Official Title: A Randomized, Double-blind, Placebo-controlled, 3-arm, Parallel-group, 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Mellitus and Severe Renal Impairment who have Inadequate Glycemic Control

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Lexicon Pharmaceuticals, Inc.

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A Randomized, Double-blind, Placebo-controlled, 3-arm, Parallel-group, 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients with Type 2 Diabetes Mellitus and Severe Renal Impairment who have Inadequate Glycemic Control

Statistical Analysis Plan

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APPROVALS

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

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VERSION HISTORY

Version Status	**Version Date**
Final 1.0	11 October 2018
Final 2.0	20 May 2019
Final 3.0	21 November 2019

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR:	albumin: creatinine ratio
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomic category
BMI:	body mass index
BP:	blood pressure
CEC:	Clinical Endpoint Committee
CI:	confidence interval
CKD:	chronic kidney disease
CRO:	contract research organization
CV:	cardiovascular
DBP:	diastolic blood pressure
DCCT:	Diabetes Control and Complications Trial
DILI:	drug-induced liver injury
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EOSI:	event of special interest
EOT:	end of treatment
ESRD:	end stage renal disease
FPG:	fasting plasma glucose
GCR:	glucose: creatinine ratio
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
IRT:	Interactive Response Technology
KM:	Kaplan-Meier
LDH:	lactic acid dehydrogenase
LLN:	lower limit of normal
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
NTX:	N-terminal telopeptide
P1NP:	type 1 procollagen N-terminal
PCSA:	potentially clinically significant abnormality
PD:	phamacodynamics
P-gp:	P-glycoprotein
PI:	Principal Investigator
PK:	pharmacokinetic
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	preferred term
PTH:	parathyroid hormone
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SE:	standard error
SGLT:	sodium-glucose cotransporter
SGLT2:	sodium-glucose cotransporter type 2
SOC:	system organ class
T2D:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
UACR:	urine albumin: creatinine ratio
UGCR:	urine glucose: creatinine ratio
UGE:	urinary glucose excretion
ULN:	upper limit of normal
UTI:	urinary tract infection
WHO-DD:	World Health Organization-Drug Dictionary
β-CTX-1:	beta-C-terminal telopeptide

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter and multinational, double-blind (single-blind Run-in Phase), placebo-controlled, parallel-group study. Patients were randomly assigned 1:1:1 to the following 3 treatment groups.

- Sotagliflozin 400 mg
- Sotagliflozin 200 mg
- Placebo

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

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

The randomization will be stratified by:

- Hemoglobin A1c (HbA1c) at the screening (≤8.5% and >8.5%)
- Mean systolic blood pressure (SBP) at the screening visit (<130 mmHg, ≥130 mmHg).

It is anticipated to randomize a total of approximately 276 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 with respect to hemoglobin A1c (HbA1c) reduction at Week 26 in patients with type 2 diabetes (T2D) who have inadequate glycemic control and severe renal impairment.

1.2.2 Secondary objectives

- To assess the effects of sotagliflozin 200 mg versus placebo based on: Change from Baseline in HbA1c at Week 26
- To assess the effects of sotagliflozin 400 mg and 200 mg versus placebo, based on:
  - Change from Baseline in fasting plasma glucose (FPG) at Week 26

- Change from Baseline in body weight at Week 26
- Change from Baseline in systolic blood pressure (SBP) at Week 12 for patients with baseline SBP ≥130 mmHg
- Change from Baseline in SBP at Week 12 for all patients
- Percentage change in urine albumin:creatinine ratio (UACR) from baseline to Week 26 (for patients with baseline UACR >30 mg/g)
- The proportion of patients with HbA1c <6.5%, <7.0% at Week 26

- To evaluate the safety of sotagliflozin 400 mg and 200 mg versus placebo over the 52 weeks of treatment.

1.2.3 Other objectives

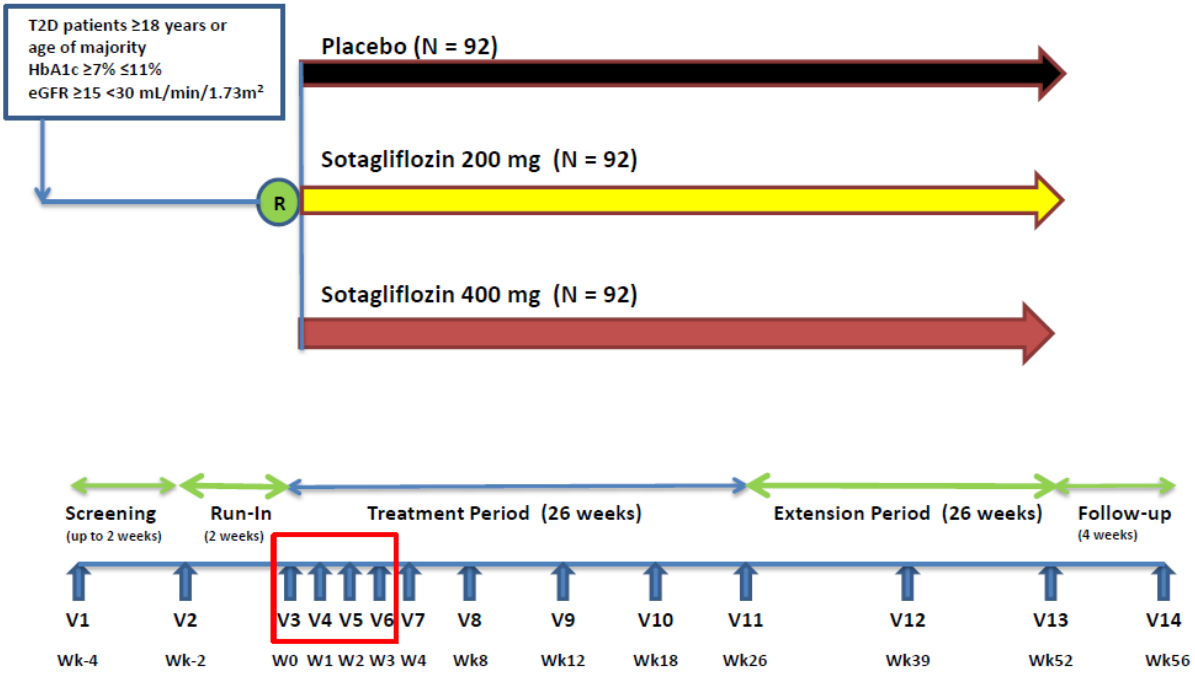
To compare sotagliflozin 400 mg and 200 mg versus placebo with respect to:

- Change from Baseline in SBP at Weeks 26 and 52 for patients with Baseline SBP ≥130 mmHg
- Change from Baseline in SBP at Weeks 26 and 52 for all patients
- Change from Baseline in HbA1c at Week 52
- Change from Baseline in FPG at Week 52
- Change from Baseline in body weight at Week 52
- Change from Baseline in estimated glomerular filtration rate (eGFR)
- Change from baseline on the following endpoints
  - Cystatin C
  - Urinary glucose excretion (UGE)
  - Urine glucose:creatinine ratio (UGCR)
  - Fructosamine
  - N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- Progression of kidney disease, based upon changes in eGFR or albuminuria
- Change from Baseline in additional measures of sitting blood pressure (BP)
- The proportion of patients requiring rescue for hyperglycemia during the 26-week double-blind treatment period
- To assess plasma levels of sotagliflozin and sotagliflozin-3-Oglucuronide in the sotagliflozin treatment arms

1.3 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations were performed based on the primary endpoint. Assuming a common standard deviation of 1.2% and using a 2-sided test at a 0.05 α-level, 92 patients in each group will provide 80% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo.

1.4 STUDY PLAN



The study flowchart can be found in Appendix E.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

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

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

The first patient was enrolled on 12 September 2017. The study analysis will be conducted in 2 steps. The first step analysis is planned when all patients have been randomized and have their data at the minimum up to Week 26 collected and validated. The second step will be conducted at the end of the study.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	13-Dec-2017	Urgent coronary revascularization not adjudicated by CEC to be consistent with outcome trials	Urgent coronary revascularization not included in adjudication related analyses.
1	13-Dec-2017	5 half-lives of sotagliflozin prolonged to 15 days considering patients with severe renal dysfunction	5 half-lives of IMP updated from 5 days to 15 days; TEAE period updated accordingly
1	13-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.
1	13-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

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	04-Oct-2018	Urgent coronary revascularization not adjudicated by CEC to be consistent with outcome trials	Urgent coronary revascularization not included in adjudication related analyses*.
1	04-Oct-2018	5 half-lives of sotagliflozin prolonged to 15 days considering patients with severe renal dysfunction	5 half-lives of IMP updated from 5 days to 15 days; TEAE period updated accordingly*
1	04-Oct-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	04-Oct-2018	The effect in body weight is considered more closely associated with the planned indication.	Change in the order of secondary objectives and endpoints for the study
1	04-Oct-2018	Clarification on EOSI renal events	Details specified on renal events to be consistent with outcome studies in Section 2.1.4.2.
1	04-Oct-2018	Clarification on ESRD	ESRD is defined in Section 2.4.4.3 consistent with CEC charter.
1	04-Oct-2018	[redacted]	[redacted]
1	04-Oct-2018	[redacted]	[redacted]
1	04-Oct-2018	Updating the wording to be consistency with CEC charter	"Unstable angina leading to hospitalization" changed to "Unstable angina requiring hospitalization"
2	05-Jun-2019	[redacted]	[redacted]
2	05-Jun-2019	Number of iterations for multiple imputation was changed	Number of iterations for multiple imputation was changed from 10000 to 2000
2	05-Jun-2019	Wording change to be consistent with CEC charter	"Heart failure leading to hospitalization" changed to "Heart failure requiring hospitalization"

SAP version number	Date approved	Rationale	Description of statistical changes
2	05-Jun-2019	MedDRA version and dictionary updated	MedDRA version was updated to V22.0 and list of PTs for selected EOSI was updated
2	05-Jun-2019	Update categories of prior antidiabetic medication to cover all patients	Add "no antidiabetic therapy"
3	This version	Change in study Sponsor led to a strategic decision not to report the first step analysis in a standalone CSR	First step analyses will be combined with the second step analysis and both will be conducted at the end of the study in a single CSR The following sections/paragraphs are not applicable Section 2.4.4.4 – the last paragraph Section 3. – the first step analysis details Section 4. – the first data base lock
3	This version	[redacted]	[redacted]
3	This version	Assess robustness of the ITT-based analyses	Identify possible need to conduct sensitivity analyses for PK anomalies
3	This version	Provide comparative analyses at Week 52 for the primary and secondary efficacy endpoints to further characterize the long-term effects of sotagliflozin	Apply statistical methods specified in Sections 1.6, 2.4.4.1, and 2.4.4.2 to the primary and secondary endpoints at Week 52
3	This version	Based on clinical guidelines for a higher A1C target for patients with chronic kidney disease.	Add another endpoint of proportion of patients with HbA1c <8%, at Week 26 and Week 52

* Change made in Protocol Amendment 1 dated 20-DEC-2017.

