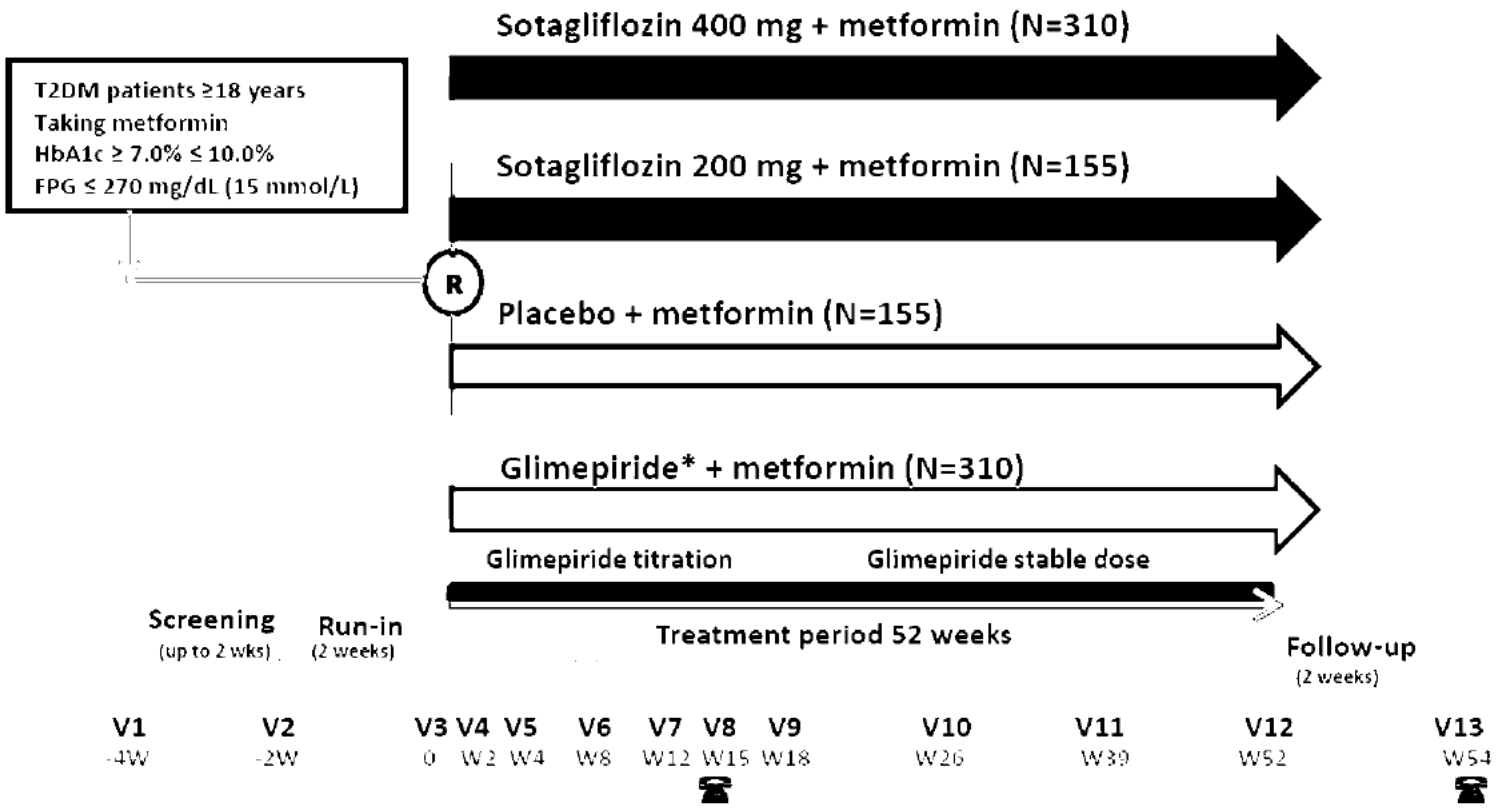
	control-based multiple imputation method, under the missing not at random frame work: • For placebo patients, missing data will be imputed based on the placebo group data. • For patients in the active groups (sotagliflozin 400 mg, sotagliflozin 200 mg, and glimepiride) missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model. Each of the complete datasets will be analyzed by the Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride and placebo), randomization strata of HbA1c at Screening (≤8.5%, >8.5%) and SBP at Screening (<130 mmHg, ≥130 mmHg), 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 52 for each treatment group, as well as the between-group difference and the 95% CI for the difference. If the upper bound of the 2-sided 95% confidence interval for the adjusted mean difference (sotagliflozin 400 mg vs glimepiride) in HbA1c change from baseline to Week 52 is <0.3%, the non-inferiority will be declared. 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 case (OC). **Analysis of secondary efficacy endpoints:** For secondary endpoints of reduction of body weight at Weeks 26 and 52, reduction of SBP at Week 12 in patients with baseline SBP ≥130 mmHg, and in all patients, reduction of HbA1c at Weeks 26 and 52, a similar approach to the primary efficacy endpoint will be used, with missing values imputed by control-based multiple imputation method: • For placebo patients, missing data will be imputed based on the placebo group data. • For patients in the active groups (sotagliflozin 400 mg, sotagliflozin 200 mg, and glimepiride) missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model. For each of the continuous secondary endpoint, each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo), randomization strata of Screening HbA1c (≤8.5%, >8.5%) and Screening SBP (<130 mmHg, ≥130 mmHg), country as fixed effects, and baseline secondary endpoint value as a covariate. Results from each complete dataset will be combined to provide the adjusted

	mean change from Baseline to Weeks 26 and 52 in HbA1c and body weight (or Week 12 for SBP) for each treatment group, as well as the between-group differences and the 95% CI for the differences. The categorical secondary endpoint the proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period, will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization strata of Screening HbA1c (≤8.5%, >8.5%) and Screening SBP (<130 mmHg, ≥130 mmHg). The proportion in each treatment group will be provided, as well as the difference of proportions between sotagliflozin and glimepiride with associated 2-sided 95% CI. To control for the family wise Type I error, a fixed-sequence testing procedure will be applied to the primary and secondary endpoints to the following order: • The non-inferiority of the HbA1c change from Baseline to Week 52 between sotagliflozin 400 mg and glimepiride. • The superiority of sotagliflozin 400 mg compared to glimepiride on: - Change in body weight from Baseline to Week 52 - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg - Change in SBP from Baseline to Week 12 in all patients - The proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period • The superiority of sotagliflozin 400 mg compared to placebo on the change in HbA1c from Baseline to Week 26. • The superiority of sotagliflozin 200 mg compared to placebo on the change in HbA1c from Baseline to Week 26. • The superiority sotagliflozin 400 mg compared to placebo on: - Change in body weight from Baseline to Week 26 - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg - Change in SBP from Baseline to Week 12 in all patients • The non-inferiority of sotagliflozin 200 mg compared to glimepiride on the change in HbA1c from Baseline to Week 52. • The superiority of sotagliflozin 400 mg compared to glimepiride on the change in HbA1c from Baseline to Week 52. **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. **Analyses of safety data:** All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. These analyses will be based on the

	safety population, which is defined as all randomized patients who receive at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Patients will be analyzed for safety analyses according to the treatment actually received. The safety analyses will be provided for the 52-week Treatment Period.
DURATION OF STUDY PERIOD (per patient)	Up to 58 weeks, including a Screening Period consisting of a Screening phase of up to 2 weeks, a 2-week single-blind placebo Run-in phase, a 52-week double-blind Treatment Period, and a 2-week post-treatment Follow-up period to collect safety information.
STUDY COMMITTEES	**Steering committee:** ☒ Yes ☐ No **Data monitoring committee:** ☒ Yes ☐ No **Clinical Endpoint Committees:** ☒ Yes ☐ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



*Glimepiride dose started at 1 mg and titrated to a maximum of 6 mg/day or the maximum tolerated dose within the first 18 weeks.
Visit 8 and Follow-up visit (Visit 13) are phone contacts

Abbreviations: FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; N = number of patients; T2DM = Type 2 diabetes mellitus; R = randomization; V = Visit; W = Week

1.2 STUDY FLOW CHART

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	1	2	3 (Randomiza -tion)	4	5	6	7	8 ☎	9	10	11	12	13 [b] ☎
Week	-4	-2	0 Baseline	2	4	8	12	15	18	26	39	52	54
Day (window [days])		(-14/+3)	1	14 (±3)	28 (±3)	56 (±3)	84 (±3)	105 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±3)	378 (±3)
Informed consent	X												
Inclusion criteria	X												
Exclusion criteria	X	X	X										
Demographics	X												
Medical/Surgical History	X												
Medication History	X												
Body weight, height [c]	X	X	X	X	X	X	X		X	X	X	X	
Vital signs [d]	X	X	X	X	X	X	X		X	X	X	X	
Physical Examination:													
Complete	X									X		X	
Abbreviated		X	X	X	X	X	X		X		X		
Diet & exercise instruction		X	X							X		X	
Instruction on basic genitourinary hygiene & hydration		X	X		X	X	X		X	X	X	X	
Interactive response technology (IRT) contact	X	X	X	X	X	X	X		X	X	X	X	X

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	**1**	**2**	**3** (Randomiza-tion)	**4**	**5**	**6**	**7**	**8** ☎	**9**	**10**	**11**	12	**13** [b] ☎
Week	**-4**	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**15**	**18**	**26**	**39**	**52**	**54**
Day (window [days])		**(-14/+3)**	**1**	**14 (±3)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**105 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±3)**	**378 (±3)**
Randomization			X										
Dispense glucose meter for self-monitoring of blood glucose		X											
Dispense diary	X	X	X	X	X	X	X		X	X	X		
Collect/review diary		X	X	X	X	X	X		X	X	X	X	
Instruction on diabetic ketoacidosis symptoms, glucose testing		X	X	X	X	X	X		X	X	X	X	
Dispense single-blind placebo		X											
Dispense double-blind IMP			X	X	X	X	X		X	X	X		
Study drug accountability & compliance assessment			X	X	X	X	X		X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-monitoring of blood glucose [e]		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [f]	X									X		X	
Laboratory testing [g]													
FPG	X		X		X	X	X		X	X	X	X	
HbA1c	X		X				X			X	X	X	
Chemistry & Hematology	X		X				X			X	X	X	

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	1	2	3 (Randomization)	4	5	6	7	8 ☎	9	10	11	12	13 [b] ☎
Week	-4	-2	0 Baseline	2	4	8	12	15	18	26	39	52	54
Day (window [days])		(-14/+3)	1	14 (±3)	28 (±3)	56 (±3)	84 (±3)	105 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±3)	378 (±3)
Fasting lipids	X		X							X		X	
Pregnancy test (WOCBP) [h]	X		X	X	X	X	X		X	X	X	X	
Serum follicle-stimulating hormone and estradiol (menopausal women only) [h]	X												
Urinalysis (dipstick and microscopy) [i]	X		X							X		X	
[redacted]													
PQAT [l]										X		X	
Evaluate for glycemic rescue				To be assessed and reported throughout the Treatment Period									
Hypoglycemia	To be assessed and reported throughout the study												
AE/SAEs/AESI/EOSI [m]	To be assessed and reported throughout the study												

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOSI = events of special interest; EOT = end of treatment; EW = early withdrawal; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; IMP = investigational medicinal product; IRT = Interactive Response Technology; NIMP = non-investigational medicinal product; PRO = patient-reported outcome; PQAT = Patient Qualitative Assessment of Treatment; SAE = serious adverse event; SMBG = self-monitoring blood glucose; UTI = urinary tract infection; WOCBP = women of childbearing potential

a All visits' dates will be scheduled based on the date of randomization within visit window allowed as per flowchart. If a patient discontinues treatment with investigational medicinal product (IMP) during the Treatment Period, the patient will have a visit as soon as possible to complete the assessments normally planned for the last dosing day with the IMP [End of Treatment/Early Withdrawal (EOT/EW) Visit], and a Follow-up Visit 2 weeks after the last dose of IMP. In addition, every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits, particularly the Week 26 and Week 52 visits. If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status.

b All patients will have a phone call Follow-up Visit 2 weeks after the last dose of the IMP to collect safety information.

c Height to be measured only at Screening.

