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

NCT Number: NCT02926950

Document Date: SAP Version 3: 13-December-2019

Lexicon Pharmaceuticals, Inc.

Protocol No.: EFC14834

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

Covance Study ID: 000000150525

Statistical Analysis Plan

Version: 3

DATE OF ISSUE: 10 December 2019

Author: [redacted]

Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, TX 77381-1160

Covance Clinical Development Services
206 Carnegie Center
Princeton, NJ 08540-6233

APPROVALS

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

Covance Approval:

[redacted]

Signature

13 Dec. 2019

Date

[redacted]

Printed Name/Title

Lexicon Approval:

[redacted]

Signature

12-Dec-2019

Date

[redacted] PhD, [redacted]

Printed Name/Title

[redacted]

Signature

13-Dec-2019

Date

[redacted] MS, FRS, [redacted]

Printed Name/Title

[redacted]

Signature

Date 13-Dec-2019

[redacted] MD, [redacted]

Printed Name/Title

[redacted]

Signature

13-Dec-2019

Date

[redacted] PhD, [redacted]

Printed Name/Title

VERSION HISTORY

Version Status	Version Date
Final 1.0	29 May 2018
Final 2.0	03 May 2019
Final 3.0	10 December 2019

TABLE OF CONTENTS

APPROVALS **2**

VERSION HISTORY **3**

TABLE OF CONTENTS **4**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **7**

1 OVERVIEW AND INVESTIGATIONAL PLAN **9**

1.1 STUDY DESIGN AND RANDOMIZATION 9

1.2 OBJECTIVES 9

1.2.1 Primary objectives 9

1.2.2 Secondary objectives 10

1.2.3 Other objectives 10

1.2.4 Objectives of ABPM substudy 10

1.3 DETERMINATION OF SAMPLE SIZE 11

1.4 STUDY PLAN 11

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL 12

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN 13

2 STATISTICAL AND ANALYTICAL PROCEDURES **18**

2.1 ANALYSIS ENDPOINTS 18

2.1.1 Demographic and baseline characteristics 18

2.1.2 Prior or concomitant medications 20

2.1.2.1 Rescue therapy 20

2.1.2.2 Prohibited prior and concomitant medications 20

2.1.3 Efficacy endpoints 21

2.1.3.1 Primary efficacy endpoint 21

2.1.3.2 Secondary efficacy endpoints 21

2.1.3.3 Other efficacy endpoints 22

2.1.3.4 ABPM substudy efficacy endpoint(s) 22

2.1.4 Safety endpoints 23

2.1.4.1 Hypoglycemia 24

2.1.4.2 AEs variables 26

2.1.4.3 Deaths 29
2.1.4.4 Laboratory safety variables 29
2.1.4.5 Vital signs variables 31
2.1.4.6 Physical examination 31
2.1.4.7 Electrocardiogram variables 31
2.1.5 Pharmacokinetic variables 31
2.2 DISPOSITION OF PATIENTS 31
2.2.1 Randomization and drug dispensing irregularities 34
2.3 ANALYSIS POPULATIONS 35
2.3.1 Efficacy populations 35
2.3.1.1 ITT population 35
2.3.1.2 ABPM substudy population 36
2.3.2 Safety population 36
2.3.3 PK population 36
2.4 STATISTICAL METHODS 36
2.4.1 Demographics and baseline characteristics 37
2.4.2 Prior or concomitant medications 37
2.4.3 Extent of investigational medicinal product exposure and compliance 38
2.4.3.1 Extent of investigational medicinal product exposure 38
2.4.3.2 Compliance 38
2.4.4 Analyses of efficacy endpoints 39
2.4.4.1 Analysis of primary efficacy endpoint(s) 39
2.4.4.2 Analyses of secondary efficacy endpoints 42
2.4.4.3 Analyses of other efficacy endpoints 43
2.4.4.4 Analysis of ABPM substudy efficacy endpoints 44
2.4.4.5 Multiplicity issues 44
2.4.5 Analyses of safety data 45
2.4.5.1 Analyses of hypoglycemia 46
2.4.5.2 Analyses of AEs 46
2.4.5.3 Deaths 50
2.4.5.4 Analyses of laboratory variables 51
2.4.5.5 Analyses of vital sign variables 52
2.4.5.6 Analyses of electrocardiogram variables 52
2.4.5.7 Analyses of physical examination variables 53
2.4.6 Analyses of pharmacokinetic variables 53
2.5 DATA HANDLING CONVENTIONS 53
2.5.1 General conventions 53
2.5.2 Data handling conventions for secondary efficacy variables 54
2.5.3 Missing data 54
2.5.4 Windows for time points/Measurements for analyses 57

2.5.5 Unscheduled visits 60
2.5.6 Pooling of centers for statistical analyses 60
2.5.7 Statistical technical issues 60

3 INTERIM ANALYSIS 61

4 DATABASE LOCK 62

5 SOFTWARE DOCUMENTATION 63

6 REFERENCES 64

7 LIST OF APPENDICES 65

APPENDIX A MAPPING OF INCLUSION AND EXCLUSION CRITERIA UNDER THE ORIGINAL PROTOCOL AND AMENDMENT 1 66

APPENDIX B SAMPLE SAS® CODE FOR ANALYSES OF EFFICACY ENDPOINTS 67

APPENDIX C AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDY 73

APPENDIX D ABPM SUBSTUDY EFFICACY VARIABLE DERIVATION 75

APPENDIX E POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA 77

APPENDIX F LIST OF PTS FOR SELECT EOSIS (MEDDRA V21.1) 83

APPENDIX G SUMMARY OF STATISTICAL ANALYSES 91

APPENDIX H STUDY FLOW CHART 95

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABPM:	ambulatory blood pressure monitoring
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
BMI:	body mass index
CEC:	Clinical Endpoint Committee(s)
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CV:	cardiovascular
DBP:	diastolic blood pressure
DILI:	drug-induced liver injury
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EOSI:	event of special interest
FPG:	fasting plasma glucose
GCR:	glucose-creatinine ratio
HbA1c:	Hemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
IFCC:	International Federation of Clinical Chemistry and Laboratory Medicine
IMP:	investigational medicinal product
IRT:	interactive response technology
KM:	Kaplan-Meier
LDL-C:	low density lipoprotein cholesterol
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation
MM:	mixed meal
MNAR:	missing not at random
NIMP:	noninvestigational medicinal product
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetic
PPG:	postprandial glucose
PRAC:	Pharmacovigilance Risk Assessment Committee
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SOC:	system organ class
TC:	total cholesterol

TEAE:	treatment-emergent adverse event
TG:	triglycerides
UACR:	urine albumin-creatinine ratio
UGE:	urinary glucose excretion
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter and multinational, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sotagliflozin added to metformin in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on metformin.

All patients will have a Screening Period consisting of a Screening phase of up to 2 weeks and a 2-week single-blind Run-in phase prior to randomization. In order to qualify for randomization, patients must demonstrate compliance based upon pill count (≥80%) during the Run-in phase.

Randomization will be performed via interactive response technology (IRT), where forced randomization is not allowed, and stratified by:

- Hemoglobin A1c (HbA1c) at Screening (≤8.0%, >8.0%)
- Mean systolic blood pressure (SBP) at Screening (<130 mmHg, ≥130 mmHg)

Following randomization, patients will have a 26-week, double-blind Core Treatment Period, a 53-week double-blind extension, and a 4-week post-treatment Follow-up period to collect safety information (patients who prematurely discontinue the study treatment are expected to continue in the study).

A total of 500 patients ≥18 years of age will be randomly assigned 1:1 to 1 of the following 2 treatment groups:

- sotagliflozin 400 mg
- Placebo

Ambulatory Blood Pressure Monitoring substudy (ABPM substudy)

Approximately 200 of the 500 enrolled patients who have a mean SBP ≥130 mmHg at screening are expected to participate in an ABPM substudy where patients will have blood pressure measured by a validated ABPM device.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo on HbA1c reduction at Week 26 in patients with T2DM who have inadequate glycemic control with metformin.

1.2.2 Secondary objectives

- To compare sotagliflozin 400 mg versus placebo for:
  - Change from Baseline in 2-hour postprandial glucose (PPG) following a mixed meal (MM) at Week 26
  - Change from Baseline in fasting plasma glucose (FPG) at Week 26
  - Change from Baseline in body weight at Week 26
  - Change from Baseline in SBP at Week 12 for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline in SBP at Week 12 for all patients
  - Proportion of patients with HbA1c <6.5%, <7.0% at Week 26;
- To evaluate the safety of sotagliflozin 400 mg versus placebo throughout the 79-week trial.

1.2.3 Other objectives

- To compare sotagliflozin versus placebo with respect to Change from Baseline on the following endpoints:
  - Urine albumin-creatinine ratio (UACR)
  - Urinary glucose excretion (UGE) and urine glucose-creatinine ratio (GCR)
  - Estimated glomerular filtration rate (eGFR)
  - Reduction in body weight by ≥2%, ≥5%, and ≥10%;
- To compare sotagliflozin versus placebo for:
  - Change from Baseline in HbA1c at Week 79
  - Change from Baseline in FPG at Week 79
  - Change from Baseline in SBP at Week 26 for all patients and for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline in SBP at Week 79 for all patients and for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline in body weight at Week 79;
- To compare the use of rescue medications for hyperglycemia in the sotagliflozin and placebo treatment groups;
- To assess plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite.

1.2.4 Objectives of ABPM substudy

The primary objective of the ABPM substudy is to compare the effect of sotagliflozin versus placebo in a subset of patients with mean SBP ≥130 mmHg at Screening on 24-hour average SBP at Week 12.

The secondary objectives of the ABPM substudy are to compare the effect of sotagliflozin versus placebo in a subset of patients with mean SBP ≥130 mmHg at Screening on the following:

- 24-hour average SBP at Week 26
- 24-hour average diastolic blood pressure (DBP) at Weeks 12 and 26
- Average adjusted awake time BP as measured by SBP and DBP at Weeks 12 and 26 with adjustment based on actigraphy
- Average adjusted sleeping time BP as measured by SBP and DBP at Weeks 12 and 26 with adjustment based on actigraphy

Full details of the ABPM substudy are provided in Appendix C.

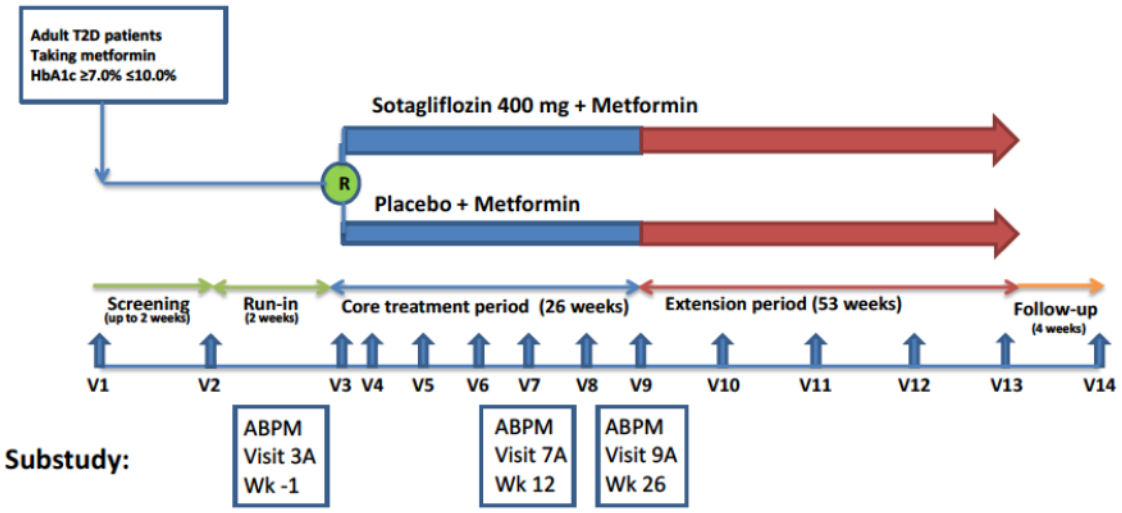
1.3 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations are based on the primary variable, 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, 250 patients per arm will have 99% power to detect a treatment difference of 0.6% in mean HbA1c Change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

The sample size/power calculations for ABPM substudy are based on the primary variable, Change from Baseline to Week 12 in average 24-hour SBP in patients with SBP ≥130 mmHg at Screening. Assuming a common SD of 15 mmHg and using a 2-sided test at a 0.05 α-level, 100 patients per arm will provide 90% power to detect a treatment difference of 7 mmHg in average 24-hour SBP Change from Baseline to Week 12 between sotagliflozin 400 mg and placebo.

1.4 STUDY PLAN

The study plan is presented graphically as follows.