The first step analysis was conducted and reported for top line results; it was not used to inform a standalone Clinical Study Report (CSR) limited to just the 6-month data. A single CSR will be written for this study and will include the results coming from the analyses specified at both the first and second steps (see Section 3 of this SAP for more details).

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

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

An alternative (back-up) imputation method will be used if the number of patients who prematurely discontinue the IMP before the Week 26 (or Week 12 for SBP) visit but have the measurement for the endpoint is < 5 in any treatment groups (ie, an insufficient number of retrieved dropouts to support the imputation method described above). This criterion will be assessed for each primary or continuous secondary efficacy endpoint.

In the back-up imputation method, missing post-baseline endpoint values at Week 26 (or Week 12 for SBP) will be imputed by the washout Multiple Imputation (MI) method under the missing not at random (MNAR) framework.

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

For patients in the sotagliflozin 400 mg and 200 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.

For the overall population each of the completed datasets after the imputation will be analyzed using the Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, 200 mg and placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed factors, and baseline HbA1c value as a covariate. Results from each analysis will be combined using Rubin's formula, to provide the adjusted mean change in HbA1c from Baseline to Week 26 (or Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg versus placebo and sotagliflozin 200 mg versus placebo) and its associated 95% confidence interval (CI).

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, and the tipping point analyses previously specified in this section.

Analysis of the primary and secondary endpoints at Week 26 as specified in Section 2.4.4.1and 2.4.4.2 will be repeated for these same measures at Week 52, even though Section 2.4.4.4 called for these analyses to be descriptive only. In addition, the sensitivity analysis methods described in this section will be applied to these variables at Week 52.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

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

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

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

Demographic characteristics

- 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 visit (data from IRT),
- Mean SBP at screening visit,
- Randomization strata of mean SBP (<130 mmHg, ≥130 mmHg) at screening visit (data from IRT),
- Baseline body mass index (BMI) (kg/m^2) derived as: (Weight in kg)/(Height in meters)^2,
- Baseline BMI categories (<30, ≥30 kg/m^2),
- Country.

Disease characteristics at screening or baseline

Disease history includes:

Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of Diabetes + 1)/365.25,

- Duration of diabetes categories: (<10, ≥10 years),
- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes – Year of birth,
- Prior use of sodium-glucose cotransporter type 2 (SGLT2) (Yes, No),
  - Prior antidiabetic medication (no antidiabetic therapy, insulin, non-insulin),
- Baseline diabetic microvascular complications (Yes, No) [ie, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy (duration of diabetic nephropathy for patients with diabetic nephropathy), diabetic peripheral neuropathy (sensory or motor), diabetic autonomic neuropathy, and diabetic foot infection],
- Baseline UACR categories (<30 mg/g [Normal], ≥30 to <300 mg/g [Microalbuminuria], and ≥300 mg/g [Macroalbuminuria]),
- eGFR at screening (mL/min/1.73m^2),
- 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 Sanofi at the time of database lock.

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

2.1.2 Prior or concomitant medications

All medications taken in the 3 months before the screening visit (any time for prior SGLT2) 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 Sanofi at the time of database lock.

- **Prior medications** are those the patient used prior to first administration of double-blind IMP. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- **Concomitant medications** are any treatments received by the patient concomitantly to the IMP, from the 1st administration of double-blind IMP to the date of last administration + 15 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 16th day after the last administration of double-blind IMP up to the end of the study.

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

2.1.2.1 Rescue therapy

Open label rescue medication(s) to treat hyperglycemia must be in accordance with local standard of care and prescribing practice for patients with CKD and will be at the discretion of the Investigator. Except for SGLT2 inhibitors and medications with specific contraindications in renal impairment, any approved medication(s) including oral antidiabetic drugs or insulin can be considered with appropriate dose modification as indicated. Rescue therapy is considered as a noninvestigational medicinal product (NIMP).

2.1.2.2 Prohibited prior and concomitant medications

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

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

  Note: short term use (<10 consecutive days) of the prohibited medication eg, short-acting insulin for treatment of acute illness or surgery is allowed.
- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin) are not allowed for rescue.
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, intra-articular, ophthalmic, nasal spray or inhaled applications are allowed).
- Investigational medicinal products in any other clinical study.
- Modification of antihypertensive medication before Week 12 is not allowed unless for safety reasons.
- Initiation of any weight loss drugs (eg, phentermine, orlistat).

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

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

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

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

2.1.3 Efficacy endpoints

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

HbA1c, FPG, UACR, UGE, urine glucose: creatinine ratio (UGCR), Cystatin C, Fructosamine, NT-proBNP and eGFR are measured/calculated in a central laboratory (see study flowchart in Appendix E). FPG, Cystatin C, Fructosamine, NT-proBNP are measured in the fasting state. Body weight, SBP and DBP (see Section 2.1.4.5) are measured at on-site visits by the investigator. Patients requiring rescue are identified as those with the reason for treatment ticked "rescue therapy" in e-CRF "Medication" page.

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

2.1.3.1 Primary efficacy endpoint(s)

Change from Baseline to Week 26 in HbA1c (%) comparing sotagliflozin 400 mg versus placebo in CKD stage 4 patients.

2.1.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Change from Baseline to Week 26 in HbA1c (%) comparing sotagliflozin 200 mg versus placebo
- Comparison sotagliflozin 400 mg and 200 mg, respectively, versus placebo for:
  - Change from Baseline in FPG at Week 26

- Change from Baseline in body weight at Week 26
- Change from Baseline in SBP at Week 12 for patients with baseline SBP ≥130 mmHg
- Change from Baseline in SBP at Week 12 for all patients
- Change in the UACR (%) from Baseline to Week 26 for patients with a UACR >30 mg/g at baseline
- Proportion of patients with HbA1c <6.5%, <7.0% at Week 26.

2.1.3.3 Other efficacy endpoints

- To compare sotagliflozin 400 mg and 200 mg versus placebo, respectively, in terms of:
  - Change from Baseline in SBP at Weeks 26 and 52 for patients with Baseline SBP ≥130 mmHg
  - Change from Baseline in SBP at Weeks 26 and 52 for all patients
  - Change from Baseline in HbA1c at Week 52
  - Change from Baseline in FPG at Week 52
  - Change from Baseline in body weight at Week 52
  - Change from Baseline in eGFR
  - Change from Baseline to Week 26 in:
    - Cystatin C
    - UGE
    - UGCR
    - Fructosamine
    - NT-proBNP
  - Proportion of patients with progression to end stage renal disease (ESRD) (dialysis or transplant) at Week 4 or any time later during the trial
  - Proportion of patients with >50% decline in eGFR from Baseline to Week 26 and Week 52
  - Proportion of patients with progression from normal to microalbuminuria or from microalbuminuria to macroalbuminuria from Baseline to Week 26 and Week 52
  - Proportion of patients with improvement from microalbuminuria to normal or from macroalbuminuria to microalbuminuria from Baseline to Week 26 and Week 52
  - Change from Baseline to Week 12 in SBP for patients with baseline SBP <130 mmHg
  - Change from Baseline to Week 12 in DBP for all patients and the subset of patients with baseline DBP ≥80 mmHg
  - Proportion of patients requiring rescue for hyperglycemia during 26-week double-blind period.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events, hypoglycemia, acute renal failure and other safety information, such as clinical laboratory data, vital signs, electrocardiogram (ECG), physical examination and marker of intestinal transit and absorption, markers of bone and calcium metabolism, etc.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first administration of the double-blind IMP.
- The **treatment** epoch is defined as the time from the first administration of double-blind IMP to the last administration of double-blind IMP. This epoch includes the 26-week double-blind core treatment period and the 26-week double-blind extension treatment period. The 26-week 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 11 (Week 26) [or Day 182 if Visit 11 (Week 26) date is missing].
- The **residual treatment** epoch is defined as the time from the last administration of the IMP to the last administration of the IMP + 15 days (1 day for hypoglycemia).

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

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

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

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

2.1.4.1 Hypoglycemia

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

Severe hypoglycemia

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

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

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

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

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

Documented symptomatic hypoglycemia

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

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

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

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

Asymptomatic hypoglycemia

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

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

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

Probable symptomatic hypoglycemia

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

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

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

Relative hypoglycemia

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

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

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

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

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

2.1.4.2 Adverse events variables

Adverse event observation period

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

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

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

AESI include:

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

EOSI include:

- Major adverse cardiovascular events (MACE [cardiovascular death, myocardial infarction, or stroke]) and other specific cardiovascular (CV) events (eg, heart failure requiring hospitalization)
- Severe hypoglycemia
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candida balanitis in males)
- Urinary tract infection
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Diarrhea
- Pancreatitis
- Bone fractures

- Venous thrombotic events, to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- Diabetic ketoacidosis
- Renal events, to include 50% decline in eGFR, end stage kidney disease, renal death
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid cancer)
- Adverse event leading to an amputation

The 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 DKA.

