Official Title: A 26-week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study with a 78-week Extension Period to Evaluate the Efficacy and Bone Safety of Sotagliflozin in Patients 55 years or Older with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

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Lexicon Pharmaceuticals, Inc.

Protocol No.: EFC15294

A 26-week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Phase 3 Study with a 78-week Extension Period to Evaluate the Efficacy and Bone Safety of Sotagliflozin in Patients 55 years or Older with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

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Statistical Analysis Plan

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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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VERSION HISTORY

Version Status	Version Date
Final 1.0	26 June 2018
Final 2.0	11 October 2018
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse events of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic class
BMD:	bone mineral density
BMI:	body mass index
BUN:	blood urea nitrogen
BW:	body weight
CEC:	clinical endpoint committee
CI:	confidence interval
CK:	creatinine phosphokinase
CMH:	Cochran-Mantel-Haenszel
CSR:	clinical study report
CV:	cardiovascular
DBP:	diastolic blood pressure
DCCT:	diabetes control and complications trial
DILI:	drug-induced liver injury
DKA:	diabetic ketoacidosis
DMC:	data monitoring committee
DXA:	dual-energy X-ray absorptiometry
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration
EOSI:	events of special interest
EOT:	end of treatment
FPG:	fasting plasma glucose
GLP-1:	glucagon-like peptide-1
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
iPTH:	parathyroide hormone
ITT:	intent-to-treat
KM:	Kaplan-Meier
LDH:	lactic acid dehydrogenase

LDL-C:	low density lipoprotein cholesterol
LLT:	lower level term
LOCF:	last-observation-carried-forward
MACE:	major adverse cardiovascular events
MDRD:	modification of diet in renal disease
MedDRA:	medical dictionary for regulatory activities
MI:	multiple imputation
MMRM:	mixed-effect model with repeated measures
MNAR:	missing not at random
NIMP:	non-investigational medicinal product
NTX:	N-terminal telopeptide
OC:	observed case
P1NP:	type 1 procollagen N-terminal
PCSA:	potentially clinically significant abnomality
PD:	pharmacodynamics
PK:	pharmacokinetics
PT:	preferred term
PTH:	parathyroid hormone
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SERMs:	selective estrogen receptor modulators
SGLT2:	sodium-glucose cotransporter-type2
SOC:	system organ class
T2D:	type 2 diabetes mellitus
TB:	total bilirubin
TC:	total cholesterol
TEAE:	treatment emergent adverse event
TG:	triglycerides
UACR:	urinary albumin to creatinine ratio
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 (single-blind Run-in Phase), placebo-controlled, parallel-group stratified study.

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 104-week double-blind Treatment Period (26-week double-blind core treatment period followed by a 78-week double-blind extension treatment period), and a 2-week post-treatment Follow-up period. Patients who prematurely discontinue the study treatment are expected to continue in the study to continue performing their respective study assessments, especially HbA1c and BMD, until the time of the last visit planned in the protocol.

Patients will be centrally randomized (using permuted block randomization schedule) via an Interactive Response Technology (IRT) in a 1:1:1 ratio to 1 of the 3 treatment groups:

- Sotagliflozin 400 mg.
- Sotagliflozin 200 mg.
- Placebo.

The randomization will be stratified by hemoglobin A1c (HbA1c) at the screening visit (≤8.5%, >8.5%) and sex (Male, Female).

It is anticipated to randomize a total of approximately 360 patients (120 per treatment group).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo with respect to HbA1c reduction at Week 26 in patients with Type 2 diabetes mellitus (T2D) who have inadequate glycemic control on diet and exercise only or with a stable antidiabetes regimen.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To compare the effects of sotagliflozin 400 mg and 200 mg versus placebo with respect to the percent change from Baseline to Week 26 in Bone Mineral Density (BMD) (lumbar spine, total hip, and femoral neck) measured by dual-energy X-ray absorptiometry (DXA) (key secondary safety objective).
- To demonstrate the superiority of sotagliflozin 400 mg versus placebo on:
  - Change from Baseline to Week 26 in body weight (BW),
  - Change from Baseline to Week 26 in fasting plasma glucose (FPG),
  - Change from Baseline to Week 12 in systolic blood pressure (SBP) for all patients,
  - Proportion of patients with HbA1c <7.0% at Week 26.
- To demonstrate the superiority of sotagliflozin 200 mg versus placebo with respect to:
  - HbA1c reduction from Baseline to Week 26,
  - Change from Baseline to Week 26 in BW,
  - Change from Baseline to Week 26 in FPG,
  - Change from Baseline to Week 12 in SBP for all patients,
  - Proportion of patients with HbA1c <7.0% at Week 26.
- To evaluate the safety of sotagliflozin 200 mg and 400 mg compared with placebo over the 104 weeks of treatment.

1.2.3 Other objectives

Other objectives of this study are to compare the effects of sotagliflozin 200 mg and 400 mg versus placebo with respect to:

- Change from Baseline to Weeks 52 and 104 in HbA1c.
- Change from Baseline to Weeks 52 and 104 in FPG.
- Change from Baseline to Weeks 52 and 104 in BW.
- Proportion of patients with HbA1c <7.0% at Weeks 52 and 104.
- Proportion of patients starting rescue therapy for hyperglycemia during the 104 weeks of treatment.
- Change from Baseline to Weeks 26 and 104 in SBP for all patients.
- Change from Baseline to Weeks 12, 26, and 104 in SBP for the subsets of patients with Baseline SBP ≥130 mmHg and <130 mmHg, respectively.

- Change from Baseline to Weeks 12, 26, and 104 in diastolic blood pressure (DBP) for all patients and the subsets of patients with Baseline DBP ≥80 mmHg and <80 mmHg, respectively.
- Changes from Baseline to Weeks 26, 52, and 104 in total body fat mass and total lean mass measured by DXA.
- Changes from Baseline to Weeks 26, 52, and 104 in serum estradiol (only for women).
- Changes from Baseline to Weeks 26, 52, and 104 in urinary albumin to creatinine ratio (UACR).
- Changes from Baseline to Weeks 26, 52, and 104 on estimated glomerular filtration rate (eGFR).

1.3 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations were performed based on the primary variable of change from Baseline to Week 26 in HbA1c (%).

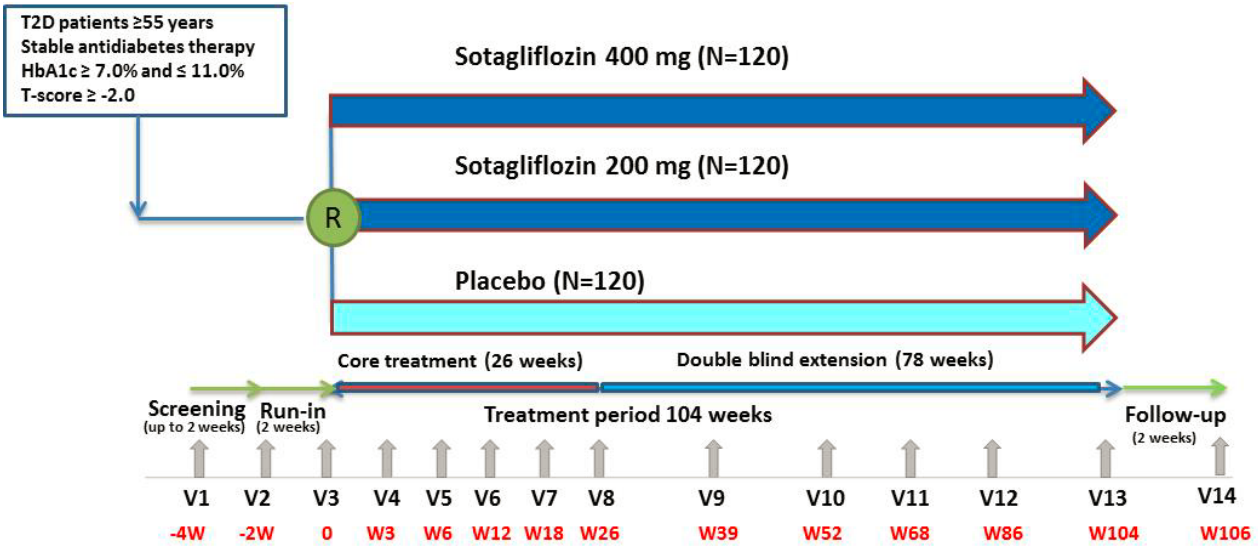
Assuming a common standard deviation (SD) of 1.2% and using a 2-sided test at a 0.05 α-level, 360 patients (120 patients per arm) will have 97% power to detect a treatment difference of -0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

This sample size will also allow to exclude a decline in BMD from Baseline of >2% with a 95% power, assuming a missing rate of 30% and an SD of 3.5%.

The total sample size will be approximately 360 patients to be randomized (120 in sotagliflozin 200 mg group, 120 in sotagliflozin 400 group, and 120 in placebo group).

Calculations were made using East 6.4 software.

1.4 STUDY PLAN



The study flowchart can be found in Appendix D.

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 statistical section of the protocol was not changed in an amendment.

The first patient was enrolled on 14-Mar-2018.

There are no planned interim analyses.

The study analysis will be conducted in 2 steps. The first step analysis is planned when all patients have been randomized and have their data at the minimum up to Week 26 collected and validated. The second step will be conducted at the end of the study.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 1 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	29-Jun-2018	Clarification on EOSI renal events	Details specified on renal events to be consistent with outcome studies in Section 2.1.4.2.
1	29-Jun-2018	[redacted]	[redacted]
1	29-Jun-2018	[redacted]	[redacted]
2	11-Oct-2018	Update to be consistent with protocol	In multiplicity issues, remove "Proportion of patients with HbA1c <7.0% at Week 26" for both sotagliflozin 400 mg and 200 mg groups.
3	This version	[redacted]	[redacted]
3	This version	Wording change to be consistency with CEC charter	"Heart failure leading to hospitalization" changed to "Heart failure requiring hospitalization"
3	This version	MedDRA dictionary updated	MedDRA version updated to V22.0; list of PTs for selected EOSI updated
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]
3	This version	[redacted]	[redacted]

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 average of all values before the first dose of double-blind IMP for patients randomized and exposed or before randomization for patients who were randomized but never exposed to IMP.

