

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

**NCT Number:** NCT03066830

**Document Date(s):** SAP Version 3: 20 February 2020

## Lexicon Pharmaceuticals, Inc.

### Protocol No.: EFC14835

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

Covance Study ID: 000000154257

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## Statistical Analysis Plan

Version: 3

DATE OF ISSUE: 19 February 2020

Author: XXXXXXXXXX

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**APPROVALS**

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

**Covance Approval:**

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**VERSION HISTORY**

<b>Version Status</b>	<b>Version Date</b>
Final 1.0	07 August 2018
Final 2.0	03 June 2019
Final 3.0	19 February 2020



## TABLE OF CONTENTS

### APPROVALS

### VERSION HISTORY

### TABLE OF CONTENTS

### LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

## 1 OVERVIEW AND INVESTIGATIONAL PLAN

### 1.1 STUDY DESIGN AND RANDOMIZATION

#### 1.2 OBJECTIVES

##### 1.2.1 Primary objectives

##### 1.2.2 Secondary objectives

##### 1.2.3 Other objectives

### 1.3 DETERMINATION OF SAMPLE SIZE

### 1.4 STUDY PLAN

### 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

### 1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

## 2 STATISTICAL AND ANALYTICAL PROCEDURES

### 2.1 ANALYSIS ENDPOINTS

#### 2.1.1 Demographic and baseline characteristics

#### 2.1.2 Prior or concomitant medications

##### 2.1.2.1 Rescue therapy

##### 2.1.2.2 Prohibited prior and concomitant medications

#### 2.1.3 Efficacy endpoints

##### 2.1.3.1 Primary efficacy endpoint(s)

##### 2.1.3.2 Secondary efficacy endpoint(s)

##### 2.1.3.3 Other efficacy endpoint(s)

#### 2.1.4 Safety endpoints

##### 2.1.4.1 Hypoglycemia

##### 2.1.4.2 Adverse events variables

##### 2.1.4.3 Deaths

##### 2.1.4.4 Laboratory safety variables

##### 2.1.4.5 Vital signs variables

##### 2.1.4.6 Physical examination

[2.1.4.7 Electrocardiogram variables](#)[2.1.5 Pharmacokinetic variables](#)[2.2 DISPOSITION OF PATIENTS](#)[2.2.1 Randomization and drug dispensing irregularities](#)[2.3 ANALYSIS POPULATIONS](#)[2.3.1 Efficacy populations](#)[2.3.1.1 Intent-to-treat population](#)[2.3.2 Safety population](#)[2.3.3 Pharmacokinetic population](#)[2.4 STATISTICAL METHODS](#)[2.4.1 Demographics and baseline characteristics](#)[2.4.2 Prior or concomitant medications](#)[2.4.3 Extent of investigational medicinal product exposure and compliance](#)[2.4.3.1 Extent of investigational medicinal product exposure](#)[2.4.3.2 Compliance](#)[2.4.4 Analyses of efficacy endpoints](#)[2.4.4.1 Analysis of primary efficacy endpoint](#)[2.4.4.2 Analyses of secondary efficacy endpoints](#)[2.4.4.3 Analyses of other efficacy endpoints](#)[2.4.4.4 Multiplicity issues](#)[2.4.5 Analyses of safety data](#)[2.4.5.1 Analyses of hypoglycemia](#)[2.4.5.2 Analyses of adverse events](#)[2.4.5.3 Deaths](#)[2.4.5.4 Analyses of laboratory variables](#)[2.4.5.5 Analyses of vital sign variables](#)[2.4.5.6 Analyses of electrocardiogram variables](#)[2.4.5.7 Analyses of physical examination variables](#)[2.4.6 Analyses of pharmacokinetic variables](#)[2.5 DATA HANDLING CONVENTIONS](#)[2.5.1 General conventions](#)[2.5.2 Data handling conventions for secondary efficacy variables](#)[2.5.3 Missing data](#)[2.5.4 Windows for time points /Measurements for analyses](#)[2.5.5 Unscheduled visits](#)[2.5.6 Pooling of centers for statistical analyses](#)[2.5.7 Statistical technical issues](#)[3 INTERIM ANALYSIS](#)

[4 DATABASE LOCK](#)

[5 SOFTWARE DOCUMENTATION](#)

[6 REFERENCES](#)

[7 LIST OF APPENDICES](#)

[APPENDIX A POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA](#)

[APPENDIX B LIST OF PTS FOR SELECT EOSIS \(MEDDRA V22.0\)](#)

[APPENDIX C SUMMARY OF STATISTICAL ANALYSES](#)

[APPENDIX D STUDY FLOW CHART](#)

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AEs:	adverse events
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BLOQ:	below limit of quantification
ATC:	anatomical therapeutic chemical
BMI:	body mass index
BUN:	blood urea nitrogen
CEC:	clinical endpoint committee
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CV:	cardiovascular, cardiovascular
DBP:	diastolic blood pressure
DCCT:	diabetes control and complications trial
DILI:	drug-induced liver injury
DMC:	Data Monitoring Committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA/PRAC:	European Medicines Agency/ Pharmacovigilance Risk Assessment Committee
EOSI:	events of special interest
EOT:	end of treatment
FPG:	fasting plasma glucose
Gd:	glibenclamide
GdMR:	glibenclamide MR
Gp:	glipizide
GpXL:	glipizide XL
Gz:	gliclazide
GzMR:	gliclazide MR
HbA1c:	hemoglobin A1c
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IFCC:	International Federation of Clinical Chemistry and Laboratory Medicine
IMP:	investigational medicinal product
INN:	international nonproprietary name
IRT:	interactive response technology
ITT:	intent-to-treat
KM:	Kaplan-Meier
LLT:	lower level term
MACE:	major adverse cardiovascular events

MAR:	missing at random
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation
MNAR:	missing not at random
NIMP:	noninvestigational medicinal product
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PK:	pharmacokinetic
PT:	preferred term
SAE:	serious adverse events
SBP:	systolic blood pressure
SD:	standard deviation
SOC:	system organ class
T2D:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
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. Patients will be randomly assigned 1:1 to the following 2 treatment groups

- Sotagliflozin 400 mg.
- Placebo.

All patients will have a Screening Period comprised of an up to 2-week Screening Phase and a 2-week, single-blind placebo Run-in Phase prior to randomization. Following randomization, patients will have a 26-week, double-blind Core Treatment Period, a 53-week double-blind Extension Period, and a 2-week post-treatment Follow-up period to collect safety information (patients who prematurely discontinue the study treatment are expected to continue in the study).

At the end of the screening period, eligible patients will be centrally randomized (using permuted block randomization schedule) via an Interactive Response Technology (IRT). The randomization will be stratified by

- Hemoglobin A1c (HbA1c) at Screening ( $\leq 8.5\%$ ,  $> 8.5\%$ ).
- Metformin use at Screening (Yes, No).
- Systolic blood pressure (SBP) at Screening ( $< 130$  mmHg,  $\geq 130$  mmHg).

It is anticipated to randomize a total of approximately 500 patients.

### 1.2 OBJECTIVES

#### 1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of sotagliflozin 400 mg versus placebo on HbA1c reduction at Week 26 in patients with type 2 diabetes mellitus (T2D) who have inadequate glycemic control with a sulfonylurea alone or in combination with metformin.

