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

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Lexicon Pharmaceuticals, Inc.

Protocol No.: EFC14868

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

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Statistical Analysis Plan

Version: Final 2.0

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APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

Covance Approval:

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VERSION HISTORY

Version Status	Version Date
Final 1.0	27 July 2018
Final 2.0	04 December 2019

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AESI:	adverse events of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BMI:	body mass index
BUN:	blood urea nitrogen
CGM:	continuous glucose monitoring
CI:	confidence interval
CPK:	creatine phosphokinase
CV:	coefficient of variability
DBP:	diastolic blood pressure, diastolic blood pressure
DCCT:	Diabetes Control and Complications Trial
DILI:	drug-induced liver injury
DMC:	Data Monitoring Committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate, estimated glomerular filtration rate
EOSI:	events of special interest
FPG:	fasting plasma glucose
HbA1c:	hemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IFCC:	International Federation of Clinical Chemistry and Laboratory Medicine
IMP:	investigational medicinal product
IQR:	interquartile range
ITT:	intent-to-treat
KM:	Kaplan-Meier
LDH:	Lactic acid dehydrogenase
LDL-C:	low density lipoprotein cholesterol
LLT:	lower level term
MAGE:	Mean Amplitude of Glycemic Excursion
MAR:	Missing at random
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation, multiple imputation
MNAR:	missing not at random, missing not at random

NIMP:	noninvestigational medicinal product
OAD:	oral antidiabetes drug
PCSA:	Potentially Clinically Significant Abnormality
PQAT:	Patient Qualitative Assessment of Treatment
PT:	preferred term
PTH:	Parathyroid hormone
SAE:	serious adverse events
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SMBG:	self-monitored blood glucose, self-monitored blood glucose
SOC:	system organ class
TC:	total cholesterol
TEAE:	treatment-emergent adverse event
TG:	triglycerides
TRIM-D:	Treatment Related Impact Measure - Diabetes
UACR:	urinary albumin creatinine ratio, urinary albumin creatinine ratio
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary, World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter, randomized, double-blind (with single-blind Run-in Phase), placebo-controlled, parallel-group stratified study. Patients are to be randomly assigned 2: 1: 1 to the following 3 treatment groups

- Sotagliflozin 400 mg
- Sotagliflozin 200 mg
- Placebo

All patients will have Screening Period comprised of a Screening Phase of up to 2 weeks and a 4-week Lantus titration/single-blind placebo titration Run-in Phase prior to randomization. Following randomization, patients will have a 52-week double-blind Treatment Period, and a 2-week post-treatment Follow-up period (patients who prematurely discontinue the study treatment are expected to continue in the study).

At the end of screening period, eligible patients are centrally randomized (using permuted block randomization schedule) via interactive response technology (IRT) in a 2:1:1 ratio to Sotagliflozin 400 mg group, Sotagliflozin 200 mg group and Placebo group. The randomization will be stratified by hemoglobin A1c (HbA1c) (≤8.5%, >8.5%) and systolic blood pressure (SBP) (<130 mmHg, ≥130 mmHg) and sulfonylureas use (Yes, No) at Week -1.

It is anticipated to randomize a total of approximately 560 patients (Sotagliflozin 400 mg: 280; Sotagliflozin 200 mg: 140; Placebo: 140).

Continuous Glucose Monitoring sub-study (CGM sub-study)

Approximately 132 eligible patients participating at a number of pre-selected sites in the United States will also be involved in the CGM sub-study with approximately 66 patients in the sotagliflozin 400 mg arm, 33 patients in the sotagliflozin 200 mg arm and 33 patients in the placebo arm. Two CGM assessment periods are planned: Baseline CGM during Week -1 for 7 consecutive days and post-randomization CGM during Week 18 and 19 for 14 consecutive days. Both patients and investigators will be masked to glucose values.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo with respect to HbA1c reduction at Week 18 in patients with type 2 diabetes mellitus (T2D) inadequate glycemic control on basal insulin alone or with OADs.

1.2.2 Secondary objectives

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

1.2.3 Other objectives

- To assess the effects of sotagliflozin 400 mg versus placebo on the proportion of patients with HbA1c < 7% or HbA1c < 6.5% at Weeks 18, 26, and 52
- To assess the effects of sotagliflozin 200 mg versus placebo on the proportion of patients with HbA1c < 7% or HbA1c < 6.5% at Weeks 18, 26, and 52
- To assess the effects of sotagliflozin 200 mg versus placebo on the change from Baseline to Week 12 in SBP for all patients
- To assess the effects of sotagliflozin 400 mg and 200 mg versus placebo on:
  - Change from baseline to Week 26 in HbA1c

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

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

1.2.4 Objectives of CGM sub-study

1.2.4.1 Primary sub-study objective

To compare the effect of sotagliflozin 400 mg versus placebo on the percentage of time within the glucose range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) over 24 hours, as assessed with CGM

1.2.4.2 Secondary sub-study objectives

- To compare the effect of sotagliflozin 200 mg versus placebo on the percentage of time spent within the glucose range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) over 24 hours, as assessed with CGM
- To compare the effect of sotagliflozin (200 and 400 mg) versus placebo over 24 hours, as assessed by CGM, on the following:
  - Mean 24 hour glucose concentration
  - Percentage of time spent within the glucose range of 70 to 140 mg/dL (3.9 to 7.8 mmol/L)
  - Coefficient of variability (CV) of glucose concentrations
  - AUC of glucose concentrations for 2 hours after a standardized mixed meal

- 2 hour postprandial plasma glucose (PPG) following a standardized mixed meal.

1.2.4.3 Other sub-study objectives

To compare the effects of sotagliflozin (200 and 400 mg) versus placebo on the following:

- Percentage of time over 24 hours with glucose levels >140 mg/dL (>7.8 mmol/L), >180 mg/dL (>10.0 mmol/L), >250 mg/dL (>13.8 mmol/L), <70 mg/dL (<3.9 mmol/L), and <54 mg/dL (<3.0 mmol/L)
- Percentage of time over 24 hours spent within the target range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) during the diurnal period (6:00 AM to 11:59 PM) and nocturnal period (0:00 AM to 5:59 AM)
- AUC of glucose concentrations over 24 hours >140 mg/dL (>7.8 mmol/L), >180 mg/dL (>10.0 mmol/L), >250 mg/dL (>13.8 mmol/L), <70 mg/dL (<3.9 mmol/L), and <54 mg/dL (<3.0 mmol/L)
- Various measures of glucose variability including Mean Amplitude of Glycemic Excursion (MAGE), standard deviation (SD) of glucose levels within and between days, and interquartile range (IQR)
- Proportion of patients (%) with at least one hypoglycemic episode defined as CGM values <70 mg/dL (<3.9 mmol/L) for ≥15 minutes.

1.3 DETERMINATION OF SAMPLE SIZE

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

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

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

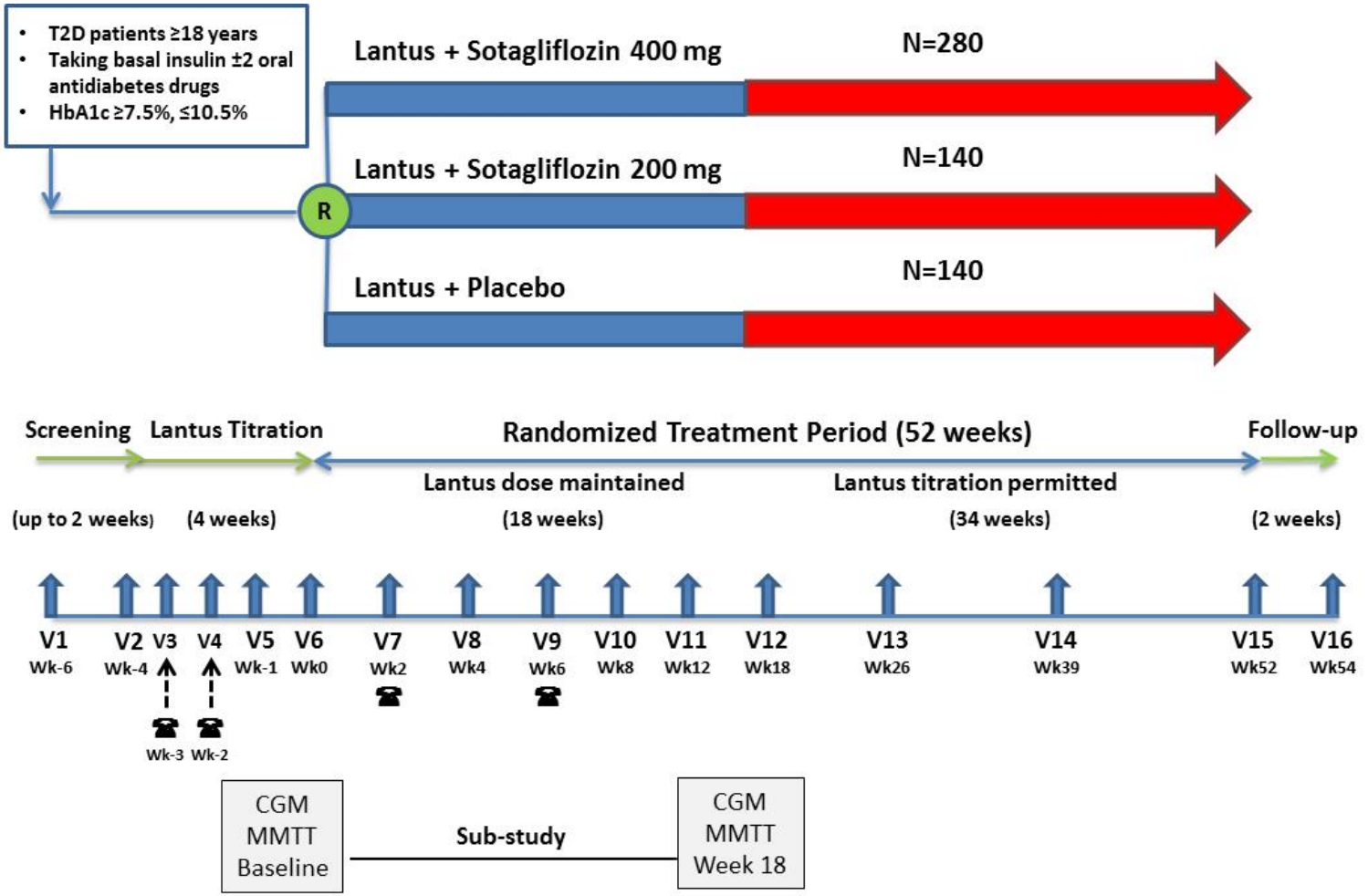
The sample size/power calculations for the CGM sub-study are based on the primary variable, change from Baseline to Week 19 in the percentage of time within the target range of 70 to 180 mg/dL over 24 hours for sotagliflozin 400 mg as compared to placebo. Assuming a common standard deviation of 18%, a common missing rate of 15% and using a 2-sided test at a 0.05 α-level, 66 patients in the sotagliflozin 400 mg arm and 33 patients in the placebo arm will

provide at least 80% power to detect a difference of 12% of time within the target range of 70 to 180 mg/dL over 24 hours between sotagliflozin 400 mg and placebo

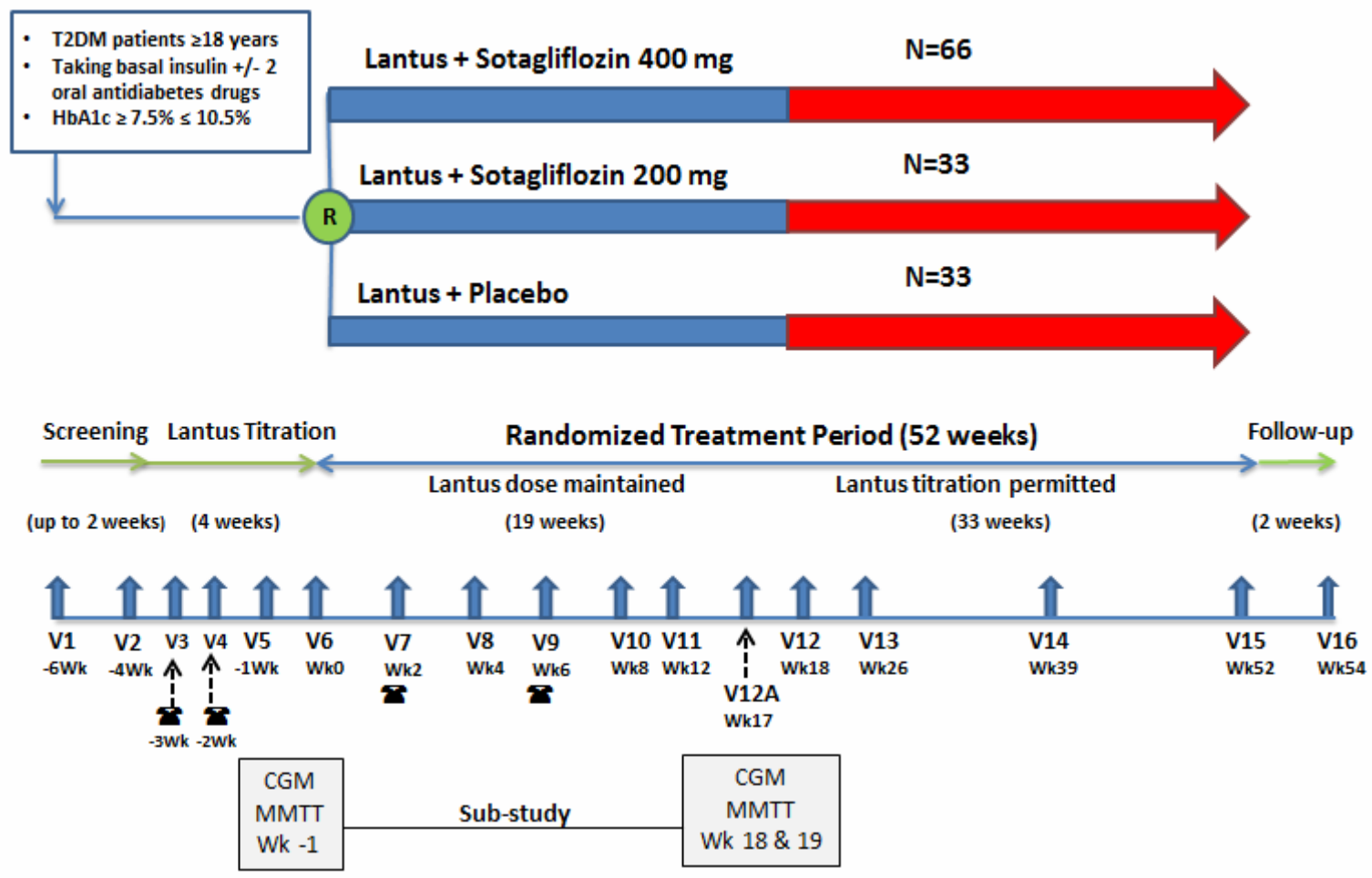
The total sample size for the CGM sub-study will be 132 patients (approximately 66 patients in sotagliflozin 400 mg arm, 33 patients in the sotagliflozin 200 mg arm, and 33 patients in the placebo arm).