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

Demographic characteristics

Demographic characteristics to be summarized are:

- Age (years) derived as: Year of informed consent - Year of birth.
- Age categories (≥55 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 (≤8.5%, >8.5%) at screening visit (data from IRT).
- Randomization strata of Gender (Male, Female) (data from IRT).
- Mean SBP at screening visit.
- Mean SBP categories (<130 mmHg, ≥130 mmHg).
- 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).
- Baseline BMD T-score (lumbar spine, total hip, or femoral neck).
- Mean serum 25-hydroxyvitamin D at screening visit.
- Country.

Disease characteristics at screening or Baseline

Disease history includes:

- Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25.
- Duration of diabetes categories: (<10, ≥10 years).
- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes – Year of Birth.
- Prior antidiabetic medication (in monotherapy or combination):
  - No antidiabetic therapy,
  - Insulin (alone or with OADs),
  - SU and/or glinide (alone or with other OADs),
  - Metformin (alone or with OADs other than SU and glinide),
  - OADs other than SU, glinide and metformin,
  - GLP-1 receptor agonist.
- Prior antidiabetic medication:
  - No antidiabetic therapy,
  - Insulin (alone or with other antihyperglycemic agents),
  - SU and/or glinide (alone or with other non-insulin antihyperglycemic agents),
  - Other (non-insulin antihyperglycemic agents except SU and glinide).
- Baseline diabetic microvascular complications (Yes, No) (ie, diabetic retinopathy, diabetic neuropathy and diabetic nephropathy, diabetic peripheral neuropathy (sensory or motor), diabetic autonomic neuropathy, and diabetic foot infection).
- Baseline UACR categories (<30 mg/g [Normal], ≥30 to <300 mg/g [Microalbuminuria], and ≥300 mg/g [Macroalbuminuria]).
- eGFR at screening (mL/min/1.73m^2).
- eGFR categories at screening (<15 mL/min/1.73m^2 [End stage renal disease], ≥15 to <30 mL/min/1.73m^2 [Severe decrease in GFR], ≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73m^2 [Normal]).
- Prior antihypertensive medication identified by therapeutic class as agents acting on the renin-angiotensin system, beta blocking agents, diuretics (a sub-category: loop diuretics identified by pharmacological class as high-ceiling diuretics), calcium channel blockers, and antihypertensives according to World Health Organization-Drug Dictionary (WHO-DD).

Medical or surgical history

Medical history and medical findings include:

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

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

Any technical details related to computation, dates and imputation 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) pages.

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 investigational medicinal product (IMP) intake. 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 first administration of double-blind IMP to the date of last administration of double-blind IMP + 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.

Background therapy consisting of a stable antidiabetes regimen in monotherapy or combination therapy (including oral antidiabetes medications, insulin, or GLP-1 agonists) for more than 12 weeks are considered as noninvestigational medicinal products (NIMP).

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 and thiazolidinediones, 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, the following medications are prohibited:

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

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

- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin) and thiazolidinediones (eg. pioglitazone, rosiglitazone) are not allowed for rescue.
- Systemic use of glucocorticoids for more than 10 consecutive days within 90 days prior to the Screening Visit (Note: topical, intra-articular, ophthalmic, nasal spray, or inhaled applications are allowed).
- Investigational medication products in any other clinical study
- Modification of antihypertensive medication before Week 12 is not allowed unless for safety reasons.
- Initiation of any weight loss drugs (eg, phentermine, orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, liraglutide).
- Initiation of medication known to affect bone mass or modify the risk of fractures:
  - Bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, teriparatide, denosumab, strontium ranelate, growth hormone,
  - Androgen deprivation therapy,
  - Aromatase inhibitors,
  - Anticonvulsants (eg. carbamazepine, phenytoin and phenobarbital),
  - Hormone replacement therapy (systemic or transdermal) that includes estrogens or androgens.

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 pharmacokinetics (PK) or pharmacodynamics (PD) of the IMP or confound interpretation of the study endpoints are allowed as needed following discussion between the Investigator and the Sponsor/CRO.

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.

It is recommended that patients receiving calcium or vitamin D at the time of screening, or initiating supplementation during the study, should maintain as stable a dose as possible throughout the study. Patients receiving replacement therapy with estrogen or testosterone for more than 24 months at the time of screening should also be advised to maintain stable dose for the duration of the study, unless if required 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, FPG, UACR, eGFR and serum estradiol are measured/calculated in a central laboratory (see study flowchart in Appendix D). 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)

The primary efficacy endpoint is the change from Baseline to Week 26 in HbA1c (%) comparing sotagliflozin 400 mg versus placebo.

2.1.3.2 Secondary efficacy/safety endpoint(s)

2.1.3.2.1 Key Secondary safety endpoint(s)

The key secondary safety endpoint is the percent change from Baseline to Week 26 in BMD (lumbar spine, total hip, and femoral neck).

Analysis of key secondary safety endpoints are detailed in Section 2.4.5.1 .

2.1.3.2.2 Secondary efficacy endpoint(s)

The main secondary efficacy endpoints are:

- Change from Baseline to Week 26 in HbA1c (sotagliflozin 200 mg only).
- Change from Baseline to Week 26 in BW.
- Change from Baseline to Week 26 in FPG.
- Change from Baseline to Week 12 in SBP for all patients.
- Proportion of patients with HbA1c <7.0% at Week 26.

2.1.3.3 Other efficacy endpoint(s)

The other secondary efficacy endpoints are:

- Change from Baseline to Weeks 52 and 104 in HbA1c.
- Change from Baseline to Weeks 52 and 104 in FPG.
- Change from Baseline to Weeks 52 and 104 in BW.
- Proportion of patients with HbA1c <7.0 % at Weeks 52 and 104.
- Proportion of patients starting rescue therapy during the 104 weeks of treatment.
- Change from Baseline to Weeks 26 and 104 in SBP for all patients.
- Change from Baseline to Weeks 12, 26, and 104 in SBP for the subsets of patients with Baseline SBP <130 mmHg and ≥130 mmHg, respectively.
- Change from Baseline to Weeks 12, 26, and 104 in DBP for all patients and the subsets of patients with Baseline DBP ≥80 mmHg and <80 mmHg, respectively.
- Change from Baseline to Weeks 26, 52, and 104 in total body fat mass and total lean mass measured by DXA.
- Change from Baseline to Weeks 26, 52, and 104 in serum estradiol (only for women).
- Change from Baseline to Weeks 26, 52, and 104 in UACR.
- Change from Baseline to Weeks 26, 52, and 104 in eGFR.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events, hypoglycemia, adjudicated bone fractures, and other safety information, such as BMD data measured by DXA, clinical laboratory data (including bone turnover markers and markers of calcium metabolism), vital signs, electrocardiogram (ECG), and physical examination, etc.

The following safety endpoints will be assessed throughout the 104 weeks of double-blind treatment:

- Adverse events, hypoglycemia (all, severe, and/or documented symptomatic hypoglycemia), EOSI, adverse events of special interest (AESI), AEs leading to discontinuation of IMP, SAEs, and deaths.
- Percent change from Baseline to Weeks 26, 52 and 104 in BMD (lumbar spine, total hip, and femoral neck).
- Proportion of patients with adjudicated bone fractures over 104 weeks.
- Proportion of patients with ≥3% decline in BMD at Week 104.
- Changes from Baseline in bone turnover markers to Week 26, 52, and 104 (serum bone resorption markers: N-terminal telopeptide of Type 1 collagen [NTX] and β-CTX-1; serum bone formation markers: P1NP and osteocalcin).

- Changes from Baseline in markers of calcium metabolism to Week 26, 52, and 104 (serum: calcium, phosphorus, magnesium, parathyroid hormone [iPTH], 25- hydroxyvitamin D and 1,25-dihydroxyvitamin D; urinary: calcium, phosphorus and magnesium).
- Clinical laboratory results, vital signs results, and 12-lead ECG.

Observation period

The observation period starts from the time when the patient gives informed consent and 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-bind 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-bind IMP. This epoch includes the 26-week double-blind core treatment period and the 78-week double-blind extension treatment period. The 26-week double-blind core treatment period is the time from the first administration of double-blind IMP to the last administration of double-blind IMP on or before Visit 8/Week 26 (or Day 182 if Visit 8/Week 26 date is missing).
- The **residual treatment** epoch is defined as the time from the last administration of the double-bind IMP up to 10 days (1 day for hypoglycemia) after the last administration of the double-bind IMP.

The treatment-emergent adverse event (TEAE) period will include both **treatment** and **residual treatment** epochs. (See the TEAE period for the 26-week core treatment period in Section 2.5.4).

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

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

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

2.1.4.1 Hypoglycemia

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

Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma.

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

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

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" 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" 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" 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" 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 TEAE 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 Medical Dictionary for Regulatory Activities (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 (DKA).
- Renal events, to include 50% decline in eGFR, end stage kidney disease, renal death.
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid cancer).
- 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 DKA.

Two independent committees will review safety events that require ongoing monitoring in a blinded manner. 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 2.

Table 2 – 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?"

AE Grouping	Criteria
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 m2 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 (eg, end date – start date+ 1 ≥90) as recorded in eCRF "Renal Event – Dialysis", OR (3b) positively adjudicated by CEC: Yes to the question ". Does the subject meet the criteria for ESRD".
Renal transplant *	(4) "Renal transplant" captured in eCRF "Other procedure form", where adjudication is not required. PTs of Renal transplant (10038533), Renal and pancreas transplant (10052278), Renal and liver transplant (10052279) based on MedDRA v22.0.
Renal death	(5) Renal death as positively adjudicated by CEC: "Death - Non-Cardiovascular (Renal)" as the primary cause of death
EOSI not adjudicated*	
Severe hypoglycemia	algorithm specified in Section 2.1.4.1 based on eCRF "Hypoglycemic Events"
Genital mycotic infections	PTs in Appendix B
Urinary tract infections	PTs in Appendix B
Clinically relevant volume depletion and events related/possibly related to volume depletion	PTs in Appendix B
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" [20000218] plus the following PTs (MedDRA v22.0): Gastroenteritis (10017888), Antidiarrhoeal supportive care (10055660), Enteritis (10014866), Enteritis leukopenic (10014877), Enterocolitis (10014893), Enterocolitis haemorrhagic (10014896)
Pancreatitis	PTs in Appendix B
Venous thrombotic events	PTs in Appendix B

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

* Search terms will be updated using the MedDRA version currently in effect at Covance at the time of database lock for EOSI identified by them.

* AE potentially leading to amputation: not one of EOSI defined in protocol, included and analyzed due to their relevance in regards to lower limb complications and amputations as an requirement from health authorities.