The study flowchart can be found in Appendix H.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

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

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

The first patient was enrolled on Dec 5, 2016. There are no planned interim analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	24-Apr-2017	To be consistent with the Vendor ([redacted])'s device's setting and property	Two secondary endpoints of ABPM substudy updated. "Change from Baseline to Week 12 and 26 in average daytime BP (awake) as measured by SBP and DBP between 09:00 and 20:59" to. "Change from Baseline to Weeks 12 and 26 in average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy". "Change from Baseline to Week 12 and 26 in average nighttime (sleep) BP as measured by SBP and DBP between 01:00 and 05:59" to. "Change from Baseline to Weeks 12 and 26 in average adjusted sleeping time BP as measured by SBP and DBP with adjustment based on actigraphy".
1	24-Apr-2017	To understand treatment effects over the entire study duration	Addition of systolic blood pressure endpoints at Week 26 and Week 79, addition of HbA1c, fasting plasma glucose and body weight endpoints at Week 79
1	24-Apr-2017	[redacted]	[redacted]

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	19-Dec-2017	5 half-lives of sotagliflozin prolonged to 10 days considering patients with moderate renal dysfunction	5 half-lives of IMP updated from 5 days to 10 days; TEAE period updated accordingly
2	19-Dec-2017	Baseline eGFR defined as recommended by CDISC Therapeutic Area Data Standards User Guide for Diabetic Kidney Disease	For serum creatinine and eGFR, the baseline value is defined as the average of all values before the first dose of double blind IMP for those randomized and exposed or before randomization for those who were randomized but never exposed to IMP.
2	19-Dec-2017	Urgent coronary revascularization not adjudicated by CEC to be consistent with outcome trials	Urgent coronary revascularization not included in adjudication related analyses.
2	19-Dec-2017	The effect in body weight is considered more closely associated with the planned indication.	Change in the order of secondary objectives, endpoints, and multiplicity adjustment

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

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

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	29-May-2018	To be consistent with the Vendor ([redacted])'s device's setting and property	Two secondary endpoints of ABPM substudy updated*: "Change from Baseline to Week 12 and 26 in average daytime BP (awake) as measured by SBP and DBP between 09:00 and 20:59" to "Change from Baseline to Weeks 12 and 26 in average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy"; "Change from Baseline to Week 12 and 26 in average nighttime (sleep) BP as measured by SBP and DBP between 01:00 and 05:59" to "Change from Baseline to Weeks 12 and 26 in average adjusted sleeping time BP as measured by SBP and DBP with adjustment based on actigraphy"

SAP version number	Date approved	Rationale	Description of statistical changes
1	29-May-2018	To understand treatment effects over the entire study duration	Addition of systolic blood pressure endpoints at Week 26 and Week 79, addition of HbA1c, fasting plasma glucose and body weight endpoints at Week 79*
1	29-May-2018	[redacted]	[redacted]
1	29-May-2018	5 half-lives of sotagliflozin prolonged to 10 days considering patients with moderate renal dysfunction	5 half-lives of IMP updated from 5 days to 10 days; TEAE period updated accordingly**
1	29-May-2018	Baseline eGFR defined as recommended by CDISC Therapeutic Area Data Standards User Guide for Diabetic Kidney Disease	For serum creatinine and eGFR, the baseline value is defined as the average of all values before the first dose of double-blind IMP for those randomized and exposed or before randomization for those who were randomized but never exposed to IMP**
1	29-May-2018	Urgent coronary revascularization not adjudicated by CEC to be consistent with outcome trials	Urgent coronary revascularization not included in adjudication related analyses**
1	29-May-2018	The effect in body weight is considered more closely associated with the planned indication.	Change in the order of secondary objectives, endpoints, and multiplicity adjustment**
1	29-May-2018	Clarification on EOSI renal events	Details specified on renal events to be consistent with outcome studies in Section 2.1.4.2.
1	29-May-2018	[redacted]	[redacted]
1	29-May-2018	[redacted]	[redacted]
2	03-May-2019	[redacted]	[redacted]

SAP version number	Date approved	Rationale	Description of statistical changes
2	03-May-2019	Wording change to be consistent with CEC charter	"Unstable angina leading to hospitalization" changed to "Unstable angina requiring hospitalization"; "Heart failure leading to hospitalization" changed to "Heart failure requiring hospitalization"
2	03-May-2019	MedDRA version and dictionary updated	MedDRA version was updated to V21.1 and list of PTs for selected EOSI were updated
2	03-May-2019	Number of iterations for multiple imputation was changed	Number of iterations for multiple imputation was changed from 10000 to 2000
3	This version	[redacted]	[redacted]
3	This version	Assess robustness of the ITT-based analyses	Sensitivity analyses of the primary and secondary efficacy endpoints and ABPM substudy endpoints will be performed due to PK anomalies.

*Change made in Protocol Amendment 1 dated 24-Apr-2017.
** Change made in Protocol Amendment 2 dated 19-DEC-2017.

The statistical methods detailed in this section will be performed in addition to those specified in other sections of the SAP. The majority of these additional assessments will serve as sensitivity analyses and will be used to support/qualify the robustness of results from the originally planned analyses.

For the primary and continuous secondary efficacy endpoints, missing 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.

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 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 400 mg 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.

Each of the completed datasets after the imputation will be analyzed using the Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed 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 versus placebo) and its associated 95% confidence interval (CI).

For ABPM substudy, the primary and secondary efficacy endpoints will be analyzed using a similar approach as described above with post-baseline missing values imputed by the retrieved dropouts method or by the washout imputation method according to the criterion specified above.

Patients in this study have undergone sampling for plasma levels of sotagliflozin and its main active metabolite in order to perform population PK analysis. Patients treated with sotagliflozin 400 mg who have no detectable levels of active study drug or metabolite in their samples (ie, Below Lower Limit of Quantification or BLLOQ) may be identified as anomalous. In addition, patients randomized to the placebo arm may also be identified as having PK anomalies if there is a detectable level of active study drug and/or metabolite in their system (i.e., above limit of detection). When sample analysis has been completed and the study has been unblinded, explanations for some of these anomalies may be found: known non-compliance or sampling occurring after treatment had been discontinued. In other cases, drug intake history relative to the randomization assignment may not be fully explained. The ITT-based analyses specified in this document provides for a conservative assessment of the efficacy data should patients have been subjected to these unexplained non-compliance findings or PK 'anomalies'. To provide a broader perspective on the impact of these apparent errors in compliance, additional sensitivity analyses of the primary efficacy endpoint and continuous efficacy endpoints will be conducted. The need to perform such analyses, their specifics, and results may be provided in the Clinical Study Report (CSR), if applicable. The analysis methods applied to the patient subpopulations defined by the occurrence of the PK anomalies (eg, exclusion of patients with PK anomalies from the ITT dataset) will include the ANCOVA model using the retrieved dropout or washout MI methods previously specified in this section.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value (with the exception of serum creatinine and eGFR) is defined as the last available value before the first dose of double-blind investigational medicinal product (IMP) or the last available value prior to randomization for patients who were randomized but never exposed to IMP.

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

Baseline safety and efficacy parameters are presented along with the summary statistics 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): Year of informed consent - Year of birth,
- Age categories: (<50, ≥50 to <65, ≥65 to <75, ≥75 years),
- Gender (Male, Female),
- Race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other pacific islander, Multiple, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown),
- HbA1c (%) at screening visit,
- Randomization strata of HbA1c (≤8%, >8%) at screening visit (data from IRT),
- Mean SBP at screening visit,
- Randomization strata of mean SBP (<130 mmHg, ≥130 mmHg) at screening visit (data from IRT),
- Baseline body mass index (BMI) (kg/m^2) derived as: (Weight in kg)/(Height in meters)^2,
- Baseline BMI categories (<30, ≥30 kg/m^2),
- Country.

Disease characteristics at screening or baseline

Disease history:

- Duration of diabetes (years): (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): Year of diagnosis of diabetes – Year of Birth,
- Duration of metformin treatment (years): (date of informed consent - date of first intake of metformin +1)/365.25,
- Daily dose of metformin(mg) at baseline,
- Categorized daily dose of metformin at baseline (<1500, ≥1500 to <2500, ≥2500 mg),
- Baseline diabetic microvascular complications (Yes, No) (ie, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, diabetic peripheral neuropathy (sensory or motor), diabetic autonomic neuropathy, and diabetic foot infection),
- Baseline UACR categories (<30 mg/g [Normal], ≥30 to <300 mg/g [Microalbuminuria], and ≥300 mg/g [Macroalbuminuria]),
- eGFR at screening (mL/min/1.73 m^2),
- eGFR categories at screening (<15 mL/min/1.73m^2 [End stage renal disease], ≥15 to <30 mL/min/1.73 m^2 [Severe decrease in GFR], ≥30 to <60 mL/min/1.73 m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73 m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73 m^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 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 Sanofi at the time of database lock.

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

2.1.2 Prior or concomitant medications

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

All medications will be coded using the World Health Organization-Drug Dictionary using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first administration of the double-blind IMP. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP from the first administration of double-blind IMP to the date of the 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 metformin is considered as a noninvestigational medicinal product (NIMP). Metformin (commercial formulations) will be administered orally according to the locally approved label.

2.1.2.1 Rescue therapy

Except for SGLT2 inhibitors, any approved medication(s) including oral antidiabetic drugs or insulin can be prescribed at the Investigator's discretion to treat the hyperglycemia. Rescue therapy is considered a NIMP.

2.1.2.2 Prohibited prior and concomitant medications

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

- Initiation of any antidiabetic agents, including oral or injectable antihyperglycemic agents other than the IMP is not allowed before the rescue therapy,
- Systemic use of glucocorticoids is not allowed for more than 10 consecutive days (topical, ophthalmic, nasal spray or inhaled applications are allowed),
- Initiation of any weight loss drugs (eg, phentermine, orlistat),
- Investigational medicinal products in any other clinical study,
- SGLT2 inhibitor (eg, canagliflozin, dapagliflozin, or empagliflozin) are not allowed for rescue.

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

Other medications which are unlikely to interfere with the pharmacokinetic (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. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

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

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

2.1.3 Efficacy endpoints

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

Efficacy variables HbA1c, 2-hour PPG, FPG, UACR, UGE, UGCR, serum creatinine, and eGFR will be measured/calculated by a central laboratory (see study flowchart in Appendix H). Body weight, SBP and DBP (see Section 2.1.4.5) will be 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

- Change from Baseline to Week 26 in HbA1c (%).

2.1.3.2 Secondary efficacy endpoints

The continuous secondary efficacy endpoints are:

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

2.1.3.3 Other efficacy endpoints

- Change from Baseline to Week 12 in SBP for patients with baseline SBP <130 mmHg
- Proportion of patients with reduction in body weight by ≥2%, ≥5%, and ≥10% from baseline
- Changes from baseline to Week 12 in DBP
- Proportion of patients achieving SBP <130 mmHg for those with baseline SBP ≥130 mmHg
- Proportion of patients achieving DBP<80 mmHg for those with baseline DBP ≥80 mmHg
- Proportion of patients requiring rescue for hyperglycemia
- Change from Baseline in:
  - UACR, UGE, and UGCR
  - Serum creatinine
  - eGFR
- Change from Baseline to Week 79 in HbA1c
- Change from Baseline to Week 79 in FPG
- Change from Baseline to Week 26 in SBP for all patients and for patients with baseline SBP ≥130 mmHg
- Change from Baseline to Week 79 in SBP for all patients and for patients with baseline SBP ≥130 mmHg
- Change from Baseline to Week 79 in body weight.

2.1.3.4 ABPM substudy efficacy endpoint(s)

Primary endpoints

The primary endpoint of the substudy is:

- Change from Baseline to Week 12 in average 24-hour SBP in a subset of patients with mean SBP ≥130 mmHg at Screening.

Secondary endpoints

The secondary endpoints of the substudy are:

- Change from Baseline to Week 26 in average 24-hour SBP
- Change from Baseline to Week 12 and 26 in average 24-hour DBP
- Change from Baseline to Week 12 and 26 in average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy

- Change from Baseline to Week 12 and 26 in average adjusted sleep time BP as measured by SBP and DBP with adjustment based on actigraphy.

2.1.4 Safety endpoints

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

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first administration of the double-blind IMP.
- The treatment epoch is defined as the time from the first administration of double-blind IMP to the last administration of double-blind IMP. This epoch includes the 26-week double-blind core treatment period and the 53-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 9/Week 26 (or Day 182 if Visit 9/Week 26 date is missing).
- The **residual treatment** epoch is defined as the time from the last administration of double-blind IMP to the last administration of double-blind IMP + 10 days (1 day for hypoglycemia).

The treatment-emergent adverse event (TEAE) period for the 79-week double-blind entire treatment period will include both **treatment** and **residual treatment** epochs (See the TEAE period for the 26-week double-blind 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 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 eCRF "Hypoglycemic Event Information" page as those documented as,

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

Documented symptomatic hypoglycemia

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

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

Documented symptomatic hypoglycemia is identified in eCRF "Hypoglycemic Event Information" page as those documented as:

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

Asymptomatic hypoglycemia

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

Asymptomatic hypoglycemia is identified in eCRF "Hypoglycemic Event Information" page as those documented as:

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

Probable symptomatic hypoglycemia

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

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

1. To the question "Countermeasure Administration", NOT ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
2. To the question "Were Symptoms Present", ticked "Yes", and
3. With no plasma glucose value before countermeasure, and
4. To the question "Did this countermeasure lead a significant improvement or prompt recovery?" ticked "Yes".

Relative hypoglycemia

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

Relative hypoglycemia is identified in eCRF "Hypoglycemic Event Information" page as those documented as,

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

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

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

2.1.4.2 AEs variables

AE observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious from the signed informed consent date up to first dose of double-blind IMP
- Treatment-emergent AEs are AEs that developed or worsened or became serious during the treatment-emergent AE period.
- Posttreatment AE are AEs that developed or worsened or became serious during the posttreatment period.

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

The occurrence of AEs (including SAEs, 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

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

EOSI

- 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 infections
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Diarrhea
- Pancreatitis
- Bone fractures
- Venous thrombotic events, to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- Diabetic ketoacidosis

- Renal events, to include 50% decline in eGFR, end stage kidney disease, renal death
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid cancer)
- AE leading to an amputation.