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

e Patients will measure their fasting glucose levels via SMBG and discuss results with site personnel at clinic or phone visits, or unscheduled phone contacts. The SMBG measurements obtained with glucose meters are displayed as plasma glucose concentration. From randomization through Week 18, glimepiride or glimepiride-matching placebo dose adjustments will be made based on algorithm provided in protocol. **Note**: Changes in blinded glimepiride dose can be made only at on-site visits (except for decreases for safety reasons related to hypoglycemia). Patients will also be requested to self-assess blood glucose levels whenever they experience any illnesses (eg, cold, flu), or symptoms of hyperglycemia or hypoglycemia. 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).

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

g All laboratory assessments occur under fasting condition and prior to IMP and NIMP administration on the day of the visit (please see the list in Table 3).

h Serum pregnancy testing only at Screening; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to beginning the Run-in phase for all women of childbearing potential (WOCBP). 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.

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

[redacted]

l Patient Reported Outcomes (PROs): Patient Qualitative Assessment of Treatment (PQAT) to be administered to English-speaking patients at Weeks 26 and 52.

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

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3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
CECs:	Clinical Endpoint Committees
CI:	confidence interval
CRF:	case report form
CRO:	contract research organization
CSR:	Clinical Study Report
CV:	cardiovascular
DBP:	diastolic blood pressure
DILIs:	drug-induced liver injuries
DKA:	diabetic ketoacidosis
DMC:	Data Monitoring Committee
DPP4:	dipeptidyl peptidase-4
DRF:	Discrepancy Resolution Form
ECG:	12-lead electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EOSI:	events of special interest
EOT:	End of Treatment
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
FSH:	follicule-stimulating hormone
G6PD:	glucose-6-phosphade dihydrogenase
GCP:	Good Clinical Practices
GI:	gastrointestinal
GLP-1:	glucagon-like peptide-1
Glut:	glucose-facilitated transporters
GU:	genitourinary
HbA1c:	hemoglobin A1c
HLGT:	high-level group term
HLT:	high-level term
HR:	heart rate
HRT:	hormone-replacement therapy
IB:	Investigator Brochure

ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
ITT:	intent-to-treat
MACEs:	major adverse cardiovascular events
MDRD:	Modification of Diet in Renal Disease
MI:	myocardial infarction
N:	number (of observations)
NIMP:	noninvestigational medicinal product
OC:	observed cases
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
P-gp:	P-glycoprotein
PI:	Principal Investigator
PK:	pharmacokinetics
PPG:	postprandial glucose
PQAT:	Patient Qualitative Assessment of Treatment
PRO:	patient reported outcome
PT:	preferred term
PYY:	peptide YY
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	steering committee
SD:	standard deviation
SE:	standard error
SGLT:	sodium-glucose transporters
SMBG:	self-monitoring blood glucose
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T1D:	type 1 diabetes
T2D:	type 2 diabetes, type 2 diabetes
TEAE:	treatment-emergent adverse event
TG:	triglycerides
UGE:	urinary glucose excretion
ULN:	upper limit of normal, upper limit of normal
UTIs:	urinary tract infections
VTEs:	venous thrombotic events
WOCBP:	women of childbearing potential

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: SOTAGLIFLOZIN AND DISEASE

Sotagliflozin is a dual inhibitor of the SGLT1 and SGLT2 being developed for use in Type 1 diabetes (T1D) and Type 2 diabetes (T2D). This way of reducing blood glucose is not an insulin-dependent mechanism; therefore hyperglycemia may be reduced while the pancreas is spared from an increased demand for insulin production that is caused by hyperglycemia. Since obesity is a significant comorbidity in T2D, and insulin resistance is increased in obesity, the caloric loss from glucose in the urine may represent an additional benefit resulting in decreased weight, which should result in decreased insulin resistance (1).

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

Although lifestyle changes, including diet, exercise, and education, are valuable components of diabetes treatment, the vast majority of people with T2D require pharmacological therapy to control the disease.

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

In patients with diabetes, it is desirable to maintain blood glucose in the normal range without exhausting the ability of the pancreatic beta-cells to produce insulin, and therefore drugs that affect plasma glucose levels without interfering with pancreatic function are desirable. Glucose is transported across the cell membrane by 2 different types of glucose transporters: glucose-facilitated transporters (Glut) and sodium-glucose transporters (SGLT) proteins, which are expressed in the kidneys, gut, and other organs (3). In the kidney, after blood is filtered by the glomerulus, glucose passes into the urine, but 99% is reabsorbed, primarily via SGLT2, which is responsible for 90% of glucose reabsorption, while 10% is reabsorbed by SGLT1. When functional SGLT2 is lacking in humans, a significant amount of glucose remains in the urine and is removed from the body (1).

The SGLT1 is expressed predominantly in the gastrointestinal (GI) tract and is responsible for the majority of glucose absorption by the small intestine (4). Inhibition of SGLT1 in the GI tract prevents glucose from being absorbed. Additionally, there is accumulating evidence that SGLT1 inhibition stimulates secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), gut hormones involved in pancreatic beta cell function and appetite control, respectively. Reduced glucose absorption in the proximal intestine leads to more glucose being delivered distally, which allows L cells in both the ileum and the colon to sense glucose and its byproducts, and as a result, they secrete GLP-1 and PYY. Although a complete lack of functional SGLT1 may be associated with symptoms of glucose and galactose malabsorption (5), pharmacologic inhibition of SGLT1 by sotagliflozin has not produced these effects in preclinical models or patients with T2D. Selective inhibitors of the SGLT1 transporter are in early stages of development.

Extensive clinical studies conducted for selective SGLT2 inhibitors have established this class as effective agents for the treatment of T2D (6, 7, 8) and have led to approvals by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Studies with sotagliflozin, a potent, dual inhibitor of SGLT2 and SGLT1, have shown that this agent produces significant glucosuria in preclinical animal models, healthy human volunteers, and patients with T2D. Single and multiple-dose administration of sotagliflozin to healthy human 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. In addition, a dose-ranging study has shown significant HbA1c reduction after 12 weeks treatment with sotagliflozin. These data suggest that sotagliflozin should be of therapeutic benefit to patients with T2D.

4.2 CLINICAL TRIALS OF SOTAGLIFLOZIN IN HUMANS

Approximately 840 subjects (698 assigned to sotagliflozin and 229 assigned to placebo) have participated in completed clinical studies of sotagliflozin. No significant safety concerns have been identified in the sotagliflozin drug program, and sotagliflozin has been well-tolerated in all studies to date. Serious adverse events (SAEs) and discontinuations due to adverse event (AEs) have been infrequent and have been balanced between treatment and comparator groups. Reports of treatment-emergent AEs (TEAE) across all sotagliflozin studies for which data are available were generally balanced between treatment and comparator groups. The most frequently reported TEAEs (≥2.0%) were headache, nausea, diarrhea, constipation, dizziness, and upper respiratory tract infection, all of which were reported at a frequency greater than 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 Brochure (IB) were observed. In general, no significant imbalances of SAE/AEs between sotagliflozin and comparators have been observed in completed studies. Cumulatively across the completed studies 8 SAEs were reported in 6 patients (4 T2D and 2 T1D), all of which were assessed as unrelated to study drug; those reported in 4 T2D patients who received sotagliflozin included pulmonary embolism, deep vein thrombosis, bile duct stone,

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

A drug interaction study with digoxin, a sensitive P-glycoprotein (P-gp) substrate, indicated that sotagliflozin acts as a weak P-gp inhibitor.

Phase 2 data indicated that sotagliflozin may reduce systolic blood pressure (SBP) by 10 to 15 mmHg in patients with SBP ≥130 mmHg at baseline, while having little effect in patients with SBP <130 mmHg, and did not induce hypotension 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.

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

4.3 RATIONALE FOR SELECTION OF DOSES

The selection of 400 mg and 200 mg once daily doses is based on the results of the Phase 2b dose-ranging study LX4211.1-202-DM. In this study sotagliflozin doses of 75 mg once daily, 200 mg once daily, 200 mg twice daily, and 400 mg once daily were tested over a 12-week, double-blind period. The sotagliflozin 400 mg and 200 mg once daily doses were chosen for further evaluation based on their HbA1c lowering effects and the overall safety and tolerability observed at these doses. At 12 weeks, the sotagliflozin 400 mg dose lowered HbA1c by a mean of 0.93% and the 200 mg dose lowered HbA1c by a mean of 0.48%, while placebo lowered HbA1c by a mean of 0.14%. The other doses did not have any advantages in efficacy, safety, or tolerability.

The overall incidence of AEs in patients receiving sotagliflozin 400 mg or 200 mg once daily was similar to that seen with placebo.

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

4.4 RATIONALE FOR STUDY DESIGN AND CONTROL GROUPS

This study is designed to demonstrate the efficacy and safety of 2 doses of sotagliflozin compared with placebo and a sulphonylurea (glimepiride) when used as add-on therapy to metformin in patients with T2D who have inadequate glycemic control on metformin monotherapy. The American Diabetes Association (ADA) and European Association for the Study of Diabetes

Update to Position Statement (8), recommends starting dual therapy in case metformin as initial monotherapy is not sufficient to control patient's glycaemia. The recommended dual therapy includes other oral antidiabetic therapies (sulfonylurea, thiazolidinediones, SGLT2-inhibitors, and dipeptidyl peptidase-4 [DPP4]-inhibitors) and injectable therapies (GLP-1 receptor agonist, insulins). A sulfonylurea is still the most frequently used second line antidiabetic treatment worldwide. Therefore, evaluation of efficacy and safety of sotagliflozin compared to glimepiride (as one of the most prescribed sulfonylureas worldwide) in line with the currently applicable guidance for active-controlled trials in diabetes (9) and the recent FDA guidance on non-inferiority trials (10), will provide valuable additional data on sotagliflozin and its use in T2D patients as a possible second line therapy when failing to reach glucose targets on metformin monotherapy.

The primary objective of this study is to demonstrate non-inferiority of sotagliflozin 400 mg compared to glimepiride on HbA1c reduction over 52 weeks, when used as add-on therapy to metformin. A placebo control group is also included in the study, allowing assessment of the superiority of sotagliflozin 400 mg and 200 mg doses in efficacy parameters compared to placebo on a background therapy of metformin. Glimepiride will be started at 1 mg per day and will be titrated to a maximum dose of 6 mg (or the maximum tolerated dose) by 1 or 2 mg dose increments based on patient pasting glucose levels as consistent with standard clinical practice. The choice of the maximum dose of glimepiride in the study is aligned with the approved labeling of glimepiride in the European Union and it is also the maximum daily dose approved in many countries globally. In the USA, the maximum recommended daily dose of glimepiride (11) is 8 mg, however it has been described that doses above the half-maximum (4 mg) provide small gains in glucose efficacy at a cost of increased hypoglycemia risk (12, 13). Titration will occur via an algorithm based on patient fasting glucose values measured by the patients at home via self-monitoring blood glucose (SMBG) readings and discussed with the Investigator during scheduled visits or unscheduled safety phone calls. If a decision to up-titrate is made during a phone contact occurred between scheduled visits, an unscheduled on-site visit will be arranged in order to provide the patient with a new treatment kit with the higher dose level. On the other hand, temporary decreases in glimepiride dose due to hypoglycemia can be done between visits as advised by the Investigator. For patients who continue to present hyperglycemia despite glimepiride titration (or mock titration of glimepiride-matching placebo), antidiabetic rescue therapy will be initiated according to a predefined algorithm. This plan will enable adequate titration of glimepiride as well as to preserve the safety of patients who may be receiving placebo.

One Patient Reported Outcome (PRO) will be assessed in this study. The Patient Qualitative Assessment of Treatment (PQAT) will be assessed at Week 26 and at the final on-treatment visit (Week 52). This instrument includes a 7-point Likert Scale for the patient to evaluate his/her subjective response to the treatment (-3 to +3 including 0 for a neutral response) and 2 free-text response questions to describe key advantages and disadvantages.

Safety, tolerability, pharmacokinetics (PK), and pharmacodynamic (PD) effects of sotagliflozin are supported by Phase 1 and Phase 2 studies and toxicology data in rats up to 26 weeks and dogs up to 39 weeks as well as 2-year carcinogenicity data in rats. These data support the use of 400 mg and 200 mg once-daily doses as safe and effective.

