Official Title:	A Randomized, Double-blind, Placebo-controlled Monotherapy in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin as Monotherapy in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control
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Lexicon Pharmaceuticals, Inc.

Protocol No.: EFC14833

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin as Monotherapy in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control

Covance Study ID: 000000150524

STATISTICAL ANALYSIS PLAN

Version: 3.0
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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.

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List of abbreviations and definition of terms

ACR:	albumin-creatinine ratio
AESI:	adverse events of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
BMI:	body mass index
BUN:	blood urea nitrogen
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CPK:	creatine phosphokinase
CV:	cardiovascular
DBP:	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
EMA:	European Medicines Agency
EOSI:	events of special interest
FPG:	fasting plasma glucose
GCR:	glucose-creatinine ratio
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
IRT:	Interactive Response Technology
ITT:	intent-to-treat
KM:	Kaplan-Meier
LDH:	Lactic acid dehydrogenase
LDL-C:	low density lipoprotein cholesterol
LLT:	lower level term
MACE:	Major adverse cardiovascular events
MAR:	Missing at random
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation
MM:	mixed meal
MNAR:	missing not at random

NIMP:	noninvestigational medicinal product
NTX:	N-terminal telopeptide
P1NP:	type 1 procollagen N-terminal
PCSA:	Potentially Clinically Significant Abnormality
PD:	pharmacodynamic
PK:	pharmacokinetic
PPG:	postprandial glucose
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	preferred term
PTH:	Parathyroid hormone
SAE:	serious adverse events
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SOC:	system organ class
T2D:	type 2 diabetes mellitus
TC:	total cholesterol
TEAE:	treatment-emergent adverse event
TG:	triglycerides
UGE:	Urinary glucose excretion
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary
β-CTX-1:	beta-C-terminal telopeptide

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group stratified study. Under the original version of the protocol, patients were randomly assigned 1:1 to the following 2 treatment groups

- Sotagliflozin 400 mg
- Placebo

The protocol was amended to include an additional dose group of sotagliflozin 200 mg after enrollment had commenced. Under Amendment 1, patients are to be randomly assigned 1:1:1 to the following 3 treatment groups

- Sotagliflozin 400 mg
- Sotagliflozin 200 mg
- Placebo

All patients will have a Screening Period comprised of an up to 2-week Screening Phase and a 2-week, single-blind placebo Run-in Phase prior to randomization. Following randomization, patients will have a 26-week double-blind Treatment Period, and a 4-week post-treatment Follow-up period (patients who prematurely discontinue the study treatment are expected to continue in the study).

At the end of the screening period, eligible patients will be centrally randomized (using permuted block randomization schedule) via an Interactive Response Technology (IRT) in a 1:1:1 ratio (1:1 ratio in the initial randomization) to 1 of the 3 treatment groups (2 treatment group in the initial randomization). The randomization will be stratified by hemoglobin A1c (HbA1c) at the screening visit (≤8%, >8%) and mean systolic blood pressure (SBP) at the screening visit (<130 mmHg, ≥130 mmHg).

It is anticipated to randomize a total of approximately 376 patients. This number includes patients randomized under the original protocol, and the patients to be randomized under Amendment 1.

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 on HbA1c reduction at Week 26 in patients with type 2 diabetes mellitus (T2D) who have inadequate glycemic control on diet and exercise.

1.2.2 Secondary objectives

- To compare sotagliflozin 400 mg versus placebo for:
  - Change from Baseline in 2-hour postprandial glucose (PPG) following a mixed meal (MM) at Week 26
  - Change from Baseline in fasting plasma glucose (FPG) at Week 26
  - Change from Baseline in body weight at Week 26,
  - Change from Baseline in SBP at Week 12 for patients with baseline SBP ≥130 mmHg,
  - Change from Baseline in SBP at Week 12 for all patients,
  - Proportion of patients with HbA1c <6.5%, <7.0% at Week 26
- To compare sotagliflozin 200 mg versus placebo for:
  - Change from Baseline in HbA1c at Week 26
  - Change from Baseline in 2-hour PPG following a MM at Week 26
  - Change from Baseline in body weight at Week 26,
  - Change from Baseline in SBP at Week 12 for all patients.
- To evaluate the safety of sotagliflozin 400 mg and 200 mg doses versus placebo

1.2.3 Other objectives

- To compare sotagliflozin 400 mg and 200 mg doses versus placebo with respect to change from Baseline for the following endpoints:
  - Urine albumin-creatinine ratio (ACR)
  - Urinary glucose excretion (UGE) and urine glucose-creatinine ratio (GCR)
  - Estimated glomerular filtration rate (eGFR)
  - Reduction in body weight by ≥2%, ≥5%, and ≥10%
- To compare sotagliflozin 200 mg versus placebo for:
  - Change from baseline in FPG at Week 26
  - Change from baseline in SBP at Week 12 for patients with Baseline SBP ≥130 mmHg
  - Proportion of patients with HbA1c <6.5%, <7.0% at Week 26
- To compare sotagliflozin 400 mg and 200 mg doses with placebo for change from Baseline in SBP at Week 26 for all patients and for patients with Baseline SBP ≥130 mmHg
- To compare sotagliflozin 400 mg and 200 mg doses with placebo in the use of rescue medications for hyperglycemia
- To assess plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite in each sotagliflozin treatment group.