2.1.4.3 Deaths

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

- Death on-study: deaths occurring during the on-study observation period.
- Death on TEAE period: deaths occurring during the TEAE period.
- Death post-treatment: deaths occurring after the treatment-emergent adverse event period until the end of the on-study period.

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, amylase, lipase, lipide profile and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and conventional units when applicable.

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

- Hematology:
  - **Red blood cells and platelets**: hemoglobin, hematocrit, red blood cell, platelets count,
  - **White blood cells**: white blood cell, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry:
  - **Metabolism**: glucose (serum), creatine phosphokinase (CK),
  - **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, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB), 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 bone and calcium metabolism:
  - Calcium,
  - Phosphorus,
  - Magnesium
  - 25-hydroxyvitamin D,
  - 1,25-dihydroxyvitamin D,
  - 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), osteocalcin.

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

- Urine dipstick includes: specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase.
- Urine microscopy includes, but is not limited to: detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment.
- Urine albumin, calcium, phosphorus, magnesium and creatinine (24-hour urine collection).

Serum glucose, calculated UACR and serum estradiol (for women) will be presented as efficacy parameters in Section 2.4.4. For creatinine and calculated eGFR, Potentially Clinically Significant Abnormality (PCSA) summaries will be presented in the safety section while descriptive summaries in the efficacy section.

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

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

2.1.4.6 Physical examination

A complete physical exam will be performed at Visit 1 (Screening) Visit 8 (Week 26) and Visit 13 (Week 104). “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 2 (Run-in), Visit 8 (Week 26) and Visit 13 (Week 104). ECG status of “normal” or “abnormal” will be reported in the e-CRF as determined by the investigator.

2.1.4.8 Bone Mineral Density

Bone mineral density at lumbar spine, total hip, and femoral neck will be assessed in all patients using DXA. Baseline DXA scans for BMD assessment will be performed during run-in (between week -2 [Visit 2] and Baseline [Visit 3]) and centrally reviewed to confirm eligibility. To assess percent change from Baseline in BMD, post-Baseline DXA scans will be performed within 2 weeks prior to the on-site visits at week 26 (Visit 8), week 52 (Visit 10), and week 104 (Visit 13). In exceptional situations, if justified based on Investigator's assessment, the DXA scan can be performed up to a maximum of 7 days after the scheduled visit. All BMD assessments will be performed locally with central review.

2.2 DISPOSITION OF PATIENTS

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

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

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

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

- Screened patients.
- Run in patients: patients who has a run-in kit allocated and recorded in IRT database.
- Screen failure patients (including failures during run-in) and reasons for screen failure.
- Nonrandomized but treated patients.
- Randomized patients.
- Randomized but not treated patients.
- Randomized and treated patients.
- Patients who complete the 26-week double-blind core treatment period (see Section 2.5.4) as scheduled.
- Patients who did not complete the 26-week double-blind core treatment period as scheduled and the reasons for permanent treatment discontinuation.
- Patients who complete the 104-week double-blind entire treatment period as scheduled.
- Patients who did not complete the 104-week double-blind entire treatment period as scheduled and the reasons for permanent treatment discontinuation.
- Patients who complete the study as scheduled.

- Patients who did not complete the study as scheduled and the reasons for study discontinuation.
- Patients' end of study status at Week 26 (ongoing, discontinued) and corresponding end of 26-week core treatment status (ongoing, discontinued).
- Patients' end of study status (completed, not completed) and corresponding end of entire 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, , as well as number of patients randomized and treated, discontinued from study treatment, and discontinued from study for each treatment for overall patients and by 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 patient randomized but 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 (≤8.5%, >8.5%) and sex (Male, Female) 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 respectively will be provided for the 104-week double-blind entire treatment period only (see Section 2.5.4). A listing of these patients, along with the reason for discontinuation treatment, study completion status and the reason for discontinuation study, will be provided.

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 and efficacy defined in Section 2.3 will be summarized in a table by number of patients on the randomized population.

- Efficacy population: intent-to-treat (ITT) population.

- Safety 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 appendix.

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

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

2.3 ANALYSIS POPULATIONS

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

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

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

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

2.3.1 Efficacy populations

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

2.3.1.1 Intent–to-treat population

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

2.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who actually 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.

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.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

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

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

Medical/surgical history will be classified into primary system organ class (SOCs) and HLTs using MedDRA and will be summarized by treatment groups. Events will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on incidence in the overall treatment group.

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 anatomic therapeutic category (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 patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

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

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

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

2.4.3 Extent of investigational medicinal product exposure and compliance

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

2.4.3.1 Extent of investigational medicinal product exposure

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

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

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number of patients exposed, mean, SD, median, minimum, and maximum) during the 26-week core treatment period and 104-week entire treatment period, respectively. In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- 1 to 28 days.
- 29 to 56 days.
- 57 to 84 days.
- 85 to 126 days.
- 127 to 182 days.
- 183 to 364 days.
- 365 to 551 days.
- 552 to 728 days.
- >728 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 double-blind IMP 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 double-blind IMP 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 double-blind IMP 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 also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% of days under-planned dose administrations.

Cases of overdose (see study protocol for further details) will constitute AEs/SAEs and will be listed 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 (de facto estimand), unless otherwise specified.

Statistical testing will be performed for primary endpoint and secondary endpoints at Week 26 (or Week 12 for SBP). The superiority tests will be two-sided tests at nominal 5% significance level. All efficacy endpoints, other than primary and main secondary efficacy endpoints, will only be summarized by descriptive statistics without formal statistical testing.

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)

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 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 groups 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.

Each of the completed datasets after the imputation will be analyzed using the Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of sex (male, female), and country as fixed factors, and baseline value of the efficacy endpoint 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 (or Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg or sotagliflozin 200mg, respectively, versus placebo) and its associated 95% confidence interval (CI).

Sensitivity analyses

Tipping point analysis based on the same MI method as applied to 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 will be provided for each penalty level. The steps to perform the tipping point analysis comparing sotagliflozin 400 mg versus placebo are as follows:

1. Missing data will be imputed using same MI method as applied for 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 rule,
5. Steps 2 to 4 will be repeated with incremental penalty at δ (ie, δ, 2δ, 3δ …) until the p-value for treatment effect of sotagliflozin 400 mg compared to placebo estimated in Step 4 is >0.05.

The above tipping point analysis will be replicated to examine the robustness of the treatment effect of sotagliflozin 200 mg (ie, adding penalty to the sotagliflozin 200 mg group instead of sotagliflozin 400 mg group in Step 2).

The tipping point analysis will be performed on the ITT population. The tipping point analyses will be performed only if the corresponding primary or secondary endpoints (change from Baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg vs placebo, or comparing sotagliflozin 200 mg vs placebo) is statistically significant at $\alpha = 0.05$ (2-sided).

In addition 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.

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 (<65, ≥65 years),
- Gender (Male, Female).
- Baseline BMI level (<30, ≥30 kg/m²).
- 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]).
- Duration of diabetes (<10, ≥10 years).
- Prior antidiabetic medication [No antidiabetic therapy, Insulin (alone or with other antihyperglycemic agents), SU and/or glinide (alone or with other non-insulin antihyperglycemic agents), other (non-insulin antihyperglycemic agents except SU, and glinide)].
- Country.

The treatment effects (sotagliflozin 400 mg and sotagliflozin 200mg, respectively, versus placebo) 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, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of sex

(male, female), 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 and sotagliflozin 200 mg versus placebo) with SE and 95% CIs will be provided as appropriate across the subgroups. A forest plot of the results will also be presented.

In the case that the subgroup factor is identical or similar to a randomization strata factor (eg, baseline HbA1c category or sex), only the subgroup factor (as a single factor and/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 entire 104-week double-blind treatment period.

2.4.4.2 Analyses of secondary efficacy endpoints

For continuous secondary efficacy endpoints (see Section 2.1.3) with missing data at Baseline, missing data will be imputed using MI under the assumption of missing at random (MAR). Missing data at Baseline will be imputed using regression method that includes randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of sex (male, female) 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. After the imputation, each of the complete datasets will be analyzed by an ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of sex (male, female), and country as fixed effects, and baseline secondary endpoint value as a covariate.

Results from each complete dataset will be combined using Rubin's rule 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 treatment group difference (comparing each sotagliflozin group to placebo group) and the 95% CI for the between-group difference.

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 (±SE) and mean change 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.

Categorical endpoint of HbA1c <7% at week 26 will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of HbA1c (≤8.5%, >8.5%), and randomization stratum of sex (male, female). Proportion of HbA1c responders in each treatment group will be provided with the difference between each sotagliflozin group and placebo group and their associated 2-sided 95% CI. To determine whether a patient is HbA1c responder or not, all measurements at week 26 will be used regardless of discontinuation of IMP or initiation of rescue medication. Patients with no HbA1c measurement at week 26 will be treated as non-responders. Summary tables and graphs will be provided by treatment group at scheduled visit.

For between-group comparison for HbA1c <7% responder analysis, a sensitivity analysis will be performed by excluding patients with baseline HbA1c <7% using the same CMH test mentioned above. Similarly, by-visit summary based on above subset of patients may 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.

The number (%) of patients who used rescue therapy will be summarized by treatment group during the 26-week core (see Section 2.5.4) and the 104-week entire double-blind treatment periods. A KM curve for the time to first rescue therapy will be presented during the 26-week core treatment period and 104-week entire double-blind treatment period (see Section 2.5.4). The list of patients who used rescue therapy will also be provided.

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

Shift tables will be provided for UACR at Week 26 and Week 104 respectively using the pre-defined categories. That is, the number (%) of patients with progression from one category at Baseline to another category at Week 26 and Week 104 will be provided by treatment group. The pre-defined categories are, for UACR, <30 mg/g creatinine [Normal], ≥30 to <300 mg/g creatinine [Microalbuminuria], and ≥300 mg/g creatinine [Macroalbuminuria].

2.4.4.4 Multiplicity issues

To control the family-wise type I error, a hierarchical testing 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 body weight,
  - Change from Baseline to Week 26 in FPG,
  - Change from Baseline to Week 12 in SBP for all patients.
- Comparing sotagliflozin 200 mg versus placebo:
  - Change from Baseline to Week 26 in HbA1c,
  - Change from Baseline to Week 26 in body weight,
  - Change from Baseline to Week 26 in FPG,
  - 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.

In addition, no further multiplicity adjustment (split of alpha) is needed for multiple analyses (ie, first step and second step analyses see Section 3). The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect and all primary and secondary efficacy endpoints will be fully evaluable at the time of the first step analysis. Analyses beyond Week 26 will be descriptive.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. The safety data will be summarized for the 26-week core treatment period and the 104-week entire treatment period separately, unless otherwise specified.