To achieve balanced randomization for assessment of the primary endpoint, randomization will be stratified based on preexisting metabolic control (baseline HbA1c ≤8.5% versus >8.5%). Another stratification factor (SBP <130 mmHg versus ≥130 mmHg) has been added to ensure balance in randomization for a secondary endpoint (change from Baseline to 12 weeks in SBP for patients with baseline SBP ≥130 mmHg).

A parallel-group, randomized active-, and placebo-controlled and double-dummy study 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.

Patients will be randomized in 2:1:2:1 ratio and any potential bias will be minimized by blinding the patients, the Investigators, and the Sponsor to the treatment allocations, and by adjudicating the endpoints in a blinded fashion.

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 study program will also provide efficacy and safety data for sotagliflozin in combination with other antidiabetic medications. In addition the program will evaluate clinical outcomes in patients with high CV risk and in patients with renal impairment. The use of sotagliflozin in the treatment of T1D is also being studied in a separate development program.

Sotagliflozin may benefit a wide variety of 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, blood pressure (BP), and triglycerides (TG) observed with sotagliflozin treatment have the potential to benefit patients with diabetes through their effects on common diabetic comorbidities.

The SGLT2 inhibitors class has been associated with small decreases of glomerular filtration rate and increased rate of genital infections, which are usually mild and well-tolerated in clinical trials. Overall, sotagliflozin has been well-tolerated in all studies to date, with the majority of events assessed as mild to moderate; most of which resolved spontaneously. Serious AEs and discontinuations due to AEs have been limited and balanced between treatment and comparator groups. Events of special interest (EOSIs) monitored closely during the clinical studies based on either their potential link to the drug's mechanism of action, events that occur in other

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

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

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to demonstrate the non-inferiority of sotagliflozin 400 mg compared to glimepiride on HbA1c reduction at Week 52 in patients with T2D who have inadequate glycemic control with metformin.

5.2 SECONDARY

- To demonstrate the superiority of sotagliflozin 400 mg compared to glimepiride on:
  - Change in body weight from Baseline to Week 52
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg
  - Change in SBP from Baseline to Week 12 in all patients
  - The proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period
- To demonstrate the superiority of sotagliflozin 400 mg compared to placebo on change in HbA1c from Baseline to Week 26 .
- To demonstrate the superiority of sotagliflozin 200 mg compared to placebo on change in HbA1c from Baseline to Week 26.
- To demonstrate the superiority of sotagliflozin 400 mg compared to placebo on:
  - Change in body weight from Baseline to Week 26
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg
  - Change in SBP from Baseline to Week 12 in all patients
- To demonstrate the non-inferiority of sotagliflozin 200 mg compared to glimepiride on change in HbA1c from Baseline to Week 52.
- To demonstrate the superiority of sotagliflozin 400 mg compared to glimepiride on change in HbA1c from Baseline to Week 52.
- To evaluate the safety of sotagliflozin compared to glimepiride and placebo over 52 weeks of treatment.

5.3 OTHER

- To evaluate sotagliflozin compared to glimepiride and placebo with respect to:
  - Change in FPG
  - The number of hospital visits due to hypoglycemia
  - Change in estimated glomerular filtration rate (eGFR)

- Change in SBP for all patients, the subset with baseline SBP <130 mmHg, and the subset with baseline SBP ≥130 mmHg
- Change in diastolic blood pressure (DBP) for all patients and the subset of patients with baseline DBP ≥80 mmHg
- The proportion of patients requiring rescue medication for hyperglycemia
- The proportion of patients with HbA1c <6.5%, <7.0%
- The proportion of patients with HbA1c <6.5%, <7.0% and no documented symptomatic hypoglycemic event (≤70 mg/dL)
- PQAT

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, double-dummy study that is anticipated to enroll approximately 930 patients.

The study will consist of a Screening phase of up to 2 weeks, a 2-week single-blind placebo Run-in phase, a 52-week double-blind Treatment Period, and a 2-week post-treatment Follow-up period. In order to qualify for randomization, patients must demonstrate compliance based upon tablet and capsule count (≥80%) and discretion of the Investigator during the Run-in phase.

6.1.1 Screening period

6.1.1.1 Screening phase (Visit 1)

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

Patients with T2D (14) will be included in this study if at Screening they have been using metformin at a stable dose of ≥1500 mg/day or the maximum tolerated dose that has been stable for at least 12 weeks.

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

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

6.1.1.2 Run-in phase (Visit 2)

The Run-in phase will last 2 weeks. Patients will be treated in a single-blind manner with 2 sotagliflozin-matching placebo tablets and 2 glimepiride-matching placebo capsules administered once daily during the Run-in phase, starting from Visit 2.

6.1.2 Double-blind Treatment Period (Week 0 to Week 52)

Eligible patients will be randomized on Day 1 (Visit 3). In order to qualify for randomization, patients must demonstrate compliance during the single-blind placebo Run-in phase based upon tablet 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)

Following randomization, patients will be treated in a double-blind manner for 52 weeks. A total of 930 patients ≥18 years of age (or ≥legal age of majority, whichever is greater) will be randomly assigned at a 2:1:2:1 ratio to the following 4 treatment groups on top of open-label metformin:

- Sotagliflozin 400 mg group: Sotagliflozin 400 mg, given as two 200 mg tablets and 2 glimepiride placebo capsules, taken orally once daily before the first meal of the day (N = 310 patients).
- Sotagliflozin 200 mg group: Sotagliflozin 200 mg, given as one 200 mg tablet and 1 sotagliflozin-matching placebo tablet, and 2 glimepiride placebo capsules, taken orally once daily before the first meal of the day (N = 155 patients).
- Glimepiride group: 2 sotagliflozin-matching placebo tablets, and combination of 2 glimepiride (or matching placebo) capsules with adequate dose strengths per dose titration (titrated up to 6 mg, see Table 2), taken orally once daily before the first meal of the day (N = 310 patients).
- Placebo group: 2 sotagliflozin-matching placebo tablets and 2 glimepiride placebo capsules, taken orally once daily before the first meal of the day (N = 155 patients).

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

All visits will be on-site with the exceptions of Visit 8 (Week 15) and Visit 13 (Week 54) which will be telephone visits.

If a patient discontinues with investigational medicinal product (IMP) early during the Treatment Period, the patient will have a Premature End of Treatment (EOT) Visit and a Follow-up phone call 2 weeks after the last dose of IMP. In addition, every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits, particularly the Week 26 and Week 52 visits.

If the patient does not agree to site visits, he/she will be contacted by telephone to inquire about safety status, particularly at the time of the initially scheduled end of study.

6.1.3 Follow-up period

Following the last dose of the IMP (either as scheduled or prematurely), a post-treatment Follow-up should be scheduled for all patients 2 weeks ± 3 days after permanent IMP discontinuation. This visit will be a phone call visit.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The total duration of the study for each patient will be up to 58 weeks and will include a Screening phase of up to 2 weeks, a 2-week single-blind Run-in phase, a 52-week double-blind Treatment Period, and a 2-week post-treatment Follow-up period.

6.2.2 Determination of end of clinical trial (all patients)

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

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

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

6.4.1 Steering committee

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

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

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

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

6.4.2 Data monitoring committee

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

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

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

6.4.3 Clinical endpoint committee(s)

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

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

6.4.4 Safety adjudication of events requiring ongoing monitoring

Two independent committees will review safety events that require ongoing monitoring to ensure timing protocol amendments in case a safety signal is identified. These events are: 1) potential cases of 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 should not be randomized more than once. In case where original screen failure was due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the patient can be rescreened once prior to entering Run-in for this study.

7.1 INCLUSION CRITERIA

I 01. Patients with T2D treated with metformin at a stable dose ≥1500 mg/day or maximum tolerated dose (documented) for at least 12 weeks prior to Screening Visit; in case of documented lack of tolerance, metformin dose <1500 mg/day is acceptable, and the dose should be stable for at least 12 weeks prior to Screening Visit.

I 02. Signed written informed consent to participate in the study in accordance with local regulations.

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

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

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

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

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

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

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

E 07. Patients with severe anemia, severe CV (including congestive heart failure New York Heart Association IV), respiratory, hepatic, neurological, psychiatric, or active malignant tumor or other major systemic disease or patients with short life expectancy that, according

to Investigator, will preclude their safe participation in this study, or will make implementation of the protocol or interpretation of the study results difficult.

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

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

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

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

E 12. Patients who have taken other investigational drugs within 12 weeks or 5 half-lives, whichever is longer, prior to Screening.

7.2.2 Exclusion criteria related to the diabetes history and treatment

E 13. Type 1 diabetes mellitus.

E 14. HbA1c <7.0% or >10% at Screening (central laboratory).

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

E 16. Previous use of any antidiabetic drug other than metformin within 12 weeks preceding the Screening Visit.

E 17. Previous use of any types of insulin for >1 month (at any time, except for treatment of gestational diabetes).

E 18. Use of a selective SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) within 3 months prior to the Screening visit.

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

E 20. History of severe hypoglycemia resulting in unconsciousness, seizure or hospitalization within 6 months prior to the Screening Visit.

E 21. Patients with contraindication to metformin as per local labeling.

7.2.3 Exclusion criteria related to the active comparator

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

E 23. History of glucose-6-phosphate dihydrogenase (G6PD) deficiency.

E 24. History of hypersensitivity reaction to glimepiride or any of the product's ingredients or history of allergic reaction to sulfonamide derivatives (hypersensitivity reactions include cutaneous eruptions with or without pruritus, as well as anaphylaxis, angioedema, or Stevens-Johnson Syndrome, dyspnea).

7.2.4 Exclusion criteria related to the current knowledge of sotagliflozin

E 25. Pregnant (confirmed by pregnancy test at the Screening) or breast-feeding women.

E 26. Women of childbearing potential not willing to use highly effective method(s) of birth control during the study treatment period and follow-up period, or who are unwilling or unable to be tested for pregnancy (see Appendix A) during the study.

E 27. Mean of 3 separate BP measurements >180 mmHg (SBP) or >100 mmHg (DBP).

E 28. History of hypertensive emergency within 12 weeks prior to Screening.

E 29. History of gastric surgery including history of gastric banding or inflammatory bowel disease within 3 years prior to the Screening Visit.

E 30. Difficulty swallowing such the patient cannot take the IMP.

E 31. Known allergies, hypersensitivity, or intolerance to SGLT2 inhibitors or any inactive component of sotagliflozin or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), unless the reaction is deemed irrelevant to the study by the Investigator.

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

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

E 33. Patients with severe renal disease as defined by an eGFR of <30 mL/min/1.73 m^2 at Screening, based on the 4 variable Modification of Diet in Renal Disease (MDRD) equation (or according to the renal function restrictions of metformin use defined in the local approved label).

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).

7.2.5 Additional exclusion criteria during or at the end of the run-in phase before randomization

E 35. Patients unwilling or unable to perform SMBG, complete the patient diary, or comply with study visits and other study procedures as required per protocol.

E 36. 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 37. Informed consent withdrawal before randomization (patient who is not willing to continue) or fails to return.

E 38. Any clinically significant abnormality identified on physical examination, laboratory tests, 12-lead electrocardiogram (ECG), or vital signs at the time of Screening or any AE during Screening Period which, in the judgment of the Investigator or any Sub-Investigator, would preclude safe completion of the study or constrains efficacy assessment.

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

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

8.1.1 Formulations

The IMPs are sotagliflozin (400 and 200 mg) and glimepiride (1 mg titrated up to 6 mg). Patients will be provided with kits containing wallets of sotagliflozin or sotagliflozin-matching placebo (supplied as tablets identical to sotagliflozin 200 mg in appearance) and kits containing wallets of glimepiride (supplied as 1, 2, and 4 mg capsules) or glimepiride-matching placebo (supplied as capsules). Treatment kits will be provided to the sites containing the appropriate number of IMP for the given Treatment Period (including visit windows). Table 1 provides a summary of each IMP.