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

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

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

Table 3 - Criteria for AESI and EOSI

AE Grouping	Criteria
AESI	
Pregnancy	eCRF "Pregnancy"
Symptomatic overdose with IMP/NIMP	"Overdose of IMP" or "Overdose of NIMP " checked and "Symptomatic overdose" checked in eCRF "Overdose"
ALT increase > 3X ULN	eCRF "ALT increase"
EOSI adjudicated	
Cardiovascular Death	Positively adjudicated by CEC: "Cardiovascular" or "Undetermined" as the primary cause of death
Myocardial infarction, Unstable Angina requiring hospitalization	Positively adjudicated by CEC: Yes to the question "Does the event meet the definition of an MI for this study?", or Yes to the question "If event is not an MI, does the event meet the definition of an UA Requiring admission to hospital or emergency room, for this study?"
Stroke	Positively adjudicated by CEC: Yes to the question "Does the event meet the definition of a Stroke for this study?"
Heart failure requiring hospitalization	Positively adjudicated by CEC: Yes to the question "Does the event meet the definition of a Heart Failure Event for this study?"
Bone fractures	Positively adjudicated by CEC: Yes to the question "Did the Fracture occur?"
Diabetic ketoacidosis	Positively adjudicated by CEC: Yes to the question "Does this event meet the criteria to be a DKA event?"
EOSI Renal events where select events adjudicated	

AE Grouping	Criteria
Sustained ≥50% decrease in eGFR	(1) For ≥50% decrease in eGFR from baseline, (1a) confirmed ≥50% decrease in GFR for ≥30 days with no reversible cause as recorded in eCRF "eGFR decrease", OR (1b) positively adjudicated by CEC: Yes to the question "Does the subject meet the criteria of CKD progression" for ≥50% decrease in eGFR.
Sustained eGFR <15 mL/min/1.73 m^2	(2) For eGFR <15 mL/min/1.73 m^2, (2a) confirmed eGFR <15 mL/min/1.73 m^2 for ≥30 days with no reversible cause as recorded in eCRF "eGFR decrease", OR (2b) positively adjudicated by CEC: Yes to the question "Does the subject meet the criteria of CKD progression".
Chronic dialysis	(3) For dialysis, (3a) dialysis lasted for ≥90 days (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 v21.1.
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 F
Urinary tract infections	PTs in Appendix F
Clinically relevant volume depletion and events related/possibly related to volume depletion	PTs in Appendix F
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" [20000218] plus the following PTs (MedDRA v21.1): Gastroenteritis (10017888), Antidiarrhoeal supportive care (10055660), Enteritis (10014866), Enteritis leukopenic (10014877), Enterocolitis (10014893), Enterocolitis haemorrhagic (10014896)
Pancreatitis	PTs in Appendix F
Venous thrombotic events	PTs in Appendix F

AE Grouping	Criteria
Malignancies of special interest	Breast cancer: Narrow search on "Breast cancer: Narrow search on "Breast neoplasms, malignant and unspecified (SMQ)" [20000149]
	Prostate cancer: Narrow search on "Prostate neoplasms, malignant and unspecified (SMQ)" [20000152]
	Leydig-cell cancer: PTs of Leydig cell tumour of the testis (10024407) and Ovarian Sertoli-Leydig cell tumour (10073270) based on MedDRA v21.1
	Thyroid cancer: PTs in Appendix F
	Renal cell cancer: PTs in Appendix F
	Pancreatic cancer: PTs in Appendix F
	Bladder cancer: PTs in Appendix F
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 F

* Search terms will be updated using the MedDRA version currently in effect at Sanofi at the time of database lock for EOSI identified by them.
AE potentially leading to an amputation: not an EOSI per individual protocol; analyzed due to their relevance to lower limb complication and amputations as a requirement from health authorities.

2.1.4.3 Deaths

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

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

2.1.4.4 Laboratory safety variables

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

Blood samples for clinical laboratories will be taken at designated visits as specified in protocol (see study flowchart in Appendix H). Clinical laboratory values will be summarized by the following groups:

- Hematology
  - **Red blood cells and platelets**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells:** white blood cell count, differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils)

- Clinical chemistry
  - **Metabolism:** glucose (serum), creatine phosphokinase (CPK)
  - **Electrolytes and minerals**: sodium, potassium, chloride, bicarbonate (ie, carbon dioxide), calcium, phosphorus, magnesium
  - **Renal function**: blood urea nitrogen (BUN), creatinine, uric acid
  - **Liver function**: total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, lactic acid dehydrogenase (LDH)
- Lipid parameters (fasting)
  - Total cholesterol (TC)
  - High density lipoprotein cholesterol (HDL-C)
  - Low density lipoprotein cholesterol (LDL-C) (calculated by Friedwald equation)
  - Non-HDLC (calculated as the difference between TC and HDLC)
  - Triglycerides (TG).
- Pancreatic enzymes: lipase, amylase.
- Blood Markers of Intestinal Transit and Absorption
  - Vitamins: B6, B12, K, E and A
  - Serum folate
  - Ferritin
- Markers of bone and calcium metabolism
  - Calcium,
  - 25-hydroxyvitamin D,
  - 1,25-dihydroxyvitamin D,
  - Phosphorus,
  - Parathyroid hormone (PTH),
  - Markers of bone resorption: N-terminal telopeptide (NTX), beta-C-terminal telopeptide (β-CTX-1),
  - Marker of bone formation: type 1 procollagen N-terminal (P1NP).

Urine samples will be collected at designated visits (see study flowchart in Appendix H) and measured by central laboratory:

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

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

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

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

2.1.4.6 Physical examination

A complete physical exam will be performed at Visit 1/Screening, Visit 9/Week 26, and Visit 13/Week 79. "Normal", "Abnormal", "Not done" as determined by the Investigator will be reported in the e-CRF by body system.

2.1.4.7 Electrocardiogram variables

12-lead ECGs will be performed at Visit 1/ Screening, Visit 3/ Randomization, Visit 9/ Week 26, and Visit 13/ Week 79. ECG status of "normal" or "abnormal" will be reported in the eCRF as determined by the Investigator.

2.1.5 Pharmacokinetic variables

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

2.2 DISPOSITION OF PATIENTS

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

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

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

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

- Screened patients
- Run in patients: patients who had a run-in record in IRT
- Screen failure patients (including failures during run-in) and reasons for screen failure (see Appendix A for details on the mapping of inclusion and exclusion criteria under the original protocol and Amendment 1)
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who have completed the 26-week double-blind core treatment period (see Section 2.5.4) as per protocol
- Patients who did not complete the 26-week double-blind core treatment period (see Section 2.5.4) as per protocol and the reasons for permanent treatment discontinuation
- Patients who have completed the 79-week double-blind entire treatment period as per protocol (double-blind core treatment period and extension treatment period)
- Patients who did not complete the 79-week double-blind entire treatment period as per protocol, and the reasons for permanent treatment discontinuation
- Patients who have completed the study as per protocol
- Patients who did not complete the study as per protocol and the reasons for study discontinuation
- 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, and treated, as well as number of patients randomized, discontinued from study treatment, and discontinued from study for each treatment group).

Patients treated but not randomized, patients randomized but not treated and patients randomized but not treated as randomized will be identified and described in separate listings. The patients of the third category (randomized and not treated as randomized) will be part of efficacy and safety analyses (Section 2.3). Patients randomized but not treated will be included in efficacy analysis. Safety data of patients treated but not randomized will be reported separately.

The randomization strata [HbA1c at Screening (≤8.0%, >8.0%) and mean SBP (<130, ≥130 mmHg)] assigned by IRT will be summarized. The percentages will be calculated using the number of randomized patients as the denominator. The discrepancy between the strata assigned by IRT and the information reported on eCRF will be listed for all randomized patients.

Kaplan-Meier (KM) plots of the cumulative incidence of double-blind IMP discontinuation due to any reason and due to AE will be provided for the entire 79-week double-blind treatment period separately (see Section 2.5.4). A listing of these patients, along with the reason for discontinuation treatment, study completion status and the reason for discontinuation study, will be provided.

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

- Patients who consented to ABPM substudy
- Patients not entering ABPM substudy and the reason for not entering
- Patients who randomized and entered ABPM substudy (ie, ABPM substudy population, see Section 2.3.1.2)
- Patients who completed ABPM substudy
- Patients who discontinued ABPM substudy and the reason for discontinuation:
  - Adverse Event
  - Study Terminated by Sponsor
  - At patient's own request
  - Lost to follow-up
  - Poor compliance to Protocol
  - Other
- Patients with good quality (see Appendix C) ABPM measurements at either Visit 7A/Week 12, or Visit 9A/Week 26 or both visits.

For patients who consented but did not entering ABPM substudy, percentages will be calculated using the number of patients consented to substudy as the denominator. All other categories of patients will be presented by treatment group and the percentages will be calculated using the number of patients randomized and entered substudy within each treatment group as the denominator. Reasons for ABPM substudy discontinuation will be supplied in tables giving numbers and percentages by treatment group. Patients prematurely discontinued the substudy, along with reasons for discontinuation, will also be listed. Patients who consented but did not enter ABPM substudy, along with reasons for not entering, will also be presented.

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

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

- Efficacy population: intent-to-treat (ITT) population
- Efficacy population for substudy: ABPM substudy population
- Safety population
- PK population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, or 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 an 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 ITT population

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

2.3.1.2 ABPM substudy population

ABPM efficacy analysis will be based on ABPM substudy population which defined as all randomized patients having:

1. signed the informed consent for ABPM substudy
2. Eligible screening SBP ≥130 mmHg
3. Baseline ABPM measurement at Visit 3A with Good Quality (see Appendix D)
4. At least one post-baseline ABPM visit recording.

2.3.2 Safety population

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

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 sotagliflozin group
- Randomized patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study treatment. If a patient is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed.

2.3.3 PK population

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

2.4 STATISTICAL METHODS

Descriptive statistics (number, mean, standard deviation (SD), median, minimum, and maximum) will be presented for continuous variable by treatment group. The number and percentage of patients in each category will be presented for categorical variables by treatment group.

2.4.1 Demographics and baseline characteristics

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

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

Demographic and disease characteristics will be summarized for ABPM substudy population by treatment group and overall (pooled across treatment groups) groups using descriptive statistics.

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

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

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

2.4.2 Prior or concomitant medications

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

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

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

Concomitant and posttreatment medications will be tabulated by anatomic and therapeutic categories and sorted by decreasing frequency in the sotagliflozin group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Prior and concomitant medications will also be presented for the ABPM substudy population for each treatment group, using counts and percentages.

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) and ABPM substudy population (see Section 2.3.1.2).

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

(Date of last double-blind IMP dose) – (date of first double-blind IMP dose) + 1 day,

regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

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

- 1 to 28 days
- 29 to 56 days
- 57 to 84 days
- 85 to 126 days
- 127 to 182 days
- 183 to 364 days
- 365 to 551 days
- >551 days

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

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

2.4.3.2 Compliance

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

Percentage of compliance for a patient will be defined as the number of days that the patient was compliant divided by the total number of days that the patient was planned to take during the

treatment epoch defined in Section 2.1.4 (ie, from the first date to the last date of double-blind IMP administration).

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

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

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with at least 1 day above-planned dose will be provided, as well as numbers and percentages of patients with (0, 20%], and >20% of days under-planned dose.

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

2.4.4 Analyses of efficacy endpoints

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

Statistical testing will be performed for primary endpoint and some secondary endpoints at Week 26 (or Week 12 for SBP) as specified in the following subsections. All efficacy variables after Week 26 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)

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

Primary analysis

The primary efficacy endpoint change in HbA1c from baseline to Week 26 will be analyzed by an ANCOVA model using HbA1c values measured at baseline and Week 26 (observed or imputed). The missing data at endpoint will be imputed by multiple imputation (MI) methods in 2 parts as detailed below. To be concise, the following texts related to imputation are generalized to accommodate primary as well as continuous secondary efficacy endpoints.

1. Missing endpoint data for patients who prematurely discontinue the IMP before the 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 (retrieved dropouts). Considering that the number of patients in each treatment group who discontinue the IMP but have the measurement for the endpoint is expected to be small, a simple imputation model based on regression will be used with baseline measurement included as the predictor. Each treatment group will have their own imputation model.

2. Missing endpoint data for all patients who stay on the IMP until the Week 26 (or Week 12 for SBP) visit, including those in the sotagliflozin 400 mg group, will be imputed separately. The wash-out imputation method will be used, where missing endpoint data in the sotagliflozin 400 mg group, as well as in the placebo group are imputed from a model estimated from patients in the placebo group who stay on the IMP until the Week 26 (or Week 12 for SBP) visit and have the endpoint data available. The imputation model will include the randomization strata and the corresponding baseline value. Missing data will be imputed using the regression method.

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, not sufficient retrieved dropouts to support the imputation method described above). This criterion will be assessed for each primary or continuous secondary efficacy endpoint separately.

In the back-up imputation method, missing post-baseline values will be imputed by control-based copy reference MI method under the missing not at random (MNAR) framework.

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

Using either imputation method, missing endpoint data will be imputed multiple times to generate multiple data sets with complete data (see sample code Part 1a or Part 2a of Appendix B). The 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 ANCOVA model with the treatment groups (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130, ≥130 mmHg), and country as fixed factors, and baseline HbA1c value as a covariate (see sample code Part 4 of Appendix B). The results from each analysis will be combined using Rubin's formula, to provide the adjusted mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as its between-group difference (comparing sotagliflozin 400 mg vs placebo) and the corresponding 95% confidence interval (CI) for the difference(see sample code Part 5 of Appendix B).

Sensitivity analyses

Tipping point analysis based on the same MI method as applied to the primary analysis will be performed to examine the robustness of the results from the primary analysis. Patients who were randomized to sotagliflozin 400 mg group and had no HbA1c data at Week 26 will be given a

penalty. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of statistical significance is changed. The tipping point is the penalty level, at which the magnitude of efficacy reduction in patients without HbA1c data at Week 26 creates a shift in the treatment effect of sotagliflozin 400 mg from being statistically significantly better than placebo to a non-statistically significant effect. LS mean difference between sotagliflozin 400 mg and placebo and its associated p-value will be provided for each penalty level. The steps to perform the tipping point analysis are as follows:

1. Missing data will be imputed using the same MI method as applied to the primary analysis (see sample code Part 3 in Appendix B),
2. The imputed HbA1c value at Week 26 in the sotagliflozin 400 mg group will be penalized by adding a penalty δ (eg, $\delta = 0.1\%$) in each complete dataset (see sample code Part 3 in Appendix B),
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 (see sample code Part 4 in Appendix B),
4. Results will be combined across complete datasets using Rubin's rule (see sample code Part 5 in Appendix B),
5. Steps 2 to 4 will be repeated with incremental penalty at δ (ie, δ, 2δ, 3δ, etc) until the p-value for treatment effect of sotagliflozin 400 mg compared to placebo estimated in Step 4 is >0.05.

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

If the retrieved dropout imputation is applied to the primary analysis, the analysis based on the control-based imputation (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 (<50, ≥50 to <65, ≥65 years) (any category with fewer than 5 patients may be combined with another category as appropriate),
- Gender (Male, Female),
- Baseline BMI level (<30, ≥30 kg/m^2),
- Baseline HbA1c (≤8.0%, >8.0%),
- Baseline HbA1c (≤8.5%, >8.5%),

- Baseline mean SBP (<130 mmHg, ≥130 mmHg),
- Baseline eGFR (≥30 to <60 mL/min/1.73 m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73 m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73 m^2 [Normal]),
- Duration of diabetes (<10, ≥10 years),
- Country.