1.4 STUDY PLAN

1.4.1 Main study



1.4.2 CGM sub-study



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

The first patient was enrolled on Nov 2, 2017. There are no planned interim analyses

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	27-Sep-2017	Addition of other endpoints following the addition of study objectives	Change in HbA1c from baseline to Week 26 and 52 are added as other endpoints and other objectives
1	27-Sep-2017	Urgent coronary revascularization not adjudicated by CEC to be consistent with outcome trials	Urgent coronary revascularization not included in adjudication related analyses.
1	27-Sep-2017	5 half-lives of sotagliflozin prolonged to 10 days considering patients with moderate renal dysfunction	5 half-lives of IMP updated from 5 days to 10 days; TEAE period updated accordingly
1	27-Sep-2017	Baseline eGFR defined as recommended by CDISC Therapeutic Area Data Standards User Guide for Diabetic Kidney Disease	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.
3	06-Mar-2018	Addition of secondary objectives to evaluate the long-term efficacy on HbA1c and body weight for 52 weeks	Change in HbA1c and body weight from baseline to Week 52 are added as secondary objectives/endpoints. The order of secondary objectives/endpoints/multiplicity adjustment updated

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan. Changes also incorporated in a protocol amendment are cross-referenced to Table 1

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	26-Jul-2018	Modification and Addition of secondary endpoints based on steering committee's recommendation	Change from baseline to Week 52 in HbA1c and body weight are added to secondary endpoints. Proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Week 18 are moved to other endpoints**. Change from baseline to Week 26 in HbA1c is added to other endpoint under Amendment 1 * Multiplicity adjustment updated to account for the modification of secondary endpoints
1	26-Jul-2018	Modification of CGM hypoglycemia definition as the result of CGM sub-study protocol amendment 1	A CGM hypoglycemic episode is defined as CGM values < 70 mg/dL (< 3.9 mmol/L) for ≥ 15 minutes instead of 10 minutes**
1	26-Jul-2018	Clarification on EOSI renal events	Details specified on renal events to be consistent with outcome studies in Section 2.1.4.2
1	26-Jul-2018	[redacted]	[redacted]
1	26-Jul-2018	[redacted]	[redacted]
2	This version	[redacted]	[redacted]
2	This version	Number of iterations for multiple imputation was changed	Number of iterations for multiple imputation was changed from 10 000 to 2000
2	This version	Wording change to be consistent with CEC charter	"Heart failure leading to hospitalization" changed to "Heart failure requiring hospitalization"
2	This version	MedDRA version and dictionary updated	MedDRA version was updated to v22.0 and list of PTs for selected EOSI was updated
2	This version	[redacted]	[redacted]

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	Lexicon process	Appendix A removed
2	This version	Assess robustness on the ITT-based analyses	Identify possible need to conduct sensitivity analyses for PK anomalies
2	This version	Numbering update	Section 2.1.4 Subsections numbering corrected; 2.1.5 and 2.1.6 re-numbered accordingly
2	This version	Consistency with other studies within the project	UGE and UGCR added to Section 2.4.4.3
2	This version	Lexicon medical group request	Clarification on the analysis of the 2-hour PPG endpoint following a standardized mixed meal to be performed based on Time 0 adjusted values added to Section 2.4.4.5

*Change made in Protocol Amendment 1 dated 27-Sep-2017.
**Change made in Protocol Amendment 2 dated 06-Mar-2018.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value (with the exception of serum creatinine and eGFR) is defined as the last available value before the first dose of double-blind investigational medicinal product (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.

All baseline safety and efficacy parameters are presented along with the summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic characteristics to be summarized are:

- Age (years) derived as: (Year of informed consent - Year of birth),
- Age categories (<50, ≥50 to <65, ≥65 to < 75, ≥75 years),
- Gender (Male, Female),
- Race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other pacific islander, Multiple, Unknown),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown),
- HbA1c (%) at Screening,
- HbA1c (%) at Visit 5 (Week -1),
- Randomization strata of HbA1c (≤8.5%, >8.5%) at Visit 5 (Week -1) (data from IRT),
- SBP at Screening,
- SBP at Visit 5 (Week -1),
- Randomization strata of SBP (<130 mmHg, ≥130 mmHg) at Visit 5 (Week -1) (data from IRT),
- Randomization strata of sulfonylureas use (yes, no) at Visit 5 (Week -1) (data from IRT),
- Baseline body mass index (BMI) (kg/m^2) derived as: (Weight in kg)/(Height in meters)^2,

- Baseline BMI categories (<30, ≥30 kg/m^2),
- Country.

Disease characteristics at screening or baseline

Disease history includes:

- Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25,
- Duration of diabetes categories: (<10, ≥10 years)
- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes – Year of birth,
- Duration of basal insulin treatment (years) derived as: (Date of informed consent – Date of first dose of basal insulin + 1)/365.25
- Prior basal insulin use at screening by type/regimen: insulin glargine 100 U/mL, insulin glargine 300 U/mL, insulin detemir, insulin degludec, NPH, and other,
- Daily dose of basal insulin (U) and daily dose of basal insulin adjusted by body weight (U/Kg) at screening,
- Daily dose of Lantus (U) and daily dose of Lantus adjusted by body weight (U/Kg) at baseline,
- Antidiabetic medication use at screening (Basal insulin only, Basal insulin and OAD(s)),
- Baseline diabetic microvascular complications (Yes, No) [ie, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, diabetic peripheral neuropathy (sensory or motor), diabetic autonomic neuropathy, and diabetic foot infection],
- Baseline urinary albumin creatinine ratio (UACR) categories (<30 mg/g [Normal], ≥30 to <300 mg/g [Microalbuminuria], and ≥300 mg/g [Macroalbuminuria]),
- eGFR at screening (mL/min/1.73m^2),
- eGFR categories at screening (<15 mL/min/1.73m^2 [End stage renal disease], ≥15 to <30 mL/min/1.73m^2 [Severe decrease in GFR], ≥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]).
- Prior antihypertensive medication identified by therapeutic class as agents acting on the renin-angiotensin system, beta blocking agents, diuretics (a sub-category: loop diuretics identified by pharmacological class as high-ceiling diuretics), calcium channel blockers, and antihypertensives according to World Health Organization-Drug Dictionary (WHO-DD).

Medical or surgical history

Medical history and medical findings include:

- Physical examination,
- Medical or surgical history,
- Medical history cardiovascular
- Surgical history amputation
- Alcohol habits,
- Tobacco smoking habits.

Medical and surgical history will be coded to a "lower level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)", and associated primary "system organ class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Covance at the time of database lock.

Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within 3 months before the screening visit (any time for prior SGLT1/SGLT2) and until the end of the study are to be reported in the electronic case report form (eCRF).

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Covance at the time of database lock.

- Prior medications are those the patient used prior to first administration of double-blind IMP. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the 1st administration of double-blind IMP to the date of last administration + 10 days. A given medication can be classified both as a prior medication and as a concomitant medication.
- Posttreatment medications are those the patient took in the period running from the 11th day after the last administration of double-blind IMP up to the end of the study.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.2.1 Rescue therapy

The recommended approach to rescue, if rescue thresholds have been reached despite up-titration of the Lantus dose, is to initiate a prandial insulin, or a GLP-1 agonist or another antidiabetic agent (except SGLT2 inhibitors) as per the Investigator's discretion and in line with local

treatment guidelines. The prandial insulin can be any injectable short-acting insulin including rapid-acting insulin analogs (Humalog, Novolog and Apidra) or regular insulin (eg, Humulin). Rescue therapy is considered a noninvestigational medicinal product (NIMP).

2.1.2.2 Prohibited prior and concomitant medications

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

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

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

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

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

The dose of all antihypertensive agents should be kept constant during the 12 weeks following randomization and no antihypertensive agents should be added or withdrawn for the 12 weeks following randomization unless it is considered necessary for safety reasons. During the Run-in Phase, adjustments to antihypertensive therapy can be made as needed. After randomization, antihypertensive regimen should be kept constant during the following 12 weeks.

2.1.3 Efficacy endpoints

All efficacy measurements collected during the study will be considered for analyses, including those obtained after IMP discontinuation or introduction of rescue therapy (see Section 2.5.4).

HbA1c, 2-hour PPG, FPG, UACR, and eGFR are measured/calculated in a central laboratory (see study flowchart in Appendix D). Body weight, SBP and DBP (see Section 2.1.5.3) are measured at on-site visits by the investigator. Patients requiring rescue are identified as those with the reason for treatment ticked "rescue therapy" in e-CRF "Medication" page or with the answer to the question "Is intended daily dose give per protocol or rescue therapy" ticked "rescue therapy" in e-CRF "Exposure-Treatment Period (Lantus)" page.

Efficacy variables will be summarized in both standard international units and conventional units when applicable.

2.1.3.1 Primary efficacy endpoint(s)

Comparison of sotagliflozin 400 mg versus placebo in change from baseline to Week 18 in HbA1c (%).

2.1.3.2 Secondary efficacy endpoint(s)

- Continuous secondary efficacy endpoints for the sotagliflozin 400 mg dose:
  - Change from Baseline to Week 18 in FPG
  - Change from Baseline to Week 18 in BW.
  - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline to Week 12 in SBP for all patients
  - Change from Baseline to Week 52 in HbA1c
  - Change from Baseline to Week 52 in BW
- Continuous secondary efficacy endpoints for the sotagliflozin 200 mg dose:
  - Change from Baseline to Week 18 in HbA1c
  - Change from Baseline to Week 18 in BW
  - Change from Baseline to Week 18 in FPG
  - Change from Baseline to Week 12 in SBP for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline to Week 52 in HbA1c
  - Change from Baseline to Week 52 in BW

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

- Proportion of patients with HbA1c <7.0% or HbA1c <6.5% at Week 18, 26 and Week 52.
- Change from Baseline to Week 26 in HbA1c
- Change from Baseline to Week 12 in SBP for all patients in the sotagliflozin 200 mg arm, and from Baseline to Weeks 26 and 52 in SBP for all patients and the subset of patients with Baseline SBP ≥130 mmHg in the sotagliflozin 400 mg and 200 mg arms
- Change from Baseline to Weeks 12, 26, and 52 in SBP in patients with Baseline SBP <130 mmHg
- Change from Baseline to Weeks 12, 26, and 52 in DBP for all patients and for the subset of patients with Baseline DBP ≥80 mmHg
- Change from Baseline to Week 52 in total daily insulin dose
- Proportion of patients requiring rescue therapy during the 52-week double-blind Treatment Period
- Change from Baseline to Week 18 and Week 52 in 7-point SMBG profile (mean daily value and at each time point)
- Change from Baseline in eGFR
- Change from Baseline in UACR during the 52-week Treatment Period
- PQAT at Weeks 18 and 52
- Change in TRIM-D from Baseline to Week 52 for total score and 5 domain scores. There will be a particular focus on the Diabetes Management domain score, to evaluate patient satisfaction of ability of treatment to control diabetes and its effects.

2.1.3.4 CGM sub-study endpoint(s)

Primary sub-study endpoint

The primary endpoint in this CGM sub-study is the change from Baseline to Week 19 in percentage of time spent within the target glucose range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) over 24 hours (sotagliflozin 400 mg and placebo arms).

Secondary sub-study endpoints

The secondary endpoints in this CGM sub-study are as follows:

- Change from Baseline to Week 19 in percentage of time spent within the target glucose range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) over 24 hours (sotagliflozin 200 mg and placebo arms)
- Change from Baseline to Week 19 in mean 24-hour glucose concentrations

- Change from Baseline to Week 19 in the percentage of time spent within the glucose range of 70 to 140 mg/dL (3.9 to 7.8 mmol/L) over 24-hours
- Change from Baseline to Week 19 in the CV of glucose concentrations over 24 hours by CGM
- Change from Baseline to Week 18 in the AUC of plasma glucose concentration 2 hours after a standardized mixed meal.
- Change from Baseline to Week 18 in 2-hour PPG following a standardized mixed meal.

Other sub-study endpoints

Other endpoints in this CGM sub-study are as follows:

- Change from Baseline to Week 19 in the percentage of time over 24 hours spent with glucose levels >140 mg/dL (>7.8 mmol/L), >180 mg/dL (>10.0 mmol/L), >250 mg/dL (> 13.8 mmol/L), <70 mg/dL (<3.9 mmol/L), and <54 mg/dL (<3.0 mmol/L)
- Change from Baseline to Week 19 in percentage of time over 24 hours spent inside the target glucose range of 70 to 180 mg/dL (3.9 to 10 mmol/L) during the diurnal period (6:00 to 11:59 pm) and during the nocturnal period (0:00 am to 5:59 am)
- Change from Baseline to Week 19 in the AUC of glucose concentrations over 24 hours >140 mg/dL (>7.8 mmol/L), >180 mg/dL (>10.0 mmol/L), >250 mg/dL (> 13.8 mmol/L), <70 mg/dL (<3.9 mmol/L), and <54 mg/dL (<3.0 mmol/L)
- Change from Baseline to Week 19 in measures of glucose variability including Mean Amplitude of Glycemic Excursion (MAGE), standard deviation (SD) of glucose levels within and between days, and interquartile range (IQR)
- Number of patients with ≥1 episode of hypoglycemia, defined as CGM values <70 mg/dL (<3.9 mmol/L) for ≥15 minutes.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events, hypoglycemia, and other safety information, such as clinical laboratory data, vital signs, electrocardiogram (ECG), and physical examination, etc.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first administration of the double-blind IMP.
- The **treatment** epoch is defined as the time from the first administration of the double-blind IMP to the last administration of the double-blind IMP.

- The **residual treatment** epoch is defined as the time from the last administration of the double-blind IMP up to 10 days (1 day for hypoglycemia) after the last administration of the double-blind IMP.

The treatment-emergent adverse event (TEAE) period will include both **treatment** and **residual treatment** epochs (see the TEAE period of the 18-week randomized core treatment period for analyses in hypoglycemia in Section 2.4.5.1).

- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the last protocol-planned visit or the resolution/stabilization of all serious adverse events (SAE), adverse events of special interest (AESI) and events of special interest (EOSI), whichever is later.

The on-study observation period is defined as the time from start of double-blind treatment until the end of the study (defined as the last scheduled visit for those who completed the study and the date collected on e-CRF page "Completion of End of Study/Follow-up" for those who did not complete the study).

The post-study observation period is defined as the time from the day after the end of the study until the resolution/stabilization of all SAE, AESI and EOSI if applicable.

2.1.4.1 Hypoglycemia

Hypoglycemia will be identified as events recorded on the dedicated e-CRF "Hypoglycemic event information" page, and will be categorized as follows (see study protocol for further details):

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.

Severe hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

To the question "Countermeasure Administration", ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and

To the question "Were Symptoms Present", ticked "Yes".

Documented symptomatic hypoglycemia

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

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

Documented symptomatic hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
- To the question "Were Symptoms Present", ticked "Yes", and
- With a plasma glucose value before countermeasure ≤3.9 mmol/L (≤70 mg/dL).

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).

Asymptomatic hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
- To the question "Were Symptoms Present", ticked "No", and
- With a plasma glucose value before countermeasure ≤3.9 mmol/L (≤70 mg/dL).

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.

Probable symptomatic hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
- To the question "Were Symptoms Present", ticked "Yes", and
- With no plasma glucose value before countermeasure, and

- To the question "Did this countermeasure lead a significant improvement or prompt recovery?", ticked "Yes".

Relative hypoglycemia

Relative hypoglycemia, recently termed "pseudo-hypoglycemia" 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).

Relative hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance"
- To the question "Were Symptoms Present", ticked "Yes", and
- With a plasma glucose value before countermeasure >3.9 mmol/L (>70 mg/dL).

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

Any hypoglycemic event fulfilling the criteria of a SAE or leading to unconsciousness, coma, or seizure will also be recorded as a SAE (see Section 2.1.4.2).

2.1.4.2 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of double-blind IMP
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period.

All adverse events (including SAE, AESI and EOSI will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA currently in effect at Covance at the time of database lock.

The occurrence of adverse events (including SAE, AESI and EOSI) will be recorded from the time of signed informed consent until the end of the study (see Section 2.1.4) or the resolution/stabilization of all SAE, AESI and EOSI.

AESI include:

- Pregnancy
- Symptomatic overdose with IMP/NIMP
- Alanine aminotransferase (ALT) increase > 3 times upper limit of normal (ULN)

EOSI include:

- MACE (CV death, myocardial infarction, or stroke) and other specific cardiovascular events (eg, heart failure requiring hospitalization)
- Severe hypoglycemia
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candida balanitis in males)
- Urinary tract infection
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Diarrhea
- Pancreatitis
- Bone fractures
- Venous thrombotic events, to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- Diabetic ketoacidosis
- Renal events, to include 50% decline in eGFR, end stage kidney disease, renal death
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid carcinoma)
- Adverse event leading to an amputation

A Clinical Endpoint Committee(s) (CEC) will in a blinded manner review and adjudicate all deaths, myocardial infarction, stroke, unstable angina requiring hospitalization, and heart failure requiring hospitalization, selected renal events, bone fracture, and diabetic ketoacidosis.

Two independent committees will review safety events that require ongoing monitoring to ensure timing protocol amendments in case a safety signal is identified. These events are: 1) potential cases of drug-induced liver injury (DILI), and 2) cases of amputations. The two committees will review the cases in a treatment-blinded manner and will present their assessment to the DMC.

AESI and EOSI will be identified based on criteria in Table 3.