#### 1.2.2 Secondary objectives

- To compare sotagliflozin 400 mg versus placebo for:
  - 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  $\geq 130$  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

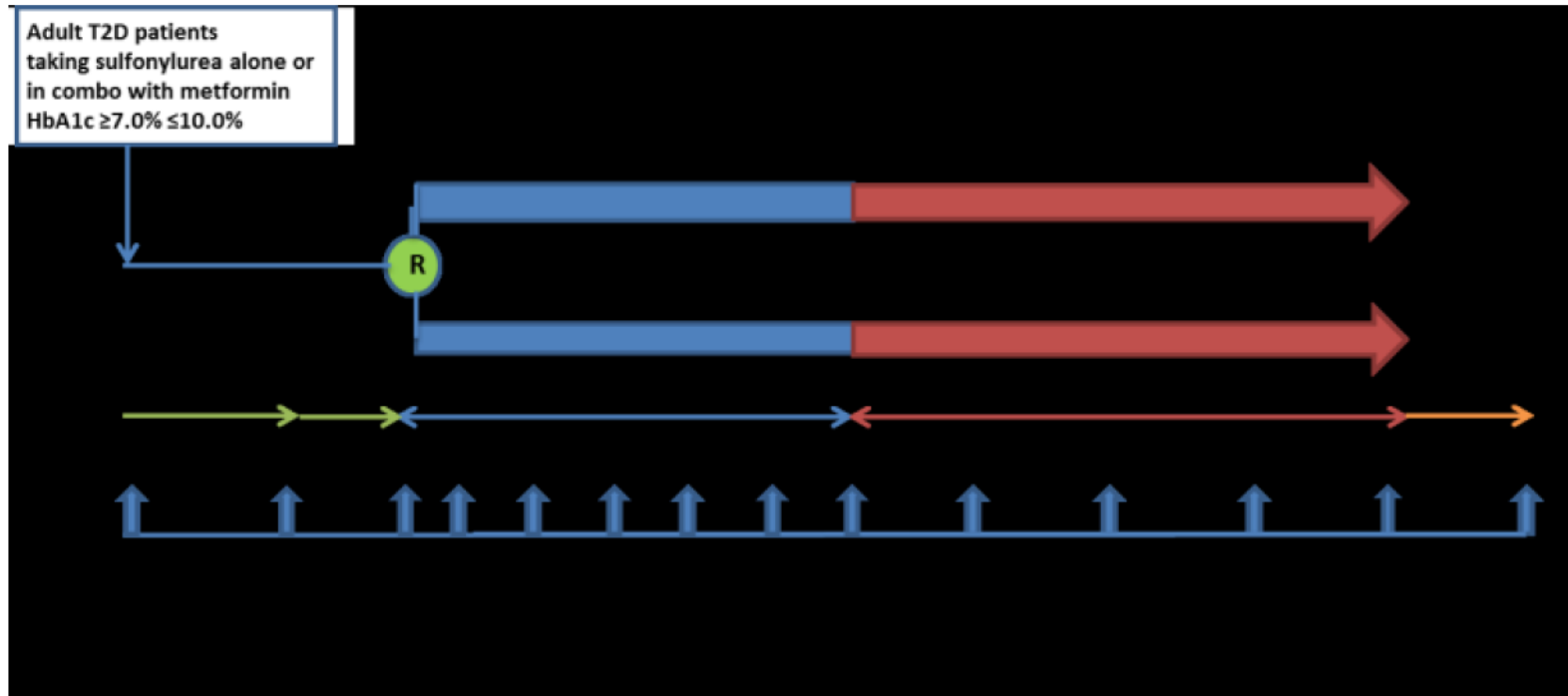
- To compare sotagliflozin versus placebo based on other blood pressure endpoints.
- To compare sotagliflozin versus placebo with respect to change from Baseline on the following endpoints:
  - Estimated glomerular filtration rate (eGFR),
  - Reduction in body weight by  $\geq 2\%$ ,  $\geq 5\%$ , and  $\geq 10\%$ .
- 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 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.

### 1.3 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  $\alpha$ -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 number of patients taking a sulfonylurea and metformin will be limited to 330 patients, to ensure sufficient numbers of sulfonylurea monotherapy patients.

### 1.4 STUDY PLAN



The study flowchart can be found in [Appendix D](#).



## 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

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

The 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 Feb 24, 2017. There were no planned interim analyses.

**Table 1 - Protocol amendment statistical changes**

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	20-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	20-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	20-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 considerations
2	20-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	20-Dec-2017	AE leading to study discontinuation is less clinically relevant than AE leading to treatment discontinuation	Delete AEs leading to discontinuation from the study from safety endpoints
2	20-Dec-2017	To understand treatment effects over the entire study duration	Several objectives/endpoints "blood pressure endpoints at Week 26 and Week 79, HbA1c, FPG and body weight endpoints at Week 79" were added

## 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	07-Aug-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	07-Aug-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	07-Aug-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 considerations*
1	07-Aug-2018	Urgent coronary revascularization not adjudicated by CEC to be consistent with outcome trials	Urgent coronary revascularization not included in adjudication related analyses*
1	07-Aug-2018	AE leading to study discontinuation is less clinically relevant than AE leading to treatment discontinuation	Delete AEs leading to discontinuation from the study from safety endpoints*
1	07-Aug-2018	To understand treatment effects over the entire study duration	Several objectives/endpoints "blood pressure endpoints at Week 26 and Week 79, HbA1c, FPG and body weight endpoints at Week 79" were added*
1	07-Aug-2018	Clarification on EOSI renal events	Details specified on renal events to be consistent with outcome studies in <a href="#">Section 2.1.4.2</a> .
1	07-Aug-2018	[REDACTED]	[REDACTED]
1	07-Aug-2018	[REDACTED]	[REDACTED]
1	07-Aug-2018	Updating the wording to be consistency with CEC charter	Unstable angina leading to hospitalization changed to Unstable angina requiring hospitalization
2	03-Jun-2019	[REDACTED]	[REDACTED]
2	03-Jun-2019	Number of iterations for multiple imputation was changed	Number of iterations for multiple imputation was changed from 10 000 to 2000
2	03-Jun-2019	Wording change to be consistent with CEC charter	"Heart failure leading to hospitalization" changed to "Heart failure requiring hospitalization"
2	03-Jun-2019	MedDRA version and dictionary updated	MedDRA version was updated to V22.0 and list of PTs for selected EOSI were updated
3	This version	[REDACTED]	[REDACTED]

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SAP version number	Date approved	Rationale	Description of statistical changes
			[REDACTED]
3	This version	[REDACTED]	[REDACTED]
3	This version	[REDACTED]	[REDACTED]
3	This version	[REDACTED]	[REDACTED]
3	This version	[REDACTED]	[REDACTED]

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\* Change made in Protocol Amendment 2 dated 20-Dec-2017.

## 2 STATISTICAL AND ANALYTICAL PROCEDURES

### 2.1 ANALYSIS ENDPOINTS

#### 2.1.1 Demographic and baseline characteristics

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

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

Baseline safety and efficacy parameters are presented along with the summary statistics for safety and efficacy sections ([Section 2.4.4](#) and [Section 2.4.5](#)).

#### *Demographic characteristics*

Demographic characteristics to be summarized are:

- Age (years) derived as: (Year of informed consent - Year of birth).
- Age categories: (<50, ≥50 to <65, ≥65 to <75, ≥75 years).
- Gender (Male, Female).
- Race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other pacific islander, Multiple, Unknown).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown).
- HbA1c (%) at screening visit.
- Randomization strata of HbA1c (≤8.5%, >8.5%) at screening (data from IRT).
- Randomization strata of metformin use (Yes, No) at screening (data from IRT).
- Mean SBP at screening.
- Randomization strata of SBP (<130 mmHg, ≥130 mmHg) at screening (data from IRT).
- Baseline body mass index (BMI) (kg/m<sup>2</sup>) derived as: (Weight in kg)/(Height in meters)<sup>2</sup>.
- Baseline BMI categories (<30, ≥30 kg/m<sup>2</sup>).
- Country.