The observation period defined in Section 2.1.4 is applicable in all safety analyses for classification of AEs, determination of treatment-emergent Potentially Clinically Significant Abnormality (PCSA) values and the last on-treatment value for laboratory, vital sign, BMD 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 last available value before the first dose of double-blind IMP. For creatinine and eGFR, the baseline value is defined as the average of all values before the first dose of double-blind IMP.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (Appendix A).
- PCSA criteria will determine which patients had at least one PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations, central laboratory/reading or local measurements (see Section 2.5.4). The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in TEAE period by treatment group on the safety population.
- For laboratory parameters cited in the protocol as efficacy endpoints (eg, HbA1c, plasma glucose, etc.), PCSA summaries will not be provided. These parameters will be summarized 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 for the 104-week entire treatment period. 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 for the 104-week entire treatment period. If this value is missing, the last on-treatment value will be the closest value prior to the last administration of IMP during the 104-week entire treatment period.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% confidence intervals may be provided, if relevant.
- Selected safety analyses will be summarized by age, gender, racial subgroups, and any pertinent subgroups (see details in Section 2.4.5.3 and Section 2.4.5.4).

2.4.5.1 Analyses of the Bone Mineral Density

Analysis of percent change from Baseline in BMD (lumbar spine, total hip, femoral neck) to Week 26, Week 52, and Week 104 will be performed on the safety population, using BMD measurements obtained during the study, regardless of IMP discontinuation and/or introduction of rescue therapy. No statistical significance tests will be performed.

All planned analyses will be performed at each location (lumbar spine, total hip, and femoral neck) separately.

Analysis of the key secondary safety endpoints of percent change from Baseline to Week 26, Week 52, and Week 104 respectively in BMD will be performed by an ANCOVA model using BMD values measured at Baseline and the corresponding time point (observed or imputed). The missing data at endpoint will be imputed by multiple imputation (MI) methods as detailed below.

Missing endpoint data at Week 26, Week 52, or Week 104 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 endpoint (Week 26, Week 52, or Week 104) but have the measurement for the endpoint (retrieved dropouts). The imputation model will include the randomization strata and the 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 (ie, ≥5 retrieved dropouts in each treatment group).

In addition, a sensitivity analysis using a pattern-based multiple imputation method will be performed. The imputation method will be implemented in 3 steps:

1. For missing data at Baseline, a monotone missingness method implemented in PROC MI with monotone regression option will be used to impute the missing data at Baseline. The imputation model will include the randomization strata and BMD measurements at Baseline.

2. In cases that a non-monotone missing data pattern occurs at the intermediate visits, these data points will be imputed using the Markov Chain Monte Carlo (MCMC) option in PROC MI to partially impute missing data at the intermediate visits in order to achieve a monotone missing pattern for all patients. The imputation model will include treatment, BMD measurements at Baseline, Week 26, Week 52, and Week 104.
3. Using the partially and monotone data sets from the MCMC of step 2, the rest of the missing data will be imputed using a sequential imputation approach. Given that the data sets have monotone missing data pattern, the approach will be to consider imputation on a visit (timepoint) by visit (timepoint) basis and conditioning on all visits (timepoints) data. The process will be to repeat, sequentially, in the order specified in the regression model, the imputation of missing values at each visit (timepoint). The imputation model will include treatment, measurements at Baseline, Week 26, Week 52, and Week 104 in the VAR statement.

A top line analysis to evaluate the efficacy will be conducted when all patients have either completed Week 26 or discontinued prior to Week 26.

The imputation model at Week 26 for the topline analysis will include treatment and measurement at Baseline, after missing baseline data imputation as described in step 1above.

The imputation method will generate multiple complete data sets. The change from Baseline to Week 26, Week 52, and Week 104 will be derived from observed and imputed BMD values.

The derived change from Baseline to each timepoint in each of the complete datasets will be analyzed by the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of sex (male, female), country as fixed effects, and baseline BMD value as a covariate.

Results from each complete data set will be combined using Rubin's rule to provide the adjusted mean change in BMD from Baseline to each timepoint (Week 26, Week 52, and Week 104) for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg or sotagliflozin 200mg vs placebo) and the 95% confidence interval (CI).

This sensitivity analysis will serve as the primary analysis at any timepoint if the number of patients who prematurely discontinue the IMP before the post-Baseline visit (Week 26, Week 52, or Week 104) with the visit data is not sufficient to perform a retrieved dropout analysis.

Descriptive analyses will be performed on the key safety endpoints to summarize the treatment effects across subgroups defined by the following baseline or screening factors:

- Age group (<65 years, ≥65 years).
- Duration of T2D (<10 years, ≥10 years).
- Sex (male, female).
- Baseline BMI level (<25; 25 to <35; ≥35 kg/m^2).
- Baseline eGFR (<45; 45 to <60; ≥60 mL/min/1.73 m^2).

The treatment effects (sotagliflozin 400 mg and sotagliflozin 200 mg versus placebo respectively) across the subgroups defined for each of these factors will be estimated for the percent change from Baseline to Week 26, Week 52, and Week 104 in BMD in the safety population, and using the same MI method as applied to each of the key safety endpoints, respectively.

The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of sex (male, female), subgroup factor, treatment-by-subgroup factor, and country as fixed effects, and baseline BMD value as covariate.

The adjusted estimates of treatment mean differences with SE and 95% CIs will be provided as appropriate across the subgroups (comparing each sotagliflozin group vs placebo group) with SE and 95% CIs will be provided as appropriate across the subgroups. A forest plot of the results will also be presented.

In the case that the subgroup factor is the sex only the subgroup factor (as a single factor and/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 (including number, mean, median, Q1, Q3, standard deviation, standard error, minimum and maximum) of BMD (lumbar spine, total hip, femoral neck) (baseline value, observed post-Baseline values, observed changes from Baseline and observed percent change from Baseline) will be provided at Week 26, Week 52 and Week 104 by treatment group. Graphical presentations will be used to examine trends over time using mean (±SE), mean change

from Baseline (±SE), and mean percent change from Baseline (±SE), at each of the scheduled visits (using OC).

The number (%) of patients with a percent change from Baseline in BMD ≥3% at Week 104 will be also summarized. The number (%) of patients will be summarized by visit for each T-score category: normal (T-score ≥-1.0); low bone density (T-score >-2.5 and <-1); osteoporosis (T-score ≤-2.5).

2.4.5.2 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 1) any hypoglycemia, 2) 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 event(s) per 100 patient-years (calculated as the number of patients with at least 1 event/ total exposure in 100 patient-years) and the total number of events per 100 patient-years (calculated as the total number of events / total exposure in 100 patient-years). Note: Note: here exposure in days is duration of treatment-emergent AE period, ie, duration of IMP treatment in days +1 (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, age group (≥55 to <65, ≥65 years), race (White, Black or African American, Asian, Other).

A KM curve will be provided by treatment group for the time to first severe hypoglycemia or documented symptomatic hypoglycemia during the TEAE period for the 104-week entire treatment period only (see Section 2.4.5).

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

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

2.4.5.3 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 present the number (n) and percentage (%) of patients experiencing an adverse event by SOC, HLGT, HLT, and PT, sorted by the internationally agreed order for SOCs and alphabetical order for HLGT, HLT and PT within the SOC. 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 26-week core treatment period and the 104-week entire treatment period respectively, 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 SOC.
- 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 similar other 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 incidence ≥2% in any treatment group) by primary SOC, HLGT, HLT and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- Common TEAEs (PTs with incidence ≥2% in any treatment group) will be provided as appropriate by primary SOC and PT and by demographic factors including gender, age group (≥55 to <65, ≥65 years), race (White, Black or African American, Asian, other), baseline SBP category (<130, ≥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]), prior antidiabetic medication [Insulin (alone or with other antihyperglycemic agents), SU and/or glinide (alone or with other non-insulin antihyperglycemic agents), Other (non-insulin antihyperglycemic agents except SU, and glinide)]. SOC will be sorted by the internationally agreed order and the PT by decreasing incidence within each SOC in the sotagliflozin 400 mg group, as described above.
- TEAEs (PTs with an incidence ≥5% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.

Analysis of all treatment emergent serious adverse event(s)

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

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

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the

internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of adverse events of special interest

The summaries of AESI will be presented for the 104-week entire treatment period only in the safety population.

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

The summaries of EOSI will be presented for the 104-week entire treatment period only in the safety population."

CV events, bone fracture and DKA

For EOSIs that are adjudicated (ie, deaths, myocardial infarction, stroke, and unstable angina requiring hospitalization, heart failure requiringhospitalization, 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", where adjudication is not required.

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 form "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 2 in Section 2.1.4.2; these PTs in Table 2 were requested by the European Medicines Agency/ Pharmacovigilance Risk Assessment Committee[EMA/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 amputation" represents the condition that commonly precedes amputation procedure, but not in all cases an amputation has occurred (as per the EMA/PRAC request).

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 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 sotagliflozin 400 mg group.

Listings

Supportive AE listings will be provided for all AEs, SAEs, and deaths, 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 TEAE; and 'P' for on-study post-treatment AE).

2.4.5.4 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, during TEAE period, poststudy).
- 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.

2.4.5.5 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(standard deviation), median, Q1, Q3, minimum and maximum) of all laboratory variables (central laboratory values and changes from Baseline, and/or percent change from Baseline [eg, lipid parameters])) will be calculated for each planned visit or study assessment (screening, Baseline, post-Baseline time point, last on-treatment) by treatment group.

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

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

In that case only the worsening of the worst case are presented.

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. The summary tables will include patients in the safety population that have at least one assessment performed during the TEAE period. When PCSA criteria are based on change from Baseline, patients must have non-missing baseline to be included in the summary. And when required by the definition of the abnormality, patients must also have available laboratory normal ranges.

A listing of patients with at least one post-Baseline measurement PCSA or out of normal range (when no PCSA is defined) will be provided and will display the patients' entire profile over time for parameters belonging to the corresponding biological function. Individual data listings will include 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 based on multiples of ULN, the parameter's value will also be expressed as multiples of ULN in the individual data presented.

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 post-Baseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post-Baseline 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 and 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..

2.4.5.6 Analyses of vital sign variables

The summary statistics (including number, mean (standard deviation), median, Q1, Q3, minimum and maximum) of all vital signs variables (central laboratory values and changes from Baseline) will be calculated for each planned visit or study assessment (Baseline, each post-Baseline time point, last on-treatment) 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 unscheduled ones, will be considered for the PCSA summaries. The summaries will include patients in the safety population who have at least one assessment performed during the TEAE period. When a PCSA definition is based on change from Baseline, patients must have a baseline to be included in the summaries.