1.3 DETERMINATION OF SAMPLE SIZE

In the original version of the protocol, the sample size/power calculations were performed based on the primary variable, change in HbA1c from baseline to Week 26. Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 120 patients per arm would have 95% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

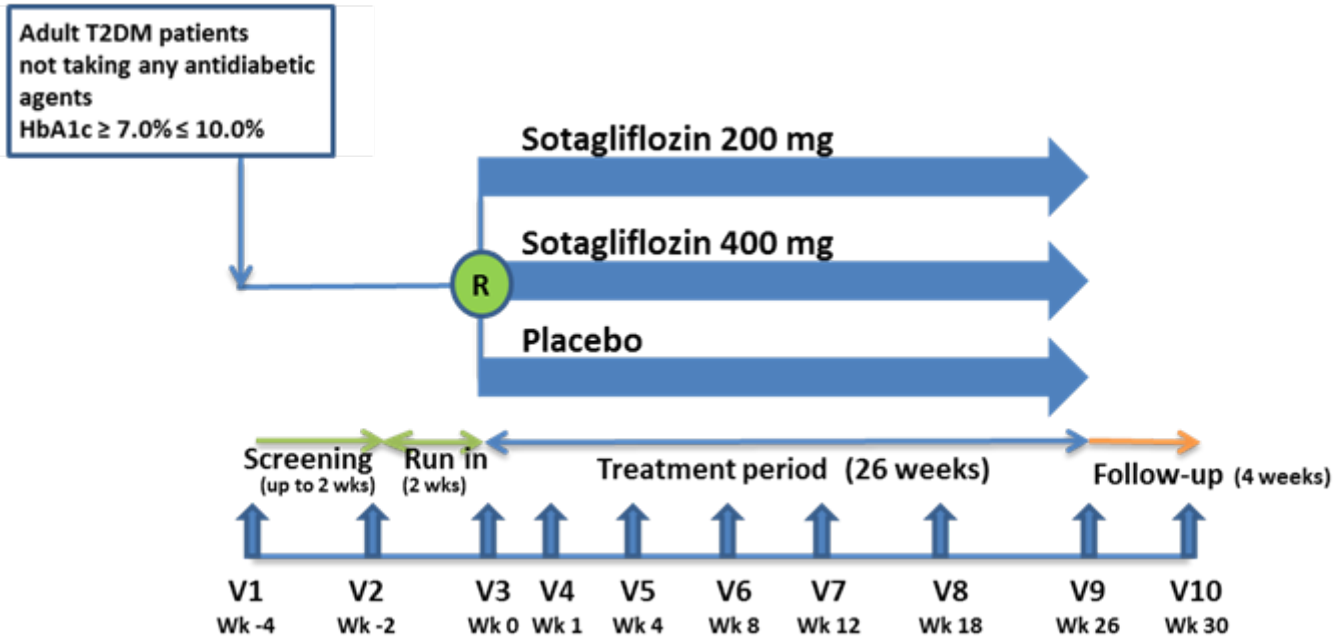
In Amendment 1, the sample size/power has been recalculated to account for the addition of the sotagliflozin 200 mg treatment group after enrollment had commenced. Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 100 patients per arm will have

- 94% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo, and
- 84% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 200 mg and placebo.

As a result, the total number of patients will include:

- 76 patients randomized (1;1) under the original protocol, balanced between placebo and sotagliflozin 400 mg, and
- Approximately 300 patients to be randomized (1:1:1) under Amendment 1, balanced among placebo, sotagliflozin 200 mg and sotagliflozin 400 mg doses.

1.4 STUDY PLAN



The study flowchart can be found in Appendix E.

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 Dec 7, 2016 under the original protocol. The first patient under Amendment 1 was enrolled on Oct 4, 2017. There are no planned interim analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	11-Apr-2017	[redacted]	[redacted]
1	11-Apr-2017	[redacted]	[redacted]
2	19-Dec-2017	Urgent coronary revascularization not adjudicated by CEC to be consistent with CV outcome trials	Urgent coronary revascularization not included in adjudication related analyses.

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	19-Dec-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
2	19-Dec-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.
2	19-Dec-2017	The effect in body weight considered more closely associated with the planned indication.	the order of secondary objectives / endpoints / multiplicity adjustment updated

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN (SAP)

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	30-May-2018	[redacted]	[redacted]
1	30-May-2018	[redacted]	[redacted]
1	30-May-2018	Randomization suspended under the original protocol	76 patients randomized under the original protocol
1	30-May-2018	As a result of the Amendment 1	Sensitivity analyses comparing sotagliflozin 400 mg versus placebo under Amendment 1 performed and presented for primary and secondary efficacy endpoints
1	30-May-2018	Urgent coronary revascularization not adjudicated by CEC to be consistent with CV outcome trials	Urgent coronary revascularization not included in adjudication related analyses **
1	30-May-2018	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	30-May-2018	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. **