***Disease characteristics at screening or baseline***

Disease history includes:

- Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25.
- Duration of diabetes categories: (<10, ≥10 years).
- Age at diagnosis of diabetes (years): (Year of diagnosis of diabetes – Year of birth).
- Metformin use at screening (Yes, No).
- Duration of metformin treatment (for those patients who used metformin at screening) (years): (date of informed consent - date of first intake of metformin +1)/365.25.
- Daily dose of metformin (mg) at baseline (for those patients who used metformin at screening).
- Categorized daily dose of metformin at baseline for those patients who used metformin at screening (<1500, ≥ 1500 to <2500, ≥2500 mg).
- Duration of sulfonylurea treatment (years): (date of informed consent - date of first intake of sulfonylurea +1)/365.25.
- Sulfonylurea at screening by international nonproprietary name (INN) and formulation.
- Daily dose of sulfonylurea at baseline by INN and formulation.
- Categorized daily dose of sulfonylurea at baseline by INN:
  - Glibenclamide (Gd) and Glibenclamide MR (GdMR):
    - <10 mg/day (Gd) or <6 mg/day (GdMR),
    - ≥10 - ≤20 mg/day (Gd) or ≥6 - ≤12 mg/day (GdMR),
    - >20 mg/day (Gd) or >12 mg/day (GdMR).
  - Gliclazide (Gz) and Gliclazide MR (GzMR):
    - <160 mg/day (Gz) or <60 mg/day (GzMR),
    - ≥160 - ≤320 mg/day (Gz) or ≥60 - ≤120 mg/day (GzMR),
    - >320 mg/day (Gz) or >120 mg/day (GzMR).
  - Glimepiride:
    - <4 mg/day,
    - ≥4 - ≤8 mg/day,
    - >8 mg/day.
  - Glipizide (Gp) and Glipizide XL (GpXL):
    - <20 mg/day (Gp) or <10 mg/day (GpXL),
    - ≥20 - ≤40 mg/day (Gp) or ≥10 - ≤20 mg/day (GpXL),



- >40 mg/day (Gp) or >20 mg/day (GpXL).
- Gliquidone:
  - <90 mg/day,
  - $\geq 90 - \leq 180$  mg/day,
  - >180 mg/day.
- 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).
- eGFR at screening (mL/min/1.73m<sup>2</sup>).
- eGFR categories at screening (<15 mL/min/1.73m<sup>2</sup> [End stage renal disease],  $\geq 15$  to <30 mL/min/1.73m<sup>2</sup> [Severe decrease in GFR],  $\geq 30$  to <60 mL/min/1.73m<sup>2</sup> [Moderate decrease in GFR],  $\geq 60$  to <90 mL/min/1.73m<sup>2</sup> [Mild decrease in GFR], and  $\geq 90$  mL/min/1.73m<sup>2</sup> [Normal]).
- Prior antihypertensive medication identified by therapeutic class as agents acting on the renin-angiotensin system, beta blocking agents, diuretics (a sub-category: loop diuretics identified by pharmacological class as high-ceiling diuretics), calcium channel blockers, and antihypertensives according to World Health Organization-Drug Dictionary (WHO-DD).

### ***Medical or surgical history***

Medical history and medical findings include:

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

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

Any technical details related to computation, dates, and imputations for missing dates are described in [Section 2.5](#).

### 2.1.2 Prior or concomitant medications

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

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

- Prior medications are those the patient used prior to first administration of 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 1<sup>st</sup> administration of double-blind IMP to the date of last administration + 10 days. A given medication can be classified both as a prior medication and as a concomitant medication.
- Posttreatment medications are those the patient took in the period running from the 11th day after the last administration of double-blind IMP up to the end of the study.

Background sulfonylurea and metformin are considered as noninvestigational medicinal products (NIMP). Sulfonylurea and metformin (commercial formulations) will be administered orally according to the locally approved label.

Any technical details related to computation, dates, imputation for missing dates are described in [Section 2.5](#).

#### 2.1.2.1 Rescue therapy

Except for SGLT2 inhibitors and additional metformin and sulfonylurea, any approved medication(s) including oral antidiabetic drugs, GLP-1 receptor agonists, or insulin can be prescribed at the Investigator's discretion to treat the hyperglycemia. Metformin will also be permitted for patients on sulfonylurea only at Screening. 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 before the rescue therapy.  
Note: short term use (<10 consecutive days) of the prohibited medication, eg, short-acting insulin for treatment of acute illness or surgery is allowed.
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, ophthalmic, nasal spray or inhaled applications are allowed).
- Initiation of any weight loss drugs (eg, phentermine, orlistat).

- Investigational medicinal products in any other clinical study.

SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin), additional sulfonylurea and metformin are not allowed for rescue or post IMP therapy until the end of study.

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 pharmacodynamic (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](#)).

HbA1c, FPG, serum creatinine, eGFR are measured/calculated in a central laboratory (see study flowchart in [D](#)). Body weight, SBP and diastolic blood pressure (DBP) (see [Section 2.1.4.5](#)) are measured at on-site visits by the investigator. Patients requiring rescue are identified as those with the reason for treatment ticked “rescue therapy” in e-CRF “Medication” page.

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

#### 2.1.3.1 Primary efficacy endpoint(s)

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

#### 2.1.3.2 Secondary efficacy endpoint(s)

- 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  $\geq$ 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 endpoint(s)

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

### 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 the double-blind IMP to the last administration of the double-blind IMP. This epoch includes the 26-week double-blind core treatment period and the 53-week double-blind extension treatment period. The 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 the double-blind IMP up to 10 days (1 day for hypoglycemia) after the last administration of double-blind IMP.

The treatment-emergent adverse event (TEAE) period will include both treatment and residual treatment epochs (See the TEAE period for the 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 TEAE period up to the last protocol-planned visit or the resolution/stabilization of all serious adverse events (SAE), adverse events of special interest (AESI) and events of special interest (EOSI), whichever is later.

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

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

#### **2.1.4.1 Hypoglycemia**

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

##### **Severe hypoglycemia**

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

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

Severe hypoglycemia is identified in e-CRF “Hypoglycemic event information” page as those documented as,

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

##### **Documented symptomatic hypoglycemia**

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

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

Documented symptomatic hypoglycemia is identified in e-CRF “Hypoglycemic event information” page as those documented as:

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

### **Asymptomatic hypoglycemia**

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

Asymptomatic hypoglycemia is identified in e-CRF “Hypoglycemic event information” page as those documented as:

1. To the question “Countermeasure Administration”, NOT ticked the option “Subject was Not Capable of Treating Self and Required Assistance”, and,
2. To the question “Were Symptoms Present”, ticked “No”, and,
3. With a plasma glucose value before countermeasure  $\leq 3.9$  mmol/L ( $\leq 70$  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  $\leq 3.9$  mmol/L [ $\leq 70$  mg/dL]), ie, symptoms treated with oral carbohydrate without a test of plasma glucose.

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

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

### **Relative hypoglycemia**

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

Relative hypoglycemia is identified in e-CRF “Hypoglycemic event information” page as those documented as,

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

In addition of the threshold of  $\leq 3.9$  mmol/L ( $\leq 70$  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 Adverse events variables**

##### **AE observation period**

- **Pretreatment AEs** are AEs that developed or worsened or became serious from the signed informed consent date up to first administration of double-blind IMP.
- **TEAEs** are AEs that developed or worsened or became serious during the TEAE period.
- **Posttreatment AEs** are AEs that developed or worsened or became serious during the posttreatment period.