Table 1 - Summary of investigational medicinal products

IMP:	Sotagliflozin 400 mg/ glimepiride-matching placebo	Sotagliflozin 200 mg/ glimepiride-matching placebo	Glimepiride/ sotagliflozin-matching placebo	Placebo (sotagliflozin and glimepiride)
Name of the IMPs	Sotagliflozin 400 mg /glimepiride- matching placebo	Sotagliflozin 200 mg/ glimepiride-matching placebo	Glimepiride/ sotagliflozin-matching placebo	Placebo (glimepiride and sotagliflozin)
Pharmaceutical form	Sotagliflozin will be supplied as 200 mg tablets/ glimepiride-matching placebo will be supplied as capsules (identical to glimepiride over-encapsulated tablets)	Sotagliflozin will be supplied as 200 mg tablets/ sotagliflozin-matching placebo will be supplied as tablets(identical to sotagliflozin 200 mg in appearance)/ glimepiride-matching placebo will be supplied as capsules	Glimepiride will be supplied as 1, 2, and 4 mg capsules/ sotagliflozin-matching placebo will be supplied as tablets	Sotagliflozin-matching placebo will be supplied as tablets/glimepiride-matching placebo will be supplied as capsules
Dose, timing and route of administration	Two 200 mg sotagliflozin tablets and 2 glimepiride-matching placebo capsules, taken orally once daily, before first meal of the day	One 200 mg sotagliflozin tablets, 1 sotagliflozin-matching placebo tablet, and 2 glimepiride-matching placebo capsules, taken orally once daily, before first meal of the day	Combination of 2 glimepiride (or matching placebo) capsules with adequate dose strengths per dose titration (titrated up to 6mg, see Table 2) and 2 sotagliflozin-matching placebo tablets taken orally once daily, before first meal of the day	Two sotagliflozin-matching placebo tablets, and 2 glimepiride-matching placebo capsules, taken orally once daily, before first meal of the day
Duration of treatment	52 weeks following randomization	52 weeks following randomization	52 weeks following randomization	54 weeks: 2 weeks during single-blind Run-in phase + 52 weeks following randomization

IMP:	Sotagliflozin 400 mg/ glimepiride-matching placebo	Sotagliflozin 200 mg/ glimepiride-matching placebo	Glimepiride/ sotagliflozin-matching placebo	Placebo (sotagliflozin and glimepiride)
Storage conditions	Sotagliflozin kit (active and placebo): Store between +15°C and +30°C (59°F and 86°F)			
	Glimepiride kit (active and placebo): Store between +2°C and +30°C (36°F and 86°F)			

IMP = Investigational medicinal product

* Glimepiride (or glimepiride placebo) will be titrated (or mock-titrated) up to 6 mg or to the maximum tolerated dose from Baseline (Visit 3) through Week 18 (Visit 9); after Week 18 (Visit 9) until Week 52 (Visit 12), patients will receive a stable dose of glimepiride.

8.1.2 Starting dose and dose adjustment

All patients will receive treatment at a fixed dose of sotagliflozin (or matching placebo) as assigned at randomization throughout the 52-week study period.

All patients will receive glimepiride (or glimepiride-matching placebo) on Day 1 starting from 1 mg daily. Glimepiride (or glimepiride-matching placebo) will be titrated (or mock-titrated) up to 6 mg (or maximum tolerated dose). Titration will be possible at 5 dose levels (1, 2, 3, 4, and 6 mg) through a combination of glimepiride (or matching placebo) capsules with different dose strengths. Table 2 provides an overview of the glimepiride dose levels.

Table 2 - Glimepiride dose levels

Dose level:	Number of glimepiride and/or placebo capsules dispensed (dose strengths)
1 mg	1 (glimepiride placebo) +1 (1 mg)
2 mg	1 (glimepiride placebo) +1 (2 mg)
3 mg	1 (1 mg) + 1 (2 mg)
4 mg	2 (2 mg)
6 mg	1 (2 mg) + 1 (4 mg)

Titration will occur during the first 18 weeks post-randomization; the glimepiride dose will have to remain stable after the first 18 weeks, unless a dose modification is required for safety reasons.

Fasting glucose values will be determined by the patient via fasting SMBG. If the average of the most recent 3 SMBG morning values (not necessarily on consecutive days) are >108 mg/dL and based on the Investigator's medical judgment and clinical assessment, the glimepiride dose will be titrated to the next level by increasing the dose by 1 or 2 mg. Note that the subject must remain on a particular glimepiride dose for at least 2 weeks, prior to uptitrating to the next level.

- The Investigator may decide to withhold titration at any time upon a documented safety rationale.
- Dose may be down titrated at any time, if necessary, based on occurrence of one episode of severe hypoglycemia, or 2 or more episodes of documented hypoglycemia within 2 weeks (symptomatic hypoglycemia with glucose measurement ≤70 mg/dL [3.9 mmol/L]). In this situation, the dose can be decreased by 1 to 2 mg, while necessary actions are taken to manage the hypoglycemia risk. The dose can subsequently be re-increased up to Week 18, inclusive.

Increase to a higher glimepiride dose level will be possible only at on-site visits. Temporary decreases due to severe or recurrent hypoglycemia are allowed if instructed by the Investigator during safety unscheduled phone visits. An on-site visit should follow as soon as possible within 7 days.

After Week 18, no further increase in the glimepiride dose will be allowed (for those subjects that have not yet reached the maximal allowed glimepiride dose of 6 mg daily) and in cases of continued poor glycemic control, appropriate rescue therapy could be considered. Note that prior to initiating rescue therapy the glimepiride dose needs to have been uptitrated to the maximal allowed or tolerated daily level if rescue is required prior to Week 18.

In case of recurrent hypoglycemia, down-titration of glimepiride (or matching placebo) can be performed at any time during the study for the patients taking a daily dose higher than 2 mg of glimepiride. In the glimepiride blister delivered to the patient, the first column will correspond to the lower dose strength. If an unscheduled phone visit is prompted due to recurrent hypoglycemia, the Investigator may use discretion to advise patients to temporarily (<7 days) decrease glimepiride/matching placebo dose by omitting the capsule of lower dose until they are able to return to the site to be evaluated and receive a new treatment kit as needed. In this case, an on-site visit should occur as soon as possible within 7 days.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT

8.2.1 Metformin

Patients are enrolled with a background therapy consisting of metformin. Background metformin is considered as a noninvestigational medicinal product (NIMP). Metformin (commercial formulation) will be administered orally according to Investigator's recommendation and the locally approved label.

The dose of metformin must be ≥1500 mg/day or maximum tolerated dose (maximum tolerated dose needs to be documented). The metformin dose must be stable for at least 12 weeks before Screening.

The dose of metformin should be stable throughout the study unless down-titration or discontinuation is required for safety reasons.

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

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

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

8.2.2 Rescue therapy

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

- From Baseline Visit (Visit 3, Day 1) to Visit 6 (Week 8) (including value at Visit 6) FPG >270 mg/dL (>15.0 mmol/L).
- From Visit 6 (Week 8) to Visit 7 (Week 12) (including value at Visit 7): FPG >240 mg/dL (>13.3 mmol/L).
- From Visit 7 (Week 12) up to the EOT Period Visit 12 (Week 52): 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 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 1 fasting SMBG value exceeds the specific glycemic limit on 1 day, the patient checks it again during the following 2 days. If all the values in the 3 consecutive days exceed the specific limit, the patients should contact the Investigator and a central laboratory FPG measurement (and HbA1c after Week 12 and onwards) is performed as soon as possible, preferably within 7 days to confirm the hyperglycemia.
- Upon receipt of a central laboratory rescue alert, a central laboratory re-test must be completed and confirmed as exceeding the criterion for rescue before rescue therapy is initiated. The re-test confirmation should be performed as soon as possible, but within 7 days of receipt by unscheduled visit.

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

- The increased FPG has been tested at a fasting status (ie, no food intake for ≥8 hours)
- IMP is given at the planned dose and glimepiride (or matching placebo) is already at the maximum titrated dose (6 mg or maximum tolerated dose) or no longer possible to be titrated during the first 18 weeks of the study.
- 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 e-CRF and the medical record).
- Stress on 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 patient is still in the first 18 weeks of the study and glimepiride is not uptitrated to the maximum dose evaluate if uptitration of glimepiride is possible.

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.

- Rescue medication can be added up to the Investigator's decision except for SGLT2 inhibitors, and sulfonylurea.
- The patient continues the study treatment (blinded) and stays in the study in order to collect efficacy and safety information. The planned visits and assessments should occur until the last scheduled visit.
- Rescue therapy is considered a NIMP. Rescue therapy is to be reported in the e-CRF. This information should include specific drug name, dose, route of administration, and frequency.

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

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

To maintain blinding, sotagliflozin and placebo tablets, glimepiride and placebo capsules, and their packaging will be blinded. Sotagliflozin versus sotagliflozin-matching placebo and glimepiride versus glimepiride-matching placebo will be 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 will generate the patient randomization list from which is allocates treatment groups to the patients.

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

The CEC members will perform adjudication in a blinded manner.

8.3.2 Randomization code breaking during the study

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

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

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

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

Patients will be randomized to receive either sotagliflozin 400 mg and glimepiride placebo, sotagliflozin 200 mg and glimepiride placebo, glimepiride and sotagliflozin placebo, or glimepiride placebo and sotagliflozin placebo once daily during the randomized double-blind Treatment Period. Randomization (ratio 2:1:2:1) will be stratified by HbA1c at Screening (≤8.5%, >8.5%), and SBP at Screening (<130 mmHg, ≥130 mmHg).

[redacted]

[redacted]At Visit 2 (Run-in) and Visit 3 (Baseline), patient eligibility will be reviewed; the IRT will be contacted at both visits for allocation of corresponding treatment packages and for randomization (Visit 3).

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

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

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

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

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

8.5 PACKAGING AND LABELING

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

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

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

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

The expiry date and storage conditions are written on the IMP labels. The IMP should be stored between +15°C and +30°C (59°F and 86°F) (Table 1).

8.7 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. 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, in order to recall the IMP and eliminate potential hazards.

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

8.7.1 Treatment accountability and compliance

Accounting and compliance for IMPs will be performed at Visit 3 and all subsequent on-site visits (excluding telephone visits).

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

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

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

If compliance is inadequate as determined by the Principal Investigator (PI), patients will be trained again and mentored. If sub-optimal compliance continues after training and mentoring, patients may be discontinued at the discretion of the PI 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 wallets[s]) at each on-site visit (or at final assessment visit in case of permanent premature discontinuation), as described in Section 1.2. IMP accounting is not required at telephone visits.

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

For NIMP not provided by the Sponsor (ie, metformin and 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 and matching placebo, and glimepiride and matching placebo.

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

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

8.8.1 Prohibited prior and concomitant medications

During the study, the following medications are prohibited:

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

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

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

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

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

8.8.2 Concomitant diabetes therapy

For patients in both groups, background NIMP metformin should be stable throughout the study unless down-titration is required for safety reasons.

The rescue medication(s) that will be used to treat hyperglycemia when a patient's hyperglycemia reaches the rescue threshold are also defined as NIMPs. Rescue medication can be added up to the Investigator's decision except for SGLT2 inhibitors and sulfonylurea. The regimen of the rescue medications will be in accordance with local standard of care and prescribing practice.

8.9 POST-STUDY 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 and glimepiride will not be provided after EOT. Patient's further treatment for diabetes and other pathologies will be at the Investigator's discretion based on his/her clinical judgment.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

The methods of assessment of efficacy endpoints are detailed in Section 9.1.5.

9.1.1 Primary efficacy (sotagliflozin 400 mg dose)

- Change from Baseline to Week 52 in HbA1c (%)

9.1.2 Secondary efficacy endpoints (sotagliflozin 400 mg dose)

- Change from Baseline to Week 26 in HbA1c
- Change from Baseline to Weeks 26 and 52 in body weight
- Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg
- Change from Baseline to Week 12 in SBP for all patients
- Proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period

9.1.3 Secondary efficacy endpoints (sotagliflozin 200 mg dose)

- Change from Baseline to Weeks 26 and 52 in HbA1c

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

- Change from Baseline to Weeks 26 and 52 in FPG
- Number of hospital visits due to hypoglycemia during the 52-week Treatment Period
- Change from Baseline in eGFR
- Change from Baseline to Week 26 and 52 in SBP for all patients and the subset with baseline SBP ≥130 mmHg
- Change from Baseline to Weeks 12, 26, and 52 in SBP for patients with baseline SBP <130 mmHg
- Change from Baseline to Weeks 12, 26, and 52 in DBP for all patients and the subset with baseline DBP ≥80 mmHg
- Proportion of patients requiring rescue treatment for hyperglycemia during the 52-week Treatment Period
- The proportion of patients with HbA1c <6.5%, <7.0% at Week 52
- The proportion of patients with HbA1c <6.5%, <7.0% at Week 52 and no documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period

- PQAT at Weeks 26 and 52

9.1.5 Assessment methods of efficacy endpoints

9.1.5.1 Hemoglobin A1c

Hemoglobin A1c will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 12 (Visit 7), Week 26 (Visit 10), Week 39 (Visit 11), and Week 52 (Visit 12).