SAP version number	Date approved	Rationale	Description of statistical changes
1	30-May-2018	The effect in body weight considered more closely associated with the planned indication.	The order of secondary objectives / endpoints / multiplicity adjustment updated **
1	30-May-2018	Clarification on EOSI renal events	Details specified on renal events to be consistent with outcome studies in Section 2.1.4.2.
1	30-May-2018	[redacted]	[redacted]
1	30-May-2018	[redacted]	[redacted]
2	07-Jun-2019	[redacted]	[redacted]
2	07-Jun-2019	For clear and concise presentation	Sensitivity analyses on sotagliflozin 400 mg versus placebo under Amendment 1 not to be presented
2	07-Jun-2019	Wording change to be consist with CEC charter	"Heart failure leading to hospitalization" changed to "Heart failure requiring hospitalization"
2	07-Jun-2019	MedDRA version and dictionary were updated	MedDRA version updated to v22.0; list of PTs for selected EOSI updated
2	07-Jun-2019	Number of iterations for multiple imputation changed	Number of iterations for multiple imputation was changed from 10000 to 2000
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]
3	This version	Assess robustness of the ITT-based analyses	Identify possible need to conduct sensitivity analyses for PK anomalies

*Change made in Protocol Amendment 1 dated 11-Apr-2017.

**Change made in Protocol Amendment 2 dated 19-Dec-2017.

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.

Baseline safety and efficacy parameters are presented along with the summary statistics for 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 visit,
- Randomization strata of HbA1c (≤8%, >8%) at screening visit (data from IRT),
- Mean SBP at screening visit,
- Randomization strata of mean SBP (<130 mmHg, ≥130 mmHg) at screening visit (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,
- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes – Year of birth,
- Baseline diabetic microvascular complications (Yes, No) [ie, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, diabetic peripheral neuropathy (sensory or motor), diabetic autonomic neuropathy, diabetic foot infection],
- Baseline urine ACR 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 SGLT2) and until the end of the study are to be reported in the electronic case report form (e-CRF).

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

Except for SGLT2 inhibitors, any approved medication(s) including oral antidiabetic drugs or insulin can be prescribed to treat the hyperglycemia at the discretion of the investigator. 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 antidiabetic agents, including oral or injectable antihyperglycemic agents other than the IMP is not allowed before the rescue therapy
- Systemic use of glucocorticoids is not allowed for more than 10 consecutive days (topical, ophthalmic, nasal spray or inhaled applications are allowed)
- Initiation of any weight loss drugs (eg, phentermine, orlistat)
- Investigational medicinal products in any other clinical study
- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin) are not allowed for rescue.

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

Reduction of digoxin dose should be considered because sotagliflozin acts as a weak P-gp inhibitor and increases systemic exposure to digoxin.

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

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

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

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, urine ACR, UGE, urine GCR, serum creatinine, and eGFR are measured/calculated in a central laboratory (see study flowchart in). Body weight, SBP and DBP (see Section 2.1.4.5) 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.

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 26 in HbA1c (%).

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- Comparison of sotagliflozin 400 mg versus placebo for,
  - Change from Baseline to Week 26 in 2-hour PPG following a MM
  - Change from Baseline to Week 26 in FPG
  - Change from Baseline to Week 26 in body weight
  - Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg
  - Change from Baseline to Week 12 in SBP for all patients
  - Proportion of patients with HbA1c <6.5%, <7.0% at Week 26

- Comparison of sotagliflozin 200 mg versus placebo for,
  - Change from Baseline to Week 26 in HbA1c
  - Change from Baseline to Week 26 in 2-hour PPG following a MM
  - Change from Baseline to Week 26 in body weight
  - Change from Baseline to Week 12 in SBP for all patients.

2.1.3.3 Other efficacy endpoint(s)

Comparison of sotagliflozin 400 mg and 200 mg doses versus placebo for,

- Change from Baseline to Week 12 in SBP for patients with baseline SBP <130 mmHg
- Changes from Baseline to Week 12 in diastolic blood pressure (DBP)
- Proportion of patients achieving SBP <130 mmHg for those with Baseline SBP ≥130 mmHg
- Proportion of patients achieving DBP <80 mmHg for those with Baseline DBP ≥80 mmHg
- Change from Baseline in:
  - Urine ACR, UGE, and urine GCR
  - Serum creatinine
  - eGFR
- Proportion of patients with reduction in body weight by ≥2%, ≥5%, and ≥10% from Baseline
- Change from Baseline to Week 26 in SBP for all patients and for patients with Baseline SBP ≥130 mmHg
- Proportion of patients requiring rescue for hyperglycemia

Comparison of sotagliflozin 200 mg versus placebo for,

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

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.

- 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 information" page as those documented as,

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

2. 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 information" page as those documented as,

1. To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
2. To the question "Were Symptoms Present", ticked "Yes", and
3. 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 information" page as those documented as,

1. To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
2. To the question "Were Symptoms Present", ticked "No", and
3. 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 information" page as those documented as,

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

4. 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 information" page as those documented as,

1. To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance"
2. To the question "Were Symptoms Present", ticked "Yes", and
3. 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:

- Major adverse cardiovascular events (MACE [cardiovascular death, myocardial infarction, or stroke]) and other specific cardiovascular (CV) 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 cancer)
- 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 "eGFR decrease", OR (2b) positively adjudicated by CEC: Yes to the question "Does the subject meet the criteria of CKD progression".
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

AE Grouping	Criteria
	(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 C
Urinary tract infections	PTs in Appendix C
Clinically relevant volume depletion and events related/possibly related to volume depletion	PTs in Appendix C
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 C
Venous thrombotic events	PTs in Appendix C
Malignancies of special interest	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 C Renal cell cancer: PTs in Appendix C Pancreatic cancer: PTs in Appendix C Bladder cancer: PTs in Appendix C
EOSI AE leading to an amputation	

AE Grouping	Criteria
Adverse event 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 C

* 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 an amputation: not an EOSI per individual protocol; analyzed due to their relevance to lower limb complication and amputations as a requirement from health authorities.