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

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

Table 3 - Criteria for AESI and EOSI

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

AE Grouping	Criteria
Bone fractures	Positively adjudicated by CEC: Yes to the question “Did the Fracture occur?”
Diabetic ketoacidosis	Positively adjudicated by CEC: Yes to the question “Does this event meet the criteria to be a DKA event?”
EOSI Renal events where select events adjudicated	
Sustained ≥50% decrease in eGFR	(1) For ≥50% decrease in eGFR from baseline, (1a) confirmed ≥50% decrease in GFR for ≥30 days with no reversible cause as recorded in eCRF “eGFR decrease”, OR (1b) positively adjudicated by CEC: Yes to the question “Does the subject meet the criteria of CKD progression”.
Sustained eGFR <15 mL/min/1.73 m^2	(2) For eGFR <15 mL/min/1.73 m^2, (2a) confirmed eGFR <15 mL/min/1.73 m^2 for >=30 days with no reversible cause as recorded in eCRF “eGFR decrease”, OR (2b) positively adjudicated by CEC: Yes to the question “Does the subject meet the criteria of CKD progression”.
Chronic dialysis	(3) For dialysis, (3a) dialysis lasted for >=90 days (e.g. end date – start date+ 1 >=90) as recorded in eCRF “Renal Event – Dialysis”, OR (3b) positively adjudicated by CEC: Yes to the question “. Does the subject meet the criteria for ESRD”.
Renal transplant	(4) “Renal transplant” captured in eCRF “Other procedure form”, where adjudication is not required. PTs of Renal transplant (10038533), Renal and pancreas transplant (10052278), Renal and liver transplant (10052279) based on MedDRA v22.0.
Renal death	(5) Renal death as positively adjudicated by CEC: “Death - Non-Cardiovascular (Renal)” as the primary cause of death
EOSI not adjudicated*	
Severe hypoglycemia	algorithm specified in Section 2.1.4.1 based on eCRF “Hypoglycemic Events”
Genital mycotic infections	PTs in Appendix C
Urinary tract infections	PTs in Appendix C,

AE Grouping	Criteria
Clinically relevant volume depletion and events related/possibly related to volume depletion	PTs in Appendix C
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" [20000218] plus the following PTs (MedDRA v22.0): Gastroenteritis (10017888), Antidiarrhoeal supportive care (10055660), Enteritis (10014866), Enteritis leukopenic (10014877), Enterocolitis (10014893), Enterocolitis haemorrhagic (10014896)
Pancreatitis	PTs in Appendix C
Venous thrombotic events	PTs in Appendix C
Malignancies of special interest	Breast cancer: Narrow search on "Breast neoplasms, malignant and unspecified (SMQ)" [20000149]
	Prostate cancer: Narrow search on "Prostate neoplasms, malignant and unspecified (SMQ)" [20000152]
	Leydig-cell cancer: PTs of Leydig cell tumour of the testis (10024407) and Ovarian Sertoli-Leydig cell tumour (10073270) based on MedDRA v22.0
	Thyroid cancer: PTs in Appendix C
	Renal cell cancer: PTs in Appendix C
	Pancreatic cancer: PTs in Appendix C
	Bladder cancer: PTs in Appendix C
EOSI AE leading to an amputation	
Adverse event leading to an amputation	"AE Correction" as the reason for amputation in eCRF "Other Procedures related to Amputation"
AE potentially leading to an amputation *	PTs in Appendix C

* Search terms will be updated using the MedDRA version currently in effect at Sanofi at the time of database lock for EOSI identified by them.
AE potentially leading to amputation: not one of EOSI defined in protocol, included and analyzed due to their relevance in regards to lower limb complications and amputations as 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 poststudy: deaths occurring after the end of the study

2.1.4.4 Laboratory safety variables

Clinical laboratory data consist 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 taken at designated visits (see study flowchart in Appendix E). The following laboratory parameters will be assessed at a central laboratory:

- Hematology
  - **Red blood cells and platelets:** hemoglobin, hematocrit, red blood cell count, platelet count,
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism:** Glucose (serum), creatine phosphokinase (CPK),
  - **Electrolytes and minerals**: sodium, potassium, chloride, calcium, phosphorus, bicarbonate (ie, carbon dioxide), magnesium
  - **Renal function**: creatinine, blood urea nitrogen (BUN), uric acid
  - **Liver function**: total protein, Albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Lactic acid dehydrogenase (LDH), total bilirubin (TB)
- Lipid parameters (fasting):
  - Total cholesterol (TC)
  - High density lipoprotein cholesterol (HDL-C)
  - Low density lipoprotein cholesterol (LDL-C) (calculated by Friedwald equation, See Section 2.5.1)
  - Non-HDL-C (calculated as the difference between TC and HDL-C),
  - Triglycerides (TG).
- Pancreatic enzymes: lipase, amylase.
- Markers of Intestinal Transit and Absorption
  - Vitamins: B6, B12, K, E and A
  - Serum folate
  - Ferritin
- Markers of bone and calcium metabolism
  - Calcium
  - 25-hydroxyvitamin D

- 1,25-dihydroxyvitamin D
- Phosphorus
- Parathyroid hormone (PTH),
- Markers of bone resorption: N-terminal telopeptide (NTX), beta-C-terminal telopeptide (β-CTX-1),
- Marker of bone formation: type 1 procollagen N-terminal (P1NP), osteocalcin

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

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

Serum glucose, UGE, calculated UACR and calculated UGCR will be presented as efficacy parameters in Section 2.4.4.

- Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

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

2.1.4.6 Physical examination

A complete physical exam will be performed at Visit 1 (Screening), Visit 11 (Week 26) and Visit 13 (Week 52). "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 ECG record is performed locally at Visit 2 (Run-in), Visit 11 (Week 26), and Visit 13 (Week 52). ECG status of "normal" or "abnormal" will be reported in the e-CRF as determined by the investigator.

2.1.5 Pharmacokinetic variables

Pharmacokinetic variables include the concentration of sotagliflozin and its 3-O-glucuronide metabolite in the sotagliflozin group (see study flowchart in Appendix E for designated visits).

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 any patients who have signed the informed consent.

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

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

- Screened patients
- Run-in patients: patient 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 completed the 26-week double-blind core treatment period (see Section 2.5.4 as scheduled).
- Patients who did not complete the 26-week double-blind core treatment period (see Section 2.5.4) as scheduled and the reasons for permanent treatment discontinuation
- Patients who completed the 52-week entire treatment period as scheduled
- Patients who did not complete the 52-week entire treatment period as scheduled , and the reasons for permanent treatment discontinuation
- Patients who completed the study as scheduled.
- Patients who did not complete the study as per protocol and the reasons for study discontinuation
- Patients' end of study status at Week 26 (ongoing, discontinued) and corresponding end of 26-week core treatment status (ongoing, discontinued)

- Patients' end of study status (completed, not completed) and corresponding end of entire treatment status (completed, not completed)
- Status at last study contact

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

A summary of the distribution of patients by country and center will also be provided (overall number of patients screened, run-in, randomized, 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 but not treated as randomized) will be part of efficacy and safety analyses (Section 2.3). Patients randomized but not treated will be included in efficacy analysis. Safety data of patients treated but not randomized will be reported separately.

The randomization strata [HbA1c at Screening (≤8.5%, >8.5%) and mean SBP at Screening (<130, ≥130 mmHg)] assigned by IRT will be summarized. The percentages will be calculated using the number of randomized patients as the denominator. The discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients.

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

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

Additionally, the analysis populations for safety, efficacy, and pharmacokinetics defined in Section 2.3.3 will be summarized in a table by number of patients in the randomized population.

- Efficacy population: intent-to-treat (ITT) population
- Safety population
- Pharmacokinetics population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

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

   OR

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

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

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

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

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

2.3 ANALYSIS POPULATIONS

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

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

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

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

2.3.1 Efficacy population

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 of double-blind IMP (regardless of the amount of treatment administered), analyzed according to the treatment actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- When a patient is exposed to both sotagliflozin and placebo, the patient will be analyzed in the appropriate sotagliflozin group (depending on the treatment kits taken [400 mg or 200 mg])
- When a patient is exposed to both sotagliflozin 400 mg (treatment kits) and 200 mg (treatment kits), the patient will be analyzed in the sotagliflozin 200 mg group
- Randomized patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study treatment. If a patient is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed.

2.3.3 PK population

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

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

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

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

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

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

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

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

2.4.2 Prior or concomitant medications

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

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

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

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

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

2.4.3 Extent of investigational medicinal product exposure and compliance

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

2.4.3.1 Extent of investigational medicinal product exposure

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

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

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum) during the 26-week core treatment period and 52-week entire treatment period, respectively. In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

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

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

Number and percentages of patients with dose interruption/reduction due to creatinine increase (identified as those who answered Yes to the question "If Actual Total Daily Dose is 0, Was the dose interruption due to creatinine increase per protocol?" in e-CRF "Exposure" page) will be summarized.

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

2.4.3.2 Compliance

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

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

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

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

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

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

2.4.4 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population using 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 secondary endpoints at Week 26 (with the exception of Week 12 for SBP). All efficacy endpoints after Week 26 will only be summarized by descriptive statistics without formal statistical testing.

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

2.4.4.1 Analysis of primary efficacy endpoint(s)

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

Primary analysis

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

1. Missing endpoint data for patients who prematurely discontinue the IMP before the Week 26 (or Week 12 for SBP) visit will be imputed using a model built separately in each treatment group and estimated from the patients in the same treatment group who prematurely discontinue the IMP before the Week 26 (or Week 12 for SBP) visit but have the measurement for the endpoint (retrieved dropouts). Considering that the number of patients in each treatment group who discontinue the IMP but have the measurement for the endpoint is expected to be small, a simple imputation model based on regression will be used with baseline measurement included as the predictor. Each treatment group will have their own imputation model.
2. Missing endpoint data for all patients who stay on the IMP until the Week 26 (or Week 12 for SBP) visit, including those in the sotagliflozin groups, will be imputed separately. The wash-out imputation method will be used, where missing endpoint data in the sotagliflozin groups, as well as in the placebo group are imputed from a model estimated from patients in the placebo group who stay on the IMP until the Week 26 (or Week 12 for SBP) visit and have the endpoint data available. The imputation model will include the randomization strata and the corresponding baseline value. Missing data will be imputed using the regression method.

An alternative (back-up) imputation method will be used if the number of patients who prematurely discontinue the IMP before the Week 26 (or Week 12 for SBP) visit but have the measurement for the endpoint is <5 in any treatment groups (ie, not sufficient retrieved dropouts to support the imputation method described above). This criterion will be assessed for each primary or continuous secondary efficacy endpoint separately.

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

To compare sotagliflozin 400 mg and 200 mg, respectively, versus placebo

- For placebo patients, missing data will be imputed based on the placebo group data,
- For patients in the sotagliflozin 400 mg and 200 mg groups, missing data will be imputed as if the patients were on placebo throughout the study, where all patients' measurements including the on-treatment measurements will be considered as if the measurements were from the placebo group in the imputation model.