Table 3 - Criteria for AESI and EOSI

AE Grouping	Criteria
AESI	
Pregnancy	eCRF "Pregnancy"
Symptomatic overdose with IMP/NIMP	"Overdose of IMP" or "Overdose of NIMP" checked and "Symptomatic overdose" checked in eCRF "Overdose"
ALT increase > 3X ULN	eCRF "ALT increase"
EOSI adjudicated	
Cardiovascular death	Positively adjudicated by CEC: "Cardiovascular" or "Undetermined" as the primary cause of death
Myocardial infarction, Unstable Angina requiring hospitalization	Positively adjudicated by CEC: Yes to the question "Does the event meet the definition of an MI for this study?", or Yes to the question "If event is not an MI, does the event meet the definition of an UA Requiring admission to hospital or emergency room, for this study?"
Stroke	Positively adjudicated by CEC: Yes to the question "Does the event meet the definition of a Stroke for this study?"
Heart failure requiring hospitalization	Positively adjudicated by CEC: Yes to the question "Does the event meet the definition of a Heart Failure Event for this study?"
Bone fractures	Positively adjudicated by CEC: Yes to the question "Did the Fracture occur?"
Diabetic ketoacidosis	Positively adjudicated by CEC: Yes to the question "Does this event meet the criteria to be a DKA event?"
EOSI Renal events where select events adjudicated	
Sustained ≥50% decrease in eGFR	(1) For ≥50% decrease in eGFR from baseline, (1a) confirmed ≥50% decrease in GFR for ≥30 days with no reversible cause as recorded in eCRF "eGFR decrease", OR (1b) positively adjudicated by CEC: Yes to the question "Does the subject meet the criteria of CKD progression" for ≥50% decrease in eGFR.
Sustained eGFR <15 mL/min/1.73 m^2	(2) For eGFR <15 mL/min/1.73 m^2, (2a) confirmed eGFR <15 mL/min/1.73 m^2 for ≥30 days with no reversible cause as recorded in eCRF form "eGFR decrease", OR (2b) positively adjudicated by CEC: Yes to the question "Does the subject meet the criteria of CKD progression".

AE Grouping	Criteria
Chronic dialysis	(3) For dialysis, (3a) dialysis lasted for ≥90 days (e.g. end date – start date+ 1 ≥90) as recorded in eCRF "Renal Event – Dialysis", OR (3b) positively adjudicated by CEC: Yes to the question ". Does the subject meet the criteria for ESRD".
Renal transplant *	(4) "Renal transplant" captured in eCRF "Other procedure form", where adjudication is not required. PTs of Renal transplant (10038533), Renal and pancreas transplant (10052278), Renal and liver transplant (10052279) based on MedDRA v22.0.
Renal death	(5) Renal death as positively adjudicated by CEC: "Death - Non-Cardiovascular (Renal)" as the primary cause of death
EOSI not adjudicated *	
Severe hypoglycemia	algorithm specified in Section 2.1.4.1 based on eCRF "Hypoglycemic Events"
Genital mycotic infections	PTs in Appendix B
Urinary tract infections	PTs in Appendix B
Clinically relevant volume depletion and events related/possibly related to volume depletion	PTs in Appendix B
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" [20000218] plus the following PTs (MedDRA v22.0): Gastroenteritis (10017888), Antidiarrhoeal supportive care (10055660), Enteritis (10014866), Enteritis leukopenic (10014877), Enterocolitis (10014893), Enterocolitis haemorrhagic (10014896)
Pancreatitis	PTs in Appendix B
Venous thrombotic events	PTs in Appendix B

AE Grouping	Criteria
Malignancies of special interest	Breast cancer: Narrow search on "Breast cancer: Narrow search on "Breast neoplasms, malignant and unspecified (SMQ)" [20000149]
	Prostate cancer: Narrow search on "Prostate neoplasms, malignant and unspecified (SMQ)" [20000152]
	Leydig-cell cancer: PTs of Leydig cell tumour of the testis (10024407) and Ovarian Sertoli-Leydig cell tumour (10073270) based on MedDRA v22.0
	Thyroid cancer: PTs in Appendix B
	Renal cell cancer: PTs in Appendix B
	Pancreatic cancer: PTs in Appendix B
	Bladder cancer: PTs in Appendix B
EOSI AE leading to an amputation	
AE leading to an amputation	"AE Correction" as the reason for amputation in eCRF "Other Procedures related to Amputation"
AE potentially leading to an amputation *	PTs in Appendix B

* Search terms will be updated using the MedDRA version currently in effect at Covance at the time of database lock for EOSI identified by them.
* AE potentially leading to amputation: not belong to the EOSI list defined in protocol, the item is included and analyzed due to their relevance in regards to lower limb complications and amputations as a requirement from health authorities.

2.1.4.3 Deaths

The deaths observation periods are per the observation periods defined below.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the TEAE period
- Death post-study: deaths occurring after the end of the study

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values will be summarized in both standard international units and conventional units when applicable.

Blood samples for clinical laboratories will be taken at designated visits (see study flowchart in Appendix D). The following laboratory data will be measured at a central laboratory:

- Hematology

  - **Red blood cells and platelets**: hemoglobin, hematocrit, red blood cell, platelets count
  - **White blood cells:** white blood cell, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism:** glucose (serum), creatine phosphokinase (CPK)
  - **Electrolytes and minerals**: sodium, potassium, chloride, bicarbonate (ie, carbon dioxide), calcium, phosphorus, magnesium
  - **Renal function**: blood urea nitrogen (BUN), creatinine, uric acid
  - **Liver function**: total protein, albumin, ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, Lactic acid dehydrogenase (LDH)
- Lipid parameters (fasting): total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) (calculated by Friedwald equation, See Section 2.5.1), Non-HDL-C (calculated as the difference between TC and HDL-C), triglycerides (TG).
- Pancreatic enzymes: lipase, amylase.
- Beta-hydroxybutyrate (BHB)
- Markers of bone and calcium metabolism
  - 25-hydroxyvitamin D,
  - 1,25-dihydroxyvitamin D,
  - Parathyroid hormone (PTH),

Urine samples will be collected at designated visits (see study flowchart in Appendix D). The following laboratory data will be measured at a central laboratory:

- 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

Serum glucose and Calculated UACR will be presented as efficacy parameters in Section 2.4.4. For calculated eGFR, PCSA summaries will be presented in the safety section while descriptive summaries in the efficacy section.

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include: heart rate (HR), systolic and diastolic blood pressure, temperature, and respiratory rate (see study flowchart in Appendix D for designated visits). They will be performed after the patient has been seated for at least 5 minutes. Blood pressure and HR will be assessed 3 times with at least 1 minute between each measurement following the 5-minute rest period. The mean of the 3 measurements will be analyzed for each vital sign variable (HR, SBP, and DBP).

2.1.4.6 Physical examination

A complete physical exam will be performed at Visit 1 (Screening) and Visit 13(Week 26). "Normal", "Abnormal" or "Not done" as determined by the Investigator will be reported in the e-CRF by body system.

2.1.4.7 Electrocardiogram variables

12-lead ECGs will be performed at Visit 1 (Screening), Visit 6 (Randomization) and Visit 13 (Week 26). ECG status of "normal" or "abnormal" will be reported in the e-CRF as determined by the investigator.

2.1.5 Pharmacokinetic variables

Pharmacokinetic variables include the plasma concentration of sotagliflozin and its 3-O-glucuronide metabolite in the sotagliflozin group.

2.1.6 Patient-reported outcome variables

The schedule of PQAT and TRIM-D are specified in the study flowchart in Appendix D. The questionnaires can be found in the study protocol.

2.1.6.1 Patient's qualitative assessment of treatment (PQAT)

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 3 free-text response questions to describe key advantages and disadvantages of treatment experienced and willingness to pursue it or not.

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

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

The general treatment-related impact on patients' health related quality of life (HRQoL) will be assessed using the TRIM-D questionnaire. The TRIM-D questionnaire is a 28-item measure comprising of 5 domains: Treatment Burden, Daily Life, Diabetes Management, Compliance, and Psychological Health (1). Table 4 below presents further technical details on this questionnaire.

Items are answered on a 5-point Likert scale ranging from (1) Not at all satisfied/convenient, or Never/Almost never, or Never/Almost never interferes to (5) Extremely satisfied/convenient, or Almost always/Always, or Almost always/Always interferes. Scales are converted into a score valued from 0 to 100 so that a higher score indicates a better health state (less negative impact). Score for each domain (called "domain score") and total score are computed. See Section 2.4.7 for more details on the scoring method.

The TRIM-D variables include TRIM-D scores (total and domain scores) and the change in TRIM-D scores from baseline to endpoint.

Table 4 - TRIM-D domains and clusters

Domains	Number of Items	Cluster of Items	Item Reversion	Direction of Domains
Treatment Burden	6	1a, 2a, 2b, 2c, 2d, 2e	No	Higher score = better health state (less negative impact)
Daily Life	5	3a, 3b, 5a, 5b, 5c	Yes, for all items	
Diabetes Management	5	4a, 4b, 4c, 4d, 4e	No	
Compliance	4	6a, 6b, 6c, 6e	Yes, for all items	
Psychological Health	8	6d, 7a, 7b, 7c, 7d, 7e, 7f, 7g	Yes, for all items	

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as all patients who signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary tables:

- Screened patients
- Run-in patients: patients who had a run-in record in IRT,
- Screen failure patients (including failures during run-in) and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who have completed the 18-week randomized core treatment period (see Section 2.5.4) as per protocol
- Patients who discontinued the IMP during the 18-week randomized core treatment period (see Section 2.5.4) and the reasons for treatment discontinuation
- Patients who have completed the entire 52-week double-blind Treatment Period
- Patients who discontinued the IMP during the entire 52-week double-blind Treatment Period and the reasons for treatment discontinuation
- Patients who have completed the study as scheduled
- Patients who discontinued the study, and the reasons for study discontinuation
- Patients' end of study status (completed, not completed) and corresponding end of treatment status (completed, not completed)
- Status at last study contact

For screened, run in, screen failure, and nonrandomized but treated patients, percentages will be calculated using the number of screened patients as the denominator. All other categories of patients will be presented by treatment group and the percentages will be calculated using the number of randomized patients within each treatment group as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. Patients prematurely discontinued from treatment and/or study, along with reasons for discontinuation, will also be listed.

A summary of the distribution of patients by country and center will also be provided (overall number of patients screened, run-in, randomized, and treated, as well as number of patients randomized, discontinued from study treatment, and discontinued from study for each treatment group).

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 patients of the third category (randomized and not treated as randomized) will be part of efficacy and safety

analyses (see Section 2.3). Patients randomized but not treated will be included in efficacy analysis. Safety data of patients treated but not randomized will be reported separately.

The randomization strata [HbA1c at Week -1 (≤8.5%, >8.5%), SBP (<130, ≥130 mmHg) at Week -1 and sulfonylurea use at Week -1 (yes, no)] assigned by IRT will be summarized. The percentages will be calculated using the number of randomized patients as the denominator. The discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients.

Kaplan-Meier (KM) plots of the cumulative incidence of double-blind IMP discontinuations due to any reason and due to AEs will be provided for the entire 52-week double-blind treatment period separately (see Section 2.5.4). A listing of these patients, along with the reason for discontinuation treatment, study completion status and the reason for discontinuation study, will be provided.

For CGM sub-study, the number of patients in each of the following categories will be summarized.

- Screened CGM sub-study population: patients who consented to CGM sub-study
- Patients who did not meet all eligibility criteria for inclusion into the CGM sub-study
- Randomized CGM sub-study population: patients who were randomized and met all eligibility criteria for inclusion into the CGM sub-study as reported in e-CRF.
- Patients who completed CGM sub-study
- Patients who discontinued CGM sub-study and the reason for discontinuation

For patients not meeting all eligibility criteria for inclusion into the CGM sub-study, percentages will be calculated using the number of patients consented to sub-study as the denominator. All other categories of patients will be presented by treatment group and the percentages will be calculated using the number of patients randomized and met all eligibility criteria for inclusion into the CGM sub-study within each treatment group as the denominator. Reasons for CGM sub-study discontinuation will be supplied in tables giving numbers and percentages by treatment group. Patients prematurely discontinued the CGM sub-study, along with reasons for discontinuation, will also be listed.

All important deviations including randomization and drug-dispensing irregularities will be summarized in tables giving numbers and percentages of deviations by randomized treatment group.

Additionally, the analysis populations for safety, efficacy, and pharmacokinetics defined in Section 2.3 will be summarized in a table by number of patients in the randomized population.

- Efficacy population: intent-to-treat (ITT) population
- Efficacy population for sub-study: CGM sub-study population

- Safety population
- PK population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

- A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

OR

A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately. Listings with additional, relevant details will be provided in appendices.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Efficacy populations

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

2.3.1.1 Intent-to treat population

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

2.3.1.2 CGM sub-study population

The CGM sub-study population will include all patients from the ITT population (see Section 2.3.1.1), who met all eligibility criteria for inclusion into the CGM sub-study.

2.3.2 Safety population

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

In addition:

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

- When a patient is exposed to both sotagliflozin and placebo, the patient will be analyzed in the appropriate sotagliflozin group (depending on the treatment kit taken [400 mg or 200 mg]).
- When a patient is exposed to both sotagliflozin 400 mg (treatment kit) and 200 mg (treatment kit), the patient will be analyzed in the sotagliflozin 200 mg group.
- Randomized patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study medication. If a patient is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed

2.3.3 PK population

For PK analyses, the PK population is defined as all safety patients who contribute with at least 1 valid plasma concentration of sotagliflozin or its 3-O-glucuronide metabolite. The PK data will be analyzed according to the treatment actually received (see Section 2.3.2).

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall (pooled across treatment groups) using descriptive statistics.

P-values on the treatment difference for the demographic and baseline characteristic data will not be calculated.

In general, no specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

In general, no specific description of the efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each efficacy analysis.

2.4.2 Prior or concomitant medications

The prior, concomitant and posttreatment medications will be presented in the randomized population for each treatment group (and overall for the summary of prior medications), using counts and percentages. No statistical test for the between-group difference will be performed.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). A given medication may be classified in more than 1 ATC class. All ATC codes corresponding to a medication will be summarized, and a patient will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, a patient may be counted several times for the same medication.

Prior medications will be presented by anatomic and therapeutic categories and sorted by decreasing frequency of ATC based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant and posttreatment medications will be presented by anatomic and therapeutic categories and sorted by decreasing frequency of ATC based on the incidence in the sotagliflozin 400 mg group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Antidiabetic medication will be presented separately by pharmacological class, chemical class and standardized medication name.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last dose date of double-blind IMP – first dose date of double-blind IMP + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number of patients exposed, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- 1 to 28 days,
- 29 to 56 days,
- 57 to 84 days,
- 85 to 126 days,
- 127 to 182 days,
- 183 to 364 days,
- >364 days.

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

Number and percentages of patients by final dose at the end of the treatment will also be presented by each treatment group.

2.4.3.2 Compliance

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

Percentage of compliance for a patient will be defined as the number of days that the patient was compliant divided by the total number of days that the patient was planned to take during the treatment epoch defined in Section 2.1.4 (ie, from the first date to the last date of double-blind IMP administration).

Above-planned dosing percentage for a patient will be defined as the number of days that the patient took a higher dose than planned divided by the total number of days that the patient was planned to take during the treatment epoch.

Under-planned dosing percentage for a patient will be defined as the number of days that the patient took a lower dose than planned divided by the total number of days that the patient was planned to take during the treatment epoch.

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with at least 1 day above-planned dose administration will be

provided, as well as numbers and percentages of patients with (0, 20%], and >20% of days under-planned dose administrations.

Cases of overdose (see study protocol for further details) will constitute AEs/SAEs and be analyzed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population using the efficacy assessments collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy, unless otherwise specified.

Missing data for efficacy analyses is identified through steps described in Section 2.5.4.

2.4.4.1 Analysis of primary efficacy endpoint(s)

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

Primary analysis

The primary efficacy endpoint of change in HbA1c from baseline to Week 18 will be analyzed by an Analysis of Covariance (ANCOVA) model using HbA1c values measured at baseline and Week 18 (observed or imputed). The missing data at endpoint will be imputed by multiple imputation (MI) methods as detailed below. To be concise, the following texts related to imputation are generalized to accommodate primary as well as continuous secondary efficacy endpoints.

Missing endpoint data at Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW) visit will be imputed using a model built separately in each treatment group and estimated from the patients in the same treatment group who prematurely discontinue the IMP before the Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW) visit but have the measurement for the endpoint (retrieved dropouts). The imputation model will include the randomization strata and the corresponding baseline value. In cases of non-convergence during the imputations, the offending stratum will be identified and then will be dropped from the model. Considering that the number of patients in each treatment group who discontinue the IMP but have the measurement for the endpoint is expected to be small, a simple imputation model based on regression will be used with baseline measurement included as the predictor. This will serve as the primary model of imputation for missing data should sampling criteria be satisfied (see below).