2.1.4.3 Deaths

The deaths observation period are per the observation periods defined above.

- 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, amylase, lipase and lipid profile) 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 collected at designated visits (see study flowchart in Appendix E). 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.
- Markers of Intestinal Transit and Absorption: Vitamins: B6, B12, K, E and A, Serum folate, and Ferritin
- Markers of bone and calcium metabolism
  - Calcium,
  - 25-hydroxyvitamin D,
  - 1,25-dihydroxyvitamin D,
  - Phosphorus,
  - Parathyroid hormone (PTH),
  - Markers of bone resorption: N-terminal telopeptide (NTX), beta-C-terminal telopeptide (β-CTX-1),
  - Marker of bone formation: type 1 procollagen N-terminal (P1NP)

Urine samples will be collected at designated visits (see study flowchart in Appendix E). 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
- Urine markers of bone and calcium metabolism: calcium and phosphorus.
- Urine albumin, calcium, glucose and creatinine

Serum glucose, UGE, calculated urine ACR and calculated urine GCR will be presented as efficacy parameters in Section 2.4.4. For creatinine and 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 E 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 9 (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 3 (Randomization) and Visit 9 (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 concentration of sotagliflozin and its 3-O-glucuronide metabolite in the sotagliflozin group.

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 have 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 (see Appendix A for details on the mapping of inclusion and exclusion criteria under the original protocol and Amendments)
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who have completed the 26-week double-blind treatment period as scheduled
- Patients who did not complete the 26-week double-blind treatment period as scheduled and the reasons for permanent treatment discontinuation
- Patients who have completed the study as scheduled
- Patients who did not complete the study as scheduled 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 Screening (≤8.0%, >8.0%) and mean SBP (<130, ≥130 mmHg)] 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 double-blind treatment period separately (see Section 2.5.4). A listing of these patients, along with the reason for discontinuation of treatment, study completion status and the reason for discontinuation study, will be provided.

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
- Safety population
- PK population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. 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

2. 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.

As described in Section 1.3, 76 patients were randomized 1:1 to receive sotagliflozin 400 mg or placebo under the original protocol and approximate 300 patients are to be randomized 1:1:1 to receive sotagliflozin 400 mg, sotagliflozin 200 mg, or placebo under Amendment 1. To ensure an unbiased comparison, the statistical analysis is planned so as to compare each sotagliflozin dose group with its matching placebo (1:1) within the same randomization, that is, sotagliflozin 400 mg versus placebo pooled under the original protocol and Amendment 1, and sotagliflozin 200 mg versus placebo under Amendment 1 only.

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, that is, sotagliflozin 400 mg versus placebo under the original protocol and Amendment 1, and sotagliflozin 200 mg versus placebo under Amendment 1.

2.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least one dose of double-blind IMP (regardless of the amount of treatment administered). Patients will be analyzed according to the treatment actually received, that is, sotagliflozin 400 mg versus placebo under the original protocol and Amendment 1, and sotagliflozin 200 mg versus placebo under Amendment 1.

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP 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 kits taken [400 mg or 200 mg])
- When a patient is exposed to both sotagliflozin 400 mg (treatment kits) and 200 mg (treatment kits), the patient will be analyzed in the sotagliflozin 200 mg group
- 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 treatment. 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 observations available, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the count and percentage of patients in each treatment group.

Parameters will be summarized based on the randomized population analyzed in the treatment group to which they were randomized, that is, sotagliflozin 400 mg versus placebo under the original protocol and Amendment 1, and sotagliflozin 200 mg versus placebo under Amendment 1. 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 (ie, randomized patients) 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.

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,
- >182 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 percentage 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 will be provided, as well as numbers and percentages of patients with (0, 20%], and >20% of days under-planned dose.

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 26 will be analyzed by an Analysis of Covariance (ANCOVA) model using HbA1c values measured at baseline and Week 26 (observed or imputed). The missing data at endpoint will be imputed by multiple imputation (MI) methods in 2 parts 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 26 (or Week 12 for SBP) 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 26 (or Week 12 for SBP) visit but have the measurement for the endpoint (ie, 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 retrieved dropout patients in each treatment group 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 method 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 26 (or Week 12 for SBP) visit but have the measurement for the endpoint is < 5 in any treatment groups (ie, an insufficient number of 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 26 (or Week 12 for SBP) will be imputed by the washout Multiple Imputation (MI) method under the missing not at random (MNAR) framework.

Missing endpoint data at the Week 26 (or Week 12 for SBP) in all treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg and placebo) are imputed from a model estimated from patients in the placebo group who have the endpoint data available.