All AEs (including SAEs, AESI and EOSI) will be coded to a LLT, PT, HLT, HLGT, and associated SOC using the version of MedDRA currently in effect at Covance 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** include

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



**EOSI include**

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

A Clinical Endpoint Committee (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
<b>AESI</b>	
Pregnancy	e-CRF "Pregnancy"
Symptomatic overdose with IMP/NIMP	"Overdose of IMP" or "Overdose of NIMP" checked and "Symptomatic overdose" checked in e-CRF "Overdose"
ALT increase >3 × ULN	e-CRF "ALT increase"
<b>EOSI adjudicated</b>	
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?"
<b>EOSI Renal events where select events adjudicated</b>	
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 e-CRF "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 <sup>2</sup>	(2) For eGFR <15 mL/min/1.73 m <sup>2</sup> , (2a) confirmed eGFR <15 mL/min/1.73 m <sup>2</sup> for ≥30 days with no reversible cause as recorded in e-CRF "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 e-CRF "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 e-CRF "Other procedure form", where adjudication is not required. PTs of Renal transplant (10038533), Renal and pancreas transplant (10052278), Renal and liver transplant (10052279) based on MedDRA v22.0.
Renal death	(5) Renal death as positively adjudicated by CEC: "Death - Non-Cardiovascular (Renal)" as the primary cause of death

AE Grouping	Criteria
<b>EOSI not adjudicated*</b>	
Severe hypoglycemia	Algorithm specified in Section 2.1.4.1 based on e-CRF "Hypoglycemic Events"
Genital mycotic infections	PTs in Appendix B
Urinary tract infections	PTs in Appendix B
Clinically relevant volume depletion and events related/possibly related to volume depletion	PTs in Appendix B
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" [20000218] plus the following PTs (MedDRA v22.0): Gastroenteritis (10017888), Antidiarrhoeal supportive care (10055660), Enteritis (10014866), Enteritis leukopenic (10014877), Enterocolitis (10014893), Enterocolitis haemorrhagic (10014896)
Pancreatitis	PTs in Appendix B
Venous thrombotic events	PTs in Appendix B
Malignancies of special interest	Breast cancer: Narrow search on "Breast cancer: Narrow search on "Breast neoplasms, malignant and unspecified (SMQ)" [20000149] Prostate cancer: Narrow search on "Prostate neoplasms, malignant and unspecified (SMQ)" [20000152] Leydig-cell cancer: PTs of Leydig cell tumour of the testis (10024407) and Ovarian Sertoli-Leydig cell tumour (10073270) based on MedDRA v22.0 Thyroid cancer: PTs in Appendix B Renal cell cancer: PTs in Appendix B Pancreatic cancer: PTs in Appendix B Bladder cancer: PTs in Appendix B
<b>EOSI AE leading to an amputation</b>	
AE leading to an amputation	"AE Correction" as the reason for amputation in e-CRF "Other Procedures related to Amputation"
AE potentially leading to an amputation *	PTs in Appendix B

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

\* AE potentially leading to an amputation: not belong to the EOSI list defined in protocol, the item is included and analyzed due to their relevance in regards to lower limb complications and amputations as a requirement from health authorities..

### 2.1.4.3 Deaths

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

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

#### 2.1.4.4 Laboratory safety variables

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

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

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

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

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

Serum glucose will be presented as efficacy parameters in [Section 2.4.4](#). For creatinine and calculated eGFR, Potentially Clinically Significant Abnormality (PCSA) summaries will be presented in the safety section while descriptive summaries in the efficacy section.

Technical formulas are described in [Section 2.5.1](#).



#### **2.1.4.5 Vital signs variables**

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

#### **2.1.4.6 Physical examination**

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

#### **2.1.4.7 Electrocardiogram variables**

12-lead ECGs will be performed at Visit 1 (Screening), Visit 9 (Week 26), and Visit 13(Week 79). ECG status of “normal” or “abnormal” will be reported in the e-CRF as determined by the investigator.

#### **2.1.5 Pharmacokinetic variables**

Pharmacokinetic variables include the plasma concentration of sotagliflozin and its 3-O-glucuronide metabolite in the sotagliflozin 400 mg group.

## **2.2 DISPOSITION OF PATIENTS**

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

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

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

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

- Screened patients.
- Run in patients: patients who had a run-in record in IRT.
- Screen failure patients (including failures during run-in) and reasons for screen failure.
- Nonrandomized but treated patients.
- Randomized patients.

- Randomized but not treated patients.
- Randomized and treated patients.
- Patients who have completed the 26-week double-blind core treatment period (see [Section 2.5.4](#)) as per protocol.
- Patients 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 entire treatment period as per protocol (double-blind core treatment period and extension treatment period).
- Patients who did not complete the 79-week 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 ( $\leq 8.5\%$ ,  $> 8.5\%$ ), Metformin use at screening (Yes, No), and mean SBP at Screening ( $< 130$ ,  $\geq 130$  mmHg)] assigned by IRT will be summarized. The percentages will be calculated using the number of randomized patients as the denominator. The discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients.

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

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

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

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

### 2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

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

OR

3. 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 CSR. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately. Listings with additional, relevant details will be provided in appendices.

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

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***Randomization and drug allocation irregularities***

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*Kit dispensation without IRT transaction*

*Erroneous kit dispensation*

*Kit not available*

*Randomization by error*

*Patient randomized twice*

*Stratification error*

*Patient switched to another site*

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## **2.3 ANALYSIS POPULATIONS**

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

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

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

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

### **2.3.1 Efficacy populations**

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

#### ***2.3.1.1 Intent-to-treat population***

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

### **2.3.2 Safety population**

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least one dose or part of a 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 placebo and sotagliflozin, the patient will be analyzed in the sotagliflozin 400 mg group.
- Randomized patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study treatment. If a patient is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed.

### 2.3.3 Pharmacokinetic population

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

## 2.4 STATISTICAL METHODS

### 2.4.1 Demographics and baseline characteristics

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

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

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

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

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

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

## 2.4.2 Prior or concomitant medications

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

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). A given medication may be classified in more than 1 ATC class. All ATC codes corresponding to a medication will be summarized, and a patient will be counted once 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 presented by anatomic and therapeutic categories and sorted by decreasing frequency in the sotagliflozin 400 mg group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

## 2.4.3 Extent of investigational medicinal product exposure and compliance

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

### 2.4.3.1 Extent of investigational medicinal product exposure

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

Duration of IMP exposure is defined as last dose date of double-blind IMP – first dose date of double-blind IMP + 1 day, regardless of unplanned intermittent discontinuations (see [Section 2.5.3](#) for calculation in case of missing or incomplete data). Duration of IMP exposure will be summarized descriptively as a quantitative variable (number of patients exposed, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- 1 to 28 days,
- 29 to 56 days,
- 57 to 84 days,
- 85 to 126 days,
- 127 to 182 days,

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

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

#### **2.4.4 Analyses of efficacy endpoints**

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



Statistical testing will be performed for primary endpoint and some secondary endpoints at Week 26 (or Week 12 for SBP) as specified in 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**

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

##### **Primary analysis**

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

Missing endpoint data at Week 26 (or Week 12 for SBP) visit will be imputed using a model built separately in each treatment group and estimated from the patients in the same treatment group who prematurely discontinue the IMP before the Week 26 (or Week 12 for SBP) visit but have the measurement for the endpoint (ie, retrieved dropouts). The imputation model will include the randomization strata and the corresponding baseline value. In cases of non-convergence during the imputations, the offending stratum will be identified and then will be dropped from the model. Considering that the number of retrieved dropout patients in each treatment group is expected to be small, a simple imputation model based on regression will be used with baseline measurement included as the predictor. This will serve as the primary method of imputation for missing data should sampling criteria be satisfied (see below).

An alternative (back-up) imputation method will be used if the number of patients who prematurely discontinue the IMP before the Week 26 (or Week 12 for SBP) visit but have the measurement for the endpoint is  $< 5$  in any treatment groups (ie, an insufficient number of retrieved dropouts to support the imputation method described above). This criterion will be assessed for each primary and 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 group with missing data at Week 26 (or Week 12 for SBP), their missing values will be imputed using observed baseline and the observed primary endpoint data from placebo completers; no intermittent values from either placebo or the active treatment groups will be used.



For placebo patients, missing data will be imputed based on the placebo group data. Intermittent observed values will be used while imputing missing values at Week 26 (or Week 12 for SBP). In cases that a non-monotone missing data pattern occurs at the intermediate visits, these data points will be first imputed in the placebo group using the Markov Chain Monte Carlo (MCMC) option in PROC MI to achieve a monotone missing pattern for all placebo patients. The Week 26 (or Week 12 for SBP) endpoint values will be subsequently imputed from the multiple copies of the original dataset where each copy will have a monotone missing pattern.