The treatment effects across the subgroups defined above will be estimated for the Change from Baseline to Week 26 in HbA1c in the ITT population using the same MI method as applied to the primary analysis. The ANCOVA model will include treatment (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130, ≥130 mmHg), subgroup factor, treatment-by-subgroup factor, and country as fixed factors and baseline HbA1c as a covariate (see sample code Part 4 of Appendix B). The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus placebo) with standard error (SE) and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided.

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

Summary statistics at scheduled visits

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

Similar presentations will be provided excluding measurements after rescue therapy during the entire 79-week double-blind treatment period.

2.4.4.2 Analyses of secondary efficacy endpoints

For continuous secondary endpoints with missing data at baseline, missing data will be imputed using MI under the missing at random (MAR) assumption. Missing data at baseline will be imputed using regression method that includes randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130, ≥130 mmHg), and baseline value in the imputation model (see sample code Part 1b or Part 2b in Appendix B).

The continuous secondary endpoints (Section 2.1.3.2) will be analyzed using similar ANCOVA model including corresponding measurements at baseline and endpoint (observed or imputed) as described in Section 2.4.4.1. The missing data at endpoint will be imputed by the retrieved dropouts & washout imputation method or by the control-based copy reference imputation method according to the criterion described in Section 2.4.4.1 . After imputation, each of the complete

datasets will be analyzed by an ANCOVA model with treatment groups (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%), randomization stratum of SBP (<130, ≥130 mmHg), and country as fixed effects, and corresponding baseline value as a covariate. For the analysis of SBP in patients with baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included in the ANCOVA model. Results from each complete dataset will be combined using Rubin's formula to provide the adjusted mean Change from Baseline to Week 26 (or Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg vs placebo) and the 95% CI for the 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 values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits. In addition, SBP will be summarized descriptively at each visit for those with baseline SBP ≥140 mmHg.

The binary efficacy variables of HbA1c (<6.5%, <7% at Week 26 respectively) will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of HbA1c (≤8.0%, >8.0%), and randomization stratum of SBP (<130, ≥130 mmHg). The proportion in each treatment group, as well as the difference of proportions between sotagliflozin 400 mg and placebo with associated 2-sided 95% CI will be provided. For HbA1c responders at Week 26 (<6.5%, <7% respectively), all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 26 will be treated as non-responders. Summary tables and graphs will also be provided by treatment group at scheduled visits.

For between-group comparison, a sensitivity analysis will be performed separately for HbA1c <6.5% responder (excluding patients with baseline HbA1c <6.5%) and for HbA1c <7% responder (excluding patients with baseline HbA1c values < 7%) by using the same CMH test as that used for the above binary variables. The summary by visit may also be provided by excluding those patients with HbA1c <6.5% or <7% respectively.

2.4.4.3 Analyses of other efficacy endpoints

The analysis of other endpoints (see Section 2.1.3.3) will be descriptive with no formal testing. Summary statistics at scheduled visits using observed values 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 core (see Section 2.5.4) and the entire double-blind treatment periods. A KM curve will be provided for the cumulative incidence of rescue therapy during the entire double-blind treatment period. The list of patients who used rescue therapy will also be provided (see Section 2.5.4).

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

Shift tables will be provided for UACR at Week 26 and Week 79 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 79 will be provided by treatment group respectively. The pre-defined categories are, for urine ACR, <30 mg/g creatinine [Normal], ≥30 to <300 mg/g creatinine [Microalbuminuria], and ≥300 mg/g creatinine [Macroalbuminuria].

2.4.4.4 Analysis of ABPM substudy efficacy endpoints

Analyses of ABPM substudy efficacy endpoints will be performed on the ABPM population using all assessment collected up to Week 26, including those obtained after IMP discontinuation or introduction of rescue therapy, unless otherwise specified.

For ABPM substudy, primary and secondary efficacy endpoints will be analyzed using a similar approach as in the main-study with post-baseline missing values imputed by the retrieved dropouts & washout imputation method or by the control-based copy reference imputation method according to the criterion described in Section 2.4.4.1. Each of the complete dataset will be analyzed using ANCOVA model including factors for treatment (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%) as fixed factor, and the baseline value of the specific dependent variable as a covariate. Results from each complete dataset will be combined using Rubin's formula to provide the adjusted mean for each treatment group, as well as the between-group difference and the associated 95% CI.

All ABPM substudy efficacy endpoints will also be summarized by descriptive statistics by scheduled visits (Visit 3/Randomization, Visit 7/Week 12 and Visit 9/Week 26). The descriptive statistics will include number, mean, SE, standard deviation, minimum, maximum.

Please refer to Appendix C and Appendix D for ABPM substudy efficacy variable derivation.

2.4.4.5 Multiplicity issues

To control the family-wise type I error, a fixed-sequence 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 main secondary efficacy variables and ABPM substudy primary endpoint 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).

- Change from Baseline to Week 26 in 2-hour PPG following an MM
- Change from Baseline to Week 26 in FPG
- Change from Baseline to Week 26 in body weight
- Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg
- Change from Baseline to Week 12 in SBP for all patients
- Change from Baseline to Week 12 in average 24-hour SBP in patients from ABPM substudy (the primary endpoint of the ABPM substudy)
- Proportion of patients with HbA1c <7.0% at Week 26.

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

2.4.5 Analyses of safety data

Safety endpoints are presented in Section 2.1.4. 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 79-week entire treatment period separately, unless otherwise specified.

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

General common rules

All safety analyses will be performed on the Safety population using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value (with the exception of serum creatinine and eGFR) is defined as the last available value before the first dose of double-blind IMP. For 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 E).
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent AE period, taking into account all evaluations performed during the treatment-emergent AE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment-emergent PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter during the treatment-emergent AE period by treatment group in the safety population.
- For laboratory parameters cited in the protocol as efficacy endpoints (including HbA1c and plasma glucose, etc), PCSA summaries will not be provided. These parameters will be summarized in Section 2.4.4. For serum creatinine, and eGFR, PCSA summaries will be presented in safety Section 2.4.5, while descriptive summaries in efficacy Section 2.4.4.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from Baseline values by visit and treatment group for the 79-week entire treatment period only. Summaries will include the last on-treatment value. The last on-treatment value is commonly defined as the value collected at the same day/time of the last administration of IMP for the 79-week entire treatment period. If this value is missing, this last on-treatment value will be the closest value prior to the last administration of IMP during the 79-week entire treatment period.

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

2.4.5.1 Analyses of hypoglycemia

Analyses of hypoglycemia will be performed on the treatment-emergent AE periods 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 Section 2.1.4.

The number (%) of patients with any hypoglycemia, severe hypoglycemia, and documented symptomatic hypoglycemia will be summarized respectively by treatment group during the treatment-emergent AE period, as well as the incidence rate in patient years. Two types of incidence rates will be presented: the number of patients with at least 1 event per 100 patient-years (calculated as the number of patients with at least 1 event / total exposure in 100 patient-years), and the number of events per 100 patient-years (calculated as the total number of events / (total exposure in 100 patient-years)). Note: here exposure in days is 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 (Male, Female), age group (<50, ≥50 to <65, ≥65 years) and race (White, Black or African American, Asian, Other).

A KM curve will also be provided by treatment group for the time to first severe hypoglycemia or documented symptomatic hypoglycemia during the treatment-emergent AE period for the 79-week entire treatment period only (see Section 2.5.4).

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

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

2.4.5.2 Analyses of AEs

Generalities

The primary focus of AE reporting will be on treatment-emergent AEs. Pretreatment and posttreatment AEs will be described separately.

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

Adverse event incidence tables will be presented by SOC, HLGT, HLT, and PT, sorted by the internationally agreed order for SOCs and alphabetic order for HLGT, HLT and PT within a SOC, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event by PT 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 group will define the presentation order for all other similar tables unless otherwise specified. In case of equal frequency regrading PTs, alphabetical order will be used.

Analysis of all treatment-emergent AEs

The following treatment-emergent AE summaries will be generated during the 26-week core and the 79-week entire treatment periods respectively in the safety population.

- Overview of treatment-emergent AEs, summarizing number (%) of patients with any
  - Treatment-emergent AE
  - Serious treatment-emergent AE
  - Treatment-emergent AE leading to death
  - Treatment-emergent AE leading to permanent treatment discontinuation.
- All treatment-emergent AEs by primary SOC, showing number (%) of patients with at least 1 treatment-emergent AE, sorted by internationally agreed order of primary SOC.
- All treatment-emergent AEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent AE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- Number (%) of patients experiencing Treatment-emergent AEs presented by PT, sorted by decreasing incidence of PT in the sotagliflozin group.
- All treatment-emergent AEs by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent AE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the sotagliflozin group. This sorting order will be applied to all other similar tables, unless otherwise specified.

- All treatment-emergent AEs 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 AE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent AEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent AE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.
- Common treatment-emergent AEs (PTs with an incidence ≥2% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.
- Summaries of common treatment-emergent AEs (PTs with an incidence ≥2% in any treatment group) will be provided as appropriate by primary SOC and PT and by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years of age), race (White, Black or African American, Asian, Other), baseline SBP category (<130 mmHg, ≥130 mmHg), and baseline eGFR category (≥30 to <60 mL/min/1.73 m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73 m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73 m^2 [Normal]). SOC will be sorted by internationally agreed order and the PT by decreasing incidence within each SOC in the sotagliflozin 400 mg group, as described above.
- TEAEs (PTs with an incidence ≥5% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.

Analysis of all treatment emergent SAE(s)

- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent AE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent SAEs 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 SAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of all treatment-emergent AE(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 79-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 during the 79-week entire treatment period only. Corresponding listings will be provided as appropriately.

Analysis of events of special interest

The summaries of EOSI will be presented for the 79-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 requiring hospitalization, bone fracture, and diabetic ketoacidosis), the number (%) of patients with an EOSI positively adjudicated by CEC will be summarized by treatment group. All EOSIs sent for adjudication and/or reported by the investigators in the specific AE forms will be listed along with the adjudication outcome.

Renal events

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

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

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

Renal death will be part of all deaths specified above.

Other EOSIs

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

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

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

Analysis of Amputation

The number (%) of patients with amputation will be summarized by treatment group and by PT and LLT during the study (ie, regardless of on- or post-treatment). Amputation is a procedure recorded in eCRF 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 3 in Section 2.1.4.2). These PTs in Table 3 were requested by the European Medicines Agency (EMA)/ Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report, 9 February 2017).The associated list will be provided as well, with patients who had an amputation procedure flagged. "AE potentially leading to an amputation" represents the condition that may potentially lead to the amputation procedure, but not in all cases an amputation has occurred.

Analysis of pretreatment and posttreatment AEs

- All pretreatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the sotagliflozin group
- All posttreatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the sotagliflozin group.

Listings

Supporting AE listings will be provided for all AEs, SAEs, death, AEs leading to treatment discontinuation and/or death, and EOSI if appropriate.

Listing of all AEs, SAEs, deaths, and AEs leading to permanent treatment discontinuation, sorted by treatment, patient ID, onset date, will include the following information: treatment, patient ID, country, age, sex, 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/NIMP, outcome, date of death if any, seriousness, seriousness criteria, and AE status ("E" for a TEAE; "P" for an on-study post-treatment AE).

2.4.5.3 Deaths

The following summaries of deaths will be generated.

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

2.4.5.4 Analyses of laboratory variables

Laboratory parameters will be grouped and summarized by biological function as described in Section 2.1.4.4.

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

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

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

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

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

A listing of patients with at least 1 post-baseline PCSA (or out of normal range when no PCSA criterion is defined) will be provided and will display the entire patients' profile across time for all 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 multiples of the ULN, the parameter's value will also be expressed as a multiple of the ULN in the individual data provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any 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, total bilirubin, and the following complementary parameters (if available): conjugated bilirubin and prothrombin time/international normalized ratio, creatine phosphokinase, serum creatinine, complete blood count, anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies, auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, Epstein-Barr virus, herpes viruses, and anti-LKM.

2.4.5.5 Analyses of vital sign variables

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

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

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

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

2.4.5.6 Analyses of electrocardiogram variables

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

2.4.5.7 Analyses of physical examination variables

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

2.4.6 Analyses of pharmacokinetic variables

Plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite will be summarized by visit and nominal sampling time (pre-dose at Weeks 4, 18, 26, 52, 79, 2 hours 30 minutes post-dose at Weeks 26 and 79) in the PK population (Section 2.3.3) in the sotagliflozin group, using descriptive statistics such as number, geometric mean, coefficient of variation, median, minimum and maximum. Individual plasma concentrations of sotagliflozin and its 3-O-glucuronide at nominal sampling times will also be listed.

[redacted]

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

HbA1c

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

IFCC-HbA1c (mmol/mol) = $(DCCT - HbA1c\ (\%)\ -\ 2.15)\ \times 10.929$.

Renal function formulas

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

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

Conventional unit: eGFR(mL/min/1.73 m^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) = $Urine\ Albumin\ (mg/dL)\ /\ Urine\ Creatinine\ (mg/dL)\ x\ 1000$

Urine GCR

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

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

Calculation of LDL-C

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

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

2.5.2 Data handling conventions for secondary efficacy variables

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

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

2.5.3 Missing data

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

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

Incomplete date of first administration of double-blind IMP

Date/time of first administration is the first non-missing start date/time of double-blind IMP completed in the eCRF "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 eCRF "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 eCRF "First dose IMP" module.

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

For the calculation of the treatment duration, the date of the last dose of double-blind IMP is equal to the date of last administration reported on the eCRF "Treatment status library" 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 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 medication missing/partial dates

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

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

Missing or partial adverse event/hypoglycemia onset dates and times will be imputed so that if the partial adverse event/hypoglycemia onset date/time information does not indicate that the AE/hypoglycemia started prior to treatment or after the treatment-emergent AE, the adverse event/hypoglycemia will be classified as treatment-emergent.