For patients in the sotagliflozin group with missing data at Week 26 (or Week 12 for SBP), 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 26 (or Week 12 for SBP). 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 26 (or Week 12 for SBP) 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 2000 times to generate multiple data sets with complete data. Other details of the imputation procedures such as the seed

number and sort ordering are specified in the SAS programs. The HbA1c change from baseline to Week 26 will be derived from observed and imputed HbA1c values at Week 26.

To impute the missing values for the primary endpoint, the imputation for the two doses of sotagloflozin will be performed separately. To compare sotagliflozin 400 mg and placebo, imputations will be performed using the pooled dataset of patients randomized to placebo and sotagliflozin 400 mg under the Original protocol plus the Amendment 1. However, for the placebo and sotagliflozin 200 mg, patients randomized to the two doses under the protocol Amendment 1 will be used for imputing missing values.

Each of the completed datasets after the imputation will be analyzed using the Analysis of Covariance (ANCOVA) model for the placebo and sotagliflozin 400 mg patients randomized under the original protocol and Amendment 1, or for the placebo and sotagliflozin 200 mg patients randomized under the protocol Amendment 1. The model will include treatment groups (sotagliflozin 400 mg and placebo; or sotagliflozin 200 mg, and placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed factors, and baseline HbA1c value as a covariate. Results from each analysis will be combined using Rubin's formula to provide the adjusted mean change in HbA1c from Baseline to Week 26 for sotagliflozin 400 mg and placebo (under the original protocol and Amendment 1) and for sotagliflozin 200 mg and placebo (under the Amendment 1), as well as the between-group differences and its associated 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 400 mg group and had no HbA1c data at Week 26 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. The tipping point is the penalty level, at which the magnitude of efficacy reduction in patients without HbA1c data at Week 26 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 for superiority will be provided for each penalty level. The steps to perform the tipping point analysis 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 26 in the sotagliflozin 400 mg group will be penalized by adding a penalty δ (eg, δ = 0.1%) in each complete dataset,
3. Change from baseline at Week 26 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 formula,
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 in Step 2) for the patients randomized to placebo and sotagliflozin 200 mg under the protocol Amendment 1.

The tipping point analysis will be performed for the primary variable only if that variable (change from baseline to Week 26 in HbA1c) is statistically significant at $\alpha = 0.05$ (2-sided).

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

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 as those who have no detectable levels of active study drug or metabolite in their samples (ie, Below Limit of Quantification or BLOQ). 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/m^2),
- Baseline HbA1c (≤8.0%, >8.0%),
- Baseline HbA1c (≤8.5%, >8.5%),

- Baseline mean SBP (<130 mmHg, ≥130 mmHg),
- Baseline eGFR (≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73m^2 [Normal])
- Country.

The treatment effect (sotagliflozin 400 mg versus placebo under the original protocol and Amendment 1 or sotagliflozin 200 mg versus placebo under the Amendment 1) across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 26 in HbA1c in the ITT population, and using the same MI method as applied to the primary analysis. The ANCOVA model will include treatment groups (sotagliflozin 400 mg and placebo; or sotagliflozin 200 mg and placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), 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 or sotagliflozin 200 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 mean SBP category), 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 26-week double-blind 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 stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), 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. Otherwise, the

washout imputation method will be used according to the criterion described in Section 2.4.1. After the imputation, each of the complete datasets will be analyzed by an ANCOVA model.

- To compare sotagliflozin 400 mg versus placebo under the original protocol and Amendment 1, the ANCOVA model will include treatment groups (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed effects, and the corresponding baseline value as a covariate.
- To compare sotagliflozin 200 mg versus placebo under Amendment 1, the ANCOVA model will include treatment groups (sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed effects, and the corresponding baseline value as a covariate.

For the analysis of SBP in patients with baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included in the ANCOVA model. Results from each complete dataset will be combined using Rubin's formula to provide the adjusted mean change from Baseline to Week 26 (or Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing each sotagliflozin dose group vs its corresponding placebo group) and the 95% CI for the difference.

Sensitivity analyses will be performed to compare sotagliflozin 200 mg and placebo under Amendment 1 for selected other endpoints such as FPG, SBP and HbA1c responders.

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 with baseline SBP ≥140 mmHg.

The categorical secondary efficacy variables of HbA1c <6.5%, <7% at Week 26 will be analyzed respectively using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of HbA1c (≤8.0%, >8.0%), and randomization stratum of SBP (<130 mmHg, ≥130 mmHg). The proportion in each treatment group will be provided, as well as the difference between each sotagliflozin group and its corresponding placebo group with the associated 2-sided 95% CI. For HbA1c responders at Week 26 (<6.5%, <7% respectively), all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 26 will be treated as non-responders. 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.

Sensitivity analyses

Tipping point analysis, similar to what is described in Section 2.4.4.1, will be performed to examine the robustness of the treatment effect of sotagliflozin 200 mg on HbA1c, using the same imputation method and ANCOVA model as described above for comparing sotagliflozin 200 mg versus placebo under Amendment 1. The tipping point analysis will be performed only if the secondary endpoint change from baseline to Week 26 in HbA1c for comparing sotagliflozin 200 mg versus placebo is statistically significant at $\alpha = 0.05$ (2-sided).