The imputation models for the washout MI method will include the randomization strata and the corresponding baseline value. Missing data will be imputed using the regression method.

In cases of non-convergence during the imputations, especially for the MCMC application in the placebo non-monotone datasets, graphical measures (eg, trace and autocorrelation plots) will be used to identify the offending variable and once detected, that variable(s) will be dropped from the model and the imputations will be re-run. These re-run models will use the same seed number and number of imputations as used in the original models.

Using either imputation method, missing endpoint data will be imputed 2000 times to generate multiple data sets with complete data. Other details of the imputation procedures such as the seed number and sort ordering are specified in the SAS programs. The HbA1c change from baseline to Week 26 (or Week 12 for SBP) will be derived from observed and imputed HbA1c values at Week 26 (or Week 12 for SBP).

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 ( $\leq 8.5\%$ ,  $> 8.5\%$ ), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP ( $< 130$  mmHg,  $\geq 130$  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).

### **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..

2. The imputed HbA1c value at Week 26 in the sotagliflozin 400 mg group will be penalized by adding a penalty  $\delta$  (eg,  $\delta = 0.1\%$ ) in each complete dataset..
3. Change from baseline at Week 26 in HbA1c will be analyzed using the same ANCOVA model as specified in the primary analysis in each complete dataset..
4. Results will be combined across complete datasets using Rubin's formula..
5. Steps 2 to 4 will be repeated with incremental penalty at  $\delta$  (ie,  $\delta, 2\delta, 3\delta, \dots$ ) 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 on the ITT population. The tipping point analysis will be performed for the primary variable only if that variable (change from baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg vs. placebo) is statistical significant at  $\alpha = 0.05$  (2-sided).

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

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

#### **Assessment of treatment effect by subgroup**

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

- Race (White, Black or African American, Asian, Other) (any race groups with fewer than 5 patients may be combined with "Other" category as appropriate).
- Ethnicity (Hispanic, Not Hispanic).
- Age group ( $<50, \geq 50$  to  $<65, \geq 65$  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<sup>2</sup>).
- Baseline HbA1c (≤8.5%, >8.5%).
- Metformin use at Screening (Yes, No).
- Baseline mean SBP (<130 mmHg, ≥130 mmHg).
- Baseline eGFR (≥30 to <60 mL/min/1.73m<sup>2</sup> [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m<sup>2</sup> [Mild decrease in GFR], and ≥90 mL/min/1.73m<sup>2</sup> [Normal]).
- Duration of diabetes (<10, ≥10 years).
- Country.

The treatment effects (sotagliflozin 400 mg versus placebo) across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 26 in HbA1c in the ITT population, and using the same MI method as applied to the primary analysis. The ANCOVA model will include treatment groups (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), subgroup factor, treatment-by-subgroup factor, and country as fixed factors and baseline HbA1c values as a covariate. The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus placebo) with standard error (SE) and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided.

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

#### **Summary statistics at scheduled visits**

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

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

#### **2.4.4.2 Analyses of secondary efficacy endpoints**

For continuous secondary efficacy parameters with missing data at baseline, missing baseline 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



( $\leq 8.5\%$ ,  $> 8.5\%$ ), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP ( $< 130$  mmHg,  $\geq 130$  mmHg), and baseline value in the imputation model..

Each continuous secondary efficacy endpoint (Section 2.1.3.2) will be analyzed using a similar ANCOVA model including the measurements at baseline and endpoint (observed or imputed). The missing data at endpoint will be imputed by the retrieved dropouts if there are at least 5 patients in each study treatment group who discontinued but have the endpoint. Otherwise, the washout imputation method will be used according to the criterion described in Section 2.4.4.1. After the imputation, each of the complete datasets will be analyzed by an ANCOVA model.

The ANCOVA model will include treatment groups (sotagliflozin 400 mg, placebo), randomization stratum of HbA1c ( $\leq 8.5\%$ ,  $> 8.5\%$ ), randomization stratum of metformin use at Screening (Yes, No), randomization stratum of SBP ( $< 130$  mmHg,  $\geq 130$  mmHg), and country as fixed effects, and the corresponding baseline secondary endpoint value as a covariate. For the analysis of SBP in patients with baseline SBP  $\geq 130$  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 versus 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 ( $\pm$ SE) and mean changes from baseline ( $\pm$ SE) at each of the scheduled visits. In addition, SBP will be summarized descriptively at each visit for those patients with baseline SBP  $\geq 140$  mmHg.

The categorical secondary efficacy variables of HbA1c  $< 6.5\%$ ,  $< 7\%$  at Week 26 will be analyzed respectively using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of HbA1c ( $\leq 8.5\%$ ,  $> 8.5\%$ ), randomization stratum of metformin use at Screening (Yes, No), and randomization stratum of SBP ( $< 130$  mmHg,  $\geq 130$  mmHg). The proportion in each treatment group will be provided, as well as the difference of proportions between sotagliflozin 400 mg and placebo with the associated 2-sided 95% CI. For HbA1c responders at Week 26 ( $< 6.5\%$ ,  $< 7\%$  respectively), all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at Week 26 will be treated as non-responders. Summary tables and graphs will also be provided by treatment group at scheduled visits.

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

### **2.4.4.3 Analyses of other efficacy endpoints**

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

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

### **2.4.4.4 Multiplicity issues**

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

Once the primary hypothesis (superiority of the change from Baseline to Week 26 in HbA1c comparing sotagliflozin 400 mg versus placebo) is statistically significant for the primary efficacy endpoint at  $\alpha = 0.05$  (2-sided), the following secondary hypothesis based on change from Baseline scores will be tested in the following prioritized order:

1. Change from Baseline to Week 26 in FPG.
2. Change from Baseline to Week 26 in body weight.
3. Change from Baseline to Week 12 in SBP for patients with baseline SBP  $\geq 130$  mmHg.
4. Change from Baseline to Week 12 in SBP for all patients.
5. Proportion of patients with HbA1c  $< 7.0\%$  at Week 26.

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

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

### **2.4.5 Analyses of safety data**

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

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 PCSA values and the last on-treatment value for the laboratory, vital sign and ECG.

### **General common rules**

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

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value (with the exception of serum creatinine and eGFR) is defined as the last available value before the first dose of double-blind IMP, with the exception of creatinine and eGFR, where the baseline value is defined as the average of all values before the first dose of double-blind IMP.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG ([Appendix A](#)).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment-emergent PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter during the TEAE period by treatment group in the safety population.
- For laboratory parameters cited in the protocol as efficacy endpoints (including HbA1c and plasma glucose etc.), PCSA summaries will not be provided. These parameters will be summarized in efficacy [Section 2.4.4](#). For creatinine and eGFR, PCSA summaries will be presented in safety [Section 2.4.5](#) while descriptive summaries in efficacy [Section 2.4.4](#).
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group 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, racial subgroups, and other pertinent subgroups (see details in [Section 2.4.5.1](#) and [Section 2.4.5.2](#)).

#### **2.4.5.1 Analyses of hypoglycemia**

Analyses of hypoglycemia will be performed on the TEAE 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 2.1.4.1](#).



The number (%) of patients with any hypoglycemia, severe hypoglycemia, and documented symptomatic hypoglycemia will be summarized respectively by treatment group during the TEAE period, as well as the incidence rate in patient years. Two types of incidence rates will be presented: the number of patients with at least 1 event per 100 patient years (calculated as the number of patients with at least 1 event / total exposure in 100 patient years), and the number of events per 100 patient-years [calculated as the total number of events / (total exposure in 100 patient-years)]. Note: here exposure (in days) is duration of TEAE 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), race (White, Black or African American, Asian, Other) and Metformin use at Screening (Yes, No).

A KM curve will also be provided by treatment group for the time to first severe hypoglycemia or documented symptomatic hypoglycemia during the TEAE period for the 79-week entire treatment period only.