An alternative (back-up) imputation method will be used if the number of patients who prematurely discontinue the IMP before the Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW) visit but have the measurement for the endpoint is <5 in any treatment groups (ie, not sufficient retrieved dropouts to support the imputation method described above). This criterion will be assessed for each primary or continuous secondary efficacy endpoint.

In the back-up imputation method, missing post-baseline endpoint values at Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW) will be imputed by washout multiple imputation (MI) method under the missing not at random (MNAR) framework.

Missing endpoint data at Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW) in the sotagliflozin group(s), as well as in the placebo group are imputed from a model estimated from patients in the placebo group who have the endpoint data available.

For patients in the sotagliflozin 400 mg and 200 mg groups with missing data at Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW), their missing values will be imputed using observed baseline and the observed primary endpoint data from placebo completers; no intermittent values from either placebo or the active treatment groups will be used.

For placebo patients, missing data will be imputed based on the placebo group data. Intermittent observed values will be used while imputing missing values at Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW). In cases that a non-monotone missing data pattern occurs at the intermediate visits, these data points will be first imputed in the placebo group using the Markov Chain Monte Carlo (MCMC) option in PROC MI to achieve a monotone missing pattern for all placebo patients. The Week 18 (or Week 12 for SBP or Week 52 for HbA1c and BW) endpoint values will be subsequently imputed from the multiple copies of the original dataset where each copy will have a monotone missing pattern.

The imputation models for the washout MI method will include the randomization strata and the corresponding baseline value. Missing data will be imputed using the regression method. In cases of non-convergence during the imputations, especially for the MCMC application in the placebo non-monotone datasets, graphical measures (eg, trace and autocorrelation plots) will be used to identify the offending variable and once detected, that variable(s) will be dropped from the model and the imputations will be re-run. These re-run models will use the same seed number and number of imputations as used in the original models.

Using either imputation method, missing endpoint data will be imputed multiple times to generate multiple data sets with complete data. The change from baseline to Week 18 will be derived from observed and imputed HbA1c value at Week 18. Each of the complete datasets after the imputation will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c ($\leq$8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, $\geq$130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and baseline HbA1c value as a covariate. Results from each complete dataset will be combined using Rubin's rule to provide the adjusted mean change in HbA1c from Baseline to Week 18 for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg, 200 mg vs placebo) and the 95% confidence interval (CI).

Sensitivity analyses

Tipping point analysis based on the same MI method as applied to the primary analysis will be performed to examine the robustness of the results from the primary analysis. Patients who were randomized to sotagliflozin groups and had no HbA1c data at Week 18 will be given a penalty. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of statistical significance is changed (see below). The tipping point is the penalty level, at which the magnitude of efficacy reduction in patients without HbA1c data at Week 18 creates a shift in the treatment effect of sotagliflozin 400 mg from being statistically significantly better than placebo to a non-statistically significant effect. LS mean difference between sotagliflozin 400 mg and placebo and its associated p-value will be provided for each penalty level. The steps to perform the tipping point analysis comparing sotagliflozin 400 mg versus placebo are as follows:

1. Missing data will be imputed using the same MI method as applied to the primary analysis,
2. The imputed HbA1c value at Week 18 in the sotagliflozin group will be penalized by adding a penalty δ (eg, $\delta = 0.1\%$) in each complete dataset,
3. Change from baseline at Week 18 in HbA1c will be analyzed using the same ANCOVA model as specified in the primary analysis in each complete dataset,
4. Results will be combined across complete datasets using Rubin's rule,
5. Steps 2 to 4 will be repeated with incremental penalty at δ (ie, δ, 2δ, 3δ, ……) until the p-value for treatment effect of sotagliflozin 400 mg compared to placebo estimated in Step 4 is >0.05.

The above tipping point analysis will be replicated to examine the robustness of the treatment effect of sotagliflozin 200 mg (ie, adding penalty to the sotagliflozin 200 mg group instead of sotagliflozin 400 mg group).

The tipping point analysis will be performed only if the corresponding primary or secondary endpoint (change from baseline to Week 18 in HbA1c comparing sotagliflozin 400 mg vs placebo, or comparing sotagliflozin 200 mg vs placebo) is statistically significant at $\alpha = 0.05$ (2-sided).

In addition, if the retrieved dropout imputation is applied to the primary analysis, the analysis based on the washout (ie, the backup imputation method) will be presented as a sensitivity analysis.

To investigate the impact of randomization stratification error of HbA1c at Week -1 (≤8.5%, >8.5%), the following sensitivity analyses will be performed for the primary or secondary endpoint (change from baseline to Week 18 in HbA1c comparing sotagliflozin 400 mg vs placebo or comparing sotagliflozin 200 mg vs placebo):

- The same model as described in the primary analysis will be performed by excluding those patients with randomization stratification error regarding HbA1c at Week -1 (≤8.5%, >8.5%).

- The same model with the same MI method as described in the primary analysis will also be performed by replacing randomization strata of HbA1c (⩽8.5%, >8.5%) at Week -1 from IRT with the actual strata calculated based on HbA1c value (⩽8.5%, >8.5%) at Week -1 from central lab in both imputation model and analysis model.

Patients in this study have undergone sampling for plasma levels of sotagliflozin and its main active metabolite in order to perform population PK analysis. Patients may be identified who have no detectable levels of active study drug or metabolite in their samples (ie, Below Lower Limit of Quantification or BLLOQ). When sample analysis has been completed and the study has been unblinded, explanations for some of these patients may be found: known non-compliance or sampling occurring after treatment had been discontinued. In other cases, drug intake history relative to the randomization assignment may not be fully explained. The ITT-based analyses specified in this document provides for a conservative assessment of the efficacy data should patients have been subjected to these unexplained non-compliance findings or PK 'anomalies'. To provide a broader perspective on the impact of these apparent errors in compliance, additional sensitivity analyses of the primary efficacy endpoint and continuous efficacy endpoints may be conducted. The need to perform such analyses, their specifics, and results will be provided in the Clinical Study Report (CSR), if applicable. The analysis methods applied to the patient subpopulations defined by the occurrence of the PK anomalies (eg., exclusion of patients with PK anomalies from the ITT dataset) will include the ANCOVA model using the retrieved dropout and/or washout MI methods previously specified in this section.

Assessment of treatment effect by subgroup

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

- Race (White, Black or African American, Asian, Other) (any race groups with fewer than 5 patients may be combined with "Other" category as appropriate),
- Ethnicity (Hispanic, Not Hispanic),
- Age group (<50, ≥50 to <65, ≥65 years) (any category with fewer than 5 patients may be combined with another category as appropriate),
- Gender (Male, Female),
- Baseline BMI level (<30, ≥30 kg/m²),
- Baseline HbA1c (≤8.5%, >8.5%),
- Baseline SBP (<130 mmHg, ≥130 mmHg),
- Sulfonylurea use at Week -1 (yes, no),
- Baseline eGFR (≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73m^2 [Normal])
- Duration of diabetes (<10, ≥10 years)

- Country.

The treatment effects (sotagliflozin 400 mg versus placebo and sotagliflozin 200 mg versus placebo) across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 18 in HbA1c in the ITT population, and using the same MI method as applied to the primary analysis. The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), subgroup factor, treatment-by-subgroup factor, and country as fixed factors and using baseline HbA1c value as a covariate. The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus placebo) with standard error (SE) and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided.

In the case that the subgroup factor is identical or similar to a randomization strata factor (eg, baseline HbA1c or baseline SBP category or Sulfonylurea use at Week -1), only the subgroup factor (as a single factor or an interaction term) will be included in the model in order to avoid the issue of collinearity in the analysis. The corresponding strata factor will not be included in the model.

Summary statistics at scheduled visits

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

Similar presentations will be provided excluding measurements after rescue therapy during the 52-week entire treatment period.

2.4.4.2 Analyses of secondary efficacy endpoints

For continuous secondary efficacy parameters (see Section 2.1.3) with missing data at baseline, missing data will be imputed using MI under the missing at random (MAR) assumption. Missing data at baseline will be imputed using regression method that includes randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and baseline value in the imputation model.

Each continuous secondary efficacy endpoint (Section 2.1.3) will be analyzed using a similar ANCOVA model including the measurements at baseline and endpoint (observed or imputed). The missing data at endpoint will be imputed by the retrieved dropouts if there are at least 5 patients in each study treatment group who discontinued but have the endpoint data. Otherwise,

the washout imputation method will be used. After the imputation, each of the complete datasets will be analyzed by an ANCOVA model.

The ANCOVA model will include treatment groups (sotagliflozin 400 mg, 200 mg, and placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and the corresponding baseline of secondary endpoint value as a covariate. For the analysis of SBP in patients with baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included. Results from each complete dataset will be combined using Rubin's formula to provide the adjusted mean change from Baseline to Week 18 (or Week 12 for SBP, week 52 for HbA1c and BW) for each treatment group, as well as the between-group differences and the 95% CIs for the differences.

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. In addition, SBP will be summarized descriptively at each visit for those patients with baseline SBP ≥140 mmHg.

The categorical secondary and other efficacy variables of HbA1c <6.5%, <7% at Week 18 will be analyzed respectively using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and randomization strata of sulfonylureas use at Week -1 (yes, no). The proportion in each treatment group will be provided, as well as the difference of proportions between sotagliflozin (400 mg, 200 mg) and placebo with associated 2-sided 95% CI. For HbA1c responders at Week 18 (<6.5%, <7% respectively), all values at Week 18 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 18 will be treated as non-responders. Summary tables and graphs will also be provided by treatment group at scheduled visits.

For between-group comparison, a sensitivity analysis will be performed respectively for HbA1c <6.5% responder analysis by excluding patients whose HbA1c values at baseline are <6.5%, and for HbA1c <7% responder analysis by excluding patients whose HbA1c values at baseline are <7% using the same CMH test mentioned above. Similarly, by-visit summary may also be provided excluding those patients.

2.4.4.3 Analyses of other efficacy endpoints

Except for PRO endpoints, the analysis of other endpoints (see Section 2.1.3) will be descriptive with no formal testing. Summary statistics at scheduled visits will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time. For the daily Lantus dose (U) and daily Lantus dose adjusted by body weight (Lantus dose/body weight in U/Kg),

summary statistics (for screening value, run-in value, baseline value, and observed values) at scheduled visits (using OC) will also be provided for each treatment group.

The change from baseline values will be summarized for UGE and UGCR. These 2 variables have been added for analyses.

For the daily Lantus dose and total daily insulin dose, the baseline value is defined as the available value on the last day prior to 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.

The number (%) of patients achieving HbA1c response (<6.5%, <7% at Week 18, Week 26 and Week 52, respectively) will be descriptive summarized at each scheduled visit.

The number (%) of patients who used rescue therapy and a KM curve for the time to first rescue therapy will be provided by treatment group during the entire 52-week treatment period (see Section 2.5.4). A list of patients who used rescue therapy will also be provided.

UACR will be log-transformed at patient level. Summary statistics of UACR in log scale will then be calculated for each treatment group at each visit and back-transformed to provide the geometric mean and its associated percent change of UACR from baseline.

Shift tables will be provided for UACR at Week 26 and Week 52 using the pre-defined categories. That is, the number (%) of patients with progression from one category at baseline to another category at Week 26 and Week 52 will be provided by treatment group. The pre-defined categories are, for UACR, <30 mg/g creatinine [Normal], ≥30 to <300 mg/g creatinine [Microalbuminuria], and ≥300 mg/g creatinine [Macroalbuminuria].

The analysis of TRIM-D scores is in Section 2.4.7.

2.4.4.4 Multiplicity issues

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

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

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

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

If any hypothesis is found to be not statistically significant, the testing procedure will be stopped and the following hypotheses will not be tested.

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

2.4.4.5 Analyses of CGM sub-study efficacy variables

The analysis of CGM endpoints will be performed on the CGM sub-study population using CGM measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

All CGM derived variables will be subject to the following criteria.

- CGM data are masked to both the patients and investigators.
- A complete 24-hour CGM profile includes 288 data points given that CGM reading is recorded every 5 minutes.
- The start and end time of a 24-hour CGM profile is defined as midnight, i.e. each CGM profile begins at midnight (0.00) and ends at midnight (23:59). Partial CGM data points prior to the first midnight and after the last midnight from the visit will not be used in the CGM parameter calculation as the partial CGM profile may introduce additional variabilities to the data.
- Useable CGM data for a day/a 24-hour CGM profile are defined as at least 80% time of records (230 data points) without a gap (missing data) lasting for ≥ 2 hours per 24 hours.
- Qualified CGM data for calculating baseline value should have at least 4 days (not necessarily consecutive) of useable 24-hour CGM data from 7-day CGM profiles. Qualified CGM data for calculating the post randomization value at Week 19 should have at least 4 days (not necessarily consecutive) of useable 24-hour CGM data from 14-day CGM profiles.

- In case that there are more than 288 data points or more than one data point per 5 minutes, usually due to recalibration or switching CGM devices, averaging the data points every 5 minutes will be performed so that there is only one data point per 5 minutes.
- For all CGM parameters except the standard deviation of glucose levels between days, AUC of glucose concentrations for 2 hours after a standardized mixed meal and 2-hour PPG, a CGM parameter will be first calculated based on each 24-hour CGM profile from the visit, the final values of the CGM parameters for the visit will be based on the average of parameter values taken on each CGM profile from each CGM visit.
- The percentage of time glucose within or outside a specific range will be calculated as time of CGM glucose within/outside the range divided by total time with valid data.

Analysis of CGM sub-study primary endpoint

The CGM primary endpoint of change in percentage of time glucose levels within the target range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) over 24 hours from baseline to Week 19 will be analyzed by an ANCOVA model using the values measured at baseline and Week 19 (observed or imputed). The missing CGM values at endpoint will be imputed by multiple imputation (MI) methods as described below.

Note that the comparison of change in percentage of time glucose levels within the target range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) over 24 hours from baseline to Week 19 between sotagliflozin 200 mg and placebo is a CGM sub-study secondary endpoint, however the analysis is identical to that of CGM primary endpoint and is detailed here for concision.

Missing endpoint data at Week 19 visit will be imputed using a model built separately in each treatment group and estimated from the patients in the same treatment group who prematurely discontinue the IMP before the Week 19 visit but have the measurement for the endpoint (retrieved dropouts). The imputation model will include the randomization strata and the corresponding baseline value. In cases of non-convergence during the imputations, the offending stratum will be identified and then will be dropped from the model. Considering that the number of patients in each treatment group who discontinue the IMP but have the measurement for the endpoint is expected to be small, a simple imputation model based on regression will be used with baseline measurement included as the predictor. This will serve as the primary model of imputation for missing data should sampling criteria be satisfied (see below).

An alternative (back-up) imputation method will be used if the number of patients who prematurely discontinue the IMP before the Week 19 visit but have the measurement for the endpoint is <5 in any treatment groups (ie, not sufficient retrieved dropouts to support the imputation method described above). This criterion will be assessed for each CGM sub-study primary or continuous secondary endpoint.

In the back-up imputation method, missing post-baseline endpoint values at Week 19 will be imputed by washout multiple imputation (MI) method under the missing not at random (MNAR) framework.

Missing endpoint data at Week 19 in the sotagliflozin group(s), as well as in the placebo group are imputed from a model estimated from patients in the placebo group who have the endpoint data available.

For patients in the sotagliflozin 400 mg and 200 mg groups with missing data at Week 19, their missing values will be imputed using observed baseline and the observed primary endpoint data from placebo completers; no intermittent values from either placebo or the active treatment groups will be used.

For placebo patients, missing data will be imputed based on the placebo group data. Intermittent observed values will be used while imputing missing values at Week 19. In cases that a non-monotone missing data pattern occurs at the intermediate visits, these data points will be first imputed in the placebo group using the Markov Chain Monte Carlo (MCMC) option in PROC MI to achieve a monotone missing pattern for all placebo patients. The Week 19 endpoint values will be subsequently imputed from the multiple copies of the original dataset where each copy will have a monotone missing pattern.

The imputation models for the washout MI method will include the randomization strata and the corresponding baseline value. Missing data will be imputed using the regression method. In cases of non-convergence during the imputations, especially for the MCMC application in the placebo non-monotone datasets, graphical measures (eg, trace and autocorrelation plots) will be used to identify the offending variable and once detected, that variable(s) will be dropped from the model and the imputations will be re-run. These re-run models will use the same seed number and number of imputations as used in the original models.