Similar to what is described in Section 2.4.4.1, the treatment effects (sotagliflozin 200 mg versus placebo under Amendment 1) across the subgroups (see Section 2.4.4.1) will be estimated for the change from Baseline to Week 26 in HbA1c in the ITT population, and using the same imputation method described above for comparing sotagliflozin 200 mg versus placebo under Amendment 1 in the full analysis dataset. The ANCOVA model will include treatment groups (sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), 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 200 mg versus placebo) with 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.

2.4.4.3 Analyses of other efficacy endpoints

The analysis of other endpoints (see Section 2.1.3) will be descriptive with no formal testing. Summary statistics at scheduled visits based on observed value will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time as appropriate.

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. A list of patients who used rescue therapy will also be provided (see Section 2.5.4).

Urine ACR will be log-transformed at patient level. Summary statistics of urine ACR 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 urine ACR from baseline.

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

The analysis of the 2-hour PPG endpoint 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 26 time points. These Time 0 adjusted values will be used to derive the Week 26 minus Baseline scores, which will serve as the measure of interest for comparative purposes.

2.4.4.4 Multiplicity issues

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

Once the primary variable (change from Baseline to Week 26 in HbA1c) 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 not to be statistically significant at $\alpha=0.05$ (2-sided).

- Comparing sotagliflozin 400 mg versus placebo,
  - Change from Baseline to Week 26 in 2-hour PPG following an MM
  - Change from Baseline to Week 26 in FPG
  - Change from Baseline to Week 26 in body weight
  - Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg
  - Change from Baseline to Week 12 in SBP for all patients
  - Proportion of patients with HbA1c <7.0% at Week 26
- Comparing sotagliflozin 200 mg versus placebo,
  - Change from Baseline to Week 26 in HbA1c
  - Change from Baseline to Week 26 in 2-hour PPG following an MM
  - Change from Baseline to Week 26 in body weight
  - Change from Baseline to Week 12 in SBP for all patients.

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

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group.

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 B].
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including 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 during the TEAE period by treatment group in 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 efficacy Section 2.4.4. For creatinine and eGFR, PCSA summaries will be presented in safety Section 2.4.5 while descriptive summaries in efficacy 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. 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 closest value prior to the last dose administration.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% CIs may be provided, if relevant.
- Selected safety analyses will be summarized by age, gender, racial subgroups, and other 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. 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).

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 (see Section 2.5.4).

Documented symptomatic hypoglycemia maybe presented by ≤3.9 mmol/L (≤70 mg/dL) and <3.0 mmol/L (<54 mg/dL) 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), 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 SAE 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 SAE regardless of relationship and related to IMP, 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

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

CV 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 eCRF "GFR decrease",
ii. recorded in eCRF "Renal Event – Dialysis",
iii. identified as "Renal transplant" in eCRF "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 and LLT 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). These PTs in Table 3 were requested by the European Medicines Agency (EMA)/ Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report, 9 February 2017). 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 may potentially lead to 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, death, 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 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 2.1.4.4.

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 applicable visit or study assessment (screening, baseline, postbaseline time points, last on-treatment value) by treatment group.

The incidence of PCSAs (list provided in Appendix B) at any time during the TEAE period will be summarized for each laboratory test 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 applicable visit or study assessment (baseline, post-baseline time points, 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 and 26 and 2 hours 30 minutes post-dose at Week 26) 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]

2.5 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)

Urine ACR

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

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

Urine GCR

Standard unit: Urine GCR = Urine Glucose (mmol/L) / Urine Creatinine (mmol/L)

Conventional unit: Urine GCR = Urine Glucose (mg/dL) / Urine Creatinine (mg/dL)

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 & washout imputation method or by the control-based copy reference 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 3 (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 e-CRF "Treatment Status Library" page.

If the date of last administration reported on the e-CRF "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 / Measurements for analyses

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 2.1.4.4 and vital signs in Section 2.1.4.5).

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 4) will be applied to re-allocate a post-baseline unscheduled measurement to a scheduled measurement.

Table 4 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 1 (Visit 4)	7	2 to 17
Week 4 (Visit 5)	28	18 to 41
Week 8 (Visit 6)	56	42 to 69
Week 12 (Visit 7)	84	70 to 104
Week 18 (Visit 8)	126	105 to 153

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 26 (Visit 9)	182	≥154

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, for parameters with PCSA defined based on normal range, local results will only be used in the PCSA summary if they are accompanied by a local laboratory normal range. For parameters with PCSA not defined based on normal range, local results will be used in the PCSA summary as appropriate.

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 the 26-week double-blind treatment period.

Patients who did not experience any event during the 26-week double-blind treatment period are considered censored observations. For time to treatment discontinuation/rescue therapy, 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 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

None.