Using either imputation method, missing endpoint data will be imputed multiple times to generate multiple data sets with complete data (see sample code Part 1a or Part 2a of Appendix A). The change from baseline to Week 26 will be derived from observed and imputed HbA1c values at Week 26. Each of the complete datasets after the imputation will be analyzed by an Analysis of Covariance (ANCOVA) model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130, ≥130 mmHg), and country as fixed factors, and baseline HbA1c value as a covariate (see sample code Part 4a of Appendix A). Results from each complete dataset will be combined using Rubin's formula, to provide the adjusted mean change in HbA1c from Baseline to Week 26 for each treatment group, as well as the between group difference (comparing sotagliflozin 400 mg, sotagliflozin 200 mg, respectively, versus placebo) and the 95% confidence interval (CI) for the between-group difference (see sample code Part 5 in Appendix A).

Sensitivity analyses

Tipping point analysis based on the same multiple imputation method as applied to the primary analysis will be performed to examine the robustness of the results from the primary analysis. Patients who were randomized to sotagliflozin groups and had no HbA1c data at Week 26 will be given a penalty. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of statistical significance is changed. The tipping point is the penalty level, at which the magnitude of efficacy reduction in patients without HbA1c data at Week 26 creates a shift in the treatment effect of sotagliflozin 400 mg from being statistically significantly better than placebo to a non-statistically significant effect. LS mean difference between sotagliflozin 400 mg and placebo and its associated p-value will be provided for each penalty level. The steps to perform the tipping point analysis comparing sotagliflozin 400 mg versus placebo are as follows:

1. Missing data will be imputed using the same MI method as applied to the primary analysis (see sample code Part 3 in Appendix A),

2. The imputed HbA1c value at Week 26 in the sotagliflozin 400 mg group will be penalized by adding a penalty δ (eg, δ= 0.1%) in each complete dataset (see sample code Part 3 in Appendix A),

3. Change from Baseline at Week 26 in HbA1c will be analyzed using the same ANCOVA model as specified in the primary analysis in each complete dataset (see sample code Part 4a in Appendix A),

4. Results will be combined across complete datasets using Rubin's rule (see sample code Part 5 in Appendix A),

5. Steps 2 to 4 will be repeated with incremental penalty at δ (ie, δ , 2δ, 3δ……) until the p-value for treatment effect of sotagliflozin 400 mg compared to placebo estimated in Step 4 is >0.05.

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

The tipping point analysis will be performed on the ITT population. The tipping point analysis will be performed only if the corresponding primary or secondary variables (change from Baseline to Week 26 in HbA1c) is statistically significant at $\alpha = 0.05$ (2-sided).

If the retrieved dropout imputation is applied to the primary analysis, the analysis based on the control-based imputation (ie, the backup imputation method) will be presented as a sensitivity analysis.

Assessment of treatment effect by subgroup

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

- Race (White, Black or African American, Asian, Other) (any race groups with fewer than 5 patients may be combined with "Other" category as appropriate),
- Ethnicity (Hispanic, Not Hispanic),
- Age group (<50, ≥50 to <65, ≥65 years) (any category with fewer than 5 patients may be combined with another category as appropriate),
- Gender (Male, Female),
- Baseline BMI level (<30, ≥30 kg/m^2),
- Baseline HbA1c (≤8.5%, >8.5%),
- Baseline mean SBP (<130 mmHg, ≥130 mmHg),
- Duration of diabetes (<10, ≥10 years),
- Prior antidiabetic medication (insulin, non-insulin),
- Country.

The treatment effect (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 as applied to the analysis for the primary efficacy endpoint. The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130, ≥130 mmHg), subgroup factor, treatment-by-subgroup factor, and country as fixed factors and using baseline HbA1c value as a covariate. The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus placebo) with standard error (SE) and 95% CIs will be provided as appropriate across the subgroups (see sample code Part 4a in Appendix A). A graphical presentation of the results (ie, forest plot) will also be provided.

Similarly, the treatment effect across the subgroups will be estimated for the comparison of sotagliflozin 200 mg versus placebo as a sensitivity analysis.

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

Summary statistics at scheduled visits

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

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

2.4.4.2 Analyses of secondary efficacy endpoints

For continuous secondary efficacy parameters (see Section 2.1.3) with missing data at baseline, missing data will be imputed using MI under the missing at random (MAR) assumption. Missing data at baseline will be imputed using regression method that includes randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130, ≥130 mmHg), and baseline value in the imputation model (see sample code Part 1 or 2b in Appendix A).

Each continuous secondary endpoints (see Section 2.1.3) will be analyzed using a similar ANCOVA model including the measurements at baseline and endpoint (observed or imputed). The missing data at endpoint will be imputed by the retrieved dropouts & washout imputation method or by the control-based copy reference imputation method according to the criterion described in Section 2.4.4.1. After the imputation, each of the complete datasets will be analyzed by an ANCOVA model.

The ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130, ≥130 mmHg), and country as fixed effects, and baseline secondary endpoint value as a covariate. For the analysis of SBP in patients with baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included in the ANCOVA model. Results from each complete dataset will be combined using Rubin's rule to provide the adjusted mean change from baseline to Week 26 (or Week 12 for SBP) for each treatment group, as well as the between-group difference (comparing sotagliflozin 400 mg, sotagliflozin 200 mg vs placebo) and the 95% CI for the difference.

UACR will be log-transformed at patient level before analysis, and geometric means (with and without ANCOVA model adjustment), differences between treatments and 95% CIs will be back-transformed to original scale. Summary statistics of UACR in log scale will then be calculated for

each treatment group at each visit and back-transformed to provide the geometric mean and its associated percent change of UACR from baseline.

For all continuous secondary endpoints, summary statistics at scheduled visits will be provided for each treatment group. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits. In addition, SBP will be summarized descriptively at each visit for those with baseline SBP ≥140 mmHg.

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

For between-group comparison, a sensitivity analysis will be performed 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 provided by treatment group during the 26-week core (see Section 2.5.4) and the 52-week entire double-blind treatment periods. A KM curve for the time to first rescue therapy will be presented during the 26-week core treatment period and 52-week entire treatment period (see Section 2.5.4). The list of patients who used rescue therapy will also be provided.

ESRD is defined as: (1) dialysis that persists for a duration of ≥90 days, or positively adjudicated as ESRD if dialysis <90 days; (2) eGFR <15 ml/min/1.73 m2 sustained for at least 30 days or positively adjudicated as chronic; or (3) renal transplant. The number (%) of patients with progression to ESRD at Week 4 or any time later during the study will be summarized. The same analysis will be provided during the period from the first administration of double-blind IMP (or the date of randomization if not exposed) to Week 4 (exclusive). A KM plot will be provided for time to first occurrence of ESRD up to Week 26 and the end of study respectively (see Section 2.5.4).

The number (%) of patients with >50% decline in eGFR from baseline at each scheduled visit (including Week 26 and Week 52) will be presented. The same analysis will be presented from Week 4 at each scheduled visit afterwards (including Week 26 and Week 52). A KM plot will be provided for time to first occurrence of >50% decline in eGFR from baseline up to Week 26 and the end of study respectively (see Section 2.5.4).

The number (%) of patients with UACR progression from baseline to Week 26 and Week 52, (ie, from normal to microalbuminuria or from microalbuminuria to macroalbuminuria) will be provided by treatment group respectively. A KM plot will be provided for time to UACR progression up to Week 26 and the end of study respectively (see Section 2.5.4). Similarly, the number (%) of patients with UACR improvement from baseline to Week 26 and Week 52 (from microalbuminuria to normal or from macroalbuminuria to microalbuminuria) will be provided, as well as the KM plot if appropriate.

2.4.4.4 Multiplicity issues

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

Once the primary variable (change from Baseline to Week 26 in HbA1c) is statistically significant at α=0.05 (2-sided), a hierarchical testing procedure will be performed to test the following secondary efficacy variables in the following prioritized order. The testing will stop as soon as an endpoint is found not to be statistically significant at α=0.05 (2-sided).

- Comparing sotagliflozin 200 mg versus placebo in change from Baseline to Week 26 in HbA1c
- Comparing sotagliflozin 400 mg versus placebo
  - Change from Baseline to Week 26 in FPG
  - Change from Baseline to Week 26 in body weight
  - Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg
  - Change from Baseline to Week 12 in SBP for all patients
  - Proportion of patients with HbA1c <7.0% at Week 26
- Comparing sotagliflozin 200 mg versus placebo
  - Change from Baseline to Week 26 in FPG
  - Change from Baseline to Week 26 in body weight
  - Change from Baseline to Week 12 in SBP for patients with baseline SBP ≥130 mmHg

Once the above secondary variables are statistically significant at α = 0.05 (2-sided), Hochberg's step-up procedure (1) will be performed to test the remaining 4 secondary variables: order a number of m (m=4 here) tests by p-values (from lowest to highest) $P_{(1)}$ ……, $P_{(m)}$ associated with tests $H_{(1)}$ ……, $H_{(m)}$, find the largest k (called R) so that $P_{(k)} \leq \alpha / (m+1-k)$, conclude $H_{(1)}$ ……, $H_{(R)}$ statistically significant.

- Percentage change in UACR from Baseline to Week 26 for patients with UACR >30 mg/g at Baseline, comparing sotagliflozin 400 mg and 200 mg, respectively, versus placebo
- Proportion of patients with HbA1c <7.0% at Week 26, comparing sotagliflozin 200 mg versus placebo
- Change from Baseline to Week 12 in SBP for all patients comparing sotagliflozin 200 mg versus placebo.

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

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

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. The safety data will be summarized for the 26-week core treatment period and the 52-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. For serum creatinine and eGFR, the baseline value is defined as the average of all values before the first dose of double-blind IMP.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (Appendix B)
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations.

The number of all such patients will be the numerator for the treatment-emergent PCSA percentage.

- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.
- For laboratory parameters cited in the protocol as efficacy endpoints (including HbA1c and plasma glucose etc), PCSA summaries will not be provided. These parameters will be summarized in 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 52-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 52-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 52-week entire treatment period.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% 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 2.5.2).

2.4.5.1 Analyses of hypoglycemia

Analyses of hypoglycemia will be performed on the TEAE period as defined in Section 2.1.4. Hypoglycemia will be classified as severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia or relative hypoglycemia (see Section 2.1.4).