No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

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

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

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

For the purpose of defining treatment-emergent AE period, the date of the last administration of double-blind IMP is equal to the date of the last administration reported on the e-CRF "Treatment Status Library" page. If the date of last administration reported on the e-CRF "Treatment Status Library" page is:

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

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

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

Handling of missing assessment of relationship of adverse events to IMP

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

Handling of missing severity/grades of adverse events

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

Handling of potentially clinically significant abnormalities

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

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

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

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

Linked adverse events that worsened or became serious

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

2.5.4 Windows for time points/Measurements for analyses

The following steps will decide how the scheduled and/or unscheduled visits will be used in efficacy analyses and by-visit summary analyses for safety variables (clinical laboratory data in Section 2.1.4.4 and vital signs in Section 2.1.4.5).

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

Step 2 After Step 1, if there are still no measurement for a given parameter at a scheduled visit, the analysis window below (Table 4) will be applied to re-allocate a post-baseline unscheduled measurement to a scheduled measurement.

Table 4 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 1 (Visit 4)	7	2 to 17
Week 4 (Visit 5)	28	18 to 41
Week 8 (Visit 6)	56	42 to 69
Week 12 (Visit 7)	83/84	70 to 104
Week 18 (Visit 8)	126	105 to 153
Week 26 (Visit 9)	181/182	154 to 227
Week 39 (Visit 10)	273	228 to 318
Week 52 (Visit 11)	365	319 to 409
Week 65 (Visit 12)	455	410 to 502
Week 79 (Visit 13)	551	>502

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 above visit 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 number) 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.

For ABPM substudy, an analysis window of 70 to 133 was used for Visit 7A, and 134-227 for Visit 9A.

Reference day

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

Baseline definition for efficacy/safety data

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

Summary statistics by visit for continuous efficacy endpoints

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

Last on-treatment value for laboratory variables and vital signs

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

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

Descriptive statistics (number, mean, SD, minimum, median, maximum) of quantitative laboratory variables and vital signs (observed data and change from baseline) during the TEAE period will be provided at scheduled visits. In addition, these summaries will also include a row

for the 'last value on-treatment' to describe the last available on-treatment value (see above). Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number, see Section 2.5.4) and labeled with the targeted approximate day/week.

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

When a patient has more than 1 measurement from the central laboratory for the same laboratory parameter on the same date, the average of the measurements will be used. For the same laboratory parameter, if a patient has more than 1 measurement on different dates for the same scheduled visit, the value closest to the date of the visit will be used for the scheduled visit. When the values for the same scheduled visit are equidistant, the last value should be used for the scheduled visit.

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 9/Week 26 (or Day 182 if Visit 9/Week 26 date is missing). This is for analyzing selected efficacy parameters (eg, rescued patients) during core treatment period.

TEAE period for the 26-week core treatment period

The TEAE period for 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 9 (or Day 182 if Visit 9 date is missing), or (2) the time from the first administration of the double-blind IMP to the administration at Visit 9/Week 26 (or Day 182 if Visit 9/Week 26 date is missing) if the patient discontinued treatment after Visit 9/Week 26. This is for the purpose of safety analyses during the core treatment period.

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 79-week double-blind treatment period.

Patients who did not experience any event during the 79-week double-blind treatment period are considered censored observations. For time to treatment discontinuation/rescue therapy, censoring date is the date of EOT. For time to severe or documented hypoglycemia, censoring date is date of EOT+1 or date of EOS, whichever is the earliest. Date of EOS will be used if date of EOT is not available. Last contact date will be used if date of EOS is not available.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline, the last on-treatment value, PCSAs and the shift summaries for safety or efficacy. They will be included in the by-visit summaries if they are re-allocated to scheduled visit (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 analysis. However, all data from the centers within each country will be pooled, and the country will be included as fixed factors if parametric statistical model (ANCOVA model, etc) are used for primary and secondary efficacy endpoints. Countries with fewer than 5 randomized patients will be grouped, if number of patients from grouped countries are still fewer than 5, they will then be further grouped with the country with the lowest number of patients that is 5 or more.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

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

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

4 DATABASE LOCK

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

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring. J Hypertens. 2013;31(9):1731-68.

7 LIST OF APPENDICES

Appendix A: Mapping of inclusion and exclusion criteria under the original protocol and Amendment 1

Appendix B: Sample SAS® code for analyses of efficacy endpoints

Appendix C: Ambulatory blood pressure monitoring substudy

Appendix D: ABPM substudy efficacy variable derivation

Appendix E: Potentially clinically significant abnormalities criteria

Appendix F: List of PTs for select EOSIs (MedDRA v21.1)

Appendix G: Summary of statistical analyses

Appendix H: Study Flow Chart

Appendix A Mapping of inclusion and exclusion criteria under the original protocol and Amendment 1

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

Appendix B Sample SAS® code for analyses of efficacy endpoints

```
* VARIABLES;
* treat - treatment;
* strata1 - stratification factor 1;
* strata2 - stratification factor 2;
* value0 - value at baseline;
* value1  … valuen - value at each post-baseline visit for a total of n visits; valuen for the endpoint visit;
* change - change from baseline;

*****************************************************************************************************************;
****Part 1: Preferred imputation method: the retrieved dropouts and washout imputation *****;
*****************************************************************************************************************;
```

/* Part 1a, for parameters with no missing data at baseline */;

```
* MI in patients who prematurely discontinued IMP before the endpoint using the endpoint data from its
own group (retrieved dropouts);
    proc sort data=ads;
        by treat ptid;
    run;
  proc mi data=ads out= disc_mi  nimpute=2000 seed=97531;
        where discontinue = "Y";
        by treat;
        var value0 valuen;
        monotone regression (valuen = value0 );
  run;

* MI in patients who stay on the IMP until the endpoint visit using the endpoint data from the placebo group
(wash-out MI);
    proc sort data=ads;
        by ptid;
    run;
  proc mi data=ads out= comp_mi  nimpute=2000 seed=75319;
        where discontinue="N" and (treat=1 or (treat ne 1 and valuen =. )); *1 denotes placebo group;
        class strata1 strata2;
        var strata1 strata2 value0 valuen;
        monotone regression (valuen = strata1 strata2  value0 );
  run;

* Repeat dataset with the same number of replications for remaining patients who have complete data at
the endpoint visit;
  data comp_trt;
        set ads (where=(discontinue="N" and  treat ne 1 and valuen ne .));
        _imputation_=0;
        do i = 1 to 2000;
                _imputation_=_imputation_+1;
                output;
        end;
```

```
   run;

* Combine three subsets of patients;
   data mi_1;
         set disc_mi comp_mi comp_trt;
   run;
```

/*Part 1b, for parameters with missing data at baseline */

```
* Impute the missing data at baseline;
     proc sort data=ads;
          by ptid;
     run;
   proc mi data=ads out=mi_base nimpute=2000 seed=13579;
          class strata1 strata2;
          var strata1 strata2 value0;
          monotone regression;
   run;
```

```
* MI in patients who prematurely discontinued IMP before the endpoint using the endpoint data from its
own group (retrieved dropouts);
     proc sort data=mi_base;
          by _imputation_ treat ptid;
     run;
   proc mi data=mi_base out= disc_mi  nimpute=1 seed=97531;
          where discontinue = "Y";
          by _imputation_ treat;
          var value0 valuen;
          monotone regression (valuen = value0 );
   run;
```

```
* MI in patients who stay on the IMP until the endpoint visit using the endpoint data from the placebo group
(wash-out MI);
     proc sort data=mi_base;
          by _imputation_ ptid;
     run;
   proc mi data=mi_base out= comp_mi  nimpute=1 seed=75319;
          where discontinue="N" and (treat=1 or (treat ne 1 and valuen =. )); *1 denotes placebo group;
          by _imputation_;
          class strata1 strata2;
          var strata1 strata2 value0 valuen;
          monotone regression (valuen = strata1 strata2  value0 );
   run;


* Combine subsets of patients;
   data mi_1;
          set disc_mi comp_mi mi_base (where=(discontinue "N" and (treat ne 1 and valuen ^=.));
```

```
run;


*****************************************************************************************;
************Part 2: Back-up imputation method: Control-based MI************;
*****************************************************************************************;
```

/*Part 2a, for parameters with no missing data at baseline*/;

```
* Partial imputations to render monotone missing data;
    proc sort data=ads;
        by treat strata1 strata2 ptid;
    Run;
  proc mi data=ads out=monotone nimpute=2000 seed=97531;
        by treat strata1 strata2;
        var value:;
        mcmc chain=multiple impute=monotone;
  run;

    * Partial imputations to render monotone missing data; Drop strata if imputation could not converge;
    proc sort data=ads;
        by treat ptid;
    Run;

    proc mi data=ads out=monotone nimpute=2000 seed=97531;
        by treat;
        var value:;
        mcmc chain=multiple impute=monotone;
    run;


* To impute the missing data at post-baseline visits;
    proc sort data= monotone;
        by _imputation_ ptid;
    run;
  proc mi data= monotone out=mi_1 nimpute=1 seed=75319;
        by _imputation_;
        class treat strata1 strata2;
        monotone reg (  / details);
        mnar model (value: / modelobs=(treat='1')); *1 denotes placebo group;
        var strata1 strata2 value:;
  run;
```

/*Part 2b, for parameters with missing data at baseline */

```
* To impute the missing data at baseline;
    proc sort data=ads;
        by ptid;
```

```
    run;
  proc mi data=ads out=mi_base nimpute=2000 seed=13579;
        class strata1 strata2;
        var strata1 strata2 value0;
        monotone regression;
  run;

* Partial imputation to render monotone missing;
    proc sort data=mi_base;
        by _imputation_ treat strata1 strata2 ptid;
    Run;

  proc mi data=mi_base out=monotone nimpute=1 seed=35791;
        by _imputation_ treat strata1 strata2;
        var value:;
        mcmc chain=multiple impute=monotone;
  run;
```

*Note for partial imputations to render monotone missing data, drop strata1 and strata2 if imputation could not converge, same as in Part 2a.

```
* To impute the missing data at post-baseline visits;
    proc sort data= monotone;
        by _imputation_ ptid;
    run;
  proc mi data=monotone out=mi_1 nimpute=1 seed=57913;
        by _imputation_;
        class treat strata1 strata2;
        monotone reg (  / details);
        mnar model (value: / modelobs=(treat='1')); *1 denotes placebo group;
        var strata1 strata2 value:;
  run;


*******************************************************************************************;
********** Part 3: Multiple imputation for tipping-point analysis **********;
*******************************************************************************************;
```

/* Part 3a, Primary imputation method: for parameters with no missing data at baseline */;

```
* MI in patients who prematurely discontinued IMP before the endpoint;
proc sort data=ads;
        by treat ptid;
  run;
  proc mi data=ads out= disc_mi  nimpute=2000 seed=97531;
        where discontinue = "Y";
        by treat;
```

```
        var value0 valuen;
        monotone regression (valuen = value0 );
        mnar adjust (valuen / shift=0.1 adjustobs=(treat='2')); *2 denotes test drug group;
  run;
```

* MI in patients who stay on the IMP until the endpoint visit using the endpoint data from the placebo group (wash-out MI);

```
  proc sort data=ads;
        by ptid;
  run;
  proc mi data=ads out= comp_mi  nimpute=2000 seed=75319;
        where discontinue="N" and (treat=1 or (treat ne 1 and valuen =. )); *1 denotes placebo group;
        class treat strata1 strata2;
        var treat strata1 strata2 value0 valuen;
        monotone regression (valuen = strata1 strata2  value0 );
        mnar adjust (valuen / shift=0.1 adjustobs=(treat='2')); *2 denotes test drug group;
  run;
```

/*Part 3b, Back-up imputation method, for parameters with no missing data at baseline*/;

* Partial imputation to render monotone missing data;

```
    proc sort data=ads;
        by treat strata1 strata2 ptid;
    run;
  proc mi data=ads out=monotone nimpute=2000 seed=97531;
        by treat strata1 strata2;
        var value:;
        mcmc chain=multiple impute=monotone;
  run;
```

*Note for partial imputations to render monotone missing data, drop strata1 and strata2 if imputation could not converge, same as in Part 2a.

* To impute the missing data at post-baseline visits with penalty in test drug group ;

```
    proc sort data= monotone;
        by _imputation_ ptid;
    run;
  proc mi data= monotone out=mi_1 nimpute=1 seed=75319;
        by _imputation_;
        class treat strata1 strata2;
        monotone reg (  / details);
        mnar model (value: / modelobs=(treat='1')); *1 denotes control group;
        mnar adjust (valuen / shift=0.1 adjustobs=(treat='2')); *2 denotes test drug group;
        var strata1 strata2 value:;
  run;
```

```
*************************************************************************************;
******************************** Part 4: ANCOVA ********************************;
*************************************************************************************;

/* For the comparison between placebo and sotagliflozin 400 mg; */
   proc mixed data=mi_2;
        by _imputation_;
        class treat strata1 strata2 country;
        model change= treat strata1 strata2 country value0;
        lsmeans treat /diff cl e;
        lsmestimate  treat "A1 Placebo"   1 0  /cl;
        lsmestimate  treat "A2 Test drug"    0 1   /cl;
        lsmestimate  treat "B1 Test drug vs Placebo"   -1 1 /cl;
        ods output LSMEstimates=lsmestimates;
   run;

* Subgroup analyses using gender as an example;
   proc mixed data=mi_2;
        by _imputation_;
        class treat strata1 strata2 country gender;
        model change= strata1 strata2 country value0 treat*gender;
        lsmeans treat*gender /diff cl;
        lsmestimate treat*gender "SA11 Placebo - Female"   1 0 0 0 /cl;
        lsmestimate treat*gender "SA12 Placebo - Male"       0 1 0 0 /cl;
        lsmestimate treat*gender “SA21 Test drug - Female” 0 0 1 0 /cl;
        lsmestimate treat*gender “SA22 Test drug - Male”     0 0 0 1 /cl;
        lsmestimate treat*gender “SB1 Test drug vs Placebo - Female” -1 0 1 0 /cl;
        lsmestimate treat*gender “SB2 Test drug vs Placebo - Male”     0 -1 0 1 /cl;
        ods output LSMEstimates=lsmestimates;
   run;


*************************************************************************************;
********** Part 5: Combining results using Rubin’s formula **********;
*************************************************************************************;
   proc sort data=lsmestimates;
        by label _imputation_;
   run;

   proc mianalyze data=lsmestimates;
        by label;
        modeleffects estimate;
        stderr stderr;
        ods output parameterestimates=ancova;
   run;
```

Appendix C Ambulatory blood pressure monitoring substudy

Background

A Phase 2 trial of sotagliflozin (LX4211.1-202) provided evidence that sotagliflozin reduced both SBP and DBP in patients with elevated SBP and DBP at baseline but not normotensive patients. In this substudy of approximately 200 patients with mean SBP ≥130 mmHg at screening, patients will have ABPM assessed for 24 hours at baseline, Week 12, and Week 26 to provide a more systematic assessment of the SBP and DBP lowering efficacy of sotagliflozin.