7 LIST OF APPENDICES

Appendix A Mapping of inclusion and exclusion criteria under the original protocol and Amendments

Order	Original Protocol	Amendment 1	Amendment 2	CSR Display
1	I01			I01
2	I02			I02
3	E01	E01		E01/E01A1
4	E02			E02
5	E03			E03
6	E04			E04
7	E05			E05
8	E06	E06		E06/E06A1
9	E07			E07
10	E08			E08
11	E09	E09	E09	E09/E09A1/E09A2
12	E10	E10	E10	E10/E10A1/E10A2
13	E11	E11		E11/E11A1
14	E12			E12
15	E13			E13
16	E14		E14	E14/E14A2
17	E15	E15		E15/E15A1
18	E16	E33		E16/E33A1
19	E17	E16		E17/E16A1
20	E18	E17		E18/E17A1
21	E19			E19
22	E20	E18		E20/E18A1
23	E21	E19		E21/E19A1
24	E22	E20		E22/E20A1
25	E23	E21		E23/E21A1
26	E24	E22	E22	E24/E22A1/E22A2
27	E25	E23		E25/E23A1
28	E26	E24		E26/E24A1
29	E27	E25		E27/E25A1
30	E28	E26		E28/E26A1
31	E29	E27		E29/E27A1
32	E30			E30
33	E31	E28		E31/E28A1
34	E32	E29		E32/E29A1
35	E33		E33	E33/E33A2
36	E34			E34
37	E35	E30	E30	E35/E30A1/E30A2
38		E31		E31A1
39		E32		E32A1
40			E34	E34A2

Appendix B 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.
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)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling

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

Parameter	PCSA	Comments
	≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	
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	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		

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

Parameter	PCSA	Comments
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.
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	

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

Parameter	PCSA	Comments
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
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	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

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

Parameter	PCSA	Comments
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix C 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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
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 D Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA_{1c}: Change from baseline at Week 26, (sotagliflozin 400 mg vs placebo)	ITT	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR framework): treatment, randomization stratum (HbA1c / SBP at screening), and country as fixed effects, and baseline HbA1c value as a covariate, under the original protocol and Amendment 1	Tipping point analysis; ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR framework) under original protocol and Amendment 1	Subgroups: race, ethnicity, age, gender, baseline BMI, baseline HbA1c, baseline SBP, baseline eGFR 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 excluding measurments after rescue therapy.
Secondary endpoints					
HbA_{1c}, 2-hour PPG, FPG, body weight: Change from Baseline to Week 26; SBP (for patients with baseline SBP ≥130 mmHg, all patients): Change from Baseline to Week 12	ITT	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI Method under MNAR framework): treatment, randomization stratum (HbA1c / SBP at screening), and country as fixed effects, and baseline HbA1c value as a covariate, comparing sotagliflozin 400 mg vs placebo under the original protocol and Amendment 1, and comparing sotagliflozin 200 mg vs placebo	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR framework) comparing sotagliflozin 200 mg (for selected other endpoints) vs placebo under Amendment 1; Tipping point analysis on HbA1c.	Subgroups on HbA1c: race, ethnicity, age, gender, baseline BMI, baseline HbA1c, baseline SBP, baseline eGFR 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.

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
		under Amendment 1.			
Proportion of patients with HbA1c <6.5%, <7.0% at Week 26	ITT	CMH method stratified on randomization strata (HbA_{1c} / SBP at screening), comparing sotagliflozin 400 mg vs placebo under the original protocol and Amendment 1, and comparing sotagliflozin 200 mg vs placebo under Amendment 1.	CMH method stratified on randomization strata (HbA_{1c} / SBP at screening): excluding patients with baseline HbA_{1c} values <6.5% (for <6.5% responders) or <7% (for <7% responders) respectively	No	By-visit summary and graphs of HbA_{1c} responders (<6.5%, <7%). By-visit frequency summary and graphs of HbA_{1c} responders (<6.5%, <7%) excluding patients with baseline HbA_{1c} values <6.5% or <7% respectively.
Other endpoints					
SBP (for patients with baseline SBP <130 mmHg), DBP, Urine ACR, UGE, and urine GCR, Serum creatinine, eGFR: 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, with reduction in body weight by ≥2%, ≥5%, and ≥10% from Baseline; achieving SBP <130 mmHg with baseline SBP ≥130 mmHg; achieving DBP <80 mmHg with baseline DBP ≥80 mmHg	ITT	By-visit frequency summary	No	No	By-visit graphical presentation as appropriate
Proportion of patients requiring rescue for hyperglycemia		Summary statistics	No	No	KM plot; List of patients rescued

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, and incidence rates in 100 patient-years.		Severe hypoglycemia or documented symptomatic hypoglycemia by subgroups: race, age, gender	KM plot time to first event of severe hypoglycemia or documented symptomatic hypoglycemia 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, 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

Appendix E Study flow chart

	Screening Period		Double Blind Treatment Period[a]							Follow-up[b]
	Screening	Run-in								
VISIT	1	2	3 (Randomization)	4	5	6	7	8	9	10
Week	Up to -4	-2	0 Baseline	1	4	8	12	18	26	30
Day (window [days])		(-7/+3)	1	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	210 (±3)
Informed consent	X									
Inclusion criteria	X									
Exclusion criteria	X		X							
Demographics	X									
Medical/Surgical History	X									
Medication History	X									
Body weight, height[c]	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X
Physical Exam:										
complete	X								X	
abbreviated		X	X	X	X	X	X	X		X
Diet & exercise instruction		X	X						X	
Instruction on basic genitourinary hygiene & hydration		X	X	X	X	X	X	X	X	
Interactive response technology (IRT) contact	X	X	X		X	X	X	X	X	X
Randomization			X							
Dispense glucose meter		X								
Dispense diary	X	X	X	X	X	X	X	X	X	
Collect/review diary		X	X	X	X	X	X	X	X	X
Instruction on diabetic ketoacidosis symptoms and glucose testing			X	X	X	X	X	X	X	