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 treatment-emergent AE period, ie, duration of IMP treatment in days +1 (Section 2.1.4).

- The summary of frequency and incidence rate in patient years for severe hypoglycemia or documented symptomatic hypoglycemia will be provided as appropriate by gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years), race (White, Black or African American, Asian, Other) and prior antidiabetic medication (no antidiabetic therapy , insulin, non-insulin).

- 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 52-week entire treatment period only (see Section 2.5.4).

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

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

2.4.5.2 Analyses of adverse events

Generalities

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

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

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

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

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the 26-week core treatment period and the 52 week entire treatment period respectively in the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary system organ class, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT in the sotagliflozin 400 mg group
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the sotagliflozin 400 mg group. This sorting order will be applied to all other similar tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related IMP by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above
- Common TEAEs (PTs with incidence ≥2% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.
- Common TEAEs (PTs with an incidence ≥2% in any treatment group) will be provided as appropriate by primary SOC, and PT and by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years of age), race (White, Black or African American, Asian, other), baseline SBP category (<130 mmHg, ≥130 mmHg), and prior antidiabetic medication (no antidiabetic therapy, insulin, non-insulin). 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 incidence ≥5% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.

- Acute renal failure (narrow search on "Acute renal failure (SMQ)" [20000003]) by PT.

Analysis of all treatment emergent serious adverse event(s)

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

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

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

Analysis of adverse events of special interest

- The summaries of AESI will be presented for the 52-week entire treatment period only in the safety population.
- Pregnancy and overdose will be included in overall AE summaries if any are reported. ALT increase >3 x ULN is included in laboratory PCSA summary if any.
- In addition, the number (%) of patients with an AESI will be summarized by PT and by treatment group. Corresponding listings will be provided as appropriately.

Analysis of events of special interest

- The summaries of EOSI will be presented for the 52-week entire treatment period only in the safety population."

CV events, bone fracture and DKA

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

Renal events

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

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

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

Renal death will be part of all deaths specified above.

Other EOSIs

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

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

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

Analysis of Amputation

The number (%) of patients with amputation will be summarized by treatment group and by PT and LLT during the study (ie, regardless of on- or post-treatment). Amputation is a procedure recorded in eCRF "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 (as identified in Table 3 in Section 2.1.4.2; these PTs in Table 3 were requested by the European Medicines Agency(EMA)/ Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report, 09 February 2017). The associated list will be provided as well, with patients who had an amputation procedure flagged. "AE potentially leading to an amputation" represents the condition that may potentially lead to the amputation procedure, but not in all cases an amputation has occurred.

Analysis of pretreatment and posttreatment adverse events

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

Listings

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

2.4.5.3 Deaths

The following summaries of deaths will be generated.

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

2.4.5.4 Analyses of laboratory variables

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

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values, changes from baseline, and/or percent change from baseline [eg, lipid parameters, albumin, total protein, hemoglobin, hematocrit]) will be calculated for each applicable visit or study assessment (screening, baseline, postbaseline time point, last on-treatment value) by treatment group. Graphical presentations may be used to examine trends over time using mean (±SE) and/or mean change from baseline (±SE) at scheduled visits (eg, creatinine, eGFR).

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

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

For creatinine, ≥50% change from baseline will be provided in addition to the PCSA criteria defined, ie, ≥150 μmol/L (Adults), ≥30% change from baseline, ≥50% change from baseline, and ≥100% change from baseline. For eGFR, ≥50% decrease from baseline will be provided in

addition to the PCSA criteria defined, ie, <15 (end stage renal disease), ≥15 - <30 (severe decrease in GFR), ≥30 - < 60 (moderate decrease in GFR), ≥60 - <90 (mild decrease in GFR), and ≥50% decrease from baseline. For parameters for which no PCSA criteria are defined, similar tables using the normal range will be provided.

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

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

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

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

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure (see Section 2.4.3.1) for each treatment group (only if a tabulation summary is necessary).

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

2.4.5.5 Analyses of vital sign variables

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

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

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

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

2.4.5.6 Analyses of electrocardiogram variables

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

2.4.5.7 Analyses of physical examination variables

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

2.4.6 Analyses of pharmacokinetic variables

Plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite will be summarized by visit and nominal sampling time (pre-dose at Weeks 4, 18, 26, 39, and 52 and 3 hours post-dose at Week 26 and Week 52) in the PK population (see Section 2.3.3) in the sotagliflozin group, using descriptive statistics such as number, geometric mean, coefficient of variation, median, minimum and maximum. Individual plasma concentrations of sotagliflozin and its 3-O-glucuronide metabolite at nominal sampling times will also be listed.

[redacted]

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

HbA1c

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

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

Renal function formulas

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

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

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

UACR

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

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

UGCR

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

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

Calculation of LDL-C

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

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

2.5.2 Data handling conventions for secondary efficacy variables

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

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

2.5.3 Missing data

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

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

Incomplete date of first administration of double-blind IMP

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

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

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing.

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

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

Handling of medication missing/partial dates

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

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

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

Handling of adverse events/hypoglycemia when date and time of first investigational medicinal product administration is missing

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

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

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

If the date of last administration reported on the e-CRF "Treatment Status Library" page is

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

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

- Partially missing, it will be imputed with a date as late as possible.

Completely missing, all adverse events occurred on or after the first administration of double-blind IMP will be considered as treatment emergent adverse events.

Handling of missing assessment of relationship of adverse events to IMP

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

Handling of missing severity/grades of adverse events

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

Handling of potentially clinically significant abnormalities

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

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

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

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

Linked adverse events that worsened or became serious

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

Handling of missing data for continuous efficacy endpoints

Please see Section 2.4.4.1 and Section 2.4.4.2.

Handling of missing data for categorical secondary efficacy endpoints

Please see Section 2.4.4.2.

2.5.4 Windows for time points

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

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

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

Table 4 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 1 (Visit 4)	7	2 to 10
Week 2 (Visit 5)	14	11 to 17
Week 3 (Visit 6)	21	18 to 24
Week 4 (Visit 7)	28	25 to 41
Week 8 (Visit 8)	56	42 to 69
Week 12 (Visit 9)	84	70 to 104
Week 18 (Visit 10)	126	105 to 153
Week 26 (Visit 11)	182	154 to 227
Week 39 (Visit 12)	273	228 to 318
Week 52 (Visit 13)	364	≥319

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

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

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

Reference day

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

Baseline definition for efficacy/safety data

For the safety analyses, the baseline for a given parameter is defined as the last available measurement (or the average of all measurements for creatinine and eGFR), including unscheduled assessments, assessed prior to the first administration of double-blind IMP. For the efficacy analyses, the baseline for a given parameter is defined as the last available measurement (or the average of all measurements for creatinine and eGFR), including unscheduled assessments, assessed prior to the first administration of double-blind IMP or the last available value (or the

average of all measurements for creatinine and eGFR) before randomization if not treated with double-blind IMP.

Summary statistics by visit for continuous efficacy endpoints

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

Last on-treatment value for laboratory variables and vital signs

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

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

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

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

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

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 11 (Week 26) (or Day 182 if Visit 11 (Week 26) date is missing). This is for defining EOT status at Week 26 and analyzing selected efficacy parameters (eg, rescued patients) during the core treatment period.

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

The TEAE period for the 26-week double-blind core treatment period is (1) the time from the first administration of the double-blind IMP up to 15 days (1 day for hypoglycemia) after the last administration of IMP if the patient discontinued treatment on or before Visit 11 (or Day 182 if Visit 11 date is missing), or (2) the time from the first administration of the double-blind IMP to the administration at Visit 11 (Week 26) (or Day 182 if Visit 11 (Week 26) date is missing) if the patient remained treated beyond Visit 11 (Week 26). This is for the purpose of safety analyses during the core treatment period.

26-week core study period

The 26-week core study period is the time from first administration of double-blind IMP to Visit 11 (Week 26) (or Day 182 if Visit 11 (Week 26) date is missing) or the end of TEAE period for the 26-week double-blind core treatment period (as defined above) whichever is later. This is for defining EOS status at Week 26.

Time to event analysis

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

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

Time to event	Censorsing date at Week 26 (1st step analysis)	Censorsing date at EOT/EOS (2nd step analysis)
Treatment discontinuation due to any reason	Not applicable	EOT
Treatment discontinuation due to AE	Not applicable	EOT
Time to rescue	min (EOT, Date of W26 visit)	EOT
Time to severe or documented hypoglycemia	See Section 3	Min (EOT+1, EOS)
Time to ESRD	min (EOS, Date of W26/re-allocated W26 eGFR value)	EOS
Time to eGFR decrease	min (EOS, Date of W26/re-allocated W26 eGFR value)	EOS
Time to UACR progression/improvement	min (EOS, Date of W26/re-allocated W26 UACR value)	EOS

Note: (1) Day 182 will be used if Date of Week 26 visit (or date of W26/re-allocated W26) is not available.
(2) Date of EOS will be used if date of EOT is not available; Last contact date will be used if date of EOS is not available.

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

Center will not be included in the statistical models for efficacy analyses. However, all centers within a country will be pooled, and country will be included as a fixed effect in a parametric statistical model (eg, ANCOVA etc) for primary and secondary efficacy endpoints. Countries with fewer than 5 randomized patients will be grouped, if patients from grouped countries are still fewer 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 since analysis of primary and secondary efficacy endpoints will be considered final at the time of first step analyses described below. The study analyses will be conducted in 2 steps.

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

The first step analyses will be conducted when all patients have been randomized and have their data at the minimum up to Week 26 collected and validated. For this analysis the common cut-off date is 15 days after the date of last patient last Week 26 visit. The first step analyses will include:

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

The first step analyses will not be used to change the conduct of the ongoing study in any aspect. Since the primary and secondary efficacy analyses would have been concluded at the time of the first step analyses, the significance level for the study remains at 0.05 (see Section 2.4.4.2).The first step analyses will be included in the submission dossier to health authorities.

- Second step: Final analyses

The second step analyses will be conducted at the end of the study. The second step analyses will include the final analyses of efficacy endpoints at Week 52 and safety endpoints, which will be descriptive only.

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

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will be applied for analyses performed at first step analysis:

- Any assessments within analysis windows up to Week 26 will be taken into account (may include few unscheduled data after the cut-off date).
- Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
  - Patients who did not complete 52-Week entire treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as “ongoing” in the disposition summary;
  - Their TEAE period, and on-study observation period will end at the cut-off date;

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

An independent 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

Two database locks will be done:

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

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. Hochberg Y. A sharper bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.