A listing of patients with at least one 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 on the direction).

2.4.5.7 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.

2.4.5.8 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.

2.5 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) = $(DCCT - HbA1c\,(\%) - 2.15) \times 10.929$.

Renal function formulas

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

Standard unit: eGFR (mL/min/1.73m^2)=

$$175 \times [Serum\ Creatinine\,(\mu mol/L)/88.4]^{-1.154} \times Age\,(year)^{-0.203} \times 1.212\,(if\ Black) \times 0.742\,(if\ Female)$$

Conventional unit: eGFR(mL/min/1.73m^2) =

$$175 \times [Serum\ Creatinine\ (mg/dL)]^{-1.154} \times Age\ (year)^{-0.203} \times 1.212\ (if\ Black) \times 0.742\ (if\ Female)$$

Urine ACR

Standard unit: UACR (mg/g) =

$$Urine\ Albumin\ (mg/dL) / (Urine\ Creatinine\ (mmol/L) \times 11.31) \times 1000$$

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

Calculation of LDL-C

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

- In Standard unit(mmol/L), TC – HDL-C – TG/2.17.
- In Conventional unit (mg/dL), TC – HDL-C – TG/5.

2.5.2 Data handling conventions for secondary efficacy variables

Scheduled measurements (Section 2.5.4) of continuous variables collected during the study will be used in the analysis 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 or by washout imputation method according to the criterion described in Section 2.4.4.1.

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

2.5.3 Missing data

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

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

Incomplete date of first administration of double-blind IMP

Date/time of first administration is the first non-missing start date/time of double-blind IMP

completed in the e-CRF "First dose IMP" module.

For patients who are randomized and dispensed a double-blind treatment kit but who are lost to follow-up just after Visit 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 IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake 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 posttreatment 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 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 when date and time of first IMP administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. 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 e-CRF "Completion of End of Study/Follow-up".
- Completely missing, it will be imputed with the date of last available information on e-CRF "Completion of End of Study/Follow-up" page.

If the date of last available information on e-CRF "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, then 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 of adverse events

If the severity 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.

Handling of missing data for key secondary safety endpoints

Please See Section 2.4.5.1

2.5.4 Windows for time points

The following will decide how 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 available; otherwise, an unscheduled measurement (including the end of treatment/study visit for those prematurely discontinued) will be used if it were on the same date as a scheduled visit;

Step 2: After step 1, if there are still no measurement for a given parameter at a scheduled visit, analysis window below (Table 3) will be applied to re-allocate a post-Baseline unscheduled measurement to the scheduled visit.

Table 3 – Analyses window definition

Scheduled visit post Baseline	Targeted study day	Analysis window in study days
Week 3 (Visit 4)	21	2 to 31
Week 6 (Visit 5)	42	32 to 62
Week 12 (Visit 6)	84	63 to 104
Week 18 (Visit 7)	126	105 to 153
Week 26 (Visit 8)	182	154 to 227
Week 39 (Visit 9)	273	228 to 318
Week 52 (Visit 10)	364	319 to 419
Week 68 (Visit 11)	476	420 to 538
Week 86 (Visit 12)	602	539 to 664
Week 104 (Visit 13)	728	≥665

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 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 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. See Section 2.1.4 and Section 2.5.4 for details.

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 one 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 one 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 one set of measurements for the same vital sign parameter (ie, SBP, DBP, or HR) on the same date.

26-week double blind core treatment period

The 26-week double-blind core treatment period is the time from first administration of double-blind IMP to the last administration of double-blind IMP on or before Visit 8/Week 26 (or Day 182 if Visit 8/Week 26 date is missing). This is for defining EOT status at Week 26 and analyzing selected efficacy parameters (eg, rescued patients) and safety during 26-week core treatment period.

TEAE period for the 26-week double blind core treatment period

The TEAE period for the 26-week double-blind core treatment period is (1) the time from the first administration of the double-blind IMP up to 10 days (1 day for hypoglycemia) after the last administration of IMP if the patient discontinued treatment on or before Visit 8 (or Day 182 if Visit 8 date is missing), or (2) the time from the first administration of the double-blind IMP to the administration at Visit 8/Week 26 (or Day 182 if Visit 8/Week 26 date is missing) if the patient remained treated beyond Visit 8/Week 26. This is for the purpose of safety analyses during the 26-week core treatment period.

26-week core study period

The 26-week core study period is the time from first administration of double-blind IMP to Visit 8/Week 26 (or Day 182 if Visit 8/Week 26 date is missing) or the end of TEAE period for the 26-week double-blind core treatment period (as defined above) whichever is later. This is for defining EOS status at Week 26.

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 respective analysis period.

Patients who did not experience any event during the respective analysis period are considered censored observations. The censoring rules are defined below:

Time to event	Censoring date at Week 26 (1st step analysis)	Censoring date at EOT/EOS (2nd step analysis)
Treatment discontinuation due to any reason	Not applicable	EOT
Treatment discontinuation due to AE	Not applicable	EOT
Time to rescue	min (EOT, Date of W26 visit)	EOT
Time to severe or documented hypoglycemia	min (EOT+1, EOS, Date of W26 visit). See Section 3	Min (EOT+1, EOS)

Note: (1) Day 182 will be used if Date of Week 26 visit (or date of W26/re-allocated W26) is not available.
(2) 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 not be included in the by-visit summaries, but 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 than5, they will 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, however analysis of primary and secondary endpoints at Week 26 will be considered final at the time of first step analyses described below. The study analyses will be conducted in 2 steps:

- First step: Efficacy analyses up to Week 26, and interim safety analyses.

  The first step analyses will be conducted when all patients have been randomized and have all their data, at the minimum up to Week 26 (Visit 8), collected and validated. For this analysis the common cut-off date is 10 days after the date of last patient last Week 26 visit. The first step analyses will include:

  - Efficacy analyses up to Week 26, which are considered as the final analyses for primary and secondary endpoints. Analyses beyond week 26 will be descriptive,
  - Safety analysis of the key secondary safety endpoint of BMD at Week 26,
  - Interim safety analyses which will be performed on all safety data collected and validated at the time of the first step analyses.

The first step analyses will not be used to change the conduct of the ongoing study in any aspect. Since the primary efficacy and secondary analyses would have been concluded at the time of the first step analyses, the significance level for the study remains at 0.05 (see Section 2.4.4.4). The first step analyses will be included in the submission dossier to health authorities.

Individuals who are involved in the unblinding of the first step analysis will not be involved in the conduct of the study afterwards.

- Second step: final analyses.

  The second step analyses will be conducted at the end of the study. The second step analyses will include the final analyses of efficacy endpoints at Week 52 and Week 104 and safety endpoints on the 104-week entire treatment period, which will be descriptive only.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as appropriate. The following additional rules will apply for the first-step analyses:

- Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
- Any assessments within analysis windows up to Week 26 will be taken into account (may include few unscheduled data after the cut-off date),
- Patients who did not complete 104-week entire treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as “ongoing” in the disposition summary,
- Their TEAE period, and on-study observation period will end at the cut-off date,

- Their treatment duration will be derived by considering date of cut-off as last administration date,
- Analyses of percentage of days with under/above-planned dosing and compliance will be performed up to last administration reported in the e-CRF before the last visit taking into consideration of the cut-off date,
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions, and deaths occurring after the cut-off date will not be included in the analyses,
- For time to severe or documented symptomatic hypoglycemia at the 1st step analysis, the censoring date is min (EOT+1, EOS, common cut-off date),
- Post-treatment epoch, post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths, and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date,
- Status at last study contact will be provided for patients who either completed or prematurely discontinued the study before or at the cut-off date.

An independent DMC will monitor and assess the safety of patients from this trial through periodic review of the accumulated safety data provided by an independent statistical group. Related details are provided in separate documents (DMC charter and DMC SAP).

4 DATABASE LOCK

Two database locks will be done:

- First database lock (for first step analysis): will include all available data on all randomized patients up to the common cut-off date as defined in Section 3. This database lock is planned to be done approximately 4 weeks after the common cut-off date.
- Final database lock (for second step analysis): will include all data, including follow-up, for all randomized patients. This database lock is planned to be done approximately 4 weeks after 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: Potentially clinically significant abnormalities (PCSA) criteria

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

Appendix C: Summary of statistical analyses

Appendix D: Study Flow Chart

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 May 21, 2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
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) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from Baseline ≥100% change from Baseline	Benichou C., 1994.
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
Potassium	<3 mmol/L	FDA Feb 2005.
	≥5.5 mmol/L	
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	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black)	Increase in WBC: not relevant.
	≥16.0 Giga/L	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)	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).
	≥185 g/L (Male); ≥165 g/L (Female)	
	Decrease from Baseline ≥20 g/L	
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female)	
	≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
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	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from Baseline ≥5% decrease from Baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 May 21, 2014)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

(From BTD-009536 May 21, 2014)

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

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

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

EOSI	Preferred term code	Preferred term
Urinary tract infections	10048709	Urosepsis
Urinary tract infections	10048837	Cystitis glandularis
Urinary tract infections	10049059	Urinary tract infection fungal
Urinary tract infections	10049100	Pyelocystitis
Urinary tract infections	10051250	Ureteritis
Urinary tract infections	10051350	Cytomegalovirus urinary tract infection
Urinary tract infections	10051959	Urinary bladder abscess
Urinary tract infections	10052238	Escherichia urinary tract infection
Urinary tract infections	10054088	Urinary tract infection bacterial
Urinary tract infections	10056351	Emphysematous cystitis
Urinary tract infections	10058523	Bladder candidiasis
Urinary tract infections	10058596	Renal cyst infection
Urinary tract infections	10059517	Bacterial pyelonephritis
Urinary tract infections	10061181	Genitourinary tract gonococcal infection
Urinary tract infections	10061182	Genitourinary tract infection
Urinary tract infections	10061395	Ureter abscess
Urinary tract infections	10062279	Urinary tract infection pseudomonal
Urinary tract infections	10062280	Urinary tract infection staphylococcal
Urinary tract infections	10064825	Urinary tract infection viral
Urinary tract infections	10064921	Urinary tract inflammation
Urinary tract infections	10065197	Cystitis viral
Urinary tract infections	10065198	Cystitis bacterial
Urinary tract infections	10065199	Cystitis helminthic
Urinary tract infections	10065213	Pyelonephritis viral
Urinary tract infections	10065214	Pyelonephritis fungal
Urinary tract infections	10065582	Urogenital infection fungal
Urinary tract infections	10065583	Urogenital infection bacterial
Urinary tract infections	10066757	Urinary tract abscess
Urinary tract infections	10068822	Emphysematous pyelonephritis
Urinary tract infections	10070300	Streptococcal urinary tract infection
Urinary tract infections	10074409	Escherichia pyelonephritis
Urinary tract infections	10075063	Urethritis mycoplasmal
Urinary tract infections	10078665	Bacterial urethritis
Urinary tract infections	10081163	Fungal urethritis
Urinary tract infections	10081262	Candida urethritis