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

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

#### **2.4.5.2 Analyses of adverse events**

##### **Generalities**

The primary focus of adverse event reporting will be on TEAEs. 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 adverse event 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, HLG, HLT, and PT, sorted by the internationally agreed order for SOCs and alphabetic order for HLG, HLT and PT within a SOC, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

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

### **Analysis of all TEAEs**

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

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE,
  - Serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, showing number (%) of patients with at least 1 TEAE, sorted by internationally agreed order of primary SOC.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT in the sotagliflozin 400mg group.
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the sotagliflozin 400mg group. This sorting order will be applied to all other similar tables, unless otherwise specified.
- All TEAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.
- Common TEAEs (PTs with an incidence  $\geq 2\%$  in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.



- Common TEAEs (PTs with an incidence  $\geq 2\%$  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,  $\geq 50$  to <65,  $\geq 65$  years of age), race (White, Black or African American, Asian, other), baseline SBP category (<130 mmHg,  $\geq 130$  mmHg), Metformin use at Screening (Yes, No), and baseline eGFR category ( $\geq 30$  to <60 mL/min/1.73m<sup>2</sup> [Moderate decrease in GFR],  $\geq 60$  to <90 mL/min/1.73m<sup>2</sup> [Mild decrease in GFR], and  $\geq 90$  mL/min/1.73m<sup>2</sup> [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  $\geq 5\%$  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 TEAE, 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 TEAE(s) leading to treatment discontinuation**

- All TEAE 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 AESI**

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.

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 EOSI**

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

Renal death will be part of all deaths specified above.

#### *Other EOSIs*

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

Severe hypoglycemia will be included in the summary of hypoglycemia (See [Section 2.5.1](#)).

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 e-CRF “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 e-CRF “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/ Pharmacovigilance Risk Assessment Committee[EMA/PRAC] Assessment Report 9 February 2017). 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 (as per the EMA/PRAC request).

### **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 400mg 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 400mg group.

### **Listings**

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

#### **2.4.5.3 Deaths**

The following summaries of deaths will be generated.

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

#### **2.4.5.4 Analyses of laboratory variables**

Laboratory parameters will be grouped and summarized by biological function as described in [Section 2.1.4.4](#).

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

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

- Normal/missing.



- Abnormal according to PCSA criterion or criteria.

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

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

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

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

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

### **Drug-induced liver injury**

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

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

#### **2.4.5.5 Analyses of vital sign variables**

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

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

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

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

#### **2.4.5.6 Analyses of electrocardiogram variables**

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

#### **2.4.5.7 Analyses of physical examination variables**

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

#### **2.4.6 Analyses of pharmacokinetic variables**

Plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite will be summarized by visit and nominal sampling time (pre-dose at Weeks 4, 18, 26, 52, and 79, and 1 hour 30 minutes post-dose at Week 26 and 79) in the PK population (see [Section 2.3.3](#)) in the sotagliflozin 400 mg group, using descriptive statistics such as number, geometric mean, coefficient of variation, median, minimum and maximum. Individual plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite at nominal sampling times will also be listed.



## 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,

$$\text{IFCC-HbA1c (mmol/mol)} = [\text{DCCT-HbA1c (\%)} - 2.15] \times 10.929.$$

#### *Renal function formulas*

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

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

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

#### *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),  $\text{TC} - \text{HDL-C} - \text{TG}/2.17$ .
- In conventional unit (mg/dL),  $\text{TC} - \text{HDL-C} - \text{TG}/5$ .

### 2.5.2 Data handling conventions for secondary efficacy variables

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

For the categorical secondary efficacy endpoints, data handling conventions are described in [Section 2.4.4.2](#).

### 2.5.3 Missing data

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



is presented.

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

#### ***Incomplete date of first administration of double-blind IMP***

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

For patients who are randomized and dispensed a double-blind treatment kit but who are lost to follow-up just after Visit 3 (eg. only the treatment kit number is reported in the e-CRF “Exposure - treatment period” module without any dose information), the date of first administration will be imputed using the date of randomization. When a patient is randomized but not exposed, “Not taken” should be ticked in the e-CRF “First dose IMP” module.

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

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

The last dose administration should be clearly identified in the e-CRF and should not be approximated by the last returned package date.

#### ***Handling of medication missing/partial dates***

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

#### ***Handling of AE/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 AEs/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 AEs/hypoglycemia when IMP end of treatment date is missing***

For the purpose of defining TEAE period, the date of the last administration of double-blind IMP is equal to the date of the last administration reported on the e-CRF “Treatment Status Library” page. If the date of last administration reported on the e-CRF “Treatment Status Library” page is

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

If the date of last available information on e-CRF “Completion of End of Study/Follow-up” page is:

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

***Handling of missing assessment of relationship of AEs to IMP***

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

***Handling of missing severity/grades of AE***

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an AE, 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  $ULN \geq 0.5$  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 AEs that worsened or became serious***

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

#### ***Handling of missing data for continuous efficacy endpoints***

See [Section 2.4.4.1](#) and [Section 2.4.4.2](#).

#### ***Handling of missing data for categorical efficacy endpoints***

See [Section 2.4.4.2](#).

### **2.5.4 Windows for time points /Measurements for analyses**

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

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

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

**Table 4 - Analyses window definition**

<b>Scheduled visit post baseline</b>	<b>Targeted study day</b>	<b>Analysis window in study days</b>
Week 4 (Visit 5)	28	2 to 55
Week 12 (Visit 7)	84	56 to 104
Week 18 (Visit 8)	126	105 to 153
Week 26 (Visit 9)	182	154 to 227
Week 39 (Visit 10)	273	228 to 318
Week 52 (Visit 11)	364	319 to 409
Week 65 (Visit 12)	455	410 to 502
Week 79 (Visit 13)	551	≥503

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



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

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

### ***Reference day***

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

### ***Baseline definition for efficacy/safety data***

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

### ***Summary statistics by visit for continuous efficacy endpoints***

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

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

### ***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 double blind 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 remained treated beyond 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 visits (see [Section 2.5.4](#)).

### 2.5.6 Pooling of centers for statistical analyses

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

### 2.5.7 Statistical technical issues

None.

### **3 INTERIM ANALYSIS**

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

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

## 4 DATABASE LOCK

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

## 5 SOFTWARE DOCUMENTATION

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

## 6 REFERENCES

None.



## 7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities criteria

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

Appendix C Summary of statistical analyses

Appendix D Study flow chart

**Appendix A Potentially clinically significant abnormalities criteria**

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

<b>Parameter</b>	<b>PCSA</b>	<b>Comments</b>
<b>Clinical Chemistry</b>		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN	FDA Feb 2005.

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

Parameter	PCSA	Comments
	>10 ULN	Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cockcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m <sup>2</sup> ) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	>408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17 <sup>th</sup> Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA May 2005. ADA Jan 2008.

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

<b>Parameter</b>	<b>PCSA</b>	<b>Comments</b>
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
<b>Hematology</b>		
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 17 <sup>th</sup> 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.
<b>Urinalysis</b>		
pH	≤4.6 ≥8	
<b>Vital signs</b>		
HR	≤50 bpm and decrease from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.