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified Level I "National Glycohemoglobin Standardization Program" central laboratory.

9.1.5.2 Body weight measurement

Body weight is measured at all on-site visits.

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. 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 e-CRF and Source Data. Self-reported weights are not acceptable; patients must not read the scales themselves.

9.1.5.3 Fasting plasma glucose measurement

Plasma glucose is measured in the fasting state at Screening (Visit 1) and all on-site visits, with the exception of Week 2 (Visit 4), during the Treatment Period. Fasting plasma glucose will be performed on the morning of the visit. For the eligibility and efficacy assessments of the study, FPG is measured at a central laboratory.

9.1.5.4 Blood pressure measurements

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

9.1.5.5 Kidney function parameter assessment

Serum creatinine will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 12 (Visit 7), Week 26 (Visit 10), and Week 52 (Visit 12). A central laboratory will analyze samples.

9.1.5.6 Proportion of patients requiring rescue for hyperglycemia

The use of rescue medications for hyperglycemia will be assessed and reported throughout the Treatment Period. Routine alerts on FPG and/or HbA1c will be sent to the Investigator from the

central laboratory to ensure that glycemic parameter results remain within predefined thresholds. For details and further actions should FPG and/or HbA1c values fall above thresholds, refer to Section 8.2.2.

9.1.5.7 Number of hospital visits due to hypoglycemia during the 52-week treatment period

Hospital visit due to hypoglycemia will include emergency room visit, outpatient visit and any hypoglycemic episodes hospitalization due to hypoglycemia. During the study, patients are instructed to document hospital visit due to hypoglycemia in their study diary.

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.

Adjudication of all deaths, MACE/other selected CV events, selected renal events, bone fracture and DKA will be performed in a blinded manner by a CEC(s) comprised of experts. Details will be provided in the charter of the CEC(s). Further details are available in Section 6.4.3.

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

The following safety endpoints will be assessed:

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

Observation period of safety endpoints

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

- The pre-Treatment Period is defined as the time between the date of 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 (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 SAE, AESI, and EOSI will be assessed. Refer to Section 10.4 to Section 10.7 for details.

9.2.1.1.1 Adverse events of special interest

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

9.2.1.1.2 Events of special interest

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

9.2.1.2 Hypoglycemia

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

9.2.1.3 Laboratory safety variables

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

Table 3 lists the hematology, clinical chemistry, and other blood safety parameters to be assessed by the central laboratory.

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

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

Table 3 - Blood safety laboratory

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

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

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

9.2.1.3.1 Urinalysis

Urinalysis (urine dipstick with microscopy) will be performed by central laboratory at Screening (Visit 1), Baseline (Visit 3), Week 26 (Visit 10), and Week 52 (Visit 12). To prevent partial unblinding, the central laboratory urinalysis dipstick will not include the measurement of urine glucose.

The central urinalysis includes:

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

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

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

9.2.1.4 Vital signs

A complete physical exam (including sitting BP and heart rate [HR]), temperature and respiratory rate) will be performed at Visit 1 (Screening), Visit 10 (Week 26), and Visit 12 (Week 52).

Abbreviated physical exams (including sitting BP and HR) will be performed at all other on-site visits. The abbreviated physical exam should focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs, if necessary.

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

9.2.1.5 Electrocardiogram variables

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

A 12-lead ECG record is performed locally at Screening (Visit 1), Week 26 (Visit 10), and Week 52 (Visit 12).

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

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

9.2.1.6 Self-monitoring of blood glucose

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

Patients will also receive a patient diary at all on-site Visits with the exception of Visit 12 (Week 52). The diary will be reviewed at all on-site visits from Visit 2 to Visit 12. Self-assessed blood glucose levels will be entered in the patient diary.

Patients will be asked to self-assess fasting blood glucose levels at least 3 times in the week before on-site or telephone study visits from the Run-in visit (Visit 2) to the end of the titration period including on day of each on-site study visit. After Visit 9 (Week 18), the Investigator can (at their own discretion) instruct patients to self-monitor blood glucose as frequently as considered needed.

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

If 1 fasting SMBG value exceeds the specific glycemic limit on 1 day, the patient checks it again during the following 2 days. If all the values in the 3 consecutive days exceed the specific limit, the patients should contact the Investigator and a central laboratory FPG measurement (and HbA1c after Week 12) is performed.

Patients will also be instructed to record SMBG values that are ≤70 mg/dL (≤3.9 mmol/L) in the patient diary. Patients should be instructed to contact the site if fasting SMBG values over 3 consecutive days are:

- >270 mg/dL (>15.0 mmol/L) from Baseline Visit (Visit 3, Day 1) to Visit 6 (Week 8) (including value at Visit 6).
- >240 mg/dL (>13.3 mmol/L) from Visit 6 (Week 8) to Visit 7 (Week 12) (including value at Visit 7).
- >200 mg/dL (>11.1 mmol/L) from Visit 7 (Week 12) up to the EOT Period Visit 12 (Week 52).

9.3 OTHER ENDPOINTS

[redacted]

[redacted]

9.3.2 Patient reported outcomes

9.3.2.1 Patient qualitative assessment of treatment

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

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

The patients will be asked to complete it electronically from home just before the on-site visits planned at Weeks 26 (Visit 10) and 52 (Visit 12). They will be asked to do it by themselves without any help from friends or relatives.

At the beginning of the Weeks 26 (Visit 10) and 52 (Visit 12) patient visits, Investigators will have to review patient answers (accessible on a web platform) in order to identify any potential AEs reported by patients within the open-ended questions. Investigators will discuss with the patient potential AEs identified; Investigators will not discuss any other aspects of the answers with the patients, and will not ask patients to change their answers. If AEs that were previously not captured are identified during this process, they should be reported as described in Section 10.4.2.

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

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

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

[redacted]

[redacted]

9.5 APPROPRIATENESS OF MEASUREMENTS

The addition of sotagliflozin to background therapy consisting of metformin is expected to lower HbA1c over 52 weeks of treatment (primary efficacy analysis).

The concentration of HbA1c reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2 to 12 weeks.

Hemoglobin A1c has also been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is known to reduce the risk of long-term microvascular complications. Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. The duration of study treatment (52 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 52 is a secondary endpoint.

Phase 2 data indicated that sotagliflozin may reduce SBP by 10 to 15 mmHg in patients with SBP $\geq$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 $\geq$80 mmHg. Although effects on BP in Phase 2 data were observed with the 400 mg dose at 12 weeks, the effects will be examined at Weeks 12, 26, and 52.

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

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

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

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

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

This is an out-patient study and consists of 11 on-site visits and 2 telephone visits, although optional on-site and/or telephone visits can be scheduled at any time for any reason during the study whenever considered necessary by the Investigator.

The patients need to be fasting for on-site visits Visit 1 through Visit 12 (Week -4 through Week 52), unless instructed otherwise by the Investigator. Throughout the study, "fasting" is defined as 8 hours without food. **Note**: If the patient is not fasting at the visits specified above, the blood sample will not be collected and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted (other procedures can be performed as scheduled). All laboratory assessments will occur prior to IMP and NIMP administration on the day of the visit.

The Run-in Visit (Visit 2) can be performed as soon as the results of all Screening tests are available and the patient is confirmed to be eligible for participation in the study. The visit window for Visit 4 through Visit 10 should occur within ± 3 days. Visit 11 should occur within ± 7 days. Visit 12 should occur during Day 361 to 367 except for Premature EOT visit. For the Follow-up (Visit 13 – phone visit), the visit should occur 2 weeks ± 3 days after Visit 12.

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 trial visits are reviewed by the Investigator and Sub-Investigators who are qualified in the treatment of T2D and are familiar with the study.

10.1.1 Screening period

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

10.1.1.1 Screening phase

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

Patients will undergo screening assessments at Visit 1 (Week -4) following signing of the ICF. Patients who meet the inclusion criteria as noted in Section 7.1 and have no exclusion criteria as noted in Section 7.2 will be randomized at Visit 3 (Day 1).

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

A patient can be rescreened once in case of manageable laboratory exclusion as deemed by the Investigator as reasonable to change. In these cases, the patient will need to sign a new ICF, be registered as a new patient in the IRT and assigned a new patient number (first Screening Visit is to be registered as screen failure in the IRT), and again complete the Screening Visit procedures/assessments.

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

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

- Obtain the informed consent:
  - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration. Written information will be provided to the patient. Written informed consent must be given by the patient and Investigator prior to any investigations.
  - [redacted]
  - [redacted]
- Complete physical examination including height, body weight, and vital signs (SBP and DBP, HR, 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 C for details).
- IRT to be notified (allocation of identification, registration of screening).
- Assessment of all inclusion/exclusion criteria.
- Collection of demographic data (age, gender, and ethnic origin).
- Assessment of the patient's medical and surgical history: to include history of T2D, treatment and complications (eye, kidney, amputations, etc); history of smoking/tobacco use; history of alcohol and drug abuse.
- Patient diary is dispensed and instructions/training are provided.
- Concomitant medication and medication history, including any prior medications for T2D.
- 12-lead ECG.
- The following laboratory testing (by the central laboratory):
  - FPG

- HbA1c
- Serum pregnancy testing for WOCBP or serum FSH and estradiol (for women of nonreproductive potential if definition of postmenopausal or premenopausal cannot be satisfied; see Appendix A)
- Clinical chemistry (including amylase, lipase) and hematology
- Fasting lipids
- Urinalysis (dipstick and microscopy)

- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Patients are instructed to return to the site in fasting status for Visit 2 (Week -2).

10.1.1.2 Run-in phase

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

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

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

- Assessment of exclusion criteria.
- Measurement of body weight.
- Abbreviated physical examination including vital signs (SBP, DBP, HR, 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 C for details).
- Diet and exercise instruction.
- Blood glucose meter is dispensed and instructions/training are provided.
- IRT to be notified.
- Instruction on DKA symptoms and basic genitourinary (GU) hygiene and hydration is provided (see Appendix B).
- Patient diary is collected and reviewed and a new one dispensed. Instructions/training are provided as needed.
- AEs/SAEs/AESI/EOSI and hypoglycemia occurring since Visit 1 (if any) are reported.
- Run-in kit/placebo is dispensed.
- Changes in concomitant medication are reported.
- Fasting SMBG is assessed.
- Patients are instructed to return to the site in the fasting state for Visit 3 (Randomization).

10.1.2 Double-blind randomized treatment period (Day 1 to Week 52)

Upon successful completion of the Run-in phase, patients will be randomly allocated to either sotagliflozin 400 mg and glimepiride placebo, sotagliflozin 200 mg and glimepiride placebo, glimepiride and sotagliflozin placebo, or glimepiride placebo and sotagliflozin placebo for the double-blind Treatment Period lasting 52 weeks. All randomized patients will be followed at regular on-site visits for the duration of the Treatment Period.

At each on-site visit, the patient must return to the investigation site in the morning in fasting condition (at least 8 hours fasting) and holding antidiabetic drug(s).

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

10.1.2.1 On-site randomization visit on 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 the Run-in phase.
- Concomitant medications are assessed.
- Measurement of body weight.
- Abbreviated physical examination including vital signs. After 5 minutes resting, seated SBP, DBP, and HR will be assessed 3 times with at least 1 minute between each measurement (see Appendix C for details).
- IMP accounting and compliance for single-blind placebo Run-in phase.
- IRT to be notified and randomization will occur.
- Diet and exercise instruction.
- Patient diary is collected/reviewed and a new one is dispensed. Instructions/training are provided as needed.
- Instruction on DKA symptoms and instruction on basic GU hygiene and hydration is provided (see Appendix B).
- Fasting SMBG is assessed.
- The following laboratory testing (by the central laboratory):
  - FPG
  - HbA1c
  - Urine pregnancy testing for WOCBP
  - Clinical chemistry (including amylase, lipase) and hematology
  - Fasting lipids

  - Urinalysis (dipstick and microscopy)
- Additional laboratory testing at this visit:
  - [redacted]
  - [redacted]
- IMP is dispensed.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Patients are instructed to return to the site in the fasting state for Visit 4 (Week 2).
- For accountability and compliance purposes, patients are instructed to return to the site with their used, unused, and in-use wallet(s) dispensed during Visit 3.