Using either imputation method, missing endpoint data will be imputed multiple times to generate multiple data sets with complete data. Each of the complete datasets after the imputation will be analyzed by the ANCOVA model with treatment arms (sotagliflozin 400 mg, sotagliflozin 200 mg, and placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 systolic blood pressure (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), Lantus injection time (morning, evening) and country, as fixed effects, and Baseline CGM percentage value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change of percentage of time inside the target range (≥70 to ≤ 180 mg/dL) from Baseline to Week 19 for each treatment group, as well as the between group difference (comparing the sotagliflozin 400 mg, 200 mg versus placebo), and the 95% confidence interval (CI).

For the purpose of categorizing Lantus injection time (morning, evening), the available Lantus injection time on the last day prior to 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 will be used. The injection time during the period of 0:00 to 11:59 will be in morning category and in evening category if the injection time is during the period of 12:00 to 23:59. If the patient is using Lantus more than once daily, the category will be based on the injection time of the largest dose. If the doses are equal, the injection time of the latest dose will be used.

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.

Analyses of CGM sub-study secondary endpoints

Continuous CGM secondary endpoints will be analyzed using a similar approach as the CGM sub-study primary endpoint, with missing post-randomization CGM values (ie, final values of the CGM parameter) imputed by the retrieved dropouts imputation method or by the washout imputation method according to the criterion described in Section 2.4.4.5.

For each of the continuous CGM sub-study secondary endpoints, each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), randomization strata of sulfonylureas use at Week -1 (yes, no), Lantus injection time (morning, evening) and country as fixed effects, and Baseline secondary endpoint value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 19 (Week 18 for MMTT related endpoints) for each treatment group, as well as the between group difference (comparing each sotagliflozin group versus placebo), and the 95% CI using contrast statement.

For all continuous CGM sub-study 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).

Mean 24-hour glucose concentration is calculated by sum of glucose values divided by total number of glucose measurements for the 24 hourly intervals and then averaged for the period before each visit.

The CV over 24-hour is calculated as the ratio of the standard deviation of the glucose values to mean of the glucose values over 24-hour profile. For each patient and visit, the CV from all CGM profiles will be averaged as the final values of the CV for the visit. It will be log-transformed before the analysis. Change from Baseline to Week 19 of CV in log scale will be analyzed. Results in the log scale will be back-transformed.

AUC of glucose concentrations for 2 hours after a standardized mixed meal will be calculated using the linear trapezoidal method. CGM data will be limited to CGM readings taken from the start of the standardized meal through 2 hours after the start of the standardized meal, inclusive.

The analysis of the 2-hour PPG endpoint following a standardized mixed meal will be based on a Time 0 adjusted value (ie, the 2-hour PPG value minus the Time 0 value, FPG sample) at both the

Baseline and Week 18 time points. These Time 0 adjusted values will be used to derive the Week 18 minus Baseline scores, which will serve as the measure of interest for comparative purposes.

Analyses of CGM sub-study other endpoints

The analysis of other sub-study endpoints (see Section 2.1.3) will be descriptive with no formal testing. Summary statistics at scheduled visits using observed cases will be provided by each treatment group.

The details for calculation AUCs outside of target ranges, MAGE and SD of glucose levels within and between days (24-hour CGM profile) are provided below.

Inter-quartile range (IQR) is determined by calculating the difference between the 75th and 25th percentile values for the 24 hourly intervals over each 24-hour CGM profile and then averaged for the period of each visit.

A hypoglycemic episode is defined as a set of any number of consecutive CGM glucoses, all of which are <70 mg/dL (< 3.9 mmol/L) for at least 15 minutes. No provisions are made for gaps in measurements.

Calculation of CGM sub-study parameters

1) ***Mean Amplitude of Glycemic Excursion (MAGE)***

   It is defined as mean glucose value by summing absolute rises and falls (local minima and maxima) of more than 1 SD (within a 24-hour CGM profile). It includes only peak-to-nadir or nadir-to-peak excursions. $MAGE_j = \sum \frac{\lambda}{n}$ if $\lambda > SD$, where λ is the glucose increase or decrease (peak-to-nadir or nadir-to-peak excursions for the j[th] 24-hour CGM profile). n is the number of peak-to-nadir or nadir-to-peak excursions for the j[th] 24-hour CGM profile.

2) ***Standard deviation of glucose levels (SD) of glucose levels within and between days and coefficient of variation***

   $SD_{within,j} = \frac{\sum (x_{ij} - \bar{x}_j)^2}{h_j - 1}$, where x_{ij} is individual CGM data points within the j[th] 24-hour CGM profile, $\bar{x}_j$ is the mean glucose reading from all CGM data points for the j[th] 24-hour CGM profile. h_j is number of CGM data points within the j[th] 24-hour CGM profile. For each patient and visit, the $SD_{within,j}$ from all CGM profiles will be averaged as the final values of the within SD for the visit.

$SD_{between} = \frac{\sum(\bar{x}_j - \bar{x})^2}{m-1}$ where $\bar{x}$ is the mean glucose reading from all evaluable CGM data points from all evaluable CGM profiles from the same visit for the patient. $\bar{x}_j$ is the mean glucose reading from all CGM data points within the j[th] 24-hour CGM profile. m is the number of evaluable 24-hour CGM profiles,

$$CV = \frac{\sum \frac{SD_{within,j}}{\bar{x}_j}}{m}$$

where $\bar{x}_j$ is the mean glucose reading from all CGM data points within the j[th] CGM 24-hour profile.

3) Calculations of glucose AUC outside target ranges (daily average over the period prior to a visit)

Calculations of glucose AUC of hyperglycemia (hypoglycemia) are described as follows.

Let t_i represent the time of each CGM glucose measurement and Δx_i equals the absolute value of change from target at each time point.

The glucose AUC outside target range at each time point will be determined using the following formulas:

- $AUC_i = (t_i - t_{i-1})(\Delta x_i + \Delta x_{i-1})/2$ if the both measurements are above (below) the target range
- $AUC_i = (t_i - t_{i-1})\left(\Delta x_i^{\,2}/(\Delta x_i + \Delta x_{i-1})\right)/2$ if the first measurement is below (above) the target range and the second measurement is above (below) the target range
- $AUC_i = (t_i - t_{i-1})\left(\Delta x_{i-1}^{\,2}/(\Delta x_i + \Delta x_{i-1})\right)/2$ if the first measurement is above (below) the target range and the second measurement is below (above) the target range
- $AUC_i = 0$ if both measurements are below (above) the target range

The CGM glucose AUC for the full 24 hours will be calculated as the sum of the AUC_i values using the available CGM data within the 24-hour CGM profile. The daily average will be calculated from this sum.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. The safety data except hypoglycemia will be summarized for the entire 52-week double-blind treatment period. The hypoglycemia will be summarized for the 18-week randomized core treatment period and the entire 52-week double-blind treatment period (see Section 2.4.5.1).

The "observation period" defined in Section 2.1.4 is applicable in all safety analyses for the classification of AEs, determination of treatment-emergent Potentially Clinically Significant Abnormality (PCSA) values and the last on-treatment value for the laboratory, vital sign and ECG.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately
- The baseline value (with the exception of serum creatinine and eGFR) is defined as the last available value before the first dose of double-blind 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.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG [Appendix A].
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment emergent PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.
- For laboratory parameters cited in the protocol as efficacy endpoints (including HbA1c and plasma glucose, etc.), PCSA summaries will not be provided. These parameters will be summarized in Section 2.4.4.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group for the entire 52-week double-blind treatment period only. Summaries will include the last on-treatment value. The last on-treatment value is commonly defined as the value collected at the same day/time of the last administration of

IMP. If this value is missing, this last on-treatment value will be the closet value prior to the last dose administration of IMP during the entire 52-week treatment period.

- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% confidence intervals may be provided, if relevant
- Selected safety analyses will be summarized by age, gender, racial subgroups, and any pertinent subgroups (see details in Section 2.4.5.1 and Section 2.4.5.2).

2.4.5.1 Analyses of hypoglycemia

Analyses of hypoglycemia will be performed on the TEAE period as defined in Section 2.1.4. For the purpose of hypoglycemia analyses during the 18-week randomized core treatment period, the TEAE period for 18-week randomized core treatment period is (1) the time from the first administration of the double-blind IMP up to 1 day after the last administration of IMP if the patient discontinued treatment on or before Visit 12 (or Day 126 if Visit 18 date is missing), or (2) the time from the first administration of the double-blind IMP to the administration at Visit 12/Week 18 (or Day 126 if Visit 12/Week 18 date is missing) if the patient remained treated beyond Visit 12/Week 18. Hypoglycemia will be classified as severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia or relative hypoglycemia (see Section 2.1.4.1).

The number (%) of patients with any hypoglycemia, severe hypoglycemia and documented symptomatic hypoglycemia will be summarized respectively by treatment group during the TEAE period, as well as the incidence rate in patient years. Two types of incidence rates will be presented: the number of patients with at least 1 event per 100 patient-years (calculated as the number of patients with at least 1 event / total exposure in 100 patient-years), and the number of events per 100 patient-years (calculated as the total number of events / total exposure in 100 patient-years). Note: here exposure (in days) is the duration of TEAE period, ie, duration of IMP treatment in days +1 (see Section 2.1.4).

The summary of frequency and incidence rate in patient years for severe hypoglycemia or documented symptomatic hypoglycemia will be provided as appropriate by gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years), race (White, Black or African American, Asian, Other), sulfonylurea use at Week -1 (yes, no).

The number (%) of patients with at least 1 severe hypoglycemia or documented symptomatic hypoglycemia during the TEAE period, as well as the corresponding number of events, will be summarized as necessary by hour of the day for each treatment group, using the following hour intervals: ≥23:00 to <06:00, ≥06:00 to <10:00, ≥10:00 to <14:00, ≥14:00 to <18:00, ≥18:00 to <23:00.

A KM curve will also be provided by treatment group for the time to first severe hypoglycemia or documented symptomatic hypoglycemia during the TEAE period for the entire 52-week double-blind treatment period only (see Section 2.5.4).

Documented symptomatic hypoglycemia maybe presented by ≤70 mg/dL (3.9 mmol/L) and <54 mg/dL (3.0 mmol/L) respectively, as appropriate.

A listing of patients for all events reported on the dedicated e-CRF "Hypoglycemic event information" page will be provided with each category flagged (ie, severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia and relative hypoglycemia).

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will be presented by SOC, HLGT, HLT, and PT, sorted by the internationally agreed order for SOCs and alphabetic order for HLGT, HLT and PT within a SOC, the number (n) and percentage (%) of patients experiencing an adverse event. 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.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all treatment-emergent adverse events presented by primary SOC and PT (sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs in the sotagliflozin 400 mg group) will define the presentation order for all other similar tables unless otherwise specified. In case of equal frequency regarding PTs, alphabetical order will be used.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary SOC, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT in the sotagliflozin 400 mg group
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the sotagliflozin 400 mg group. This sorting order will be applied to all other similar tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related to IMP by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above
- Common TEAEs (PTs with an incidence ≥2% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.
- Common TEAEs (PTs with an incidence ≥2% in any treatment group) will be provided as appropriate by primary SOC, and PT and by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years of age), race (White, Black or African American, Asian, other), sulfonylurea use at Week -1 (yes, no), baseline SBP category

(<130 mmHg, ≥130 mmHg), and baseline eGFR category (≥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]). SOC will be sorted by internationally agreed order and the PT by decreasing incidence within each SOC in the sotagliflozin 400 mg group, as described above.

- TEAEs (PTs with an incidence ≥5% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

Analysis of adverse events of special interest

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

In addition, the number (%) of patients with an AESI will be summarized by PT and by treatment group. Corresponding listings will be provided as appropriately.

Analysis of events of special interest

Cardiovascular events, bone fracture and DKA

For EOSIs that are adjudicated (ie, deaths, myocardial infarction, stroke, and unstable angina requiring hospitalization, heart failure requiring hospitalization, bone fracture, and diabetic ketoacidosis), the number (%) of patients with an EOSI positively adjudicated by CEC will be summarized by treatment group. All EOSIs sent for adjudication and/or reported by the investigators in the specific AE forms will be listed along with the adjudication outcome.

Renal events

For the EOSI renal events where selected events are adjudicated, the number (%) of patients with any renal events identified in Table 3 in Section 2.1.4.2 will be summarized by treatment group.

The following renal events will be listed along with the adjudication outcome if applicable, including events,

i. recorded in e-CRF "GFR decrease",
ii. recorded in e-CRF "Renal Event – Dialysis",
iii. identified as "Renal transplant" in e-CRF "Other procedure",

Renal death will be part of all deaths specified above.

Other EOSIs

For EOSIs that are not adjudicated, the number (%) of patients with at least one event will be summarized by treatment group and by PT (as identified in Table 3 in Section 2.1.4.2.

Severe hypoglycemia will be included in the summary of hypoglycemia (See Section 2.4.5.1)

AE leading to an amputation is described in the section below.

Analysis of Amputation

The number (%) of patients with amputation will be summarized by treatment group and by PT during the study (ie, regardless of on- or post-treatment). Amputation is a procedure recorded in eCRF "Other Procedures related to Amputation". Patients who had a procedure related to amputation will be listed.

The number (%) of patients with an "AE leading to an amputation" will be summarized by treatment group and by PT. The "AE leading to an amputation" is determined by the AE identifier recorded in eCRF "Other Procedures related to Amputation" when "AE correction" is chosen as the reason for the amputation procedure.

In addition, the number (%) of patients with an "AE potentially leading to an amputation" will be summarized by treatment group and by PT (as identified in **Table 3** in Section 2.1.4.2). The associated list will be provided as well, with patients who had an amputation procedure flagged. "AE potentially leading to an amputation" represents the condition that commonly precedes the amputation procedure, but not in all cases an amputation has occurred.

Analysis of pretreatment and posttreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the sotagliflozin 400 mg group

- All posttreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the sotagliflozin 400 mg group

Listings

Supportive AE listings will be provided for all AEs, SAEs, AEs leading to treatment discontinuation and/or death, and EOSI as appropriate. Listing of all AEs, SAEs and AEs leading to treatment discontinuation and/or death, sorted by treatment, patient identification and onset date, will include at least the following information: treatment, patient identification, country, age, gender, race, BMI, primary SOC, PT, reported term, onset date, study day (relative day to the start date of double-blind treatment), AE duration, duration of exposure, intensity, corrective treatment, action taken with IMP, date of treatment discontinuation (if relevant), relationship to IMP or NIMP, outcome, date of death (if any), seriousness, seriousness criteria, and AE status ("E" for a TEAE; and "P" for an on-study post-treatment AE).

2.4.5.3 Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.

2.4.5.4 Analyses of laboratory variables

Laboratory parameters will be grouped and summarized by biological function as described in Section 2.1.5.2.

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (screening, run-in, baseline, postbaseline time point, last on-treatment value) by treatment group.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. These summaries will include patients in the safety population who have at least 1 assessment performed during the TEAE period. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries, and when required by the definition of the abnormality, patients must also have available laboratory normal ranges.

A listing of patients with at least 1 post-baseline PCSA (or out of normal range when no PCSA criterion is defined) will be provided which will display the entire patients' profile across time for all parameters belonging to the corresponding biological function. Individual data listings will include the following flags when applicable:

- Baseline values will be flagged "B".
- Normal laboratory ranges, available for most laboratory parameters, will be identified as ULN and LLN. Baseline, last on-treatment value, and individual data will be flagged "L" if the value is below the LLN and will be flagged "H" if it is above the ULN.
- Laboratory PCSA criteria will be used for the corresponding laboratory parameters. Values reaching a PCSA limit will be flagged (+, ++, -, or -- depending upon the direction and level of the abnormality). Flags for WBC and differential counts will be determined using data expressed in international units.

For parameters whose PCSA criteria are multiples of the ULN, the parameter's value will also be expressed as a multiple of the ULN in the individual data provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group (only if a tabulation summary is necessary).

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters (if available): conjugated bilirubin and prothrombin time/international normalized ratio, creatine phosphokinase, serum creatinine, complete blood count, anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies, auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, Epstein-Barr virus, herpes viruses, and anti-LKM.

2.4.5.5 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of heart rate, temperature and respiratory rate (observed values, or mean of observed values, and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment value) by treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group for SBP, DBP and HR. All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. The summaries will include patients in the safety population who have at least 1 assessment performed during the TEAE period. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries.