7 LIST OF APPENDICES

Appendix A Sample SAS® code for analyses of efficacy endpoints

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

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

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

```
* MI in patients who prematurely discontinued IMP before the endpoint using the endpoint data from its
own group (retrieved dropouts);
    proc sort data=ads;
        by treat ptid;
    run;


    proc mi data=ads out=disc_mi  nimpute=2000 seed=97531;
        where discontinue = “Y";
        by treat;
        var value0 valuen;
        monotone regression (valuen = value0 );
    run;

* MI in patients who stay on the IMP until the endpoint visit using the endpoint data from the placebo group
(wash-out MI);
    proc sort data=ads;
        by ptid;
    run;


    proc mi data=ads out=comp_mi  nimpute=2000 seed=75319;
        where discontinue="N" and (treat=1 or (treat ne 1 and valuen =. )); *1 denotes placebo group;
        class strata1 strata2;
        var strata1 strata2 value0 valuen;
        monotone regression (valuen = strata1 strata2  value0 );
    run;

* Repeat dataset with the same number of replications for remaining patients who have complete data at
the endpoint visit;
    data comp_trt;
```

```
        set ads (where=(discontinue="N" and  treat ne 1 and valuen ne .));
        _imputation_=0;
        do i = 1 to 2000;
                _imputation_=_imputation_+1;
                output;
        end;
    run;

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

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

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


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

* MI in patients who prematurely discontinued IMP before the endpoint using the endpoint data from its own group (retrieved dropouts);

```
    proc sort data=mi_base;
        by _imputation_ treat ptid;
    run;


   proc mi data=mi_base out=disc_mi  nimpute=1 seed=97531;
        where discontinue = “Y";
        by _imputation_ treat ;
        var value0 valuen;
        monotone regression (valuen = value0 );
   run;
```

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

```
    proc sort data=mi_base;
        by _imputation_ ptid;
    run;


   proc mi data= mi_base out=comp_mi  nimpute=1 seed=75319;
```

```
        where discontinue="N" and (treat=1 or (treat ne 1 and valuen =. )); *1 denotes control group;
        by _imputation_;
        class strata1 strata2;
        var strata1 strata2 value0 valuen;
        monotone regression (valuen = strata1 strata2 value0 );
    run;

    * Combine datasets;
    data mi_1;
        set disc_mi  comp_mi  mi_base (where=( discontinue="N" and  treat ne 1 and valuen ^=.));
    run;


**********************************************************************************************;
**********Part 2:  Backup imputation method : Control-based copy reference multiple imputations
**********;
**********************************************************************************************;

/* Data  preparation */;

/*For categorical variables with more than 2 levels, dummy binary variables have to be created
before using SAS procedure to generate monotone missing data since MCMC method does not
take categorical variables */;
/*Below using a treatment group of 3 levels as an example*/;

    data ads1;
        set ads0 (keep=ptid treat);
    run;

     * Output dataset ADS1 contains the original variable TREAT & dummy variables TREAT1, TREAT2;

    proc transreg data=ads1 design;
        model class (treat / zero= last);  * proper sorting needed to ensure correct reference group;
        output out=ads2 (drop=_type_ _name_ intercept);
         id ptid;
    run;

    data ads;
        merge ads0 ads2;
        by ptid;
    run;


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

    * Partial imputations to render monotone missing data;
    proc sort data=ads;
        by treat1 treat2 strata1 strata2 strata3 ptid;
    Run;


    proc mi data=ads out=monotone nimpute=2000 seed=97531;
```

```
        by treat1 treat2 strata1 strata2 ;
        var value:;
        mcmc chain=multiple impute=monotone;
    run;

    * Partial imputations to render monotone missing data; Drop strata if not converge;
    proc sort data=ads;
        by treat1 treat2 ptid;
    Run;

    proc mi data=ads out=monotone nimpute=2000 seed=97531;
        by treat1 treat2;
        var value:;
        mcmc chain=multiple impute=monotone;
    run;


     * To impute the missing data at post-baseline visits;
    proc sort data= monotone;
        by _imputation_ ptid;
    run;

    proc mi data= monotone out=mi_1 nimpute=1 seed=75319;
        by _imputation_;
        class treat strata1 strata2;
        monotone reg (  / details);
        mnar model (value: / modelobs=(treat='1')); *1 denotes placebo group;
        var strata1 strata2 value:;
   run;
```

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

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


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

   * Partial imputation to render monotone missing;
    proc sort data=ads;
```

```
        by _imputation_ treat1 treat2 strata1 strata2 ptid;
    Run;


   proc mi data=ads out=monotone nimpute=1 seed=97531;
        by _imputation_ treat1 treat2 strata1 strata2 ;
        var value:;
        mcmc chain=multiple impute=monotone;
    run;
    * Partial imputations to render monotone missing data; see Part 2a for dropping strata if not converge;


   * To impute the missing data at post-baseline visits;
    proc sort data= monotone;
        by _imputation_ ptid;
    run;


    proc mi data=monotone out=mi_1 nimpute=1 seed=57913;
        by _imputation_;
        class treat strata1 strata2;
        monotone reg (  / details);
        mnar model (value: / modelobs=(treat='1')); *1 denotes placebo group;
        var strata1 strata2 value:;
    run;


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

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

```
* MI in patients who prematurely discontinued IMP before the endpoint using the endpoint data from its
own group (retrieved dropouts);
   proc sort data=ads;
        by treat ptid;
   run;


   proc mi data=ads out=disc_mi  nimpute=2000 seed=97531;
        where discontinue = "Y";
        by treat;
        var value0 valuen;
        monotone regression (valuen = value0 );
        mnar adjust (valuen / shift=0.1 adjustobs=(treat='2')); *2 denotes test drug group of lower dose;
              adjust (valuen / shift=0.1 adjustobs=(treat='3')); *2 denotes test drug group of higher dose;
   run;
```

```
* MI in patients who stay on the IMP until the endpoint visit using the endpoint data from the placebo group
(wash-out MI);
   proc sort data=ads;
        by ptid;
   run;


   proc mi data=ads out=comp_mi  nimpute=2000 seed=75319;
        where discontinue="N" and (treat=1 or (treat ne 1 and valuen =. )); *1 denotes placebo group;
        class treat strata1 strata2;
        var treat strata1 strata2 value0 valuen;
        monotone regression (valuen = strata1 strata2 value0 );
        mnar adjust (valuen / shift=0.1 adjustobs=(treat='2')); *2 denotes test drug group of lower dose;
             adjust (valuen / shift=0.1 adjustobs=(treat='3')); *3 denotes test drug group of higher dose;
   run;
```

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

```
    * Partial imputation to render monotone missing data;
     proc sort data=ads;
          by treat1 treat2 strata1 strata2 ptid;
     run;


     proc mi data=ads out=monotone nimpute=2000 seed=97531;
          by treat1 treat2  strata1 strata2;
          var value:;
          mcmc chain=multiple impute=monotone;
     run;
* Partial imputations to render monotone missing data; see Part 2a for dropping strata if not converge;

    * To impute the missing data at post-baseline visits with penalty in test drug group ;
     proc sort data= monotone;
          by _imputation_ ptid;
     run;


     proc mi data= monotone out=mi_1 nimpute=1 seed=75319;
          by _imputation_;
          class treat strata1 strata2;
          monotone reg (  / details);
          mnar model (value: / modelobs=(treat='1')); *1 denotes placebo group;
          mnar adjust (valuen / shift=0.1 adjustobs=(treat='2')); *2 denotes test drug group of lower dose;
               adjust (valuen / shift=0.1 adjustobs=(treat='3')); *3 denotes test drug group of higher dose;
          var strata1 strata2 value:;
```

```
    run;


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

    proc mixed data=mi_2;
        by _imputation_;
        class treat strata1 strata2 country;
        model change= treat strata1 strata2 country value0;
        lsmeans treat /diff cl;
        lsmestimate  treat "A1 Placebo"   1 0 0 /cl;
        lsmestimate  treat "A2 200mg drug"    0 1 0  /cl;
        lsmestimate  treat "A3 400mg drug"    0 0 1  /cl;
        lsmestimate  treat "B1 200mg drug vs Placebo"   -1 1 0 /cl;
        lsmestimate  treat "B2 400mg drug vs Placebo"   -1 0 1/cl;
        ods output LSMEstimates=LSMEstimates;
    run;
```

*** Subgroup analyses using gender as an example;**

```
proc mixed data=mi_2;
        by _imputation_;
        class treat strata1 strata2 country gender;
        model change= strata1 strata2 country value0 treat*gender;
        lsmeans treat*gender /diff cl;
        lsmestimate treat*gender "SA11 Placebo - Female" 1 0 0 0 /cl;
        lsmestimate treat*gender "SA12 Placebo - Male" 0 1 0 0 /cl;
        lsmestimate treat*gender  "SA21 Test drug - Female"  0 0 1 0 /cl;
        lsmestimate treat*gender  "SA22 Test drug - Male"  0 0 0 1 /cl;
        lsmestimate treat*gender  "SB1 Test drug vs Placebo - Female"  -1 0 1 0 /cl;
        lsmestimate treat*gender  "SB2 Test drug vs Placebo - Male"  0 -1 0 1 /cl;
        ods output Diffs=diffs Lsmestimates = lsmestimates;
run;

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

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

run;

Appendix B Potentially clinically significant abnormalities criteria

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

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

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

(From BTD-009536 May 21, 2014)

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

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

(From BTD-009536 May 21, 2014)

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

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

(From BTD-009536 May 21, 2014)

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

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

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	Categories are cumulative
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	> 220 ms	
	>220 ms and increase from baseline ≥25%	
	> 240 ms	
	> 240 ms and increase from baseline ≥25%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