10.1.2.2 On-site visits at Weeks 2 to 39 (Visits 4 to 11)

The following will be performed at these visits:

- Measurement of body weight.
- Abbreviated physical examination including vital signs (SBP, DBP, HR, 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 (all visits except Visit 10, see Appendix C for details). At Visit 10 (Week 26), a complete physical examination will be performed (Section 9.2.1.4).
- Diet and exercise instruction (Visit 10 only).
- Instruction on DKA symptoms and basic GU hygiene and hydration (all visits except Visit 4; see Appendix B) is provided.
- IRT to be notified.
- Patient diary is collected/reviewed and a new one is dispensed. Instructions/training are provided as needed.
- IMP dispensed.
- IMP accounting and compliance.
- Concomitant medications are assessed.
- Fasting SMBG is assessed.
- 12-lead ECG (Visit 10 only).
- The following laboratory testing (by the central laboratory):
  - FPG (all visits except Visit 4)
  - HbA1c (Visit 7, 10, and 11)
  - Urine pregnancy testing for WOCBP
  - Clinical chemistry (including amylase, lipase, and hematology; Visits 7, 10, and 11)
  - Fasting lipids (Visit 10 only)

  - Urinalysis (dipstick and microscopy; Visit 10 only)
- Additional laboratory testing at this visit:
  - [redacted]
- PQAT (Visit 10 only).
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Patients are evaluated for glycemic rescue (see Section 9.1.5.6).
- Patients are instructed to return to the site in the fasting state for their next visit.
- For accountability and compliance purposes, patients are instructed to return to the site with their used, unused, and in-use wallet(s) at the next visit.

10.1.2.3 Phone call visit at Week 15 (Visit 8)

The following will be performed at this visit:

- Concomitant medications are assessed.
- Fasting SMBG is assessed.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- Patients are evaluated for glycemic rescue (see Section 9.1.5.6).
- Patients are instructed to return to the site in the fasting state for their next visit (Visit 9).

10.1.2.4 On-site Visit 12 (Week 52) or end of treatment

The following will be performed at this visit:

- Measurement of body weight.
- Complete physical examination including vital signs (SBP and DBP, HR, 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 C for details).
- Diet and exercise instruction is provided.
- Instruction on DKA symptoms basic GU hygiene and hydration (see Appendix B) is provided.
- IMP accounting and compliance.
- Patient diary, including hypoglycemia log, is collected/reviewed.
- Concomitant medications are assessed.
- Fasting SMBG is assessed.
- 12-lead ECG.
- The following laboratory testing (by the central laboratory):
  - FPG

- HbA1c
- Clinical chemistry (including amylase, lipase) and hematology
- Fasting lipids
- Urine pregnancy testing for WOCBP
- Urinalysis (dipstick and microscopy)

- Additional laboratory testing at this visit:
  - [redacted]
- PQAT
- IRT to be notified.
- AEs/SAEs/AESI/EOSI and hypoglycemia (if any) are reported.
- A telephone call for last study visit (Visit 13) is scheduled in 2 weeks.

10.1.3 Post-treatment follow-up period

The post-treatment Follow-up period will include a Follow-up phone call 2 weeks after the last dose of IMP.

10.1.3.1 Follow-up phone call Visit 13 (Week 54)

The following information will be discussed during this phone call:

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

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient's file

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

- Agreement and signature of ICF with the study identification.
- Study identification (name).
- Patient number, confirmation of randomization, treatment batch number, dates and doses of study medication administration.

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

10.2.2 Source data verification requirements for screen failures

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

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

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

10.3.1 Temporary treatment discontinuation with investigational medicinal product

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Lower extremity complications (such as skin ulcers, infection, osteomyelitis and gangrene) requiring treatment should lead to temporary discontinuation of IMP. Reinitiating treatment with

the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered, according to his/her best medical judgment, that the occurrence of the concerned event was unlikely to be related to the IMP.

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

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

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

Use of any other anti-hyperglycemic medication during the time of temporary treatment discontinuation (eg, insulin during a hospitalization) is recorded as concomitant medication with the name and doses recorded in the e-CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

10.3.3 List of criteria for permanent treatment discontinuation

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

The following reasons lead to permanent discontinuation:

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

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

For patients who prematurely discontinue the IMP, the assessments planned at the EOT visit (see Section 10.1.2.4) will be performed as soon as possible after treatment discontinuation. The reason(s) for IMP discontinuation will be clearly specified. This EOT assessment may occur at a regularly scheduled or unscheduled visit.

10.3.4 Handling of patients after permanent treatment discontinuation

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

If a patient decides to discontinue IMP early, a Premature EOT visit (see Section 10.1.2.4) 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. For patients that discontinue treatment but remain in the study, remaining study visits should occur as scheduled where possible. The IRT should be notified of EOT.

After permanent treatment discontinuation, of the investigational products, any treatments (other than SGLT2 inhibitors) are permitted, as deemed necessary by the Investigator.

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

10.3.5 Procedure and consequence for patient withdrawal from study

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

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

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

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

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

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

- Results in death, or
- Is life-threatening, or
- **Note**: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect
- 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 times ULN + total bilirubin >2 times ULN or asymptomatic ALT increase >10 times ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study.
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

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

The AESI for this study are:

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

intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.

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

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

10.4.1.4 Events of special interest

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

The EOSI for this study are:

- Major adverse cardiovascular events (MACE [CV death, MI, or stroke]) and other specific CV events (eg, heart failure leading to hospitalization)
- Severe hypoglycemia (see Section 9.2.1.2)
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candida balanitis in males)
- UTIs
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Diarrhea
- Pancreatitis
- Bone fractures
- VTE to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- DKA
- Renal events to include 50% decline in eGFR, end stage kidney disease, renal death
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid carcinoma)
- Adverse events leading to amputation

10.4.2 General guidelines for reporting adverse events

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

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the Monitoring team and Pharmacovigilance after approval of the Investigator within the e-CRF.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and 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 e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper case report form [CRF] process) is available and should be used when the e-CRF system does not work.

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

10.4.4 Guidelines for reporting adverse events of special interest

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

10.4.5 Guidelines for reporting events of special interest

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

10.4.6 Guidelines for management of specific laboratory abnormalities

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

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

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

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSARs), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.

- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- The following AESIs to those regulatory authorities who require such reporting:
  - Pregnancy
  - Symptomatic overdose
  - ALT increase >3 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

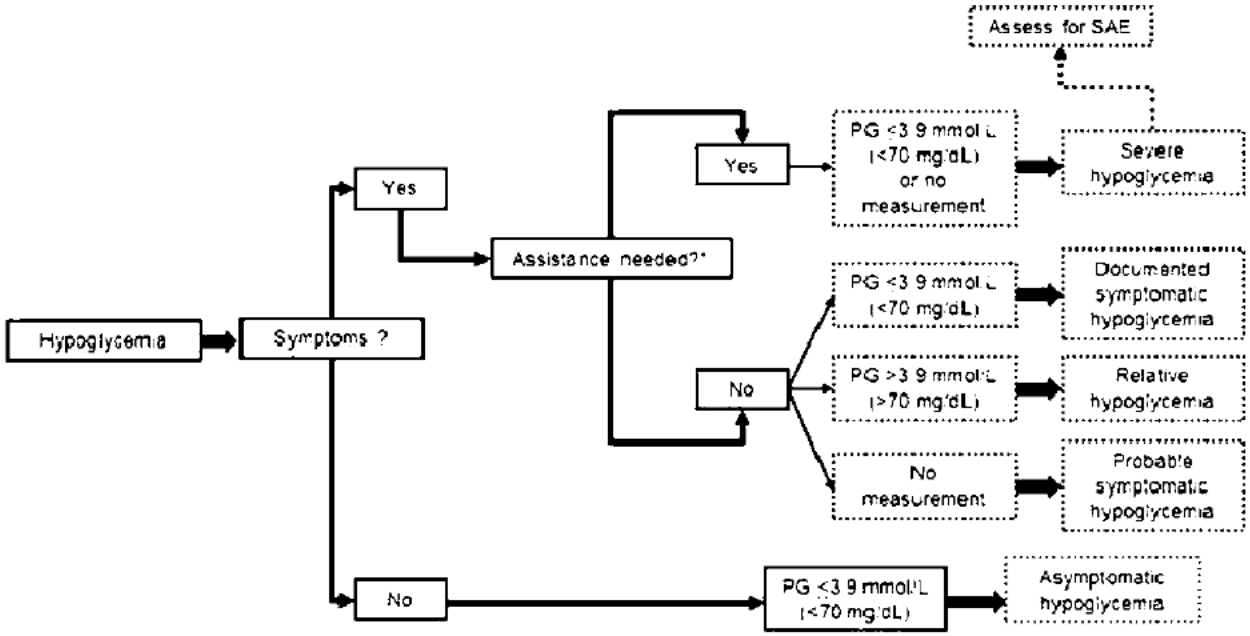
10.6.1 Hypoglycemia

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

Hypoglycemia is categorized according to the ADA workgroup on hypoglycemia classification (15) 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 EFC14838



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

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

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

Documented symptomatic hypoglycemia

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

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

Asymptomatic hypoglycemia

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

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

Probable symptomatic hypoglycemia

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

Relative hypoglycemia

Relative hypoglycemia, recently termed "pseudo-hypoglycemia" (15), is an event during which the patient reports typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >3.9 mmol/L (>70 mg/dL).

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations were performed based on the primary endpoint of the change of HbA1c from Baseline to Week 52 in the intent-to-treat (ITT) population. Assuming a common standard deviation (SD) of 1.1%, and the true difference between sotagliflozin 400 mg and glimepiride is zero, 310 patients in the sotagliflozin 400 mg and glimepiride groups will ensure that the upper bound of the 2-sided 95% confidence interval (CI) of the adjusted mean difference is below 0.3% with at least 90% power. This sample size will have 80% power to test the non-inferiority of the change of HbA1c from Baseline to Week 52 in completers, with 30%.dropout rate.

A sample size of 310 patients in sotagliflozin 400 mg group and 155 patients in placebo group will have >99% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo (SD 1.2%; 2-sided 5% significance level).

A sample size of 155 patients in sotagliflozin 200 mg group and 155 patients in placebo group will have 95% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 200 mg and placebo (SD 1.2%; 2-sided 5% significance level).

The total sample size will be 930 patients to be randomized (sotagliflozin 400 mg group: 310; sotagliflozin 200 mg group: 155; glimepiride: 310; placebo: 155).

11.2 DISPOSITION OF PATIENTS

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

- Screened patients: patients who have signed the ICF.
- Run-in patients.
- Randomized patients: patients with a treatment kit number allocated and recorded in IRT database, and regardless of whether the treatment kit was used or not.
- The safety population (ie, randomized and treated patients).
- The ITT population (as defined in Section 11.3.2 and analyzed as randomized).
- The randomization strata (HbA1c at Screening [≤8.5%, >8.5%], SBP at Screening [<130, ≥130 mmHg]). The discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients.
- Patients who have completed the 52-week Treatment Period.
- Patients who discontinued the IMP during the 52-week Treatment Period, and the reasons for treatment discontinuation.

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

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

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

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

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

11.3.2 Intent–to-treat population

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

11.3.3 Safety population

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

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

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

- When a patient is exposed to both sotagliflozin and placebo, the patient will be analyzed in the sotagliflozin group (depending on the treatment kits taken [400 mg or 200 mg]).
- When a patient is exposed to both sotagliflozin 400 mg (treatment kits) and 200 mg (treatment kits), the patient will be analyzed in the sotagliflozin 200 mg group.
- When a patient is exposed to both sotagliflozin and glimepiride, the patient will be analyzed in the sotagliflozin group (depending on the treatment kits taken [400 mg or 200 mg]).
- When a patient is exposed to both glimepiride and placebo, the patient will be analyzed in the glimepiride group.
- Randomized patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study medication.

11.4 STATISTICAL METHODS

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

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

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

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

Analysis of demographics and baseline characteristics, prior and concomitant medications will be provided in detail in the statistical analysis plan (SAP).