A listing of patients with at least 1 post-baseline PCSA will be provided and will display the patient's profile over time of all vital sign parameters. Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged (+, or - depending of the direction).

2.4.5.6 Analyses of electrocardiogram variables

Shift tables will be provided to present ECG status according to baseline status (Normal/Missing, Abnormal) for each treatment group during the TEAE period. Supportive listings of patients with abnormal ECG status at any post-baseline visit will be provided.

2.4.5.7 Analyses of physical examination variables

Shift tables will be provided to present physical examination findings by body system according to baseline status (Normal/Missing, Abnormal) for each treatment group during the TEAE period. Supportive listings of patients with abnormal findings at any post-baseline visit will be provided.

2.4.6 Analyses of pharmacokinetic variables

Plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite will be summarized by visit and nominal sampling time (pre-dose at Weeks 4, 18, 26 and 52) in the PK population (see Section 2.3.3) in the sotagliflozin group, using descriptive statistics such as number, geometric mean, coefficient of variation, median, minimum and maximum. Individual plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite at nominal sampling times will also be listed.

[redacted]

2.4.7 Analyses of patient reported outcomes

2.4.7.1 Scoring methods

TRIM-D is scored [1] in the following steps:

Step 1: Reverse the scale of the 17 items that need to be reverse coded (see Table 4).

Step 2: Sum the raw score across items in each domain for domain scores and the raw score of all items for total score.

Note: A domain score is calculated if at least half of the items in a multi-item domain are answered (or half plus 1 in the case of domains with an odd number of items). Total score is calculated if 14 or more items are answered.

Step 3: Transform the raw score to a score ranging from 0 (worst) to 100 (best) using the following:

Domain score = [(raw score – lowest possible raw score) / possible raw score range] * 100

Lowest possible raw score and possible raw score range are provided in Table 5.

Table 5 - TRIM-D range of scores

Domains	Cluster of Items	Lowest / Highest possible raw scores	Possible raw score range
Treatment Burden	1a, 2a, 2b, 2c, 2d, 2e	6/30	24
Daily Life	3a, 3b, 5a, 5b, 5c	5/25	20
Diabetes Management	4a, 4b, 4c, 4d, 4e	5/25	20
Compliance	6a, 6b, 6c, 6e	4/20	16
Psychological Health	6d, 7a, 7b, 7c, 7d, 7e, 7f, 7g	8/40	32
Total	All items	28 / 140	112

2.4.7.2 Analysis methods

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

For TRIM-D scores (total and domain scores), descriptive statistics (mean, median, SD, minimum and maximum) for absolute values and for changes from baseline will be presented by treatment group at baseline, Week 18, Week 26, Week 39 and Week 52.

The change in TRIM-D scores from Baseline to endpoint will be analyzed using a similar approach to the primary efficacy endpoint, with missing post-baseline values imputed by the retrieved dropouts imputation method or by the washout imputation method according to the criterion described in Section 2.4.4.1.

After the imputation, each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization strata of Week -1 HbA1c (≤8.5%, >8.5%), randomization strata of Week -1 SBP (<130 mmHg, ≥130 mmHg), and randomization strata of sulfonylureas use at Week -1 (yes, no), and country as fixed effects, and TRIM-D scores at Baseline as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change from Baseline to Week 52 for each treatment group, as well as the between group difference (comparing each sotagliflozin group versus placebo) and the 95% CI using contrast statements.

Cumulative distribution functions of scores change from baseline to endpoint will be displayed by treatment groups for TRIM-D scores (total and domain scores).

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

HbA1c

The formula to convert HbA1c from Diabetes Control and Complications Trial (DCCT) aligned value to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized value is,

IFCC-HbA1c (mmol/mol) = [DCCT-HbA1c (%) - 2.15] x 10.929.

Renal function formulas

The estimated GFR (mL/min/1.73 m^2) will be calculated using the 4 variable Modification of Diet in Renal Disease (MDRD) formula:

Standard unit: eGFR (mL/min/1.73 m^2) = 175 x [Serum Creatinine (µmol/L)/88.4] $^{-1.154}$ x Age (year) $^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)

Conventional unit: eGFR (mL/min/1.73 m^2) = 175 x Serum Creatinine (mg/dL) $^{-1.154}$ x Age (year) $^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)

UACR

Standard unit: UACR (mg/g) = Urine Albumin (mg/dL) / [Urine Creatinine (mmol/L) x 11.31] x 1000

Conventional unit: UACR (mg/g) = Urine Albumin (mg/dL) / Urine Creatinine (mg/dL) x 1000

Calculation of LDL-C

When TG is lower than or equal to 4.52 mmol/L (400 mg/dL), LDL-C is calculated using the Friedewald equation as:

- in standard unit (mmol/L), TC – HDL-C – TG/2.17;
- in conventional unit (mg/dL), TC – HDL-C – TG/5.

2.5.2 Data handling conventions for secondary efficacy variables

Scheduled measurements (see Section 2.5.4) of continuous efficacy variables collected during the study will be used in the analyses including those obtained after IMP discontinuation or introduction of rescue therapy. Continuous secondary efficacy endpoints will be analyzed with missing values imputed by the retrieved dropouts imputation method or by the washout imputation method according to the criterion described in Section 2.4.4.1.

For the categorical secondary efficacy endpoints, data handling conventions are described in Section 2.4.4.2.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Derived variables will be considered missing if any of the original variables required to calculate them are missing. For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then change from baseline at endpoint will be missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

Incomplete date of first administration of double-blind IMP

Date/time of first administration is the first non-missing start date/time of double-blind IMP completed in the e-CRF “First dose IMP” module.

For patients who are randomized and dispensed a double-blind treatment kit but who are lost to follow-up just after Visit 6 (eg. only the treatment kit number is reported in the e-CRF “Exposure

- treatment period" module without any dose information), the date of first administration will be imputed using the date of randomization. When a patient is randomized but not exposed, "Not taken" should be ticked in the e-CRF "First dose IMP" module.

Handling of computation of treatment duration if IMP end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of double-blind IMP is equal to the date of last administration reported on the e-CRF "Treatment status library" page. If this date is missing, the exposure duration should be left as missing.

The last dose administration should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

Missing or partial adverse event/hypoglycemia onset dates and times will be imputed so that if the partial adverse event/hypoglycemia onset date/time information does not indicate that the adverse event/hypoglycemia started prior to treatment or after the treatment-emergent adverse event period, the adverse event/hypoglycemia will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events/hypoglycemia when date and time of first IMP administration is missing

When the date and time of the first double-blind IMP administration is missing, the day of randomization should be considered as the start date of TEAE period (see Section 2.1.4). The exposure duration should be kept as missing.

Handling of adverse events/hypoglycemia when IMP end of treatment date is missing

For the purpose of defining TEAE period, the date of the last administration of double-blind IMP is equal to the date of the last administration reported on the eCRF "Treatment Status Library" page.

If the date of last administration reported on the eCRF "Treatment Status Library" page is

- Partially missing, it will be imputed with a date as late as possible before or on the date of last available information on eCRF "Completion of End of Study/Follow-up".

- Completely missing, it will be imputed with the date of last available information on eCRF "Completion of End of Study/Follow-up" page.

If the date of last available information on eCRF "Completion of End of Study/Follow-up" page is

- Partially missing, it will be imputed with a date as late as possible.
- Completely missing, all adverse events occurred on or after the first administration of double-blind IMP will be considered as treatment emergent adverse events.

Handling of missing assessment of relationship of adverse events to IMP

If the assessment of the relationship to IMP is missing, the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Linked adverse events that worsened or became serious

An AE that worsened or became serious will have a separate record in the data from the original event record with an AE identification number that links the new record to the original record. An AE that worsened or became serious will be considered a new recurring AE in the summary of recurrent events or in the summary of events by time intervals.

Handling of missing data for continuous efficacy endpoints

Please see Section 2.4.4.1 and Section 2.4.4.2.

Handling of missing data for categorical secondary efficacy endpoints

Please see Section 2.4.4.2.

2.5.4 Windows for time points

The following steps will decide how the scheduled and/or unscheduled visits will be used in the analyses on efficacy variables and the by-visit summaries for safety variables (clinical laboratory data in Section 2.1.5.2 and vital signs in Section 2.1.5.3).

Step 1 A scheduled measurement will be used if it is available; otherwise, an unscheduled measurement (including the end of treatment/study visit for those prematurely discontinued) will be used if it happens to be on the same date as the date of the scheduled visit.

Step 2 After Step 1, if there are still no measurement for a given parameter at a scheduled visit, the analysis window below (Table 6) will be applied to re-allocate a post-baseline unscheduled measurement to a scheduled measurement.

Table 6 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 4 (Visit 8)	28	2 to 41
Week 8 (Visit 10)	56	42 to 69
Week 12 (Visit 11)	84	70 to 104
Week 18 (Visit 12)	126	105 to 153
Week 26 (Visit 13)	182	154 to 227
Week 39 (Visit 14)	273	228 to 318
Week 52 (Visit 15)	364	≥319

Study days are calculated from the day of first administration of double-blind IMP; the day of first administration of IMP (or the day of randomization if not exposed) is Day 1.

After applying the above time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. In case of equality, the last measurement will be used. Re-allocated scheduled visits (ie, visit numbers) should be sequential if ordered by the date of measurement.

After Step 2, if there are still no measurement for a given parameter at a scheduled visit, data is considered missing for efficacy analyses, where multiple imputation would be applied as appropriately as described in Section 2.4.4.

Reference day

The reference day for the calculation of extent of exposure, time to onset, and relative days will be the day of the first administration of double-blind IMP or the day of randomization if not exposed to double-blind IMP, denoted as Day 1.

Baseline definition for efficacy/safety data

For the safety analyses, the baseline for a given parameter is defined as the last available measurement (or the average of all measurements for creatinine and eGFR), including unscheduled assessments, assessed prior to the first administration of double-blind IMP. For the efficacy analyses, the baseline for a given parameter is defined as the last available measurement (or the average of all measurements for creatinine and eGFR), including unscheduled assessments, assessed prior to the first administration of double-blind IMP or the last available value (or the average of all measurements for creatinine and eGFR) before randomization if not treated with double-blind IMP.

Summary statistics by visit for continuous efficacy endpoints

Summary statistics (number, mean, SD, SE, minimum, median, maximum) of continuous efficacy endpoints (observed data and change from baseline) will be provided at scheduled visits as per protocol. Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number, see Section 2.5.4) and labeled with the targeted approximate day/week.

Last on-treatment value for laboratory variables and vital signs

The last on-treatment value is the final measurement assessed during the treatment epoch, regardless of the introduction of rescue therapy, including measurements at unscheduled visits. Please see details in Section 2.1.4 and Section 2.4.5

Display of safety data by visit (laboratory variables and vital signs)

Descriptive statistics (number, mean, SD, minimum, median, maximum) of quantitative laboratory variables and vital signs (observed data and change from baseline) during the TEAE period will be provided at scheduled visits. In addition, these summaries will also include a row for the 'last value on-treatment' to describe the last available on-treatment value (see above). Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number, see Section 2.5.4) and labeled with the targeted approximate day/week.

As specified in the study protocol, laboratory data from scheduled visits are reported by central laboratories. The local results will not be used in the efficacy analyses or in the definition of baseline for both safety and efficacy analyses. In the safety analyses, local results will only be used in the PCSA summary if they are accompanied by a local laboratory normal range.

When a patient has more than 1 measurement from the central laboratory for the same laboratory parameter on the same date, the average of the measurements will be used. For the same laboratory parameter, if a patient has more than 1 measurement on different dates for the same

scheduled visit, the value closest to the date of the visit will be used for the scheduled visit. When the values for the same scheduled visit are equidistant, the last value should be used for the scheduled visit. Similar rules will be applicable to a patient who has more than 1 set of measurements for the same vital sign parameter (ie, SBP, DBP, or HR) on the same date.

Time to event analysis

For time to event analysis/KM plot, time to event (eg, treatment discontinuation, rescue therapy, hypoglycemia, etc) is defined as the number of days from the date of the first administration of double-blind IMP (or the date of randomization if not exposed) to the start date of the first occurrence of the event during entire 52-week double-blind treatment period.

Patients who did not experience any event during the entire 52-week double-blind treatment period are considered censored observations. For treatment discontinuation and time to rescue, censoring date is the date of EOT. For time to severe or documented hypoglycemia, censoring date is date of EOT+1 or date of EOS, whichever is the earliest. Date of EOS will be used if date of EOT is not available. Last contact date will be used if date of EOS is not available.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline, the last on-treatment value, PCSAs, and the shift summaries for safety or efficacy. They will be included in the by-visit summaries if they are re-allocated to scheduled visits (see Section 2.5.4).

2.5.6 Pooling of centers for statistical analyses

Center will not be included in the statistical models for efficacy analyses. However, all centers within a country will be pooled, and country will be included as a fixed effect in a parametric statistical model (eg, ANCOVA, etc) for primary and secondary efficacy endpoints. Countries with fewer than 5 randomized patients will be grouped, if patients from grouped countries are still fewer than 5, they will then be further grouped with the country with the country with the lowest number of patients that is 5 or more.

2.5.7 Statistical technical issues

None

3 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 Data Monitoring Committee (DMC) will be used to 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).

4 DATABASE LOCK

The database is planned to be locked approximately 4 weeks after the last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS® version 9.2 or higher.

6 REFERENCES

1. Savre I, Mapi Research Trust. TRIM-D Treatment Related Impact Measure-Diabetes. Information booklet. 1st ed. Hojbjerre L, Novo Nordisk. France. Mapi Research Trust; c2013. 41 p.

7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities criteria

Appendix B List of PTs for select EOSIs (MedDRA v22.0)

Appendix C Summary of statistical analyses

Appendix D Study flow chart

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
Amylasemia	≥3 ULN	
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male); ≤0.32 v/v (Female) ≥0.55 v/v (Male); ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4): 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms >500 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix B List of PTs for select EOSIs (MedDRA v22.0)

EOSI	Preferred Term Code	Preferred Term
Genital Mycotic Infections	10004074	Balanitis candida
Genital Mycotic Infections	10018143	Genital candidiasis
Genital Mycotic Infections	10047784	Vulvovaginal candidiasis
Genital Mycotic Infections	10061180	Genital infection fungal
Genital Mycotic Infections	10064899	Vulvovaginal mycotic infection
Genital Mycotic Infections	10065582	Urogenital infection fungal
Genital Mycotic Infections	10071209	Candida cervicitis
Genital Mycotic Infections	10079521	Fungal balanitis
Urinary tract infections	10011781	Cystitis
Urinary tract infections	10011790	Cystitis escherichia
Urinary tract infections	10011797	Cystitis klebsiella
Urinary tract infections	10011799	Cystitis pseudomonal
Urinary tract infections	10017525	Fungal cystitis
Urinary tract infections	10018185	Genitourinary chlamydia infection
Urinary tract infections	10023424	Kidney infection
Urinary tract infections	10037584	Pyelitis
Urinary tract infections	10037596	Pyelonephritis
Urinary tract infections	10037597	Pyelonephritis acute
Urinary tract infections	10037601	Pyelonephritis chronic
Urinary tract infections	10037603	Pyelonephritis mycoplasmal
Urinary tract infections	10037653	Pyonephrosis
Urinary tract infections	10038351	Renal abscess
Urinary tract infections	10044828	Tuberculosis of genitourinary system
Urinary tract infections	10046424	Urethral abscess
Urinary tract infections	10046480	Urethritis
Urinary tract infections	10046482	Urethritis chlamydial
Urinary tract infections	10046483	Urethritis gonococcal
Urinary tract infections	10046490	Urethritis ureaplasmal
Urinary tract infections	10046571	Urinary tract infection
Urinary tract infections	10046572	Urinary tract infection enterococcal
Urinary tract infections	10046704	Urogenital trichomoniasis
Urinary tract infections	10048302	Tubulointerstitial nephritis
Urinary tract infections	10048709	Urosepsis
Urinary tract infections	10048837	Cystitis glandularis
Urinary tract infections	10049059	Urinary tract infection fungal
Urinary tract infections	10049100	Pyelocystitis
Urinary tract infections	10051250	Ureteritis
Urinary tract infections	10051350	Cytomegalovirus urinary tract infection
Urinary tract infections	10051959	Urinary bladder abscess
Urinary tract infections	10052238	Escherichia urinary tract infection