Sub-study procedures

Patients with SBP ≥130 mmHg at screening will be provided with information on the ABPM substudy, and separate informed consent taken before ABPM substudy-specific procedures are performed.

Patients in the ABPM substudy will have 3 additional visits to the site for placement of the ABPM device, namely Visits 3A, 7A and 9A. Visit 3A will occur at Week -1, 1 week before randomization. Visits 7A and 9A will occur, respectively, on the day before Visit 7 (Week 12) and Visit 9 (Week 26).

Patients do not need to be fasting for Visits 3A, 7A and 9A. Once the ABPM device has been placed at Visit 3A, patients will be instructed to remove it after 24 hours and return it to the site by post in appropriate packaging provided by the site. Twenty-four hours after Visits 7A and 9A, patients will return to the site in a fasting state at Visits 7 and 9, respectively, and the device will be removed. All ABPM data will be reviewed following return of the device to ensure quality of the recording; Patients with ABPM data not of sufficient quality will be asked to repeat the process as soon as possible. Patients with ABPM data not of sufficient quality at Visit 3A should not be randomized until the baseline ABPM recording has been repeated.

Ambulatory blood pressure monitoring will be performed with a validated device provided by the Sponsor or Sponsor representative. Each recording will start in the morning preferably between 8:00 and 10:00 immediately after the administration of study medication, and will end after at least 24 hours of recording on the following day. The blood pressure cuff will be applied preferentially on the non-dominant arm. The monitor will be programmed to measure blood pressure every 20 minutes between 08:00 and 21:59, and every 30 minutes between 22:00 and 07:59. Patients will remain blinded to all collected ABPM values by switching off the display of the device. Patients will be instructed to follow their usual daily routines, but to remain still and avoid arm movement during each automated measurement. Patients will be asked to avoid strenuous activity, bathing, or taking a shower and to record the time of sleep and any unusual events or poor sleep quality during the ABPM recording period in their study log.

Sub-study objectives

The primary objective of the ABPM substudy is to compare the effect of sotagliflozin versus placebo in a subset of patients with SBP ≥130 mmHg at screening on 24-hour average SBP at Week 12.

The secondary objectives of the ABPM substudy are to compare the effect of sotagliflozin versus placebo in a subset of patients with SBP ≥130 mmHg at screening on the following:

- 24-hour average SBP at Week 26
- 24-hour average DBP at Weeks 12 and 26
- Average adjusted awake time BP as measured by SBP and DBP at Weeks 12 and 26 with adjustment based on actigraphy
- Average adjusted sleep time BP as measured by SBP and DBP at Weeks 12 and 26 with adjustment based on actigraphy.

Sub-study endpoints

The primary endpoint of the substudy is:

- Change from Baseline to Week 12 in average 24-hour SBP in a subset of patients with SBP ≥130 mmHg at screening.

The secondary endpoints of the substudy are:

- Change from Baseline to Week 26 in average 24-hour SBP
- Change from Baseline to Week 12 and 26 in average 24-hour DBP
- Change from Baseline to Week 12 and 26 in average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy
- Change from Baseline to Week 12 and 26 in average adjusted sleep time BP as measured by SBP and DBP with adjustment based on actigraphy.

Statistical analyses

The quality of a visit recording will be considered insufficient if the visit recording does not meet the criteria below (1):

1. Visit Recording does not contain greater than or equal to 17 non-consecutive hours of data where each hour has at least one valid BP measurement.
2. Visit Recording has less than 44 total measurements.

ABPM substudy endpoints will be analyzed using a similar approach as the primary efficacy endpoint with missing values imputed by the retrieved dropouts & washout imputation method or the control-based multiple imputation method under the missing not at random frame work. Each of the complete dataset will be analyzed using ANCOVA model including factors for treatment (sotagliflozin, placebo), randomization stratum of HbA1c (≤8.0%, >8.0%) as fixed effects, and the baseline value of the specific dependent variable as a covariate.

Appendix D ABPM substudy efficacy variable derivation

All following derivation of the efficacy variables for ABPM substudy will be performed and provided by vendor [redacted] (specialized in ABPM device) by using validated software [redacted] and following [redacted] Project Requirement Specifications as follows:

All ABPM substudy efficacy measurements will be recorded by validated ABPM Ambulo 2400 device. The device's inflation plan is set up to collect patient's BP measurements every 20 minutes during 8:00-21:59 and every 30 minutes during 22:00-7:59 over at least 24 hour time interval. The device will start recording patient's blood pressure after its inflation is initiated, which composes a patient's visit recording. All individual measurements will be analyzed by [redacted] and be assigned a status of successful included, successful excluded manual inflations, error or event.

Successful excluded measurements are valid device log entries related to manual device initiation of inflation by the patient and will be excluded from analysis.

Error measurements are any attempted inflation that results in a 0 value for one of the four values the device captures: systolic, diastolic, mean atrial pressure, or pulse pressure. Examples of errors are "cuff leak," device error, movement error, etc. These errors could be the result of a hole in the hose or patient movement (during inflation or deflation of the cuff).

Events refer to non-inflation events which appear in the data with 0 values for systolic, diastolic, mean atrial pressure, and pulse pressure. Examples of these events are USB disconnect, sequence trigger, and power on reset.

Usually, occurrence of events will not impact the quality of the recording. Both events and errors are excluded from analysis.

Successful included measurements are device log entries during the time interval after device automatic initiation based on the inflation plan (daytime, nighttime, or 24-hour period) that are neither successful excluded manual inflation plan, error, nor event. The successful included measurement captured systolic, diastolic, mean atrial pressure, and pulse pressure.

The quality of each recording at each visit will be considered Not Good Quality and not acceptable for analysis if the visit recording meets the criteria below:

1. Visit Recording does not contain greater than or equal to 17 non-consecutive hours of data where each hour has at least one valid BP measurement.
2. Visit Recording has less than 44 total measurements.

A valid measurement is a measurement having non-missing values for systolic, diastolic, pulse pressure and mean arterial pressure (MAP). [redacted] will analyze the recording from the first valid inflation (after device initiated) up to 24 hours thereafter to determine the quality of the recording. If the quality of the visit recording is of Not Good Quality, the efficacy variable of the patient at that visit will be considered as missing value. Otherwise, the efficacy variable of the patient at the visit will be calculated as follow:

Summing over all successful included systolic/diastolic measurements collected during the time interval (24-hour, actigraphy reported sleep time or actigraphy reported wake time), then divide the total by number of successful included measurements.

The actigraphy can detect the patient's sleep or wake time based on the patient's activity intensity. If the patient has interruptive sleep periods, the actigraphy will report the first inactivity period of the patient as the patient's sleep time. Wake time will be the time outside the sleep interval. Each patient will only have one sleep time and one wake time reported by the device.

Appendix E Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
CPK	>3 ULN	FDA Feb 2005.
	>10 ULN	Am J Cardiol Apr 2006.
		Categories are cumulative.
		First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min)	<15 (end stage renal disease)	FDA draft Guidance 2010
(Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥30 - < 60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥ 90 (normal GFR)	
eGFR (mL/min/1.73 m^2)	<15 (end stage renal disease)	FDA draft Guidance 2010
(Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥30 - < 60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥ 90 (normal GFR)	
Creatinine	≥150 µmol/L (Adults)	Benichou C, 1994.
	≥30% change from baseline	
	≥100% change from baseline	
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	
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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
ECG		Ref.: International Council for Harmonisation (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	Categories are cumulative
	>90 bpm	
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
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%	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
QRS	>110 ms	Categories are cumulative
	>110 ms and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
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 F List of PTs for select EOSIs (MedDRA v21.1)

EOSI	Preferred Term Code	Preferred Term
Genital Mycotic Infections	10004074	Balanitis candida
Genital Mycotic Infections	10018143	Genital candidiasis
Genital Mycotic Infections	10047784	Vulvovaginal candidiasis
Genital Mycotic Infections	10061180	Genital infection fungal
Genital Mycotic Infections	10064899	Vulvovaginal mycotic infection
Genital Mycotic Infections	10065582	Urogenital infection fungal
Genital Mycotic Infections	10071209	Candida cervicitis
Genital Mycotic Infections	10079521	Fungal balanitis
Urinary tract infections	10011781	Cystitis
Urinary tract infections	10011790	Cystitis escherichia
Urinary tract infections	10011797	Cystitis klebsiella
Urinary tract infections	10011799	Cystitis pseudomonal
Urinary tract infections	10017525	Fungal cystitis
Urinary tract infections	10018185	Genitourinary chlamydia infection
Urinary tract infections	10023424	Kidney infection
Urinary tract infections	10037584	Pyelitis
Urinary tract infections	10037596	Pyelonephritis
Urinary tract infections	10037597	Pyelonephritis acute
Urinary tract infections	10037601	Pyelonephritis chronic
Urinary tract infections	10037603	Pyelonephritis mycoplasmal
Urinary tract infections	10037653	Pyonephrosis
Urinary tract infections	10038351	Renal abscess
Urinary tract infections	10044828	Tuberculosis of genitourinary system
Urinary tract infections	10046424	Urethral abscess
Urinary tract infections	10046480	Urethritis
Urinary tract infections	10046482	Urethritis chlamydial
Urinary tract infections	10046483	Urethritis gonococcal
Urinary tract infections	10046490	Urethritis ureaplasmal
Urinary tract infections	10046571	Urinary tract infection
Urinary tract infections	10046572	Urinary tract infection enterococcal
Urinary tract infections	10046704	Urogenital trichomoniasis
Urinary tract infections	10048302	Tubulointerstitial nephritis
Urinary tract infections	10048709	Urosepsis
Urinary tract infections	10048837	Cystitis glandularis
Urinary tract infections	10049059	Urinary tract infection fungal
Urinary tract infections	10049100	Pyelocystitis
Urinary tract infections	10051250	Ureteritis
Urinary tract infections	10051350	Cytomegalovirus urinary tract infection
Urinary tract infections	10051959	Urinary bladder abscess
Urinary tract infections	10052238	Escherichia urinary tract infection
Urinary tract infections	10054088	Urinary tract infection bacterial

Urinary tract infections	10056351	Emphysematous cystitis
Urinary tract infections	10058523	Bladder candidiasis
Urinary tract infections	10058596	Renal cyst infection
Urinary tract infections	10059517	Bacterial pyelonephritis
Urinary tract infections	10061181	Genitourinary tract gonococcal infection
Urinary tract infections	10061182	Genitourinary tract infection
Urinary tract infections	10061395	Ureter abscess
Urinary tract infections	10062279	Urinary tract infection pseudomonal
Urinary tract infections	10062280	Urinary tract infection staphylococcal
Urinary tract infections	10064825	Urinary tract infection viral
Urinary tract infections	10064921	Urinary tract inflammation
Urinary tract infections	10065197	Cystitis viral
Urinary tract infections	10065198	Cystitis bacterial
Urinary tract infections	10065199	Cystitis helminthic
Urinary tract infections	10065213	Pyelonephritis viral
Urinary tract infections	10065214	Pyelonephritis fungal
Urinary tract infections	10065582	Urogenital infection fungal
Urinary tract infections	10065583	Urogenital infection bacterial
Urinary tract infections	10066757	Urinary tract abscess
Urinary tract infections	10068822	Emphysematous pyelonephritis
Urinary tract infections	10070300	Streptococcal urinary tract infection
Urinary tract infections	10071736	Acute focal bacterial nephritis
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
Volume depletion	10005697	Blood osmolarity increased
Volume depletion	10005731	Blood pressure ambulatory decreased
Volume depletion	10005734	Blood pressure decreased
Volume depletion	10005737	Blood pressure diastolic decreased
Volume depletion	10005748	Blood pressure immeasurable
Volume depletion	10005758	Blood pressure systolic decreased
Volume depletion	10005761	Blood pressure systolic inspiratory decreased
Volume depletion	10007979	Central venous pressure decreased
Volume depletion	10009192	Circulatory collapse
Volume depletion	10012174	Dehydration
Volume depletion	10013578	Dizziness postural
Volume depletion	10021097	Hypotension
Volume depletion	10021137	Hypovolaemia
Volume depletion	10021138	Hypovolaemic shock
Volume depletion	10026983	Mean arterial pressure decreased
Volume depletion	10031127	Orthostatic hypotension
Volume depletion	10036653	Presyncope
Volume depletion	10037327	Pulmonary arterial wedge pressure decreased
Volume depletion	10042772	Syncope
Volume depletion	10046640	Urine flow decreased