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

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

EOSI	Preferred term code	Preferred term
Urinary tract infections	10049059	Urinary tract infection fungal
Urinary tract infections	10049100	Pyelocystitis
Urinary tract infections	10051250	Ureteritis
Urinary tract infections	10051350	Cytomegalovirus urinary tract infection
Urinary tract infections	10051959	Urinary bladder abscess
Urinary tract infections	10052238	Escherichia urinary tract infection
Urinary tract infections	10054088	Urinary tract infection bacterial
Urinary tract infections	10056351	Emphysematous cystitis
Urinary tract infections	10058523	Bladder candidiasis
Urinary tract infections	10058596	Renal cyst infection
Urinary tract infections	10059517	Bacterial pyelonephritis
Urinary tract infections	10061181	Genitourinary tract gonococcal infection
Urinary tract infections	10061182	Genitourinary tract infection
Urinary tract infections	10061395	Ureter abscess
Urinary tract infections	10062279	Urinary tract infection pseudomonal
Urinary tract infections	10062280	Urinary tract infection staphylococcal
Urinary tract infections	10064825	Urinary tract infection viral
Urinary tract infections	10064921	Urinary tract inflammation
Urinary tract infections	10065197	Cystitis viral
Urinary tract infections	10065198	Cystitis bacterial
Urinary tract infections	10065199	Cystitis helminthic
Urinary tract infections	10065213	Pyelonephritis viral
Urinary tract infections	10065214	Pyelonephritis fungal
Urinary tract infections	10065582	Urogenital infection fungal
Urinary tract infections	10065583	Urogenital infection bacterial
Urinary tract infections	10066757	Urinary tract abscess
Urinary tract infections	10068822	Emphysematous pyelonephritis
Urinary tract infections	10070300	Streptococcal urinary tract infection
Urinary tract infections	10074409	Escherichia pyelonephritis
Urinary tract infections	10075063	Urethritis mycoplasmal
Urinary tract infections	10078665	Bacterial urethritis
Urinary tract infections	10081163	Fungal urethritis
Urinary tract infections	10081262	Candida urethritis
Urinary tract infections	10082040	Nephritis bacterial
Volume depletion	10005697	Blood osmolarity increased

EOSI	Preferred term code	Preferred term
Volume depletion	10005731	Blood pressure ambulatory decreased
Volume depletion	10005734	Blood pressure decreased
Volume depletion	10005737	Blood pressure diastolic decreased
Volume depletion	10005748	Blood pressure immeasurable
Volume depletion	10005758	Blood pressure systolic decreased
Volume depletion	10005761	Blood pressure systolic inspiratory decreased
Volume depletion	10007979	Central venous pressure decreased
Volume depletion	10009192	Circulatory collapse
Volume depletion	10012174	Dehydration
Volume depletion	10013578	Dizziness postural
Volume depletion	10021097	Hypotension
Volume depletion	10021137	Hypovolaemia
Volume depletion	10021138	Hypovolaemic shock
Volume depletion	10026983	Mean arterial pressure decreased
Volume depletion	10031127	Orthostatic hypotension
Volume depletion	10036653	Presyncope
Volume depletion	10037327	Pulmonary arterial wedge pressure decreased
Volume depletion	10042772	Syncope
Volume depletion	10046640	Urine flow decreased
Volume depletion	10047235	Venous pressure decreased
Volume depletion	10047239	Venous pressure jugular decreased
Volume depletion	10047689	Volume blood decreased
Volume depletion	10050760	Blood urea nitrogen/creatinine ratio increased
Volume depletion	10050905	Decreased ventricular preload
Volume depletion	10053356	Blood pressure orthostatic decreased
Volume depletion	10059895	Urine output decreased
Volume depletion	10060089	Left ventricular end-diastolic pressure decreased
Volume depletion	10060231	Pulmonary arterial pressure decreased
Volume depletion	10063080	Postural orthostatic tachycardia syndrome
Volume depletion	10063927	Orthostatic intolerance
Volume depletion	10066077	Diastolic hypotension
Volume depletion	10069431	Orthostatic heart rate response increased
Volume depletion	10069583	Pulse volume decreased
Volume depletion	10072370	Prerenal failure
Pancreatitis	10033625	Pancreatic haemorrhage

EOSI	Preferred term code	Preferred term
Pancreatitis	10033635	Pancreatic pseudocyst
Pancreatitis	10033636	Pancreatic pseudocyst drainage
Pancreatitis	10033645	Pancreatitis
Pancreatitis	10033647	Pancreatitis acute
Pancreatitis	10033649	Pancreatitis chronic
Pancreatitis	10033650	Pancreatitis haemorrhagic
Pancreatitis	10033654	Pancreatitis necrotising
Pancreatitis	10033657	Pancreatitis relapsing
Pancreatitis	10048984	Pancreatic abscess
Pancreatitis	10052400	Oedematous pancreatitis
Pancreatitis	10056277	Pancreatorenal syndrome
Pancreatitis	10056975	Pancreatic phlegmon
Pancreatitis	10056976	Hereditary pancreatitis
Pancreatitis	10056977	Alcoholic pancreatitis
Pancreatitis	10058096	Pancreatic necrosis
Pancreatitis	10065189	Pancreatitis helminthic
Pancreatitis	10066127	Ischaemic pancreatitis
Pancreatitis	10069002	Autoimmune pancreatitis
Pancreatitis	10074894	Traumatic pancreatitis
Pancreatitis	10076058	Haemorrhagic necrotic pancreatitis
Venous thrombotic events	10003192	Arteriovenous fistula thrombosis
Venous thrombotic events	10003880	Axillary vein thrombosis
Venous thrombotic events	10006537	Budd-Chiari syndrome
Venous thrombotic events	10007830	Cavernous sinus thrombosis
Venous thrombotic events	10008138	Cerebral venous thrombosis
Venous thrombotic events	10014522	Embolism venous
Venous thrombotic events	10019713	Hepatic vein thrombosis
Venous thrombotic events	10023237	Jugular vein thrombosis
Venous thrombotic events	10027402	Mesenteric vein thrombosis
Venous thrombotic events	10034272	Pelvic venous thrombosis
Venous thrombotic events	10034324	Penile vein thrombosis
Venous thrombotic events	10036206	Portal vein thrombosis
Venous thrombotic events	10037377	Pulmonary embolism
Venous thrombotic events	10037421	Pulmonary microemboli
Venous thrombotic events	10037437	Pulmonary thrombosis

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

EOSI	Preferred term code	Preferred term
Thyroid cancer	10033701	Papillary thyroid cancer
Thyroid cancer	10043744	Thyroid neoplasm
Thyroid cancer	10055107	Thyroid cancer metastatic
Thyroid cancer	10066136	Huerthle cell carcinoma
Thyroid cancer	10066474	Thyroid cancer
Thyroid cancer	10070567	Thyroid cancer stage 0
Thyroid cancer	10071027	Thyroid cancer stage I
Thyroid cancer	10071028	Thyroid cancer stage II
Thyroid cancer	10071029	Thyroid cancer stage III
Thyroid cancer	10071030	Thyroid cancer stage IV
Thyroid cancer	10072162	Thyroid cancer recurrent
Thyroid cancer	10072613	Thyroid B-cell lymphoma
Thyroid cancer	10073153	Familial medullary thyroid cancer
Thyroid cancer	10076603	Poorly differentiated thyroid carcinoma
Renal cell cancer	10038389	Renal cancer
Renal cell cancer	10038390	Renal cancer recurrent
Renal cell cancer	10038391	Renal cancer stage I
Renal cell cancer	10038392	Renal cancer stage II
Renal cell cancer	10038393	Renal cancer stage III
Renal cell cancer	10038394	Renal cancer stage IV
Renal cell cancer	10038410	Renal cell carcinoma recurrent
Renal cell cancer	10038411	Renal cell carcinoma stage I
Renal cell cancer	10038412	Renal cell carcinoma stage II
Renal cell cancer	10038413	Renal cell carcinoma stage III
Renal cell cancer	10038414	Renal cell carcinoma stage IV
Renal cell cancer	10050018	Renal cancer metastatic
Renal cell cancer	10050513	Metastatic renal cell carcinoma
Renal cell cancer	10061482	Renal neoplasm
Renal cell cancer	10067944	Hereditary leiomyomatosis renal cell carcinoma
Renal cell cancer	10067946	Renal cell carcinoma
Renal cell cancer	10073251	Clear cell renal cell carcinoma
Renal cell cancer	10078493	Papillary renal cell carcinoma
Pancreatic cancer	10018404	Glucagonoma
Pancreatic cancer	10022498	Insulinoma
Pancreatic cancer	10025997	Malignant neoplasm of islets of Langerhans

EOSI	Preferred term code	Preferred term
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

EOSI	Preferred term code	Preferred term
Bladder cancer	10005009	Bladder cancer stage I, without cancer in situ
Bladder cancer	10005010	Bladder cancer stage II
Bladder cancer	10005011	Bladder cancer stage III
Bladder cancer	10005012	Bladder cancer stage IV
Bladder cancer	10005056	Bladder neoplasm
Bladder cancer	10005075	Bladder squamous cell carcinoma recurrent
Bladder cancer	10005076	Bladder squamous cell carcinoma stage 0
Bladder cancer	10005077	Bladder squamous cell carcinoma stage I
Bladder cancer	10005078	Bladder squamous cell carcinoma stage II
Bladder cancer	10005079	Bladder squamous cell carcinoma stage III
Bladder cancer	10005080	Bladder squamous cell carcinoma stage IV
Bladder cancer	10005081	Bladder squamous cell carcinoma stage unspecified
Bladder cancer	10005084	Bladder transitional cell carcinoma
Bladder cancer	10051690	Urinary bladder sarcoma
Bladder cancer	10057352	Metastatic carcinoma of the bladder
Bladder cancer	10066749	Bladder transitional cell carcinoma stage 0
Bladder cancer	10066750	Bladder transitional cell carcinoma recurrent
Bladder cancer	10066751	Bladder transitional cell carcinoma stage I
Bladder cancer	10066752	Bladder transitional cell carcinoma stage IV
Bladder cancer	10066753	Bladder transitional cell carcinoma stage II
Bladder cancer	10066754	Bladder transitional cell carcinoma stage III
Bladder cancer	10071664	Bladder transitional cell carcinoma metastatic
Bladder cancer	10078341	Neuroendocrine carcinoma of the bladder
Potentially leading to amputation	10003084	Areflexia
Potentially leading to amputation	10003178	Arterial thrombosis
Potentially leading to amputation	10003210	Arteriosclerosis
Potentially leading to amputation	10003222	Arteriosclerotic gangrene
Potentially leading to amputation	10006784	Burning sensation
Potentially leading to amputation	10007904	Cellulitis enterococcal
Potentially leading to amputation	10007905	Cellulitis gangrenous
Potentially leading to amputation	10007921	Cellulitis staphylococcal
Potentially leading to amputation	10007922	Cellulitis streptococcal
Potentially leading to amputation	10012174	Dehydration
Potentially leading to amputation	10012665	Diabetic gangrene
Potentially leading to amputation	10012679	Diabetic neuropathic ulcer