	Screening Period		Double Blind Treatment Period[a]							Follow-up[b]
	Screening	Run-in								
VISIT	1	2	3 (Randomization)	4	5	6	7	8	9	10
Week	Up to -4	-2	0 Baseline	1	4	8	12	18	26	30
Day (window [days])		(-7/+3)	1	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	210 (±3)
Dispense IMP		X	X		X	X	X	X		
IMP accounting & compliance			X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Self-monitored blood glucose[e]		X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X		X						X	
Standard mixed meal tolerance test[g]			X						X	
Laboratory testing[h]										
FPG	X		X	X	X	X	X	X	X	
HbA1c	X		X		X	X	X	X	X	
Chemistry (including amylase and lipase)	X		X		X	X	X	X	X	X
Hematology	X		X				X		X	
Fasting lipids	X		X		X	X	X	X	X	
Pregnancy test (WOCBP)[i]	X		X		X	X	X	X	X	
Serum follicle stimulating hormone and estradiol (menopausal women only)[i]	X									
Plasma concentration[j]					X			X	X	
Markers of intestinal transit & absorption[k]			X						X	X
Markers of bone & calcium metabolism[l]			X						X	
Urinalysis (dipstick and microscopy)[m]	X		X						X	

	Screening Period		Double Blind Treatment Period[a]							Follow-up[b]
	Screening	Run-in								
VISIT	1	2	3 (Randomization)	4	5	6	7	8	9	10
Week	Up to -4	-2	0 Baseline	1	4	8	12	18	26	30
Day (window [days])		(-7/+3)	1	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	210 (±3)
Urine albumin, calcium, glucose & creatinine			X	X	X	X	X	X	X	X
[redacted]										
Evaluate for glycemic rescue				To be assessed and reported throughout the treatment period						
Hypoglycemia	To be assessed and reported throughout the study									
AEs/SAEs/AESIs/EOSIs	To be assessed and reported throughout the study[p]									

a If a patient discontinues treatment with IMP early during the Treatment Period, the patient will have a Premature EOT Visit, and a Follow-up Visit 4 weeks after the last dose of IMP. However, every effort will be made to have all patients return to the site for all scheduled visits, in particular the Week 26 Visit. If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status. If a patient discontinues (or completes) treatment and study at the same time, a single visit will be performed using the procedure normally planned for the EOT visit.

b Four weeks after the last dose of IMP.

c Height to be measured only at screening

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

e See protocol Section 9.2.1.6 for details of SMBG measurements. Glucose meters used for SMBG display results as plasma glucose concentration. Patients should measure their fasting plasma glucose at least 3 times per week (including on day of each on-site study visit).

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

g Postprandial plasma glucose will be assessed by central laboratory at Baseline and 2 hours after consuming a standard mixed liquid breakfast meal and via a mixed meal tolerance test (MMTT) on Day 1 and Week 26. If a patient withdraws from IMP early, please see protocol Section 10.3.4.

h All laboratory assessments occur prior to first dose of double-blind IMP. The first dose of double-blind IMP occurs after samples for the mixed liquid meal have been collected. All visit dates will be scheduled based on the date of randomization with a ±3 days visit window allowed during the treatment period. Serum chemistry parameters (clinical chemistry [including amylase and lipase], hematology, and other blood parameters) are listed in protocol Table 2.

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

j Plasma concentration samples (ie, for sotagliflozin and sotagliflozin-3-O-glucuronide) on Weeks 4 and Week 18 should be drawn with the other laboratory assessments. For Week 26, plasma concentration samples should be drawn at predose and 2 hours 30 minutes, immediately after the respective glucose assessments during the MMTT. PK samples (except the 2 hours 30 minute sample during the MMTT) MUST be collected before administration of IMP. The date and time of the last intake of IMP prior to visits where PK samples are taken should be recorded by the patient in the patient diary. Patients should be reminded of this at visits preceding PK time points to ensure these details are captured. In the case of Premature IMP discontinuation, PK samples should not be drawn at the Premature EOT visit, nor at any subsequent visits.

k The markers of intestinal transit and absorption include vitamins B6, B12, K, E, and A, serum folate, and ferritin.

l Markers of bone and calcium metabolism include: serum and urinary calcium, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum and urinary phosphorus, serum parathyroid hormone, markers of bone resorption (serum NTX, serum β-CTX-1), and bone formation (serum P1NP).

m Urinalysis includes urine dipstick and microscopy. Dipstick includes assessment of specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. Microscopy includes detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment. In the event of abnormal urinalysis findings suspicious of urinary tract infection, urine culture should be performed. Positive urine culture determination will be based upon the criteria of the reporting laboratory.

[redacted]

p All serious adverse events (SAEs), adverse events (AEs), AEs of special interest (AESIs), and Events of Special Interest (EOSIs) will be collected starting with signing informed consent and continue until the end of the study. All AEs that occur during treatment should be followed until study completion (or until patients leave the study) or until the event has resolved, the condition has stabilized, or the patient is lost to follow-up. All patients will have a follow-up contact 4 weeks after the last dose of IMP to collect safety information.