Volume depletion	10047235	Venous pressure decreased
Volume depletion	10047239	Venous pressure jugular decreased
Volume depletion	10047689	Volume blood decreased
Volume depletion	10050760	Blood urea nitrogen/creatinine ratio increased
Volume depletion	10050905	Decreased ventricular preload
Volume depletion	10053356	Blood pressure orthostatic decreased
Volume depletion	10059895	Urine output decreased
Volume depletion	10060089	Left ventricular end-diastolic pressure decreased
Volume depletion	10060231	Pulmonary arterial pressure decreased
Volume depletion	10063080	Postural orthostatic tachycardia syndrome
Volume depletion	10063927	Orthostatic intolerance
Volume depletion	10066077	Diastolic hypotension
Volume depletion	10069431	Orthostatic heart rate response increased
Volume depletion	10069583	Pulse volume decreased
Volume depletion	10072370	Prerenal failure
Pancreatitis	10033625	Pancreatic haemorrhage
Pancreatitis	10033635	Pancreatic pseudocyst
Pancreatitis	10033636	Pancreatic pseudocyst drainage
Pancreatitis	10033645	Pancreatitis
Pancreatitis	10033647	Pancreatitis acute
Pancreatitis	10033649	Pancreatitis chronic
Pancreatitis	10033650	Pancreatitis haemorrhagic
Pancreatitis	10033654	Pancreatitis necrotising
Pancreatitis	10033657	Pancreatitis relapsing
Pancreatitis	10048984	Pancreatic abscess
Pancreatitis	10052400	Oedematous pancreatitis
Pancreatitis	10056277	Pancreatorenal syndrome
Pancreatitis	10056975	Pancreatic phlegmon
Pancreatitis	10056976	Hereditary pancreatitis
Pancreatitis	10056977	Alcoholic pancreatitis
Pancreatitis	10058096	Pancreatic necrosis
Pancreatitis	10065189	Pancreatitis helminthic
Pancreatitis	10066127	Ischaemic pancreatitis
Pancreatitis	10069002	Autoimmune pancreatitis
Pancreatitis	10074894	Traumatic pancreatitis
Pancreatitis	10076058	Haemorrhagic necrotic pancreatitis
Venous thrombotic events	10003192	Arteriovenous fistula thrombosis
Venous thrombotic events	10003880	Axillary vein thrombosis
Venous thrombotic events	10006537	Budd-Chiari syndrome
Venous thrombotic events	10007830	Cavernous sinus thrombosis
Venous thrombotic events	10008138	Cerebral venous thrombosis
Venous thrombotic events	10014522	Embolism venous
Venous thrombotic events	10019713	Hepatic vein thrombosis
Venous thrombotic events	10023237	Jugular vein thrombosis
Venous thrombotic events	10027402	Mesenteric vein thrombosis
Venous thrombotic events	10034272	Pelvic venous thrombosis

Venous thrombotic events	10034324	Penile vein thrombosis
Venous thrombotic events	10036206	Portal vein thrombosis
Venous thrombotic events	10037377	Pulmonary embolism
Venous thrombotic events	10037421	Pulmonary microemboli
Venous thrombotic events	10037437	Pulmonary thrombosis
Venous thrombotic events	10037459	Pulmonary venous thrombosis
Venous thrombotic events	10038547	Renal vein embolism
Venous thrombotic events	10038548	Renal vein thrombosis
Venous thrombotic events	10038908	Retinal vein thrombosis
Venous thrombotic events	10041659	Splenic vein thrombosis
Venous thrombotic events	10042567	Superior sagittal sinus thrombosis
Venous thrombotic events	10043570	Thrombophlebitis
Venous thrombotic events	10043581	Thrombophlebitis migrans
Venous thrombotic events	10043595	Thrombophlebitis superficial
Venous thrombotic events	10043605	Thrombosed varicose vein
Venous thrombotic events	10044457	Transverse sinus thrombosis
Venous thrombotic events	10047193	Vena cava embolism
Venous thrombotic events	10047195	Vena cava thrombosis
Venous thrombotic events	10047249	Venous thrombosis
Venous thrombotic events	10048591	Post thrombotic syndrome
Venous thrombotic events	10049446	Subclavian vein thrombosis
Venous thrombotic events	10050216	Paget-Schroetter syndrome
Venous thrombotic events	10050902	Postoperative thrombosis
Venous thrombotic events	10051055	Deep vein thrombosis
Venous thrombotic events	10053182	Arteriovenous graft thrombosis
Venous thrombotic events	10061251	Intracranial venous sinus thrombosis
Venous thrombotic events	10061408	Venous thrombosis limb
Venous thrombotic events	10063363	Brachiocephalic vein thrombosis
Venous thrombotic events	10063909	Post procedural pulmonary embolism
Venous thrombotic events	10066881	Deep vein thrombosis postoperative
Venous thrombotic events	10067270	Thrombosis corpora cavernosa
Venous thrombotic events	10069909	Metastatic pulmonary embolism
Venous thrombotic events	10072059	Ovarian vein thrombosis
Venous thrombotic events	10074349	Ophthalmic vein thrombosis
Venous thrombotic events	10077623	Portosplenomesenteric venous thrombosis
Venous thrombotic events	10077829	Visceral venous thrombosis
Venous thrombotic events	10078810	Hepatic vein embolism
Thyroid cancer	10002240	Anaplastic thyroid cancer
Thyroid cancer	10016935	Follicular thyroid cancer
Thyroid cancer	10027105	Medullary thyroid cancer
Thyroid cancer	10033701	Papillary thyroid cancer
Thyroid cancer	10043744	Thyroid neoplasm
Thyroid cancer	10055107	Thyroid cancer metastatic
Thyroid cancer	10066136	Huerthle cell carcinoma
Thyroid cancer	10066474	Thyroid cancer
Thyroid cancer	10070567	Thyroid cancer stage 0
Thyroid cancer	10071027	Thyroid cancer stage I

Thyroid cancer	10071028	Thyroid cancer stage II
Thyroid cancer	10071029	Thyroid cancer stage III
Thyroid cancer	10071030	Thyroid cancer stage IV
Thyroid cancer	10072162	Thyroid cancer recurrent
Thyroid cancer	10072613	Thyroid B-cell lymphoma
Thyroid cancer	10073153	Familial medullary thyroid cancer
Thyroid cancer	10076603	Poorly differentiated thyroid carcinoma
Renal cell cancer	10038389	Renal cancer
Renal cell cancer	10038390	Renal cancer recurrent
Renal cell cancer	10038391	Renal cancer stage I
Renal cell cancer	10038392	Renal cancer stage II
Renal cell cancer	10038393	Renal cancer stage III
Renal cell cancer	10038394	Renal cancer stage IV
Renal cell cancer	10038410	Renal cell carcinoma recurrent
Renal cell cancer	10038411	Renal cell carcinoma stage I
Renal cell cancer	10038412	Renal cell carcinoma stage II
Renal cell cancer	10038413	Renal cell carcinoma stage III
Renal cell cancer	10038414	Renal cell carcinoma stage IV
Renal cell cancer	10050018	Renal cancer metastatic
Renal cell cancer	10050513	Metastatic renal cell carcinoma
Renal cell cancer	10061482	Renal neoplasm
Renal cell cancer	10067944	Hereditary leiomyomatosis renal cell carcinoma
Renal cell cancer	10067946	Renal cell carcinoma
Renal cell cancer	10073251	Clear cell renal cell carcinoma
Renal cell cancer	10078493	Papillary renal cell carcinoma
Pancreatic cancer	10018404	Glucagonoma
Pancreatic cancer	10022498	Insulinoma
Pancreatic cancer	10025997	Malignant neoplasm of islets of Langerhans
Pancreatic cancer	10029341	Neurotensinoma
Pancreatic cancer	10033609	Pancreatic carcinoma
Pancreatic cancer	10033610	Pancreatic carcinoma metastatic
Pancreatic cancer	10033613	Pancreatic carcinoma recurrent
Pancreatic cancer	10041329	Somatostatinoma
Pancreatic cancer	10047430	Vipoma
Pancreatic cancer	10051709	Gastrinoma malignant
Pancreatic cancer	10052747	Adenocarcinoma pancreas
Pancreatic cancer	10055006	Pancreatic sarcoma
Pancreatic cancer	10055007	Carcinoid tumour of the pancreas
Pancreatic cancer	10059320	Pancreatic carcinoma stage 0
Pancreatic cancer	10059321	Pancreatic carcinoma stage I
Pancreatic cancer	10059322	Pancreatic carcinoma stage II
Pancreatic cancer	10059323	Pancreatic carcinoma stage III
Pancreatic cancer	10059326	Pancreatic carcinoma stage IV
Pancreatic cancer	10061902	Pancreatic neoplasm
Pancreatic cancer	10067517	Pancreatic neuroendocrine tumour
Pancreatic cancer	10068909	Pancreatic neuroendocrine tumour metastatic
Pancreatic cancer	10069345	Solid pseudopapillary tumour of the pancreas

Pancreatic cancer	10073363	Acinar cell carcinoma of pancreas
Pancreatic cancer	10073364	Ductal adenocarcinoma of pancreas
Pancreatic cancer	10073365	Intraductal papillary-mucinous carcinoma of pancreas
Pancreatic cancer	10073367	Pancreatoblastoma
Bladder cancer	10004986	Bladder adenocarcinoma recurrent
Bladder cancer	10004987	Bladder adenocarcinoma stage 0
Bladder cancer	10004988	Bladder adenocarcinoma stage I
Bladder cancer	10004989	Bladder adenocarcinoma stage II
Bladder cancer	10004990	Bladder adenocarcinoma stage III
Bladder cancer	10004991	Bladder adenocarcinoma stage IV
Bladder cancer	10004992	Bladder adenocarcinoma stage unspecified
Bladder cancer	10005003	Bladder cancer
Bladder cancer	10005005	Bladder cancer recurrent
Bladder cancer	10005006	Bladder cancer stage 0, with cancer in situ
Bladder cancer	10005007	Bladder cancer stage 0, without cancer in situ
Bladder cancer	10005008	Bladder cancer stage I, with cancer in situ
Bladder cancer	10005009	Bladder cancer stage I, without cancer in situ
Bladder cancer	10005010	Bladder cancer stage II
Bladder cancer	10005011	Bladder cancer stage III
Bladder cancer	10005012	Bladder cancer stage IV
Bladder cancer	10005056	Bladder neoplasm
Bladder cancer	10005075	Bladder squamous cell carcinoma recurrent
Bladder cancer	10005076	Bladder squamous cell carcinoma stage 0
Bladder cancer	10005077	Bladder squamous cell carcinoma stage I
Bladder cancer	10005078	Bladder squamous cell carcinoma stage II
Bladder cancer	10005079	Bladder squamous cell carcinoma stage III
Bladder cancer	10005080	Bladder squamous cell carcinoma stage IV
Bladder cancer	10005081	Bladder squamous cell carcinoma stage unspecified
Bladder cancer	10005084	Bladder transitional cell carcinoma
Bladder cancer	10051690	Urinary bladder sarcoma
Bladder cancer	10057352	Metastatic carcinoma of the bladder
Bladder cancer	10066749	Bladder transitional cell carcinoma stage 0
Bladder cancer	10066750	Bladder transitional cell carcinoma recurrent
Bladder cancer	10066751	Bladder transitional cell carcinoma stage I
Bladder cancer	10066752	Bladder transitional cell carcinoma stage IV
Bladder cancer	10066753	Bladder transitional cell carcinoma stage II
Bladder cancer	10066754	Bladder transitional cell carcinoma stage III
Bladder cancer	10071664	Bladder transitional cell carcinoma metastatic
Bladder cancer	10078341	Neuroendocrine carcinoma of the bladder
Potentially leading to amputation	10003084	Areflexia
Potentially leading to amputation	10003178	Arterial thrombosis
Potentially leading to amputation	10003210	Arteriosclerosis
Potentially leading to amputation	10003222	Arteriosclerotic gangrene
Potentially leading to amputation	10006784	Burning sensation
Potentially leading to amputation	10007904	Cellulitis enterococcal
Potentially leading to amputation	10007905	Cellulitis gangrenous

Potentially leading to amputation	10007921	Cellulitis staphylococcal
Potentially leading to amputation	10007922	Cellulitis streptococcal
Potentially leading to amputation	10012174	Dehydration
Potentially leading to amputation	10012665	Diabetic gangrene
Potentially leading to amputation	10012679	Diabetic neuropathic ulcer
Potentially leading to amputation	10012680	Diabetic neuropathy
Potentially leading to amputation	10017711	Gangrene
Potentially leading to amputation	10020937	Hypoaesthesia
Potentially leading to amputation	10021137	Hypovolaemia
Potentially leading to amputation	10021519	Impaired healing
Potentially leading to amputation	10021784	Infected skin ulcer
Potentially leading to amputation	10022562	Intermittent claudication
Potentially leading to amputation	10024774	Localised infection
Potentially leading to amputation	10028862	Necrosis ischaemic
Potentially leading to amputation	10029331	Neuropathy peripheral
Potentially leading to amputation	10031149	Osteitis
Potentially leading to amputation	10031252	Osteomyelitis
Potentially leading to amputation	10031253	Osteomyelitis acute
Potentially leading to amputation	10031256	Osteomyelitis chronic
Potentially leading to amputation	10031262	Osteomyelitis salmonella
Potentially leading to amputation	10031264	Osteonecrosis
Potentially leading to amputation	10033775	Paraesthesia
Potentially leading to amputation	10034568	Peripheral coldness
Potentially leading to amputation	10034576	Peripheral ischaemia
Potentially leading to amputation	10034620	Peripheral sensory neuropathy
Potentially leading to amputation	10034636	Peripheral vascular disorder
Potentially leading to amputation	10036155	Poor peripheral circulation
Potentially leading to amputation	10036410	Postoperative wound infection
Potentially leading to amputation	10040026	Sensory disturbance
Potentially leading to amputation	10040840	Skin erosion
Potentially leading to amputation	10040872	Skin infection
Potentially leading to amputation	10040943	Skin ulcer
Potentially leading to amputation	10042343	Subcutaneous abscess
Potentially leading to amputation	10043607	Thrombosis
Potentially leading to amputation	10048031	Wound dehiscence
Potentially leading to amputation	10048038	Wound infection
Potentially leading to amputation	10049927	Dry gangrene
Potentially leading to amputation	10050473	Abscess limb
Potentially leading to amputation	10050502	Neuropathic ulcer
Potentially leading to amputation	10051548	Burn infection
Potentially leading to amputation	10052428	Wound
Potentially leading to amputation	10052949	Arterial therapeutic procedure
Potentially leading to amputation	10053692	Wound complication
Potentially leading to amputation	10053716	Wound necrosis
Potentially leading to amputation	10054044	Diabetic microangiopathy
Potentially leading to amputation	10056340	Diabetic ulcer
Potentially leading to amputation	10056418	Arterial bypass operation
Potentially leading to amputation	10056673	Peripheral sensorimotor neuropathy
Potentially leading to amputation	10057518	Peripheral artery angioplasty
Potentially leading to amputation	10057525	Peripheral artery occlusion
Potentially leading to amputation	10058041	Wound sepsis