EOSI	Preferred term code	Preferred term
Urinary tract infections	10082040	Nephritis bacterial
Volume depletion	10005697	Blood osmolarity increased
Volume depletion	10005731	Blood pressure ambulatory decreased
Volume depletion	10005734	Blood pressure decreased
Volume depletion	10005737	Blood pressure diastolic decreased
Volume depletion	10005748	Blood pressure immeasurable
Volume depletion	10005758	Blood pressure systolic decreased
Volume depletion	10005761	Blood pressure systolic inspiratory decreased
Volume depletion	10007979	Central venous pressure decreased
Volume depletion	10009192	Circulatory collapse
Volume depletion	10012174	Dehydration
Volume depletion	10013578	Dizziness postural
Volume depletion	10021097	Hypotension
Volume depletion	10021137	Hypovolaemia
Volume depletion	10021138	Hypovolaemic shock
Volume depletion	10026983	Mean arterial pressure decreased
Volume depletion	10031127	Orthostatic hypotension
Volume depletion	10036653	Presyncope
Volume depletion	10037327	Pulmonary arterial wedge pressure decreased
Volume depletion	10042772	Syncope
Volume depletion	10046640	Urine flow decreased
Volume depletion	10047235	Venous pressure decreased
Volume depletion	10047239	Venous pressure jugular decreased
Volume depletion	10047689	Volume blood decreased
Volume depletion	10050760	Blood urea nitrogen/creatinine ratio increased
Volume depletion	10050905	Decreased ventricular preload
Volume depletion	10053356	Blood pressure orthostatic decreased
Volume depletion	10059895	Urine output decreased
Volume depletion	10060089	Left ventricular end-diastolic pressure decreased
Volume depletion	10060231	Pulmonary arterial pressure decreased
Volume depletion	10063080	Postural orthostatic tachycardia syndrome
Volume depletion	10063927	Orthostatic intolerance
Volume depletion	10066077	Diastolic hypotension
Volume depletion	10069431	Orthostatic heart rate response increased
Volume depletion	10069583	Pulse volume decreased

EOSI	Preferred term code	Preferred term
Volume depletion	10072370	Prerenal failure
Pancreatitis	10033625	Pancreatic haemorrhage
Pancreatitis	10033635	Pancreatic pseudocyst
Pancreatitis	10033636	Pancreatic pseudocyst drainage
Pancreatitis	10033645	Pancreatitis
Pancreatitis	10033647	Pancreatitis acute
Pancreatitis	10033649	Pancreatitis chronic
Pancreatitis	10033650	Pancreatitis haemorrhagic
Pancreatitis	10033654	Pancreatitis necrotising
Pancreatitis	10033657	Pancreatitis relapsing
Pancreatitis	10048984	Pancreatic abscess
Pancreatitis	10052400	Oedematous pancreatitis
Pancreatitis	10056277	Pancreatorenal syndrome
Pancreatitis	10056975	Pancreatic phlegmon
Pancreatitis	10056976	Hereditary pancreatitis
Pancreatitis	10056977	Alcoholic pancreatitis
Pancreatitis	10058096	Pancreatic necrosis
Pancreatitis	10065189	Pancreatitis helminthic
Pancreatitis	10066127	Ischaemic pancreatitis
Pancreatitis	10069002	Autoimmune pancreatitis
Pancreatitis	10074894	Traumatic pancreatitis
Pancreatitis	10076058	Haemorrhagic necrotic pancreatitis
Venous thrombotic events	10003192	Arteriovenous fistula thrombosis
Venous thrombotic events	10003880	Axillary vein thrombosis
Venous thrombotic events	10006537	Budd-Chiari syndrome
Venous thrombotic events	10007830	Cavernous sinus thrombosis
Venous thrombotic events	10008138	Cerebral venous thrombosis
Venous thrombotic events	10014522	Embolism venous
Venous thrombotic events	10019713	Hepatic vein thrombosis
Venous thrombotic events	10023237	Jugular vein thrombosis
Venous thrombotic events	10027402	Mesenteric vein thrombosis
Venous thrombotic events	10034272	Pelvic venous thrombosis
Venous thrombotic events	10034324	Penile vein thrombosis
Venous thrombotic events	10036206	Portal vein thrombosis
Venous thrombotic events	10037377	Pulmonary embolism

EOSI	Preferred term code	Preferred term
Venous thrombotic events	10037421	Pulmonary microemboli
Venous thrombotic events	10037437	Pulmonary thrombosis
Venous thrombotic events	10037459	Pulmonary venous thrombosis
Venous thrombotic events	10038547	Renal vein embolism
Venous thrombotic events	10038548	Renal vein thrombosis
Venous thrombotic events	10038908	Retinal vein thrombosis
Venous thrombotic events	10041659	Splenic vein thrombosis
Venous thrombotic events	10042567	Superior sagittal sinus thrombosis
Venous thrombotic events	10043570	Thrombophlebitis
Venous thrombotic events	10043581	Thrombophlebitis migrans
Venous thrombotic events	10043595	Thrombophlebitis superficial
Venous thrombotic events	10043605	Thrombosed varicose vein
Venous thrombotic events	10044457	Transverse sinus thrombosis
Venous thrombotic events	10047193	Vena cava embolism
Venous thrombotic events	10047195	Vena cava thrombosis
Venous thrombotic events	10047249	Venous thrombosis
Venous thrombotic events	10048591	Post thrombotic syndrome
Venous thrombotic events	10049446	Subclavian vein thrombosis
Venous thrombotic events	10050216	Paget-Schroetter syndrome
Venous thrombotic events	10050902	Postoperative thrombosis
Venous thrombotic events	10051055	Deep vein thrombosis
Venous thrombotic events	10053182	Arteriovenous graft thrombosis
Venous thrombotic events	10061251	Intracranial venous sinus thrombosis
Venous thrombotic events	10061408	Venous thrombosis limb
Venous thrombotic events	10063363	Brachiocephalic vein thrombosis
Venous thrombotic events	10063909	Post procedural pulmonary embolism
Venous thrombotic events	10066881	Deep vein thrombosis postoperative
Venous thrombotic events	10067270	Thrombosis corpora cavernosa
Venous thrombotic events	10069909	Metastatic pulmonary embolism
Venous thrombotic events	10072059	Ovarian vein thrombosis
Venous thrombotic events	10074349	Ophthalmic vein thrombosis
Venous thrombotic events	10077623	Portosplenomesenteric venous thrombosis
Venous thrombotic events	10077829	Visceral venous thrombosis
Venous thrombotic events	10078810	Hepatic vein embolism
Thyroid cancer	10002240	Anaplastic thyroid cancer

EOSI	Preferred term code	Preferred term
Thyroid cancer	10016935	Follicular thyroid cancer
Thyroid cancer	10027105	Medullary thyroid cancer
Thyroid cancer	10033701	Papillary thyroid cancer
Thyroid cancer	10043744	Thyroid neoplasm
Thyroid cancer	10055107	Thyroid cancer metastatic
Thyroid cancer	10066136	Huerthle cell carcinoma
Thyroid cancer	10066474	Thyroid cancer
Thyroid cancer	10070567	Thyroid cancer stage 0
Thyroid cancer	10071027	Thyroid cancer stage I
Thyroid cancer	10071028	Thyroid cancer stage II
Thyroid cancer	10071029	Thyroid cancer stage III
Thyroid cancer	10071030	Thyroid cancer stage IV
Thyroid cancer	10072162	Thyroid cancer recurrent
Thyroid cancer	10072613	Thyroid B-cell lymphoma
Thyroid cancer	10073153	Familial medullary thyroid cancer
Thyroid cancer	10076603	Poorly differentiated thyroid carcinoma
Renal cell cancer	10038389	Renal cancer
Renal cell cancer	10038390	Renal cancer recurrent
Renal cell cancer	10038391	Renal cancer stage I
Renal cell cancer	10038392	Renal cancer stage II
Renal cell cancer	10038393	Renal cancer stage III
Renal cell cancer	10038394	Renal cancer stage IV
Renal cell cancer	10038410	Renal cell carcinoma recurrent
Renal cell cancer	10038411	Renal cell carcinoma stage I
Renal cell cancer	10038412	Renal cell carcinoma stage II
Renal cell cancer	10038413	Renal cell carcinoma stage III
Renal cell cancer	10038414	Renal cell carcinoma stage IV
Renal cell cancer	10050018	Renal cancer metastatic
Renal cell cancer	10050513	Metastatic renal cell carcinoma
Renal cell cancer	10061482	Renal neoplasm
Renal cell cancer	10067944	Hereditary leiomyomatosis renal cell carcinoma
Renal cell cancer	10067946	Renal cell carcinoma
Renal cell cancer	10073251	Clear cell renal cell carcinoma
Renal cell cancer	10078493	Papillary renal cell carcinoma
Pancreatic cancer	10018404	Glucagonoma