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

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

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

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

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

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in patient years 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 imputations will be made for patients with missing or incomplete data.

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

11.4.2 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population.

Statistical testing will be performed for the primary endpoint at Week 52 and for the secondary endpoints at Weeks 26 and 52 (or Week 12 for SBP). All other efficacy endpoints will only be summarized by descriptive statistics without formal statistical testing.

11.4.2.1 Analysis of primary efficacy endpoint

For the primary efficacy endpoint, the following null and alternative hypotheses will be tested:

- H_0: $\mu_T - \mu_C \geq 0.3\%$
- H_1: $\mu_T - \mu_C < 0.3\%$

Where μ_T and μ_C are the mean changes from Baseline in HbA1c at Week 52 for sotagliflozin and glimepiride groups, respectively.

The null hypothesis will be tested at a 1-sided alpha level of 0.025 using a non-inferiority margin of 0.3% of HbA1c change.

Analysis of the primary efficacy endpoint will be performed using the ITT population, using HbA1c measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

The primary efficacy endpoint of change in HbA1c from Baseline to Week 52 will be analyzed with missing values imputed by controlled-based multiple imputation method under the missing not at random frame work:

- For placebo patients, missing data will be imputed based on the placebo group data.
- For patients in the active treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, and glimepiride) 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 400mg, sotagliflozin 200 mg, glimepiride, and placebo), randomization strata of HbA1c at Screening (≤8.5%, >8.5%) and SBP at Screening (<130 mmHg, ≥130 mmHg), 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 52 for each treatment group, as well as the between-group difference and the 95% CI for the difference. If the upper bound of the 2-sided 95% CI for the adjusted mean difference (sotagliflozin 400 mg versus glimepiride) in HbA1c change from Baseline to Week 52 is <0.3%, the non-inferiority will be declared.

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

A sensitivity analysis will be conducted with the 52-week treatment completers (ie, all patients who complete the 52-week Treatment Period and do not start rescue therapy) using the Week 52 values and the same ANCOVA model described above.

Assessment of treatment effect by subgroup

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

- Race
- Ethnicity (Hispanic, Not Hispanic)
- Age group (<50 years, ≥50 to <65 years, ≥65 years)
- Gender
- Baseline BMI level (<30, ≥30 kg/m^2)
- Baseline HbA1c (≤8.5%, >8.5%)

- Baseline SBP (<130 mmHg, ≥130 mmHg)
- 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)
- Country

The treatment effects across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 52 in HbA1c in the ITT population, and using a similar approach (ie, control-based MI method under MNAR framework) as applied to the analysis for the primary efficacy endpoint. The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo), randomization strata of HbA1c at Screening (≤8.5%, >8.5%) and SBP at Screening (<130 mmHg, ≥130 mmHg), subgroup factor, treatment-by-subgroup factor, country as fixed effects, and baseline HbA1c value as a covariate. The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus glimepiride) with SE and 95% CIs will be provided as appropriate across the subgroups.

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

11.4.2.2 Analyses of secondary efficacy endpoints

For secondary endpoints of reduction of body weight at Weeks 26 and 52, reduction of SBP at Week 12 in patients with baseline SBP ≥130 mmHg, and in all patients, reduction of HbA1c at Weeks 26 and 52, a similar approach to the primary efficacy endpoint will be used, with missing values imputed by control-based multiple imputation method under the missing not at random framework:

- For placebo patients, missing data will be imputed based on the placebo group data.
- For patients in the active group (sotagliflozin 400 mg, sotagliflozin 200 mg, and glimepiride) missing data will be imputed as if the patients were on placebo group throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model.

For each of the continuous secondary endpoint, each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo), randomization strata of Screening HbA1c (≤8.5%, >8.5%) and Screening SBP (<130 mmHg, ≥130 mmHg), country as fixed effects, and baseline secondary endpoint value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Weeks 26 and 52 (or Week 12 for SBP) for each treatment group, as well as the between-group differences and the 95% CI for the differences.

The categorical secondary endpoint, the proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period, will be analyzed using a Cochran-Mantel-Haenszel method stratified by randomization strata of

Screening HbA1c (≤8.5%, >8.5%) and Screening SBP (<130 mmHg, ≥130 mmHg).
The proportion in each treatment group will be provided, as well as the difference of proportions between groups with associated 2-sided 95% CI.

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

11.4.2.3 Analysis of other efficacy endpoints

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

11.4.2.4 Multiplicity considerations

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

The primary endpoint of the HbA1c change from Baseline to Week 52 comparing sotagliflozin 400 mg versus glimepiride will be tested at $\alpha = 0.025$ (1-sided) using a non-inferiority margin of 0.3% of HbA1c change. Once the non-inferiority is declared (the upper bound of the 2-sided 95% CI of the adjusted mean difference between sotagliflozin 400 mg and glimepiride is <0.3%), a hierarchical testing procedure will be performed to test the following key secondary endpoints by the following prioritized order. The testing will stop as soon as an endpoint is found to be not statistically significant at $\alpha = 0.05$ (2-sided):

- The superiority of sotagliflozin 400 mg compared to glimepiride on:
  - Change in body weight from Baseline to Week 52
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg
  - Change in SBP from Baseline to Week 12 in all patients
  - The proportion of patients with at least 1 documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period
- The superiority of sotagliflozin 400 mg compared to placebo on the change in HbA1c from Baseline to Week 26
- The superiority of sotagliflozin 200 mg compared to placebo on the change in HbA1c from Baseline to Week 26
- The superiority of sotagliflozin 400 mg compared to placebo on:
  - Change in body weight from Baseline to Week 26
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg

- Change in SBP from Baseline to Week 12 in all patients

- The non-inferiority of sotagliflozin 200 mg compared to glimepiride on the change in HbA1c from Baseline to Week 52
- The superiority of sotagliflozin 400 mg compared to glimepiride on the change in HbA1c from Baseline to Week 52

11.4.3 Analyses of safety data

All safety summaries will be descriptive; no statistical significance tests will be performed on safety data.

Safety endpoints are presented in Section 9.2. The summary of safety results will be presented by treatment group. 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:

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

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

11.4.3.1 Analysis of adverse events

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

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

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

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

All adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (N) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Summaries of all TEAEs in each treatment group will include:

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

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

Death and serious adverse events

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

The following deaths summaries will be generated:

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

Adverse events leading to permanent treatment discontinuation

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

11.4.3.2 Analyses of hypoglycemia

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

11.4.3.3 Analyses of adverse events of special interest

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

11.4.3.4 Analyses of events of special interest

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

11.4.3.5 Analyses of laboratory variables

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

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

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

11.4.3.6 Analyses of vital sign variables

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

treatment group. Tabular and graphical methods may be used to present the results for parameters of interest. Listings will be provided with flags indicating the PCSA values.

11.4.3.7 Analyses of 12 lead electrocardiogram status

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

11.5 INTERIM ANALYSIS

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

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

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

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

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

[redacted]

The ICFs 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(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR OR SERVICE PROVIDER

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

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

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

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

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

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

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

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Patient race and ethnicity (race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, unknown; ethnicity: Hispanic, Not Hispanic) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for FDA, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on Chinese population for the Chinese FDA).

[redacted]

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

14.6 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 to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

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

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

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

Reproductive potential (WOCBP)

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

CONTRACEPTIVE GUIDANCE

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

Female patients:

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

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION

Male patients with partners of reproductive potential who become pregnant

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

Female patients who become pregnant

- The Investigator will collect pregnancy information on any female patient, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE
- A spontaneous abortion is always considered to be an SAE and will be reported as such
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.3. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting

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

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

For females:

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

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

For uncircumcised males:

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

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

Maintaining Hydration:

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

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

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

- Dehydration is when your body loses too much fluid, frequently due to diarrhea or increased urination
- Consider increasing the amount of fluids you drink if:
  - You sense greater thirst than usual
  - You have a dry mouth or cracked lips

- You have a fever
- You have diarrhea or vomiting
- You urinate more frequently or in larger amounts than usual
- You get up in the middle of the night to urinate (more than usual)
- You feel dizzy or light-headed
- You exercise, or when it is hot outside"

Recognizing Diabetic Ketoacidosis

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

Appendix C Measurement of blood pressure and pulse rate

Equipment

1. Blood pressure measurements will be taken by an automated BP monitor or a manual sphygmomanometer
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 Visit 1 (week -4), seated BP should be measured in both arms after 5-minute rest period, and then again after 1 minutes in both arms in seated position. The arm with the highest SBP will be determined at this visit, and blood pressure should be measured in this arm throughout the study.

Measurement Technique

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

At all other on-site visits, following the 5-minute rest period, 3 separate seated BPs should be measured in the 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 e-CRF. The mean of the 3 seated BPs will constitute the BP value for that visit.

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

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

NEUTROPENIA

Neutrophils < 1500/mm^3 or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm^3

Neutrophils < 1500/mm^3 confirmed with signs of infection	Neutrophils < 1500/mm^3 confirmed with no signs of infection
1. **DISCONTINUE** Investigational Medicinal Product, hospitalization should be considered 2. **PERFORM** biological investigations for infection	1. **DISCONTINUE** Investigational Medicinal Product 2. **INVESTIGATE** for infection