Potentially leading to amputation	10058042	Wound abscess
Potentially leading to amputation	10059245	Angiopathy
Potentially leading to amputation	10059385	Extremity necrosis
Potentially leading to amputation	10059442	Wound infection staphylococcal
Potentially leading to amputation	10059444	Wound infection pseudomonas
Potentially leading to amputation	10060734	Diabetic foot
Potentially leading to amputation	10060803	Diabetic foot infection
Potentially leading to amputation	10060963	Arterial disorder
Potentially leading to amputation	10060965	Arterial stenosis
Potentially leading to amputation	10061627	Amputation
Potentially leading to amputation	10061655	Arterial graft
Potentially leading to amputation	10061657	Arterial stent insertion
Potentially leading to amputation	10061666	Autonomic neuropathy
Potentially leading to amputation	10061815	Diabetic vascular disorder
Potentially leading to amputation	10062198	Microangiopathy
Potentially leading to amputation	10062255	Soft tissue infection
Potentially leading to amputation	10062585	Peripheral arterial occlusive disease
Potentially leading to amputation	10062599	Arterial occlusive disease
Potentially leading to amputation	10062610	Ischaemic limb pain
Potentially leading to amputation	10062932	Wound treatment
Potentially leading to amputation	10064250	Staphylococcal osteomyelitis
Potentially leading to amputation	10064601	Iliac artery occlusion
Potentially leading to amputation	10065237	Osteomyelitis bacterial
Potentially leading to amputation	10065239	Osteomyelitis fungal
Potentially leading to amputation	10065240	Wound infection bacterial
Potentially leading to amputation	10065242	Wound infection fungal
Potentially leading to amputation	10068653	Bone abscess
Potentially leading to amputation	10069379	Peripheral arterial reocclusion
Potentially leading to amputation	10072170	Skin wound
Potentially leading to amputation	10072557	Peripheral artery restenosis
Potentially leading to amputation	10072560	Peripheral endarterectomy
Potentially leading to amputation	10072561	Peripheral artery bypass
Potentially leading to amputation	10072562	Peripheral artery stent insertion
Potentially leading to amputation	10072563	Peripheral artery stenosis
Potentially leading to amputation	10072564	Peripheral artery thrombosis
Potentially leading to amputation	10074396	Penetrating atherosclerotic ulcer
Potentially leading to amputation	10075118	Subperiosteal abscess
Potentially leading to amputation	10075714	Vasculitic ulcer

Appendix G Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA1c: Change from Baseline at Week 26	ITT	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR assumption): treatment, randomization stratum (HbA1c / SBP at screening), and country as fixed effects, and baseline HbA1c value as a covariate	Tipping point analysis; ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR assumption)	Subgroups: race, ethnicity, age group, gender, baseline BMI, baseline HbA1c, baseline SBP, Baseline eGFR, Duration of diabetes, and country.	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit. By-visit summary and graph excluding measurements after rescue therapy.
Secondary endpoints					
2-hour PPG, FPG, body weight: Change from Baseline to Week 26; SBP (for patients with baseline SBP ≥130 mmHg, all patients): Change from Baseline to Week 12	ITT	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR assumption): treatment, randomization stratum (HbA1c / SBP at screening), and country as fixed effects, and baseline endpoint value as a covariate	No	No	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit.

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Proportion of patients with HbA1c <6.5%, <7.0% at Week 26	ITT	CMH method stratified on randomization strata (HbA1c / SBP at screening)	CMH method stratified on randomization strata (HbA1c / SBP at screening): excluding patients with baseline HbA1c values <6.5% (for <6.5% responders) or <7% (for <7% responders) respectively	No	By-visit summary and graphs of HbA1c responders (<6.5%, <7%). By-visit frequency summary and graphs of HbA1c responders (<6.5%, <7%) excluding patients with baseline HbA1c values <6.5% or <7% respectively.
Other endpoints					
UACR, UGE, and UGCR, serum creatinine, eGFR: Change from Baseline	ITT	Summary statistics for observed values and changes from baseline by visit.	No	No	Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit as appropriate.
SBP (for patients with baseline SBP <130 mmHg), DBP: Change from Baseline to Week 12		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 (for all patients and patients with baseline SBP≥130 mmHg): Change from Baseline to Week 26		Summary statistics for observed values and changes from baseline by visit.	No	No	No
HbA1c, FPG, SBP (for all patients and patients with baseline SBP≥130 mmHg), body weight: Change from Baseline to Week 79		Summary statistics for observed values and changes from baseline by visit.	No	No	No

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Proportion of patients: achieving SBP <130 mmHg for those with baseline SBP ≥130 mmHg, achieving DBP <80 mmHg for those with baseline DBP ≥80 mmHg, with reduction in body weight by ≥2%, ≥5%, and ≥10% from baseline	ITT	By-visit frequency summary	No	No	By-visit graphical presentation as appropriate
Proportion of patients requiring rescue for hyperglycemia	ITT	Summary statistics	No	No	KM plot, List of patients rescued
ABPM Substudy	***ABPM population***				
Primary endpoint					
Change from Baseline to Week 12 in average 24-hour SBP in a subset of patients with SBP ≥130 mmHg at Screening	ABPM population	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based MI method under MNAR assumption): treatment, randomization stratum (HbA1c), and country as fixed effects, and baseline SBP value as a covariate	No	No	Summary statistics for observed values and changes from baseline by visit.
Secondary endpoint					
Average 24-hour SBP: Change from Baseline to Week 26 Average 24-hour DBP, average adjusted awake time BP as measured by SBP and DBP with adjustment based on actigraphy, average adjusted sleep time BP as measured by SBP and DBP with adjustment based on actigraphy: Change from Baseline to Week 12 and 26	ABPM population	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based MI method under MNAR framework): treatment, randomization stratum (HbA1c), and country as fixed effects, and baseline SBP value as a covariate	No	No	Summary statistics for observed values and changes from baseline by visit.

SAFETY ANALYSES

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

Appendix H Study Flow Chart

	Screening Period			Double-Blind Core Treatment Period[a]									Double-Blind Extension Period[b]				Follow-up
	Screening	Run-in															
VISIT	1	2	3A (ABPM placement) [c]	3 (Randomization)	4	5	6	7A (ABPM placement)[c]	7	8	9A (ABPM placement) [c]	9	10	11	12	13	14[d]
Week	Up to -4	-2	-1	0 Baseline	1	4	8	12	12	18	26	26	39	52	65	79	83
Day (window [days])		(-7/+3)	-7 (±2)	1	7 (±3)	28 (±3)	56 (±3)	83 (±2)	84 (±3)	126 (±3)	181 (±2)	182 (±3)	273 (±7)	365 (±7)	455 (±7)	551 (-3 to +4)	579 (±3)
Informed consent	X																
Inclusion criteria	X																
Exclusion criteria	X			X													
Demographics	X																
Medical/Surgical History	X																
Medication History	X																
Hepatitis serology	X																
Body weight, height[e]	X	X		X	X	X	X		X	X		X	X	X	X	X	X
Vital signs[f]	X	X		X	X	X	X		X	X		X	X	X	X	X	X
Physical Examination:																	
Complete	X											X				X	
Abbreviated		X		X	X	X	X		X	X			X	X	X		X
Diet & exercise instruction		X		X								X		X		X	
Instruction on basic genitourinary hygiene & hydration		X		X	X	X	X		X	X		X	X	X	X	X	

	Screening Period			Double-Blind Core Treatment Period[a]									Double-Blind Extension Period[b]				Follow-up
	Screening	Run-in															
VISIT	1	2	3A (ABPM placement) [c]	3 (Randomization)	4	5	6	7A (ABPM placement)[c]	7	8	9A (ABPM placement) [c]	9	10	11	12	13	14[d]
Week	Up to -4	-2	-1	0 Baseline	1	4	8	12	12	18	26	26	39	52	65	79	83
Day (window [days])		(-7/+3)	-7 (±2)	1	7 (±3)	28 (±3)	56 (±3)	83 (±2)	84 (±3)	126 (±3)	181 (±2)	182 (±3)	273 (±7)	365 (±7)	455 (±7)	551 (-3 to +4)	579 (±3)
IRT contact[g]	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	X	
Collect/review diary		X		X	X	X	X		X	X		X	X	X	X	X	X
Instruction on diabetic ketoacidosis symptoms, glucose testing				X	X	X	X		X	X		X	X	X	X	X	
Dispense 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	
Concomitant Medication	X	X		X	X	X	X		X	X		X	X	X	X	X	X
Self-monitoring of blood glucose[h]		X		X	X	X	X		X	X		X	X	X	X	X	X
12-lead ECG[i]	X			X								X				X	
Standard mixed meal tolerance test[j]				X								X				X	
Laboratory testing[k]																	
FPG	X			X	X	X	X		X	X		X	X	X	X	X	

	Screening Period			Double-Blind Core Treatment Period[a]									Double-Blind Extension Period[b]				Follow-up
	Screening	Run-in															
VISIT	1	2	3A (ABPM placement) [c]	3 (Randomization)	4	5	6	7A (ABPM placement)[c]	7	8	9A (ABPM placement) [c]	9	10	11	12	13	14[d]
Week	Up to -4	-2	-1	0 Baseline	1	4	8	12	12	18	26	26	39	52	65	79	83
Day (window [days])		(-7/+3)	-7 (±2)	1	7 (±3)	28 (±3)	56 (±3)	83 (±2)	84 (±3)	126 (±3)	181 (±2)	182 (±3)	273 (±7)	365 (±7)	455 (±7)	551 (-3 to +4)	579 (±3)
HbA1c	X			X		X	X		X	X		X	X	X	X	X	
Chemistry (including amylase and lipase)	X			X		X	X		X	X		X	X	X	X	X	X
Hematology	X			X					X			X	X	X	X	X	
Fasting lipids	X			X		X	X		X	X		X				X	
Pregnancy test (WOCBP)[l]	X			X		X	X		X	X		X	X	X	X	X	
Serum follicle stimulating hormone and estradiol (menopausal women only)[l]	X																
Plasma concentration[m]						X				X		X		X		X	
Markers of intestinal transit & absorption[n]				X								X				X	X
Markers of bone & calcium metabolism[o]				X								X				X	
Urinalysis (dipstick and microscopy)[p]	X			X								X				X	

	Screening Period			Double-Blind Core Treatment Period[a]									Double-Blind Extension Period[b]				Follow-up
	Screening	Run-in															
VISIT	1	2	3A (ABPM placement) [c]	3 (Randomization)	4	5	6	7A (ABPM placement)[c]	7	8	9A (ABPM placement) [c]	9	10	11	12	13	14[d]
Week	Up to -4	-2	-1	0 Baseline	1	4	8	12	12	18	26	26	39	52	65	79	83
Day (window [days])		(-7/+3)	-7 (±2)	1	7 (±3)	28 (±3)	56 (±3)	83 (±2)	84 (±3)	126 (±3)	181 (±2)	182 (±3)	273 (±7)	365 (±7)	455 (±7)	551 (-3 to +4)	579 (±3)
Urine albumin, calcium, glucose & creatinine				X	X	X	X		X	X		X	X	X	X	X	X
[redacted]																	
ABPM placement[c]			X					X			X						
ABPM removal and assessment				X					X			X					
Evaluate for glycemic rescue					To be assessed and reported throughout the treatment period												
Hypoglycemia	To be assessed and reported throughout the study																
AEs/SAEs/AESIs/EOSIs	To be assessed and reported throughout the study[s]																

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

b If a patient completes the Core Treatment, but discontinues IMP during the Extension Period, the patient will have a Premature EOT Visit, and a Follow-up Visit 4 weeks after the last dose of IMP. Every effort will be made to have all patients return to the site at the time corresponding to their quarterly visits (ie, every 13 weeks) during the Extension Period. At the time corresponding to their Week 79 Visit, all attempts will be made to contact the patient to inquire about safety status. If a patient discontinues (or completes) treatment and study at the same time, a single visit will be performed using the procedure normally planned for the EOT visit.

c Ambulatory Blood Pressure Monitoring (ABPM) substudy visits for a subset of patients will occur 1 week before the randomization Visit; patients will return the ABPM device by post after 24-hour monitoring is complete. Patients in the ABPM substudy will also have visits for placement of the ABPM device the day before Week 12 and Week 26 visits.

d Four weeks after the last dose of IMP.

e Height to be measured only at screening.

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

g Interactive response Technology (IRT) contact not required for patients who discontinue IMP early after they have attended the EOT Visit.

h See Section 9.2.1.6 for details of SMBG measurements. Glucose meters used for SMBG display results as plasma glucose concentration. Patients should measure their fasting plasma glucose at least 3 times per week (including on day of each on-site study visit). After Visit 9 (Week 26), if fasting SMBG values are <120 mg/dL, over a 2-week period, the Investigator can instruct patients to self-monitor blood glucose once a week (on day of on-site study visit for weeks with on-site study visits).

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

j Postprandial plasma glucose will be assessed by central laboratory at Baseline and 2 hours after consuming a standard mixed liquid breakfast meal and via a mixed meal tolerance test (MMTT) on Day 1, Week 26, and Week 79. If a patient withdraws from IMP early, please see Section 10.3.4.

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

l Serum pregnancy testing only at screening; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to beginning the Run-in phase for all women of childbearing potential (WOCBP) unless there is documented history of menopause (based on documented follicle-stimulating hormone [FSH] and estradiol levels – if results not documented then FSH and estradiol will be tested at Screening visit) or they are surgically sterile. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

m Plasma concentration samples (ie, for sotagliflozin and Sotagliflozin-3-O-glucuronide) on Week 4, Week 18, and Week 52 should be drawn with the other laboratory assessments. For Week 26 and Week 79, plasma concentration samples should be drawn at Time 0 and 150 minutes (2 hour 30 minutes) immediately after the respective glucose assessments during the MMTT. Pharmacokinetic (PK) samples (except the 2 hour 30 minute sample during the MMTT) MUST be collected before administration of IMP. The date and time of the last intake of IMP prior to visits where PK samples are taken should be recorded by the patient in the patient diary. Patients should be reminded of this at visits preceding PK time points to ensure these details are captured. In the case of premature IMP discontinuation, PK samples should not be drawn at the Premature EOT visit, nor at any subsequent visits.

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

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

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

[redacted]

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