EOSI	Preferred term code	Preferred term
Pancreatic cancer	10022498	Insulinoma
Pancreatic cancer	10025997	Malignant neoplasm of islets of Langerhans
Pancreatic cancer	10029341	Neurotensinoma
Pancreatic cancer	10033609	Pancreatic carcinoma
Pancreatic cancer	10033610	Pancreatic carcinoma metastatic
Pancreatic cancer	10033613	Pancreatic carcinoma recurrent
Pancreatic cancer	10041329	Somatostatinoma
Pancreatic cancer	10047430	Vipoma
Pancreatic cancer	10051709	Gastrinoma malignant
Pancreatic cancer	10052747	Adenocarcinoma pancreas
Pancreatic cancer	10055006	Pancreatic sarcoma
Pancreatic cancer	10055007	Carcinoid tumour of the pancreas
Pancreatic cancer	10059320	Pancreatic carcinoma stage 0
Pancreatic cancer	10059321	Pancreatic carcinoma stage I
Pancreatic cancer	10059322	Pancreatic carcinoma stage II
Pancreatic cancer	10059323	Pancreatic carcinoma stage III
Pancreatic cancer	10059326	Pancreatic carcinoma stage IV
Pancreatic cancer	10061902	Pancreatic neoplasm
Pancreatic cancer	10067517	Pancreatic neuroendocrine tumour
Pancreatic cancer	10068909	Pancreatic neuroendocrine tumour metastatic
Pancreatic cancer	10069345	Solid pseudopapillary tumour of the pancreas
Pancreatic cancer	10073363	Acinar cell carcinoma of pancreas
Pancreatic cancer	10073364	Ductal adenocarcinoma of pancreas
Pancreatic cancer	10073365	Intraductal papillary-mucinous carcinoma of pancreas
Pancreatic cancer	10073367	Pancreatoblastoma
Bladder cancer	10004986	Bladder adenocarcinoma recurrent
Bladder cancer	10004987	Bladder adenocarcinoma stage 0
Bladder cancer	10004988	Bladder adenocarcinoma stage I
Bladder cancer	10004989	Bladder adenocarcinoma stage II
Bladder cancer	10004990	Bladder adenocarcinoma stage III
Bladder cancer	10004991	Bladder adenocarcinoma stage IV
Bladder cancer	10004992	Bladder adenocarcinoma stage unspecified
Bladder cancer	10005003	Bladder cancer
Bladder cancer	10005005	Bladder cancer recurrent
Bladder cancer	10005006	Bladder cancer stage 0, with cancer in situ

EOSI	Preferred term code	Preferred term
Bladder cancer	10005007	Bladder cancer stage 0, without cancer in situ
Bladder cancer	10005008	Bladder cancer stage I, with cancer in situ
Bladder cancer	10005009	Bladder cancer stage I, without cancer in situ
Bladder cancer	10005010	Bladder cancer stage II
Bladder cancer	10005011	Bladder cancer stage III
Bladder cancer	10005012	Bladder cancer stage IV
Bladder cancer	10005056	Bladder neoplasm
Bladder cancer	10005075	Bladder squamous cell carcinoma recurrent
Bladder cancer	10005076	Bladder squamous cell carcinoma stage 0
Bladder cancer	10005077	Bladder squamous cell carcinoma stage I
Bladder cancer	10005078	Bladder squamous cell carcinoma stage II
Bladder cancer	10005079	Bladder squamous cell carcinoma stage III
Bladder cancer	10005080	Bladder squamous cell carcinoma stage IV
Bladder cancer	10005081	Bladder squamous cell carcinoma stage unspecified
Bladder cancer	10005084	Bladder transitional cell carcinoma
Bladder cancer	10051690	Urinary bladder sarcoma
Bladder cancer	10057352	Metastatic carcinoma of the bladder
Bladder cancer	10066749	Bladder transitional cell carcinoma stage 0
Bladder cancer	10066750	Bladder transitional cell carcinoma recurrent
Bladder cancer	10066751	Bladder transitional cell carcinoma stage I
Bladder cancer	10066752	Bladder transitional cell carcinoma stage IV
Bladder cancer	10066753	Bladder transitional cell carcinoma stage II
Bladder cancer	10066754	Bladder transitional cell carcinoma stage III
Bladder cancer	10071664	Bladder transitional cell carcinoma metastatic
Bladder cancer	10078341	Neuroendocrine carcinoma of the bladder
Potentially leading to amputation	10003084	Areflexia
Potentially leading to amputation	10003178	Arterial thrombosis
Potentially leading to amputation	10003210	Arteriosclerosis
Potentially leading to amputation	10003222	Arteriosclerotic gangrene
Potentially leading to amputation	10006784	Burning sensation
Potentially leading to amputation	10007904	Cellulitis enterococcal
Potentially leading to amputation	10007905	Cellulitis gangrenous
Potentially leading to amputation	10007921	Cellulitis staphylococcal
Potentially leading to amputation	10007922	Cellulitis streptococcal
Potentially leading to amputation	10012174	Dehydration

EOSI	Preferred term code	Preferred term
Potentially leading to amputation	10012665	Diabetic gangrene
Potentially leading to amputation	10012679	Diabetic neuropathic ulcer
Potentially leading to amputation	10012680	Diabetic neuropathy
Potentially leading to amputation	10017711	Gangrene
Potentially leading to amputation	10020937	Hypoaesthesia
Potentially leading to amputation	10021137	Hypovolaemia
Potentially leading to amputation	10021519	Impaired healing
Potentially leading to amputation	10021784	Infected skin ulcer
Potentially leading to amputation	10022562	Intermittent claudication
Potentially leading to amputation	10024774	Localised infection
Potentially leading to amputation	10028862	Necrosis ischaemic
Potentially leading to amputation	10029331	Neuropathy peripheral
Potentially leading to amputation	10031149	Osteitis
Potentially leading to amputation	10031252	Osteomyelitis
Potentially leading to amputation	10031253	Osteomyelitis acute
Potentially leading to amputation	10031256	Osteomyelitis chronic
Potentially leading to amputation	10031262	Osteomyelitis salmonella
Potentially leading to amputation	10031264	Osteonecrosis
Potentially leading to amputation	10033775	Paraesthesia
Potentially leading to amputation	10034568	Peripheral coldness
Potentially leading to amputation	10034576	Peripheral ischaemia
Potentially leading to amputation	10034620	Peripheral sensory neuropathy
Potentially leading to amputation	10034636	Peripheral vascular disorder
Potentially leading to amputation	10036155	Poor peripheral circulation
Potentially leading to amputation	10036410	Postoperative wound infection
Potentially leading to amputation	10040026	Sensory disturbance
Potentially leading to amputation	10040840	Skin erosion
Potentially leading to amputation	10040872	Skin infection
Potentially leading to amputation	10040943	Skin ulcer
Potentially leading to amputation	10042343	Subcutaneous abscess
Potentially leading to amputation	10043607	Thrombosis
Potentially leading to amputation	10048031	Wound dehiscence
Potentially leading to amputation	10048038	Wound infection
Potentially leading to amputation	10049927	Dry gangrene
Potentially leading to amputation	10050473	Abscess limb

EOSI	Preferred term code	Preferred term
Potentially leading to amputation	10050502	Neuropathic ulcer
Potentially leading to amputation	10051548	Burn infection
Potentially leading to amputation	10052428	Wound
Potentially leading to amputation	10052949	Arterial therapeutic procedure
Potentially leading to amputation	10053692	Wound complication
Potentially leading to amputation	10053716	Wound necrosis
Potentially leading to amputation	10054044	Diabetic microangiopathy
Potentially leading to amputation	10056340	Diabetic ulcer
Potentially leading to amputation	10056418	Arterial bypass operation
Potentially leading to amputation	10056673	Peripheral sensorimotor neuropathy
Potentially leading to amputation	10057518	Peripheral artery angioplasty
Potentially leading to amputation	10057525	Peripheral artery occlusion
Potentially leading to amputation	10058041	Wound sepsis
Potentially leading to amputation	10058042	Wound abscess
Potentially leading to amputation	10059245	Angiopathy
Potentially leading to amputation	10059385	Extremity necrosis
Potentially leading to amputation	10059442	Wound infection staphylococcal
Potentially leading to amputation	10059444	Wound infection pseudomonas
Potentially leading to amputation	10060734	Diabetic foot
Potentially leading to amputation	10060803	Diabetic foot infection
Potentially leading to amputation	10060963	Arterial disorder
Potentially leading to amputation	10060965	Arterial stenosis
Potentially leading to amputation	10061627	Amputation
Potentially leading to amputation	10061655	Arterial graft
Potentially leading to amputation	10061657	Arterial stent insertion
Potentially leading to amputation	10061666	Autonomic neuropathy
Potentially leading to amputation	10061815	Diabetic vascular disorder
Potentially leading to amputation	10062198	Microangiopathy
Potentially leading to amputation	10062255	Soft tissue infection
Potentially leading to amputation	10062585	Peripheral arterial occlusive disease
Potentially leading to amputation	10062599	Arterial occlusive disease
Potentially leading to amputation	10062610	Ischaemic limb pain
Potentially leading to amputation	10062932	Wound treatment
Potentially leading to amputation	10064250	Staphylococcal osteomyelitis
Potentially leading to amputation	10064601	Iliac artery occlusion

EOSI	Preferred term code	Preferred term
Potentially leading to amputation	10065237	Osteomyelitis bacterial
Potentially leading to amputation	10065239	Osteomyelitis fungal
Potentially leading to amputation	10065240	Wound infection bacterial
Potentially leading to amputation	10065242	Wound infection fungal
Potentially leading to amputation	10068653	Bone abscess
Potentially leading to amputation	10069379	Peripheral arterial reocclusion
Potentially leading to amputation	10072170	Skin wound
Potentially leading to amputation	10072557	Peripheral artery restenosis
Potentially leading to amputation	10072560	Peripheral endarterectomy
Potentially leading to amputation	10072561	Peripheral artery bypass
Potentially leading to amputation	10072562	Peripheral artery stent insertion
Potentially leading to amputation	10072563	Peripheral artery stenosis
Potentially leading to amputation	10072564	Peripheral artery thrombosis
Potentially leading to amputation	10074396	Penetrating atherosclerotic ulcer
Potentially leading to amputation	10075118	Subperiosteal abscess
Potentially leading to amputation	10075714	Vasculitic ulcer
Potentially leading to amputation	10076246	Spontaneous amputation

Appendix C Summary of statistical analyses

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA1c: Change from Baseline at Week 26	ITT	ANCOVA (with missing values imputed by retrieved dropouts imputation method or by washout imputation method under MNAR): Trt, randomization strata (HbA1c, Sex) and country as fixed effects, and baseline HbA1c value as a covariate	ANCOVA (with missing values imputed by washout imputation method under MNAR Tipping point analysis; ANCOVA (with missing values imputed by retrieved dropouts imputation method or by washout imputation method under MNAR)	Subgroups: race, ethnicity, age group, gender, baseline BMI, baseline HbA1c, baseline mean SBP, Duration of diabetes, Prior antidiabetic medication 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.
Key Secondary safety endpoint					
BMD (lumbar spine, total hip, and femoral neck): Percent change from Baseline at Week 26	Safety	ANCOVA (with missing values imputed using retrieved dropouts method or by ANCOVA (LOCF)): Trt, randomization strata (HbA1c, Sex) and country as fixed effects, and baseline BMD value as a covariate	ANCOVA (LOCF)	Subgroups: age group, gender, baseline BMI, baseline eGFR, Duration of diabetes.	Summary statistics for observed values, changes and percent changes from Baseline by visit. Graphical presentations for mean percent changes from Baseline (±SE) and mean values (±SE) by visit.