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

Parameter	PCSA	Comments
	≥120 bpm and increase from baseline ≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB		
Orthostatic DBP	≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm  >90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative       Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms	Categories are cumulative



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

Parameter	PCSA	Comments
	>110 msec and increase from baseline $\geq$ 25%	
	>120 ms	
	>120 ms and increase from baseline $\geq$ 25%	
QT	>500 ms	
QTc	<u>Absolute values (ms)</u>	To be applied to any kind of QT correction formula.
	>450 ms	Absolute values categories are cumulative
	>480 ms	
	>500 ms	QTc >480 ms and $\Delta$ QTc >60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	<u>Increase from baseline</u>	
	Increase from baseline ]30-60] ms	
	Increase from baseline >60 ms	

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

<b>EOSI</b>	<b>Preferred Term Code</b>	<b>Preferred Term</b>
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 ureaplasma
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

**Statistical Analysis Plan**

**Version: 3**

Lexicon Pharmaceuticals Protocol No. EFC14835

**Date of Issue: 19 February 2020**

Covance Study ID:000000154257

Urinary tract infections	10051350	Cytomegalovirus urinary tract infection
Urinary tract infections	10051959	Urinary bladder abscess
Urinary tract infections	10052238	Escherichia urinary tract infection
Urinary tract infections	10054088	Urinary tract infection bacterial
Urinary tract infections	10056351	Emphysematous cystitis
Urinary tract infections	10058523	Bladder candidiasis
Urinary tract infections	10058596	Renal cyst infection
Urinary tract infections	10059517	Bacterial pyelonephritis
Urinary tract infections	10061181	Genitourinary tract gonococcal infection
Urinary tract infections	10061182	Genitourinary tract infection
Urinary tract infections	10061395	Ureter abscess
Urinary tract infections	10062279	Urinary tract infection pseudomonal
Urinary tract infections	10062280	Urinary tract infection staphylococcal
Urinary tract infections	10064825	Urinary tract infection viral
Urinary tract infections	10064921	Urinary tract inflammation
Urinary tract infections	10065197	Cystitis viral
Urinary tract infections	10065198	Cystitis bacterial
Urinary tract infections	10065199	Cystitis helminthic
Urinary tract infections	10065213	Pyelonephritis viral
Urinary tract infections	10065214	Pyelonephritis fungal
Urinary tract infections	10065582	Urogenital infection fungal
Urinary tract infections	10065583	Urogenital infection bacterial
Urinary tract infections	10066757	Urinary tract abscess
Urinary tract infections	10068822	Emphysematous pyelonephritis
Urinary tract infections	10070300	Streptococcal urinary tract infection
Urinary tract infections	10074409	Escherichia pyelonephritis
Urinary tract infections	10075063	Urethritis mycoplasmal
Urinary tract infections	10078665	Bacterial urethritis
Urinary tract infections	10081163	Fungal urethritis
Urinary tract infections	10081262	Candida urethritis
Urinary tract infections	10082040	Nephritis bacterial
Volume depletion	10005697	Blood osmolarity increased
Volume depletion	10005731	Blood pressure ambulatory decreased
Volume depletion	10005734	Blood pressure decreased
Volume depletion	10005737	Blood pressure diastolic decreased
Volume depletion	10005748	Blood pressure immeasurable
Volume depletion	10005758	Blood pressure systolic decreased
Volume depletion	10005761	Blood pressure systolic inspiratory decreased
Volume depletion	10007979	Central venous pressure decreased
Volume depletion	10009192	Circulatory collapse
Volume depletion	10012174	Dehydration
Volume depletion	10013578	Dizziness postural

**Statistical Analysis Plan**

**Version: 3**

Lexicon Pharmaceuticals Protocol No. EFC14835

**Date of Issue: 19 February 2020**

Covance Study ID:000000154257

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



**Statistical Analysis Plan**

**Version: 3**

Lexicon Pharmaceuticals Protocol No. EFC14835

**Date of Issue: 19 February 2020**

Covance Study ID:000000154257

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



**Statistical Analysis Plan**

**Version: 3**

Lexicon Pharmaceuticals Protocol No. EFC14835

**Date of Issue: 19 February 2020**

Covance Study ID:000000154257

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

Statistical Analysis Plan

Version: 3

Lexicon Pharmaceuticals Protocol No. EFC14835

Date of Issue: 19 February 2020

Covance Study ID:000000154257

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

Statistical Analysis Plan

Version: 3

Lexicon Pharmaceuticals Protocol No. EFC14835

Date of Issue: 19 February 2020

Covance Study ID:000000154257

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



**Statistical Analysis Plan**

**Version: 3**

Lexicon Pharmaceuticals Protocol No. EFC14835

**Date of Issue: 19 February 2020**

Covance Study ID:000000154257

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

**Statistical Analysis Plan**

**Version: 3**

Lexicon Pharmaceuticals Protocol No. EFC14835

**Date of Issue: 19 February 2020**

Covance Study ID:000000154257

Potentially leading to amputation	10061627	Amputation
Potentially leading to amputation	10061655	Arterial graft
Potentially leading to amputation	10061657	Arterial stent insertion
Potentially leading to amputation	10061666	Autonomic neuropathy
Potentially leading to amputation	10061815	Diabetic vascular disorder
Potentially leading to amputation	10062198	Microangiopathy
Potentially leading to amputation	10062255	Soft tissue infection
Potentially leading to amputation	10062585	Peripheral arterial occlusive disease
Potentially leading to amputation	10062599	Arterial occlusive disease
Potentially leading to amputation	10062610	Ischaemic limb pain
Potentially leading to amputation	10062932	Wound treatment
Potentially leading to amputation	10064250	Staphylococcal osteomyelitis
Potentially leading to amputation	10064601	Iliac artery occlusion
Potentially leading to amputation	10065237	Osteomyelitis bacterial
Potentially leading to amputation	10065239	Osteomyelitis fungal
Potentially leading to amputation	10065240	Wound infection bacterial
Potentially leading to amputation	10065242	Wound infection fungal
Potentially leading to amputation	10068653	Bone abscess
Potentially leading to amputation	10069379	Peripheral arterial reocclusion
Potentially leading to amputation	10072170	Skin wound
Potentially leading to amputation	10072557	Peripheral artery restenosis
Potentially leading to amputation	10072560	Peripheral endarterectomy
Potentially leading to amputation	10072561	Peripheral artery bypass
Potentially leading to amputation	10072562	Peripheral artery stent insertion
Potentially leading to amputation	10072563	Peripheral artery stenosis
Potentially leading to amputation	10072564	Peripheral artery thrombosis
Potentially leading to amputation	10074396	Penetrating atherosclerotic ulcer
Potentially leading to amputation	10075118	Subperiosteal abscess
Potentially leading to amputation	10075714	Vasculitic ulcer
Potentially leading to amputation	10076246	Spontaneous amputation



## Appendix C Summary of statistical analyses

### *EFFICACY ANALYSIS*

<b>Endpoint</b>	<b>Analysis population</b>	<b>Primary analysis</b>	<b>Supportive analysis</b>	<b>Subgroup analysis</b>	<b>Other analyses</b>
<i>Primary endpoint</i>					
HbA1c: Change from Baseline at Week 26	ITT	ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by <b>washout</b> MI method under MNAR framework): treatment, randomization stratum (HbA1c /metformin use/ SBP at screening), and country as fixed effects, and baseline HbA1c value as a covariate	Tipping point analysis;	Subgroups: race, ethnicity, age, gender, baseline BMI, baseline HbA1c, baseline SBP, metformin use at screening, 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 ( $\pm$ SE) and mean values ( $\pm$ SE) by visit. By-visit summary and graph excluding measurements after rescue therapy.
<i>Secondary endpoints</i>					
FPG, body weight: Change from baseline to Week 26; SBP (for patients with Baseline SBP $\geq$ 130 mmHg, all patients): Change from Baseline to Week 12	ITT	ANCOVA (with missing values imputed by the retrieved dropouts imputation method or by <b>washout</b> MI Method under MNAR framework): treatment, randomization stratum (HbA1c /metformin use / SBP at screening), and country as fixed effects, and baseline value as a covariate	No	No	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline ( $\pm$ SE) and mean values ( $\pm$ SE) by visit. SBP will be summarized descriptively at each visit for those with baseline SBP $\geq$ 140 mmHg
Proportion of patients with HbA1c <6.5%, <7.0% at Week 26	ITT	CMH method stratified on randomization strata (HbA1c /metformin use / SBP at screening),	CMH method stratified on randomization strata (HbA1c /metformin use/ SBP at screen: excluding	No	By-visit summary and graphs of HbA <sub>1c</sub> responders (<6.5%, <7%). By-visit frequency summary and graphs of HbA <sub>1c</sub> responders (<6.5%, <7%)