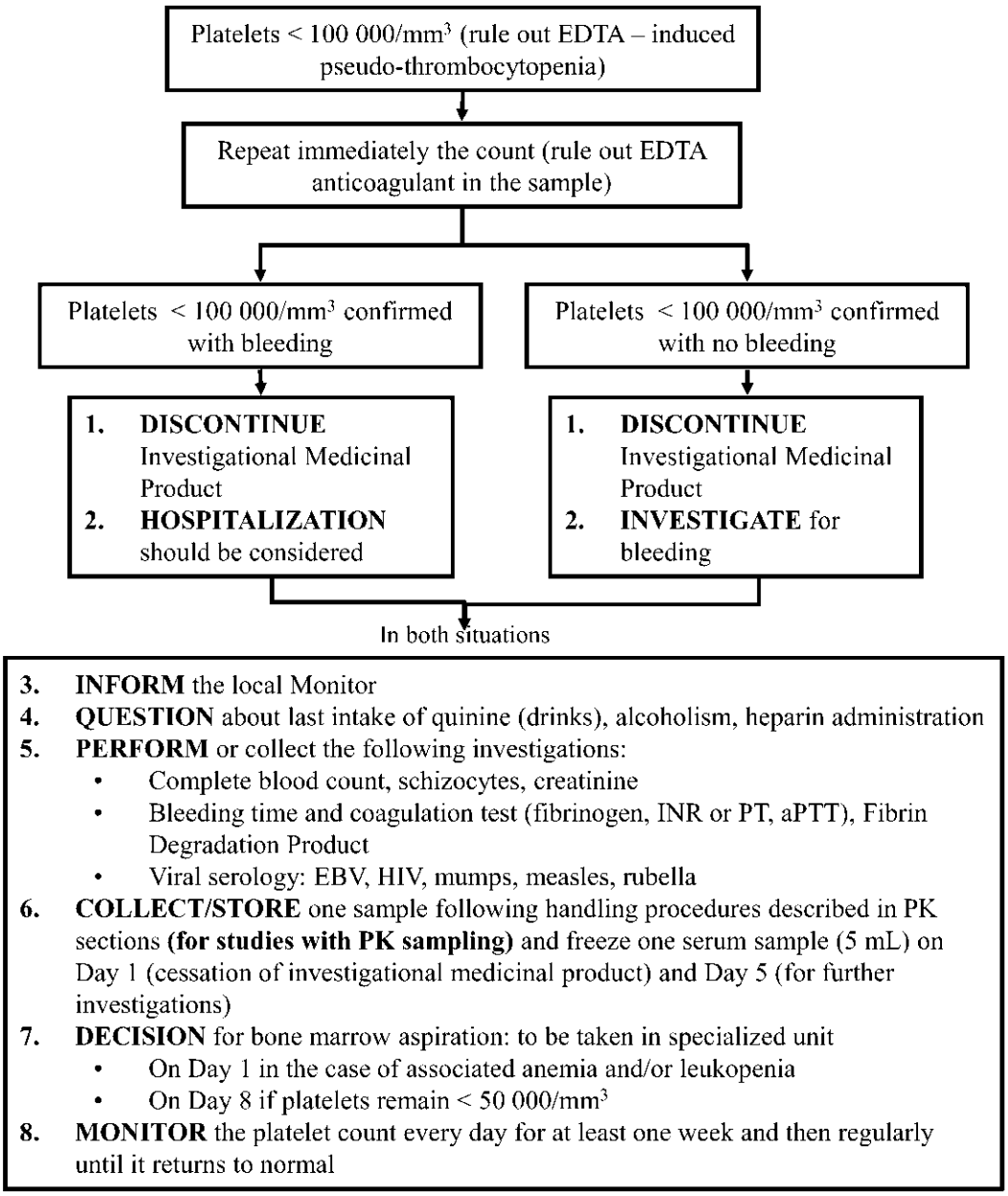
In both situations

3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

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

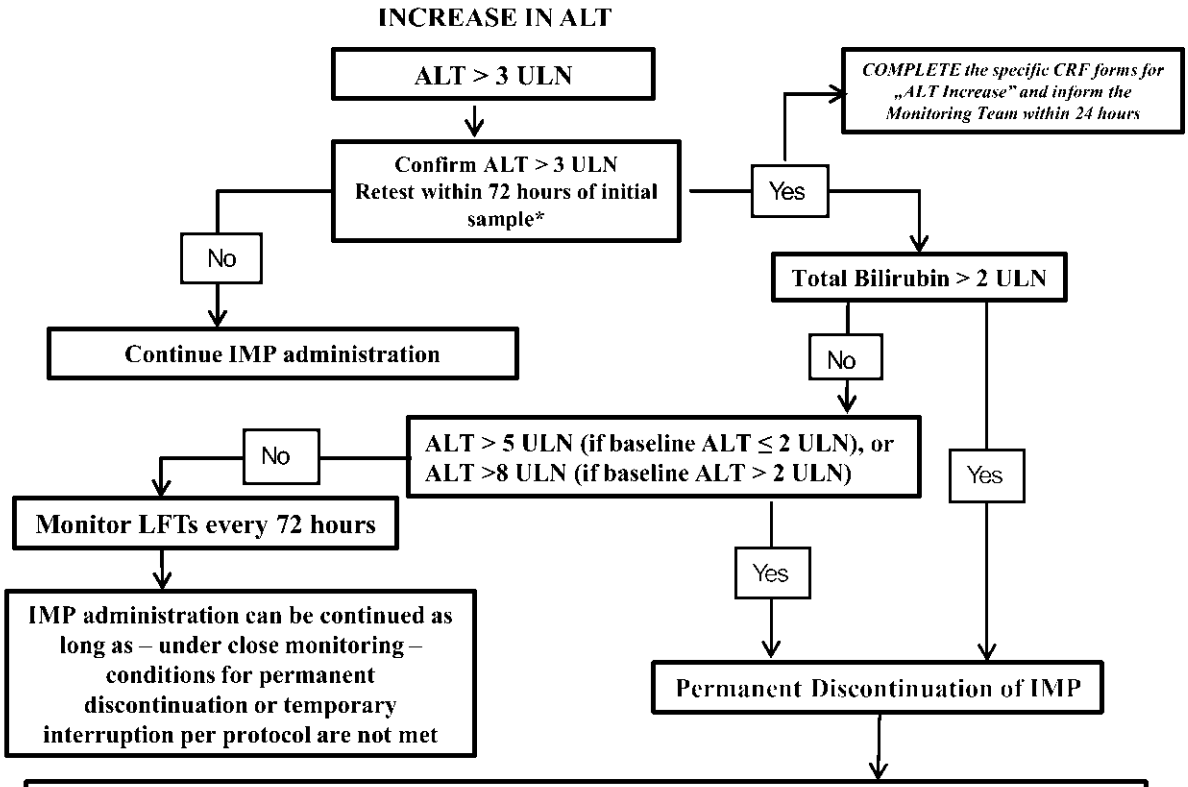
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

THROMBOCYTOPENIA



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

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



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

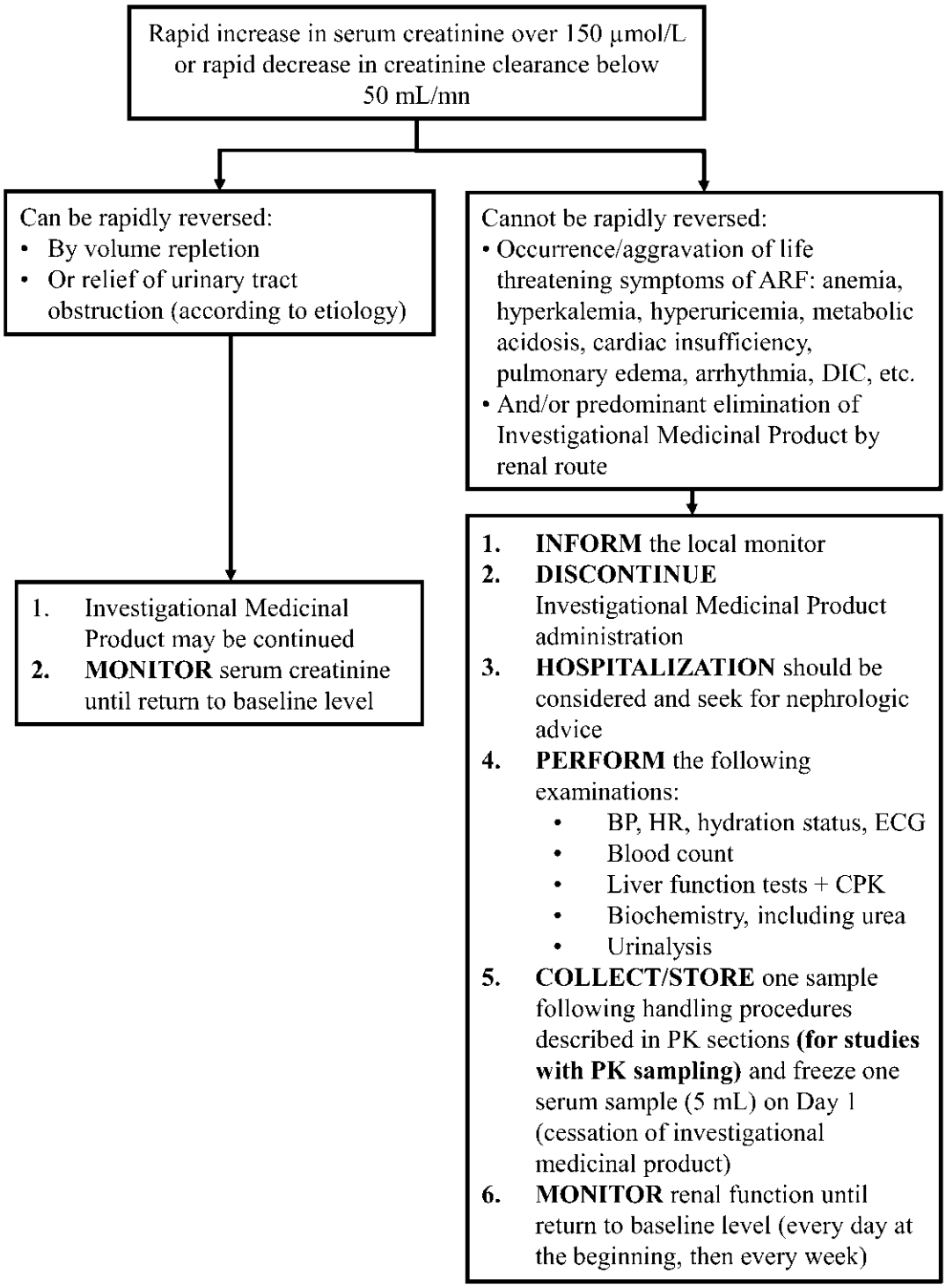
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following 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 re-test in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

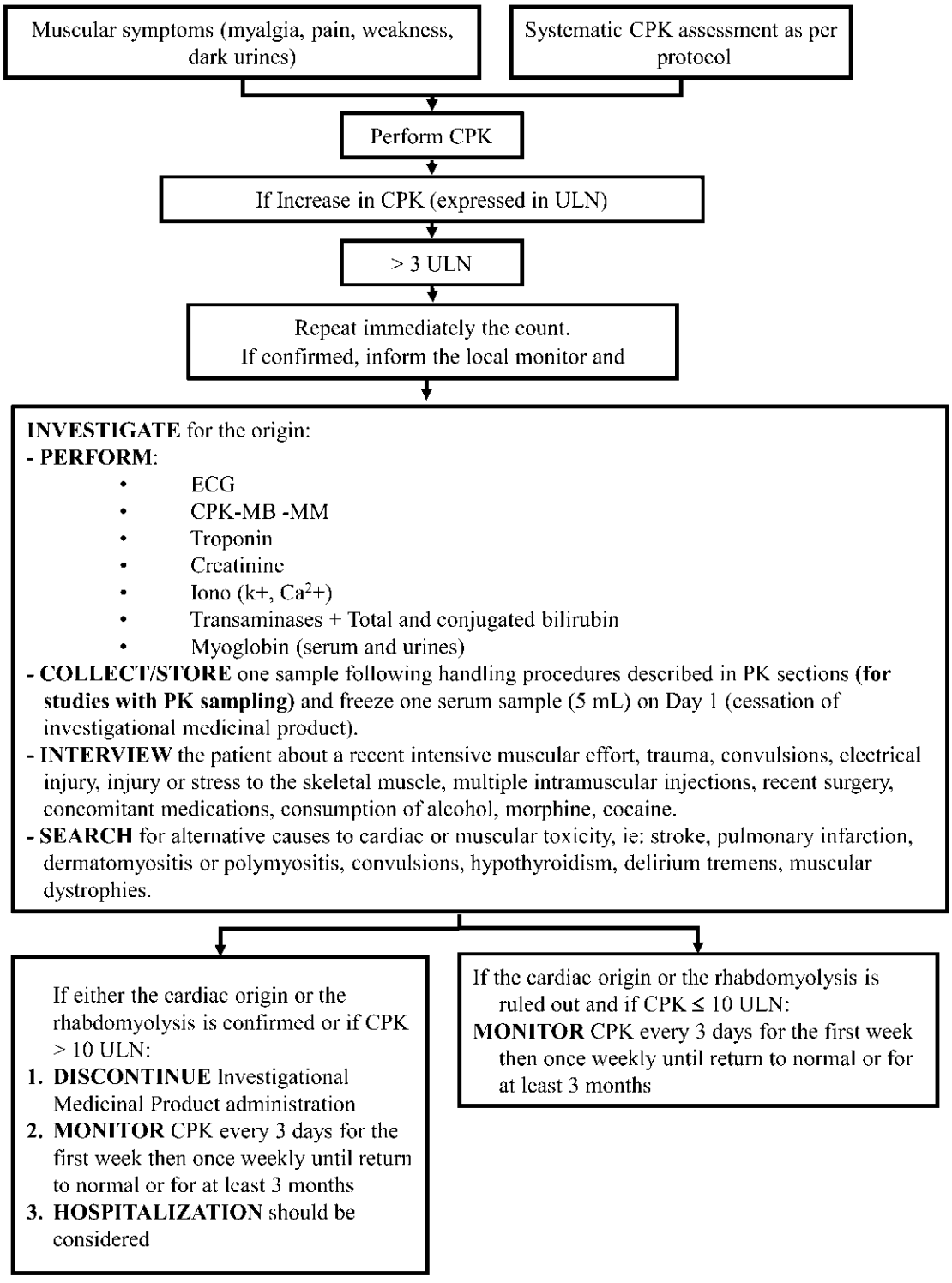
- "Baseline" refers to ALT sampled at Baseline visit; or if baseline value unavailable, to the latest ALT sampled before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during Screening
- See Section 10.4 for guidance on safety reporting
- Normalization is defined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

ACUTE RENAL FAILURE



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

SUSPICION OF RHABDOMYOLYSIS



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

Appendix E Patient Qualitative Assessment of Treatment (PQAT)

Week 26 Assessment

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

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

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

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

Yes ☐ No ☐

Please explain why?

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

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

Week 52 Assessment

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

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

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

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

Yes ☐ No ☐

Please explain why?

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

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

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	11-Apr-2018 10:07 GMT+0200
[redacted]	Regulatory Approval	11-Apr-2018 16:43 GMT+0200
[redacted]	Clinical Approval	11-Apr-2018 17:41 GMT+0200