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Secondary efficacy endpoints					
Continuous: HbA1c(sotagliflozin 200 mg vs placebo),FPG, body weight: Change from Baseline to Week 26; SBP:Change from Baseline at Week 12	ITT	ANCOVA (with missing values imputed by retrieved dropouts imputation method or by washout imputation method under MNAR): Trt, randomization strata (HbA1c, Sex) and country as fixed effects, and Baseline value as a covariate	For Hba1c (sotagliflozin 200 mg vs placebo) change from Baseline to Week 26 only: ANCOVA (with missing values imputed by washout imputation method under MNAR Tipping point analysis; ANCOVA (with missing values imputed by retrieved dropouts mputation method or by washout imputation method under MNAR)	For Hba1c sotagliflozin (200 mg vs placebo) change from Baseline to Week26 only: Subgroups: race, ethnicity, age group, gender, baseline BMI, baseline HbA1c, baseline mean SBP, Duration of diabetes, Prior antidiabetic medication 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.
Categorical: Proportion of patients with HbA1c <7% at Week 26	ITT	CMH stratified on randomization strata (HbA1c, Sex)	CMH method stratified on randomization strata (HbA1c / Sex): excluding patients with Baseline HbA1c values <7% responders)	No	By-visit summary and graphs of HbA1c responders <7%). By-visit frequency summary and graphs of HbA1c responders (<7%) excluding patients with Baseline HbA1c values <7%.

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Other efficacy endpoints					
Continuous:					
HbA1c, FPG, body weight: Change from Baseline to weeks 52 & 104	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
SBP (according to baseline SBP<130 mmHg/≥130 mmHg & all), DBP(according to baseline DBP<80 mmHg/≥80 mmHg & all),: Change from Baseline to Weeks 12, 26 & 104					
Serum estradiol, total body fat mass, total lean mass, UACR, eGFR: Change from Baseline to Weeks 26, 52 & 104					
Categorical:					
Proportion of patients with HbA1c <7% at Weeks 52 & 104	ITT	By-visit summary and graphs of HbA1c responders <7%).	No	No	
Proportion of patients requiring rescue for hyperglycemia during the 104 weeks	ITT	Summary statistics	No	No	KM plot , List of patients rescued

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Other safety endpoints					
BMD (lumbar spine, total hip, and femoral neck): Percent change from Baseline at Weeks 52 & 104	Safety	ANCOVA (with missing values imputed using retrieved dropouts method or by ANCOVA (MMRM) Trt, randomization strata (HbA1c, Sex), visit, trt-by-visit interaction and country as fixed effects, and Baseline BMD value-by-visit interaction as a covariate	ANCOVA (MMRM)	No	Summary statistics for observed values, changes and percent changes from Baseline by visit. Graphical presentations for mean percent changes from Baseline (±SE) and mean values (±SE) by visit.
SAFETY ANALYSES					
Hypoglycemia	Safety	Follow safety guidelines Number (%) of patients with any investigator reported 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 group, gender	Severe hypoglycemia or documented symptomatic hypoglycemia: frequency summary of first event / recurrent event by weekly time intervals; frequency summary of any event by hour; KM plot time to first event 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

ITT = intent-to-treat; ANCOVA = analysis of covariance

Appendix D Study Flow Chart

	Screening Period		Double-blind Treatment Period[a]											Follow-up Period[b]
	Screening	Run-in	Randomized Double-blind Core Treatment Period						Randomized Double-blind Extension Period					
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-4**	**-2**	**0**	**3**	**6**	**12**	**18**	**26**	**39**	**52**	**68**	**86**	**104**	**106**
Day (window [days])	**-28**	**-14 (±3)**	**1**	**21 (±3)**	**42 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**476 (±7)**	**602 (±7)**	**728 (±3)**	**742 (±3)**
Informed consent	X													
Inclusion criteria	X													
Exclusion criteria	X	X	X											
Patient demography	X													
Medical/surgical history	X													
Prior medication history	X													
Body weight, height[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination:														
Complete	X							X					X	
Abbreviated[e]		X	X	X	X	X	X		X	X	X	X		X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SMBG[f]			X	X	X	X	X	X	X	X	X	X	X	X
Diet & exercise instruction		X	X					X		X	X	X		
Instruction on basic GU hygiene & hydration		X	X	X	X	X	X	X	X	X	X	X		

	Screening Period		Double-blind Treatment Period[a]											Follow-up Period[b]
	Screening	Run-in	Randomized Double-blind Core Treatment Period						Randomized Double-blind Extension Period					
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-4**	**-2**	**0**	**3**	**6**	**12**	**18**	**26**	**39**	**52**	**68**	**86**	**104**	**106**
Day (window [days])	**-28**	**-14 (±3)**	**1**	**21 (±3)**	**42 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**476 (±7)**	**602 (±7)**	**728 (±3)**	**742 (±3)**
IRT contact	X	X	X	X	X	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	X	X	X	
Collect/review diary			X	X	X	X	X	X	X	X	X	X	X	X
Dispense single-blind placebo		X												
Dispense double-blind IMP			X	X	X	X	X	X	X	X	X	X		
IMP accounting & compliance			X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[g]		X						X					X	
Laboratory assessments[h]														
Serum 25 hydroxyvitamin D screening	X													
FPG [i]			X	X	X	X		X		X		X	X	
HbA1c	X		X			X		X		X		X	X	
Safety laboratory	X		X	X	X	X		X		X		X	X	X
Hematology	X		X			X		X		X		X	X	X
Fasting lipids			X					X					X	

	Screening Period		Double-blind Treatment Period[a]											Follow-up Period[b]
	Screening	Run-in	Randomized Double-blind Core Treatment Period						Randomized Double-blind Extension Period					
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-4**	**-2**	**0**	**3**	**6**	**12**	**18**	**26**	**39**	**52**	**68**	**86**	**104**	**106**
Day (window [days])	**-28**	**-14 (±3)**	**1**	**21 (±3)**	**42 (±3)**	**84 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±7)**	**476 (±7)**	**602 (±7)**	**728 (±3)**	**742 (±3)**
FSH and estradiol for documentation of menopausal status[j]	X													
Estradiol (only for women)			X					X		X			X	
Bone turnover markers[k]			X					X		X			X	
Markers of calcium metabolism[l]			X					X		X			X	
Collection of home 24-hour urine for albumin, creatinine, albumin-creatinine ratio, calcium, magnesium, and phosphorus[m]			X					X		X			X	
Urinalysis w/microscopy[n]	X		X			X		X		X		X	X	
DXA scan [o]		X						X		X			X	
Evaluate for glycemic rescue	To be assessed and reported throughout the Treatment Period													
Hypoglycemia	To be assessed and reported throughout the study													
AE/SAE/AESI/EOSI recording[p]	To be assessed and reported throughout the study													

Abbreviations: AE = adverse event, AESI = adverse event of special interest, BMD = bone mineral density, BP = blood pressure, DXA = dual-energy X-ray absorptiometry, ECG = electrocardiogram, EOSI = event of special interest, EOT = End of Treatment, FPG = fasting plasma glucose, FSH = follicle-stimulating hormone, GU = genito-urinary, HbA1c = hemoglobin A1C, HR = heart rate, IMP = investigational medicinal product, iPTH = parathyroid hormone, IRT = Interactive Response Technology, NIMP = noninvestigational medicinal product, NTX = N-terminal telopeptide of Type 1 collagen, P1NP = Type 1 procollagen N-terminal propeptide, SAE = serious adverse event, SMBG = self-monitoring of blood glucose, β-CTX-1 = beta C-terminal telopeptide of Type 1 collagen.

a. If a patient discontinues treatment with IMP early during the Treatment Period, the patient will have a Premature EOT Visit, and a Follow-up Visit, 2 weeks after the last dose of IMP. However, every effort will be made to have the patients return to the site for all scheduled visits, in particular, the visits at Week 26 (Visit 8) and Week 104 (Visit 13). If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status.

b. The Follow-up Visit will take place 2 weeks ± 3 days after the last dose of IMP. All attempts will be made to contact the patient to inquire about safety status.

c. Height to be measured only at Screening, Week 52, Week 104, and at the Premature EOT Visit.

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

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

f. Patients will be instructed to measure their fasting glucose levels via SMBG and discuss results with site personnel at clinic visits or phone contacts. The frequency of the fasting SMBG measurements will be determined by the Investigator according to the clinical need and background diabetes treatment, but it is recommended to be done at least once a week. Patients will also be instructed to self-assess blood glucose levels whenever they experience any illnesses (eg, cold, flu), or symptoms of hyperglycemia or hypoglycemia. Note that the SMBG measurements obtained with glucose meters are displayed as plasma glucose concentration. The SMBGs ≤70 mg/dL will be reported on the hypoglycemia specific electronic case report form page.

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

h. All laboratory assessments occur prior to dose of double-blind IMP and NIMP.

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

j. The FSH and serum estradiol is performed in all women at Screening to confirm menopausal status as needed.

k. Markers of bone turnover include: markers of bone resorption (serum NTX, serum β-CTX-1) and bone formation (serum P1NP and osteocalcin).

l. Markers of calcium metabolism include: serum and urinary calcium (adjusted for creatinine), serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum and urinary phosphorus (adjusted for serum phosphorus, and creatinine), serum and urinary magnesium (adjusted for serum magnesium and creatinine), serum iPTH.

m. 24-hour urine samples for calcium, phosphorus, and magnesium will be collected at Weeks 0, 26, 52, and 104. Patients will be instructed to initiate the 24-hour urine collection on the day before the visits. In exceptional situations, the 24-hour urine collection can be done up to 2 days maximum prior to or after the visit, and the specimen should be sent to the study site as soon as possible.

n. Urinalysis will be done at central laboratory and 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, urine cultures should be performed (microbial testing). Additionally, urine cultures should be performed if at any point the Principal Investigator suspects the presence of a urinary tract infection.

o. Baseline DXA scans for BMD assessment will be performed during Run-in and centrally reviewed for eligibility assessment. All BMD assessments will be performed locally with a central review. Post-Baseline DXA scans will be performed within 2 weeks prior to the on-site visits at Weeks 26, 52, and 104, or no later than 7 days after the visit. Body composition by DXA will be performed at the same visits when the BMD is measured.

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