Urinary tract infections	10054088	Urinary tract infection bacterial
Urinary tract infections	10056351	Emphysematous cystitis
Urinary tract infections	10058523	Bladder candidiasis
Urinary tract infections	10058596	Renal cyst infection
Urinary tract infections	10059517	Bacterial pyelonephritis
Urinary tract infections	10061181	Genitourinary tract gonococcal infection
Urinary tract infections	10061182	Genitourinary tract infection
Urinary tract infections	10061395	Ureter abscess
Urinary tract infections	10062279	Urinary tract infection pseudomonal
Urinary tract infections	10062280	Urinary tract infection staphylococcal
Urinary tract infections	10064825	Urinary tract infection viral
Urinary tract infections	10064921	Urinary tract inflammation
Urinary tract infections	10065197	Cystitis viral
Urinary tract infections	10065198	Cystitis bacterial
Urinary tract infections	10065199	Cystitis helminthic
Urinary tract infections	10065213	Pyelonephritis viral
Urinary tract infections	10065214	Pyelonephritis fungal
Urinary tract infections	10065582	Urogenital infection fungal
Urinary tract infections	10065583	Urogenital infection bacterial
Urinary tract infections	10066757	Urinary tract abscess
Urinary tract infections	10068822	Emphysematous pyelonephritis
Urinary tract infections	10070300	Streptococcal urinary tract infection
Urinary tract infections	10074409	Escherichia pyelonephritis
Urinary tract infections	10075063	Urethritis mycoplasmal
Urinary tract infections	10078665	Bacterial urethritis
Urinary tract infections	10081163	Fungal urethritis
Urinary tract infections	10081262	Candida urethritis
Urinary tract infections	10082040	Nephritis bacterial
Volume depletion	10005697	Blood osmolarity increased
Volume depletion	10005731	Blood pressure ambulatory decreased
Volume depletion	10005734	Blood pressure decreased
Volume depletion	10005737	Blood pressure diastolic decreased
Volume depletion	10005748	Blood pressure immeasurable
Volume depletion	10005758	Blood pressure systolic decreased
Volume depletion	10005761	Blood pressure systolic inspiratory decreased
Volume depletion	10007979	Central venous pressure decreased
Volume depletion	10009192	Circulatory collapse
Volume depletion	10012174	Dehydration
Volume depletion	10013578	Dizziness postural
Volume depletion	10021097	Hypotension
Volume depletion	10021137	Hypovolaemia
Volume depletion	10021138	Hypovolaemic shock
Volume depletion	10026983	Mean arterial pressure decreased
Volume depletion	10031127	Orthostatic hypotension
Volume depletion	10036653	Presyncope

Volume depletion	10037327	Pulmonary arterial wedge pressure decreased
Volume depletion	10042772	Syncope
Volume depletion	10046640	Urine flow decreased
Volume depletion	10047235	Venous pressure decreased
Volume depletion	10047239	Venous pressure jugular decreased
Volume depletion	10047689	Volume blood decreased
Volume depletion	10050760	Blood urea nitrogen/creatinine ratio increased
Volume depletion	10050905	Decreased ventricular preload
Volume depletion	10053356	Blood pressure orthostatic decreased
Volume depletion	10059895	Urine output decreased
Volume depletion	10060089	Left ventricular end-diastolic pressure decreased
Volume depletion	10060231	Pulmonary arterial pressure decreased
Volume depletion	10063080	Postural orthostatic tachycardia syndrome
Volume depletion	10063927	Orthostatic intolerance
Volume depletion	10066077	Diastolic hypotension
Volume depletion	10069431	Orthostatic heart rate response increased
Volume depletion	10069583	Pulse volume decreased
Volume depletion	10072370	Prerenal failure
Pancreatitis	10033625	Pancreatic haemorrhage
Pancreatitis	10033635	Pancreatic pseudocyst
Pancreatitis	10033636	Pancreatic pseudocyst drainage
Pancreatitis	10033645	Pancreatitis
Pancreatitis	10033647	Pancreatitis acute
Pancreatitis	10033649	Pancreatitis chronic
Pancreatitis	10033650	Pancreatitis haemorrhagic
Pancreatitis	10033654	Pancreatitis necrotising
Pancreatitis	10033657	Pancreatitis relapsing
Pancreatitis	10048984	Pancreatic abscess
Pancreatitis	10052400	Oedematous pancreatitis
Pancreatitis	10056277	Pancreatorenal syndrome
Pancreatitis	10056975	Pancreatic phlegmon
Pancreatitis	10056976	Hereditary pancreatitis
Pancreatitis	10056977	Alcoholic pancreatitis
Pancreatitis	10058096	Pancreatic necrosis
Pancreatitis	10065189	Pancreatitis helminthic
Pancreatitis	10066127	Ischaemic pancreatitis
Pancreatitis	10069002	Autoimmune pancreatitis
Pancreatitis	10074894	Traumatic pancreatitis
Pancreatitis	10076058	Haemorrhagic necrotic pancreatitis
Venous thrombotic events	10003192	Arteriovenous fistula thrombosis
Venous thrombotic events	10003880	Axillary vein thrombosis
Venous thrombotic events	10006537	Budd-Chiari syndrome
Venous thrombotic events	10007830	Cavernous sinus thrombosis
Venous thrombotic events	10008138	Cerebral venous thrombosis
Venous thrombotic events	10014522	Embolism venous

Venous thrombotic events	10019713	Hepatic vein thrombosis
Venous thrombotic events	10023237	Jugular vein thrombosis
Venous thrombotic events	10027402	Mesenteric vein thrombosis
Venous thrombotic events	10034272	Pelvic venous thrombosis
Venous thrombotic events	10034324	Penile vein thrombosis
Venous thrombotic events	10036206	Portal vein thrombosis
Venous thrombotic events	10037377	Pulmonary embolism
Venous thrombotic events	10037421	Pulmonary microemboli
Venous thrombotic events	10037437	Pulmonary thrombosis
Venous thrombotic events	10037459	Pulmonary venous thrombosis
Venous thrombotic events	10038547	Renal vein embolism
Venous thrombotic events	10038548	Renal vein thrombosis
Venous thrombotic events	10038908	Retinal vein thrombosis
Venous thrombotic events	10041659	Splenic vein thrombosis
Venous thrombotic events	10042567	Superior sagittal sinus thrombosis
Venous thrombotic events	10043570	Thrombophlebitis
Venous thrombotic events	10043581	Thrombophlebitis migrans
Venous thrombotic events	10043595	Thrombophlebitis superficial
Venous thrombotic events	10043605	Thrombosed varicose vein
Venous thrombotic events	10044457	Transverse sinus thrombosis
Venous thrombotic events	10047193	Vena cava embolism
Venous thrombotic events	10047195	Vena cava thrombosis
Venous thrombotic events	10047249	Venous thrombosis
Venous thrombotic events	10048591	Post thrombotic syndrome
Venous thrombotic events	10049446	Subclavian vein thrombosis
Venous thrombotic events	10050216	Paget-Schroetter syndrome
Venous thrombotic events	10050902	Postoperative thrombosis
Venous thrombotic events	10051055	Deep vein thrombosis
Venous thrombotic events	10053182	Arteriovenous graft thrombosis
Venous thrombotic events	10061251	Intracranial venous sinus thrombosis
Venous thrombotic events	10061408	Venous thrombosis limb
Venous thrombotic events	10063363	Brachiocephalic vein thrombosis
Venous thrombotic events	10063909	Post procedural pulmonary embolism
Venous thrombotic events	10066881	Deep vein thrombosis postoperative
Venous thrombotic events	10067270	Thrombosis corpora cavernosa
Venous thrombotic events	10069909	Metastatic pulmonary embolism
Venous thrombotic events	10072059	Ovarian vein thrombosis
Venous thrombotic events	10074349	Ophthalmic vein thrombosis
Venous thrombotic events	10077623	Portosplenomesenteric venous thrombosis
Venous thrombotic events	10077829	Visceral venous thrombosis
Venous thrombotic events	10078810	Hepatic vein embolism
Thyroid cancer	10002240	Anaplastic thyroid cancer
Thyroid cancer	10016935	Follicular thyroid cancer
Thyroid cancer	10027105	Medullary thyroid cancer
Thyroid cancer	10033701	Papillary thyroid cancer

Thyroid cancer	10043744	Thyroid neoplasm
Thyroid cancer	10055107	Thyroid cancer metastatic
Thyroid cancer	10066136	Huerthle cell carcinoma
Thyroid cancer	10066474	Thyroid cancer
Thyroid cancer	10070567	Thyroid cancer stage 0
Thyroid cancer	10071027	Thyroid cancer stage I
Thyroid cancer	10071028	Thyroid cancer stage II
Thyroid cancer	10071029	Thyroid cancer stage III
Thyroid cancer	10071030	Thyroid cancer stage IV
Thyroid cancer	10072162	Thyroid cancer recurrent
Thyroid cancer	10072613	Thyroid B-cell lymphoma
Thyroid cancer	10073153	Familial medullary thyroid cancer
Thyroid cancer	10076603	Poorly differentiated thyroid carcinoma
Renal cell cancer	10038389	Renal cancer
Renal cell cancer	10038390	Renal cancer recurrent
Renal cell cancer	10038391	Renal cancer stage I
Renal cell cancer	10038392	Renal cancer stage II
Renal cell cancer	10038393	Renal cancer stage III
Renal cell cancer	10038394	Renal cancer stage IV
Renal cell cancer	10038410	Renal cell carcinoma recurrent
Renal cell cancer	10038411	Renal cell carcinoma stage I
Renal cell cancer	10038412	Renal cell carcinoma stage II
Renal cell cancer	10038413	Renal cell carcinoma stage III
Renal cell cancer	10038414	Renal cell carcinoma stage IV
Renal cell cancer	10050018	Renal cancer metastatic
Renal cell cancer	10050513	Metastatic renal cell carcinoma
Renal cell cancer	10061482	Renal neoplasm
Renal cell cancer	10067944	Hereditary leiomyomatosis renal cell carcinoma
Renal cell cancer	10067946	Renal cell carcinoma
Renal cell cancer	10073251	Clear cell renal cell carcinoma
Renal cell cancer	10078493	Papillary renal cell carcinoma
Pancreatic cancer	10018404	Glucagonoma
Pancreatic cancer	10022498	Insulinoma
Pancreatic cancer	10025997	Malignant neoplasm of islets of Langerhans
Pancreatic cancer	10029341	Neurotensinoma
Pancreatic cancer	10033609	Pancreatic carcinoma
Pancreatic cancer	10033610	Pancreatic carcinoma metastatic
Pancreatic cancer	10033613	Pancreatic carcinoma recurrent
Pancreatic cancer	10041329	Somatostatinoma
Pancreatic cancer	10047430	Vipoma
Pancreatic cancer	10051709	Gastrinoma malignant
Pancreatic cancer	10052747	Adenocarcinoma pancreas
Pancreatic cancer	10055006	Pancreatic sarcoma
Pancreatic cancer	10055007	Carcinoid tumour of the pancreas
Pancreatic cancer	10059320	Pancreatic carcinoma stage 0

Pancreatic cancer	10059321	Pancreatic carcinoma stage I
Pancreatic cancer	10059322	Pancreatic carcinoma stage II
Pancreatic cancer	10059323	Pancreatic carcinoma stage III
Pancreatic cancer	10059326	Pancreatic carcinoma stage IV
Pancreatic cancer	10061902	Pancreatic neoplasm
Pancreatic cancer	10067517	Pancreatic neuroendocrine tumour
Pancreatic cancer	10068909	Pancreatic neuroendocrine tumour metastatic
Pancreatic cancer	10069345	Solid pseudopapillary tumour of the pancreas
Pancreatic cancer	10073363	Acinar cell carcinoma of pancreas
Pancreatic cancer	10073364	Ductal adenocarcinoma of pancreas
Pancreatic cancer	10073365	Intraductal papillary-mucinous carcinoma of pancreas
Pancreatic cancer	10073367	Pancreatoblastoma
Bladder cancer	10004986	Bladder adenocarcinoma recurrent
Bladder cancer	10004987	Bladder adenocarcinoma stage 0
Bladder cancer	10004988	Bladder adenocarcinoma stage I
Bladder cancer	10004989	Bladder adenocarcinoma stage II
Bladder cancer	10004990	Bladder adenocarcinoma stage III
Bladder cancer	10004991	Bladder adenocarcinoma stage IV
Bladder cancer	10004992	Bladder adenocarcinoma stage unspecified
Bladder cancer	10005003	Bladder cancer
Bladder cancer	10005005	Bladder cancer recurrent
Bladder cancer	10005006	Bladder cancer stage 0, with cancer in situ
Bladder cancer	10005007	Bladder cancer stage 0, without cancer in situ
Bladder cancer	10005008	Bladder cancer stage I, with cancer in situ
Bladder cancer	10005009	Bladder cancer stage I, without cancer in situ
Bladder cancer	10005010	Bladder cancer stage II
Bladder cancer	10005011	Bladder cancer stage III
Bladder cancer	10005012	Bladder cancer stage IV
Bladder cancer	10005056	Bladder neoplasm
Bladder cancer	10005075	Bladder squamous cell carcinoma recurrent
Bladder cancer	10005076	Bladder squamous cell carcinoma stage 0
Bladder cancer	10005077	Bladder squamous cell carcinoma stage I
Bladder cancer	10005078	Bladder squamous cell carcinoma stage II
Bladder cancer	10005079	Bladder squamous cell carcinoma stage III
Bladder cancer	10005080	Bladder squamous cell carcinoma stage IV
Bladder cancer	10005081	Bladder squamous cell carcinoma stage unspecified
Bladder cancer	10005084	Bladder transitional cell carcinoma
Bladder cancer	10051690	Urinary bladder sarcoma
Bladder cancer	10057352	Metastatic carcinoma of the bladder
Bladder cancer	10066749	Bladder transitional cell carcinoma stage 0
Bladder cancer	10066750	Bladder transitional cell carcinoma recurrent
Bladder cancer	10066751	Bladder transitional cell carcinoma stage I
Bladder cancer	10066752	Bladder transitional cell carcinoma stage IV

Bladder cancer	10066753	Bladder transitional cell carcinoma stage II
Bladder cancer	10066754	Bladder transitional cell carcinoma stage III
Bladder cancer	10071664	Bladder transitional cell carcinoma metastatic
Bladder cancer	10078341	Neuroendocrine carcinoma of the bladder
Potentially leading to amputation	10003084	Areflexia
Potentially leading to amputation	10003178	Arterial thrombosis
Potentially leading to amputation	10003210	Arteriosclerosis
Potentially leading to amputation	10003222	Arteriosclerotic gangrene
Potentially leading to amputation	10006784	Burning sensation
Potentially leading to amputation	10007904	Cellulitis enterococcal
Potentially leading to amputation	10007905	Cellulitis gangrenous
Potentially leading to amputation	10007921	Cellulitis staphylococcal
Potentially leading to amputation	10007922	Cellulitis streptococcal
Potentially leading to amputation	10012174	Dehydration
Potentially leading to amputation	10012665	Diabetic gangrene
Potentially leading to amputation	10012679	Diabetic neuropathic ulcer
Potentially leading to amputation	10012680	Diabetic neuropathy
Potentially leading to amputation	10017711	Gangrene
Potentially leading to amputation	10020937	Hypoaesthesia
Potentially leading to amputation	10021137	Hypovolaemia
Potentially leading to amputation	10021519	Impaired healing
Potentially leading to amputation	10021784	Infected skin ulcer
Potentially leading to amputation	10022562	Intermittent claudication
Potentially leading to amputation	10024774	Localised infection
Potentially leading to amputation	10028862	Necrosis ischaemic
Potentially leading to amputation	10029331	Neuropathy peripheral
Potentially leading to amputation	10031149	Osteitis
Potentially leading to amputation	10031252	Osteomyelitis
Potentially leading to amputation	10031253	Osteomyelitis acute
Potentially leading to amputation	10031256	Osteomyelitis chronic
Potentially leading to amputation	10031262	Osteomyelitis salmonella
Potentially leading to amputation	10031264	Osteonecrosis
Potentially leading to amputation	10033775	Paraesthesia
Potentially leading to amputation	10034568	Peripheral coldness
Potentially leading to amputation	10034576	Peripheral ischaemia
Potentially leading to amputation	10034620	Peripheral sensory neuropathy
Potentially leading to amputation	10034636	Peripheral vascular disorder
Potentially leading to amputation	10036155	Poor peripheral circulation
Potentially leading to amputation	10036410	Postoperative wound infection
Potentially leading to amputation	10040026	Sensory disturbance
Potentially leading to amputation	10040840	Skin erosion
Potentially leading to amputation	10040872	Skin infection
Potentially leading to amputation	10040943	Skin ulcer
Potentially leading to amputation	10042343	Subcutaneous abscess
Potentially leading to amputation	10043607	Thrombosis
Potentially leading to amputation	10048031	Wound dehiscence
Potentially leading to amputation	10048038	Wound infection
Potentially leading to amputation	10049927	Dry gangrene