Statistical Analysis Plan

Version: 3

Lexicon Pharmaceuticals Protocol No. EFC14835

Date of Issue: 19 February 2020

Covance Study ID:000000154257

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
			patients with baseline HbA <sub>1c</sub> values <6.5% (for <6.5% responders) or <7% (for <7% responders) respectively		excluding patients with baseline HbA <sub>1c</sub> values <6.5% or <7% respectively.
<b>Other endpoints</b>					
SBP (for patients with baseline SBP <130 mmHg), DBP, Serum creatinine, eGFR: change from Baseline	ITT	Summary statistics for observed values and changes from baseline by visit.	No	No	Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit as appropriate.
Proportion of patients, with reduction in body weight by ≥2%, ≥5%, and ≥10% from Baseline; achieving SBP <130 mmHg with baseline SBP ≥130 mmHg; achieving DBP <80 mmHg with baseline DBP ≥80 mmHg	ITT	By-visit frequency summary	No	No	By-visit graphical presentation as appropriate
Proportion of patients requiring rescue for hyperglycemia		Summary statistics	No	No	KM plot; List of patients rescued

***SAFETY ANALYSES***

<b>Endpoint</b>	<b>Analysis Population</b>	<b>Primary analysis</b>	<b>Supportive Analysis</b>	<b>Subgroup analysis</b>	<b>Other analyses</b>
Hypoglycemia	Safety	Follow safety guidelines Number (%) of patients with any hypoglycemia, severe hypoglycemia, documented symptomatic hypoglycemia during TEAE period, and incidence rates in 100 patient-years.		Severe hypoglycemia or documented symptomatic hypoglycemia by subgroups: race, age, gender, metformin use	KM plot time to first event of severe hypoglycemia or documented symptomatic hypoglycemia Documented symptomatic hypoglycemia maybe presented by <3.0 mmol/L (<54 mg/dL) as appropriate.
Adverse Events	Safety	Follow safety guidelines	No	Common TEAEs by subgroups: race, age, gender, baseline SBP, metformin use, baseline eGFR	To be updated for EOSI
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 D Study flow chart

	Screening Period		Double-Blind Core Treatment Period <sup>a</sup>							Double-Blind Extension Period <sup>b</sup>				Follow-up
	Screening	Run-In	3 Baseline	4 ☎	5	6 <sup>c</sup> ☎	7	8	9	10	11	12	13	14 ☎
VISIT	1	2	3 Baseline	4 ☎	5	6 <sup>c</sup> ☎	7	8	9	10	11	12	13	14 ☎
Week	-4	-2	0	1	4	8	12	18	26	39	52	65	79	81
Day (window [days])		-14 (±3)	1 (-)	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	455 (±7)	551 (-3 to +4)	565 (±3)
Informed consent	X													
Inclusion criteria	X													
Exclusion criteria	X	X	X											
Demographics	X													
Medical/Surgical History	X													
Medication History	X													
Body weight, height <sup>d</sup>	X	X	X		X		X	X	X	X	X	X	X	
Vital signs <sup>e</sup>	X	X	X		X		X	X	X	X	X	X	X	
Physical Examination:														
Complete	X								X				X	
Abbreviated <sup>f</sup>		X	X		X		X	X		X	X	X		
Diet & exercise instruction		X	X						X		X		X	
Instruction on basic GU hygiene & hydration		X	X	X	X	X	X	X	X	X	X	X	X	



Statistical Analysis Plan

Version: 3  
Lexicon Pharmaceuticals Protocol No. EFC14835

Date of Issue: 19 February 2020  
Covance Study ID:000000154257

	Screening Period		Double-Blind Core Treatment Period <sup>a</sup>							Double-Blind Extension Period <sup>b</sup>				Follow-up
	Screening	Run-In	3 Baseline	4 ☎	5	6 <sup>c</sup> ☎	7	8	9	10	11	12	13	14 ☎
VISIT	1	2												
Week	-4	-2	0	1	4	8	12	18	26	39	52	65	79	81
Day (window [days])		-14 (±3)	1 (-)	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	455 (±7)	551 (-3 to +4)	565 (±3)
Interactive response technology (IRT) contact	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		
Collect/review diary		X	X		X		X	X	X	X	X	X	X	
Instruction on diabetic ketoacidosis symptoms, glucose testing			X	X	X	X	X	X	X	X	X	X	X	
Dispense IMP		X	X		X		X	X	X	X	X	X		
IMP accounting & compliance			X		X		X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SMBG <sup>g</sup>		X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG <sup>h</sup>	X								X				X	
Laboratory testing <sup>i</sup>														
Hepatitis serology	X													
FPG	X		X		X		X	X	X	X	X	X	X	

Statistical Analysis Plan

Version: 3

Lexicon Pharmaceuticals Protocol No. EFC14835

Date of Issue: 19 February 2020

Covance Study ID:000000154257

VISIT	Screening Period		Double-Blind Core Treatment Period <sup>a</sup>							Double-Blind Extension Period <sup>b</sup>				Follow-up
	Screening	Run-In	3 Baseline	4 ☎	5	6 <sup>c</sup> ☎	7	8	9	10	11	12	13	14 ☎
Week	-4	-2	0	1	4	8	12	18	26	39	52	65	79	81
Day (window [days])		-14 (±3)	1 (-)	7 (±3)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±7)	455 (±7)	551 (-3 to +4)	565 (±3)
HbA1c	X		X		X		X		X	X	X	X	X	
Clinical chemistry, hematology <sup>j</sup>	X		X				X		X	X	X	X	X	
Fasting lipids	X								X		X		X	
Pregnancy test (WOCBP) <sup>k</sup>	X		X		X		X	X	X	X	X	X	X	
FSH and/or estradiol as needed <sup>k</sup>	X													
Plasma concentration <sup>l</sup>					X			X	X		X		X	
Urinalysis (dipstick and microscopy) <sup>m</sup>	X		X						X				X	
Evaluate for glycemic rescue					To be assessed and reported throughout the treatment period									
Hypoglycemia	To be assessed and reported throughout the study													
AEs/SAEs/AESIs/EOSIs	To be assessed and reported throughout the study <sup>p</sup>													

a If a patient discontinues treatment IMP early during the 26-Week Core Treatment Period, the patient will have a Premature End-of-Treatment (EOT) Visit and a Follow-up Visit 2 weeks after the last dose of IMP. In addition, every effort will be made to have all patients return to the site at the time corresponding to their scheduled visits, particularly 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 2 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* At Visits 4 (Week 1), 6 (Week 8) and 14 (2 weeks after the last dose of IMP) patients will be contacted by telephone, and not seen on-site.
- d* Height to be measured only at screening.
- e* Vital sign measurements (sitting blood pressure and heart rate): 3 separate seated blood pressure and heart rate measurements should be taken with at least 1 minute between readings, following a 5-minute rest period and prior to phlebotomy.
- f* The abbreviated physical exam should focus on cardiac and respiratory systems, as well as any areas important for assessment of adverse events if necessary.
- g* 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).
- h* The 12-lead ECG recordings should be obtained prior to IMP administration. The ECG will be evaluated as "normal" or "abnormal".
- i* All laboratory assessments occur prior to IMP administration on the day of the visit.
- j* Clinical chemistry, hematology: please see list in Table 2 in protocol.
- k* Serum pregnancy testing only at screening; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to the Run-In phase for all 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.
- l* Pre-dose plasma concentration samples (ie, of sotagliflozin and sotagliflozin-3-O-glucuronide) should be drawn with the other laboratory assessments at Week 4, Week 18, Week, 26, Week 52, and Week 79. Post-dose plasma concentration samples should be drawn 1 hour 30 minutes after sotagliflozin administration at Week 26 and Week 79. The date and time of the last intake of study drug 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.
- m* Urinalysis performed by the central laboratory 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. Additionally, urine culture should be performed if at any point the Principal Investigator suspects the presence of a UTI.
- p* All SAEs, AEs, AESIs, and 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 2 weeks after the last dose of IMP to collect safety information.