Potentially leading to amputation	10050473	Abscess limb
Potentially leading to amputation	10050502	Neuropathic ulcer
Potentially leading to amputation	10051548	Burn infection
Potentially leading to amputation	10052428	Wound
Potentially leading to amputation	10052949	Arterial therapeutic procedure
Potentially leading to amputation	10053692	Wound complication
Potentially leading to amputation	10053716	Wound necrosis
Potentially leading to amputation	10054044	Diabetic microangiopathy
Potentially leading to amputation	10056340	Diabetic ulcer
Potentially leading to amputation	10056418	Arterial bypass operation
Potentially leading to amputation	10056673	Peripheral sensorimotor neuropathy
Potentially leading to amputation	10057518	Peripheral artery angioplasty
Potentially leading to amputation	10057525	Peripheral artery occlusion
Potentially leading to amputation	10058041	Wound sepsis
Potentially leading to amputation	10058042	Wound abscess
Potentially leading to amputation	10059245	Angiopathy
Potentially leading to amputation	10059385	Extremity necrosis
Potentially leading to amputation	10059442	Wound infection staphylococcal
Potentially leading to amputation	10059444	Wound infection pseudomonas
Potentially leading to amputation	10060734	Diabetic foot
Potentially leading to amputation	10060803	Diabetic foot infection
Potentially leading to amputation	10060963	Arterial disorder
Potentially leading to amputation	10060965	Arterial stenosis
Potentially leading to amputation	10061627	Amputation
Potentially leading to amputation	10061655	Arterial graft
Potentially leading to amputation	10061657	Arterial stent insertion
Potentially leading to amputation	10061666	Autonomic neuropathy
Potentially leading to amputation	10061815	Diabetic vascular disorder
Potentially leading to amputation	10062198	Microangiopathy
Potentially leading to amputation	10062255	Soft tissue infection
Potentially leading to amputation	10062585	Peripheral arterial occlusive disease
Potentially leading to amputation	10062599	Arterial occlusive disease
Potentially leading to amputation	10062610	Ischaemic limb pain
Potentially leading to amputation	10062932	Wound treatment
Potentially leading to amputation	10064250	Staphylococcal osteomyelitis
Potentially leading to amputation	10064601	Iliac artery occlusion
Potentially leading to amputation	10065237	Osteomyelitis bacterial
Potentially leading to amputation	10065239	Osteomyelitis fungal
Potentially leading to amputation	10065240	Wound infection bacterial
Potentially leading to amputation	10065242	Wound infection fungal
Potentially leading to amputation	10068653	Bone abscess
Potentially leading to amputation	10069379	Peripheral arterial reocclusion
Potentially leading to amputation	10072170	Skin wound
Potentially leading to amputation	10072557	Peripheral artery restenosis
Potentially leading to amputation	10072560	Peripheral endarterectomy
Potentially leading to amputation	10072561	Peripheral artery bypass
Potentially leading to amputation	10072562	Peripheral artery stent insertion
Potentially leading to amputation	10072563	Peripheral artery stenosis

Potentially leading to amputation	10072564	Peripheral artery thrombosis
Potentially leading to amputation	10074396	Penetrating atherosclerotic ulcer
Potentially leading to amputation	10075118	Subperiosteal abscess
Potentially leading to amputation	10075714	Vasculitic ulcer
Potentially leading to amputation	10076246	Spontaneous amputation

Appendix C Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA1c: Change from baseline at Week 18, (sotagliflozin 400 mg vs placebo)	ITT	ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by washout MI method under MNAR framework): treatment, randomization stratum (HbA1c / SBP/SU use at Week -1), and country as fixed effects, and baseline HbA1c value as a covariate	Tipping point analysis; ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by washout MI method under MNAR framework) ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by washout MI method under MNAR framework): excluding patients with randomization stratification error of HbA1c; use HbA1c (≤8.5%, >8.5%) factor instead of randomization stratum of HbA1c.	Subgroups: race, ethnicity, age, gender, baseline BMI, baseline HbA1c, baseline SBP, SU use at Week -1, baseline eGFR, duration of diabetes and country.	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit. By-visit summary and graph for patients who completed the 18-week randomized core treatment period.
Secondary endpoints					
HbA1c, FPG, body weight: Change from Baseline to Week 18; HbA1c and body weight: change from	ITT	ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by washout MI Method under MNAR	Tipping point analysis on HbA1c	Subgroups on HbA1c: race, ethnicity, age, gender, baseline	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
baseline to Week 52 SBP (for patients with baseline SBP ≥130 mmHg, all patients): Change from Baseline to Week 12		framework): treatment, randomization stratum (HbA1c / SBP/SU use at Week -1), and country as fixed effects, and baseline endpoint value as a covariate.		BMI, baseline HbA1c, baseline SBP, baseline eGFR and country.	baseline (±SE) and mean values (±SE) by visit.
Other endpoints					
Proportion of patients with HbA1c <6.5%, <7.0% at Week 18	ITT			No	By-visit summary and graphs of HbA_{1c} responders (<6.5%, <7%).
SBP (for patients with baseline SBP <130 mmHg, ≥130 mmHg), DBP (for patients with baseline DBP ≥ 80 mmHg, all patients), total insulin dose, 7-point SMBG, UACR, eGFR, UGE, UGCR: change from baseline	ITT	Summary statistics for observed values and changes from baseline by visit.	No	No	Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit as appropriate.
Proportion of patients requiring rescue for hyperglycemia		Summary statistics	No	No	KM plot; List of patients rescued
TRIM-D (total score and 5 domain scores): change from baseline		ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by washout MI Method under MNAR framework): treatment, randomization stratum (HbA1c /	No	No	Summary statistics for observed values and changes from baseline by visit.

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
		SBP/SU use at Week -1), and country as fixed effects, and baseline TRIM-D value as a covariate.			

SAFETY ANALYSES

Endpoint	Analysis Population	Primary analysis	Supportive Analysis	Subgroup analysis	Other analyses
Hypoglycemia	Safety	Follow safety guidelines Number (%) of patients with any hypoglycemia, severe hypoglycemia, documented symptomatic hypoglycemia during TEAE period of 18-week randomized core treatment period and entire 52-week double-blind treatment period, and incidence rates in 100 patient-years.		Severe hypoglycemia or documented symptomatic hypoglycemia by subgroups: race, age, gender, SU use at Week -1	KM plot time to first event of severe hypoglycemia or documented symptomatic hypoglycemia Summary of frequency/events of documented symptomatic hypoglycemia by hour during the TEAE period Documented symptomatic hypoglycemia maybe presented by <54 mg/dL (3.0 mmol/L) as appropriate.
Adverse Events	Safety	Follow safety guidelines	No	Common TEAEs by subgroups: race, age, gender, SU use at Week -1, baseline SBP, baseline eGFR	
Clinical laboratory data	Safety	Follow safety guidelines	Descriptive	No	No
Vital signs	Safety	Follow safety guidelines	Descriptive	No	No
ECG, Physical examination	Safety	Follow safety guidelines	Frequency summary	No	No

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
CGM sub-study primary endpoint					
Percentage of time within the target glucose range of 70 to 180 mg/dL over 24 hours: Change from baseline to Week 19, (sotagliflozin 400 mg vs placebo)	CGM	ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by washout MI method under MNAR framework): treatment, randomization stratum (HbA1c / SBP/SU use at Week -1), and country as fixed effects, and baseline CGM percentage value as a covariate	No	No	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit.
CGM sub-study secondary endpoints					
Mean 24-hour glucose concentration, percentage of time within the glucose range of 70 to 140 mg/dL, CV of glucose concentrations over 24 hours: change from baseline to Week 19; AUC of plasma glucose concentrations 2 hours after a standardized mixed meal, 2-hour PPG: change from baseline to Week 18	CGM	ANCOVA (with missing values imputed by retrieved dropouts imputation method or by washout MI Method under MNAR framework): treatment, randomization stratum (HbA1c / SBP/SU use at Week -1), and country as fixed effects, and baseline endpoint value as a covariate.	No	No	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit.
CGM sub-study other endpoints					

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Percentage of time over 24 hours with glucose levels >140 mg/dL, >180 mg/dL, >250 mg/dL, <70 mg/dL, <54 mg/dL, 70-180 mg/dL (diurnal, nocturnal period); AUC of glucose concentrations over 24 hours >140 mg/dL, >180 mg/dL, >250 mg/dL, <70 mg/dL, <54 mg/dL; MAGE, SD of glucose levels within and between days: change from baseline	CGM	Summary statistics for observed values and changes from baseline by visit.	No	No	Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit as appropriate.
Percentage of patients with ≥ 1 episode of hypoglycemia with CGM values < 70 mg/dL for ≥ 10 minutes.	CGM	Summary statistics	No	No	No

Appendix D Study flow chart

MAIN STUDY FLOW CHART

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

	Screening Period					Double-Blind Treatment Period[a]										FU Period
	Screen - ing	Run-in (Lantus titration, single-blind placebo Run-in)				No titration of Lantus (except for safety)							Lantus titration permitted			
VISIT	**1**	**2**	**3☎[b]**	**4☎[b]**	**5**	**6**	**7☎**	**8**	**9☎**	**10**	**11**	**12**	**13**	**14**	**15**	**16[c]**
Week	**-6**	**-4**	**-3**	**-2**	**-1**	**0**	**2**	**4**	**6**	**8**	**12**	**18**	**26**	**39**	**52**	**54**
Day (window [days])	**-42**	**-28 (±3)**	**-21 (±2)**	**-14 (±2)**	**-7 (±2)**	**1 (-)**	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**378 (±3)**
Diet & exercise instruction		X			X	X							X		X	
Instruction on basic GU hygiene & hydration					X	X		X		X	X	X	X	X	X	
Interactive response technology (IRT) contact	X	X				X		X		X	X	X	X	X	X	X
Randomization						X										
Dispense glucose meter, Beta-hydroxybutyrate (BHB) meter		X														
Dispense glucose test strips and BHB strips		X				X		X		X	X	X	X	X	X	
Measurement of capillary BHB at the site						X		X		X		X	X	X	X	
Dispense diary	X	X				X		X		X	X	X	X	X	X	
Collect/review diary		X			X	X		X		X	X	X	X	X	X	X
Instruction on diabetic ketoacidosis symptoms, glucose testing		X			X	X		X		X	X	X	X	X	X	
Dispense IMP and Lantus		X				X		X		X	X	X	X	X		
IMP and Lantus accounting & compliance					X	X		X		X	X	X	X	X	X	

	Screening Period					Double-Blind Treatment Period[a]										FU Period
	Screen - ing	Run-in (Lantus titration, single-blind placebo Run-in)				No titration of Lantus (except for safety)							Lantus titration permitted			
VISIT	**1**	**2**	**3☎[b]**	**4☎[b]**	**5**	**6**	**7☎**	**8**	**9☎**	**10**	**11**	**12**	**13**	**14**	**15**	**16[c]**
Week	**-6**	**-4**	**-3**	**-2**	**-1**	**0**	**2**	**4**	**6**	**8**	**12**	**18**	**26**	**39**	**52**	**54**
Day (window [days])	**-42**	**-28 (±3)**	**-21 (±2)**	**-14 (±2)**	**-7 (±2)**	**1 (-)**	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**378 (±3)**
Review results of SMBG and recommend Lantus dose adjustments as necessary[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record results of a 7-point SMBG[h]						X						X			X	
12-lead ECG[i]	X					X							X			
Laboratory Assessments[j]																
FPG[k]	X					X		X		X	X	X	X	X	X	
BHB						X		X		X		X	X	X	X	
HbA1c	X				X	X		X		X	X	X	X	X	X	
Clinical Chemistry[l]	X				X	X		X		X	X	X	X	X	X	X
Hematology	X					X					X		X	X	X	
Fasting lipids						X						X			X	
Pregnancy test (WOCBP)[m]	X					X		X		X	X	X	X	X	X	
FSH and/or estradiol as needed[m]	X															
Plasma concentration[n]								X				X	X		X	
Markers of calcium metabolism[o]						X							X			

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

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

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

c Two weeks after the last dose of IMP.

d Height to be measured only at Screening.

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

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

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

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

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

j All laboratory assessments occur prior to dose of double-blind IMP (when applicable).

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

l Clinical chemistry includes amylase and lipase: please see the list in Table 4 in the protocol.

m Serum pregnancy testing only at Screening; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to beginning the Run-in Phase for all women of childbearing potential (WOCBP, Appendix A). Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations. For women of non-reproductive potentials (Appendix A), follicle-stimulating hormone [FSH] and/or estradiol levels should be tested in case the definition of postmenopausal or premenopausal can't be satisfied, eg, no medical documents of hysterectomy or cessation of menses without an alternative medical cause is < 12 months.

n Plasma concentration samples for sotagliflozin and sotagliflozin-3-O-glucuronide collected on Weeks 4 18, 26, and 52 may be drawn with the other laboratory assessments but MUST be collected before administration of IMP.

o All patients will have lab assessments for markers of calcium metabolism. The markers of calcium metabolism include: serum calcium, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum phosphorus, and serum parathyroid hormone.

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

q Patients will collect overnight urine at Weeks 0, 12, 26, 52 and 54. Patients will be instructed to bring triplicate first of the day voids. Urinary albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine) and glucose will be assessed. The urine before sleep will be discarded and the urine during sleep and the first morning urine (after getting up) will be collected.

[redacted]

t Patient Reported Outcomes (PROs): Patient Qualitative Assessment of Treatment (PQAT) to be administered to approximately 70 English-speaking patients at Week 18 and 52; Treatment Related Impact Measure - Diabetes (TRIM-D) to be administered to all patients included in the study at Screening, Baseline, and Weeks 18, 26, 39, and 52.

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

CGM SUB-STUDY FLOW CHART

	Screening period					Double Blind Treatment Period											FU period
	Scr	Run-in Lantus titration, single-blind placebo				No titration of Lantus (except for safety)								Lantus titration permitted			
VISIT	**1**	**2**	**3☎**	**4☎**	**5**	**6**	**7☎**	**8**	**9☎**	**10**	**11**	**12A[a]**	**12[b]**	**13**	**14**	**15**	**16**
Week	**-6**	**-4**	**-3**	**-2**	**-1**	**0**	**2**	**4**	**6**	**8**	**12**	**17**	**18**	**26**	**39**	**52**	**54**
Day (window [days])	**-42**	**-28 (±3)**	**-21 (±2)**	**-14 (±2)**	**-7 (±2)**	**1 (-)**	**14 (±3)**	**28 (±3)**	**42 (±3)**	**56 (±3)**	**84 (±3)**	**119 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**378 (±3)**
CGM sub-study procedures					**Baseline CGM**							**Post-randomization CGM**					
Informed consent	X																
Eligibility	X					X											
CGM Training/Review					X							X					
Dispense CGM supplies					X							X					
CGM sensor insertion					X	X[c]						X	X				
CGM start					X							X					
Mixed-Meal Tolerance Test[d] (MMTT)						X							X				
Collect CGM supplies						X							X				
Upload CGM data to PC and review the quality report						X							X				

a Patients in the CGM sub-study will return to the study site for an additional visit (Visit 12A) at the end of Week 17 for insertion of CGM sensors for the post-randomization CGM assessment which will be conducted over Weeks 18 and 19. If a patient discontinued the IMP before Visit 12A, the post-randomization CGM and the MMTT will not be performed.

b For patients in the CGM sub-study, at Visit 12 the CGM sensors will be replaced for continuing the next 7-day CGM. For patients in the CGM sub-study, during Week 19 the total Lantus dose should remain stable (dose change less than ±10%, or less than ±4 Units, whichever is less). At the end of Week 19 patients will remove the CGM sensor at home and return the device and supplies (including sensor, transmitter, and receiver) to the study site in person or via mail using the provided packaging. Following removal of the CGM sensor, Lantus titration may resume as needed.

c Repeat 7-day CGM assessment conducted ONLY for patients who fail to provide adequately usable CGM data during the previous 7 days. In such a case, randomization will be postponed for 7 days and MMTT will be repeated.

d Mixed meal tolerance test is to be performed while CGM sensor is in place and functioning.