EOSI	Preferred term code	Preferred term
Potentially leading to amputation	10012680	Diabetic neuropathy
Potentially leading to amputation	10017711	Gangrene
Potentially leading to amputation	10020937	Hypoaesthesia
Potentially leading to amputation	10021137	Hypovolaemia
Potentially leading to amputation	10021519	Impaired healing
Potentially leading to amputation	10021784	Infected skin ulcer
Potentially leading to amputation	10022562	Intermittent claudication
Potentially leading to amputation	10024774	Localised infection
Potentially leading to amputation	10028862	Necrosis ischaemic
Potentially leading to amputation	10029331	Neuropathy peripheral
Potentially leading to amputation	10031149	Osteitis
Potentially leading to amputation	10031252	Osteomyelitis
Potentially leading to amputation	10031253	Osteomyelitis acute
Potentially leading to amputation	10031256	Osteomyelitis chronic
Potentially leading to amputation	10031262	Osteomyelitis salmonella
Potentially leading to amputation	10031264	Osteonecrosis
Potentially leading to amputation	10033775	Paraesthesia
Potentially leading to amputation	10034568	Peripheral coldness
Potentially leading to amputation	10034576	Peripheral ischaemia
Potentially leading to amputation	10034620	Peripheral sensory neuropathy
Potentially leading to amputation	10034636	Peripheral vascular disorder
Potentially leading to amputation	10036155	Poor peripheral circulation
Potentially leading to amputation	10036410	Postoperative wound infection
Potentially leading to amputation	10040026	Sensory disturbance
Potentially leading to amputation	10040840	Skin erosion
Potentially leading to amputation	10040872	Skin infection
Potentially leading to amputation	10040943	Skin ulcer
Potentially leading to amputation	10042343	Subcutaneous abscess
Potentially leading to amputation	10043607	Thrombosis
Potentially leading to amputation	10048031	Wound dehiscence
Potentially leading to amputation	10048038	Wound infection
Potentially leading to amputation	10049927	Dry gangrene
Potentially leading to amputation	10050473	Abscess limb
Potentially leading to amputation	10050502	Neuropathic ulcer
Potentially leading to amputation	10051548	Burn infection

EOSI	Preferred term code	Preferred term
Potentially leading to amputation	10052428	Wound
Potentially leading to amputation	10052949	Arterial therapeutic procedure
Potentially leading to amputation	10053692	Wound complication
Potentially leading to amputation	10053716	Wound necrosis
Potentially leading to amputation	10054044	Diabetic microangiopathy
Potentially leading to amputation	10056340	Diabetic ulcer
Potentially leading to amputation	10056418	Arterial bypass operation
Potentially leading to amputation	10056673	Peripheral sensorimotor neuropathy
Potentially leading to amputation	10057518	Peripheral artery angioplasty
Potentially leading to amputation	10057525	Peripheral artery occlusion
Potentially leading to amputation	10058041	Wound sepsis
Potentially leading to amputation	10058042	Wound abscess
Potentially leading to amputation	10059245	Angiopathy
Potentially leading to amputation	10059385	Extremity necrosis
Potentially leading to amputation	10059442	Wound infection staphylococcal
Potentially leading to amputation	10059444	Wound infection pseudomonas
Potentially leading to amputation	10060734	Diabetic foot
Potentially leading to amputation	10060803	Diabetic foot infection
Potentially leading to amputation	10060963	Arterial disorder
Potentially leading to amputation	10060965	Arterial stenosis
Potentially leading to amputation	10061627	Amputation
Potentially leading to amputation	10061655	Arterial graft
Potentially leading to amputation	10061657	Arterial stent insertion
Potentially leading to amputation	10061666	Autonomic neuropathy
Potentially leading to amputation	10061815	Diabetic vascular disorder
Potentially leading to amputation	10062198	Microangiopathy
Potentially leading to amputation	10062255	Soft tissue infection
Potentially leading to amputation	10062585	Peripheral arterial occlusive disease
Potentially leading to amputation	10062599	Arterial occlusive disease
Potentially leading to amputation	10062610	Ischaemic limb pain
Potentially leading to amputation	10062932	Wound treatment
Potentially leading to amputation	10064250	Staphylococcal osteomyelitis
Potentially leading to amputation	10064601	Iliac artery occlusion
Potentially leading to amputation	10065237	Osteomyelitis bacterial
Potentially leading to amputation	10065239	Osteomyelitis fungal

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

Appendix D Summary of statistical analyses

Efficacy Analysis

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA1c: Change from baseline at Week 26, (sotagliflozin 400 mg vs placebo)	ITT	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR framework): treatment, randomization stratum (HbA1c / SBP at screening), and country as fixed effects, and baseline HbA1c value as a covariate	Tipping point analysis; ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI method under MNAR framework)	Subgroups: race, ethnicity, age, gender, baseline BMI, baseline HbA1c, baseline SBP, duration of diabetes and country.	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit. *By-visit summary and graph excluding measurements after rescue therapy.* See Section 1.6 for additional planned analyses.
Secondary endpoints					
HbA1c (sotagliflozin 200 mg vs placebo), FPG, body weight: Change from Baseline to Week 26; SBP (for patients with baseline SBP ≥130 mmHg, all patients): Change from Baseline to Week 12 UACR (for patients with baseline UACR >30 mg/g, all patients): Change from Baseline to Week 26	ITT	ANCOVA (with missing values imputed by the retrieved dropouts & washout imputation method or by control-based copy reference MI Method under MNAR framework): treatment, randomization stratum (HbA1c / SBP at screening), and country as fixed effects, and baseline HbA1c value as a covariate,	No	No	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit. See Section 1.6 for additional planned analyses.
Proportion of patients with HbA1c <6.5%, <7.0% at	ITT	CMH method stratified on randomization strata (HbA1c / SBP	CMH method stratified on randomization strata (HbA1c	No	By-visit summary and graphs of HbA1c responders

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Week 26		at screening)	/ SBP at screening): excluding patients with baseline HbA1c values <6.5% (for <6.5% responders) or <7% (for <7% responders) respectively		(<6.5%, <7%). By-visit frequency summary and graphs of HbA1c responders (<6.5%, <7%) excluding patients with baseline HbA1c values <6.5% or <7% respectively. See Section 1.6 for additional planned analyses.
Other endpoints					
SBP (for patients with baseline SBP <130 mmHg), DBP (for all patients and patients with baseline≥80 mmHg), UACR, UGE, and UGCR, 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 >50% decline in eGFR; with progression to end-stage renal disease, with progression/improvement of UACR categories,	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

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

Appendix E Study Flow Chart

	Screening Period		Double-Blind Treatment Period[a]									Extension		Follow-up[a]
	Screening	Run-in												
Visit	1	2	3 Random-ization	4	5	6	7	8	9	10	11	12	13	14
Week	-4	-2	0 Baseline	1	2	3	4	8	12	18	26	39	52	56
Day (window [days])		(±3)	1	7 (±5)	14 (±5)	21 (±5)	28 (±5)	56 (±5)	84 (±5)	126 (±5)	182 (±5)	273 (±5)	364 (±5)	392 (±5)
Informed consent	X													
Inclusion criteria	X													
Exclusion criteria	X		X											
Demographics	X													
Medical/Surgical History	X													
Medication History	X													
Body weight, height[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam:														
complete	X										X		X	
abbreviated[d]		X	X			X	X	X	X	X		X		X
Diet & exercise instruction		X	X	X	X	X	X				X		X	
Instruction on basic genito-urinary hygiene & hydration	X	X	X			X	X	X	X	X	X	X	X	
Interactive response technology (IRT) contact[e]	X	X	X			X	X	X	X	X	X	X	X	X
Randomization			X											
Dispense glucose meter		X												
Collect glucose meter														X
Dispense diary	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Instruction on diabetic ketoacidosis symptoms and glucose testing			X			X	X	X	X	X	X	X	X	
Dispense IMP		X	X				X	X	X	X	X	X		

	Screening Period		Double-Blind Treatment Period[a]									Extension		Follow-up[a]
	Screening	Run-in												
Visit	1	2	3 Random-ization	4	5	6	7	8	9	10	11	12	13	14
Week	-4	-2	0 Baseline	1	2	3	4	8	12	18	26	39	52	56
Day (window [days])		(±3)	1	7 (±5)	14 (±5)	21 (±5)	28 (±5)	56 (±5)	84 (±5)	126 (±5)	182 (±5)	273 (±5)	364 (±5)	392 (±5)
IMP accounting & compliance			X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-monitored blood glucose[f]		X	X			X	X	X	X	X	X	X	X	X
12-lead ECG[g]		X									X		X	
Laboratory testing [h]														
Hepatitis serology		X												
FPG	X		X				X	X	X	X	X	X	X	
HbA1c	X		X					X	X	X	X	X	X	
Fructosamine			X				X	X	X	X	X	X	X	
Safety laboratory[i]	X		X	X	X	X	X	X	X	X	X[l]	X	X[l]	X
Cystatin C			X	X	X	X	X		X		X	X	X	X
NT-proBNP			X	X	X	X	X		X		X	X	X	
Fasting lipids			X								X	X	X	
Pregnancy test (WOCBP)[j]	X		X				X	X	X	X	X	X	X	
FSH and/or estradiol (menopausal women only)[j]	X													
Sotagliflozin Plasma concentration [k]							X			X	X[l]	X	X[l]	
Markers of intestinal transit & absorption [m]			X	X	X	X	X				X		X	
Markers of bone & calcium metabolism [n]			X	X	X	X	X				X		X	

	Screening Period		Double-Blind Treatment Period[a]									Extension		Follow-up[a]
	Screening	Run-in												
Visit	1	2	3 Random-ization	4	5	6	7	8	9	10	11	12	13	14
Week	-4	-2	0 Baseline	1	2	3	4	8	12	18	26	39	52	56
Day (window [days])		(±3)	1	7 (±5)	14 (±5)	21 (±5)	28 (±5)	56 (±5)	84 (±5)	126 (±5)	182 (±5)	273 (±5)	364 (±5)	392 (±5)
Urinalysis (dipstick and microscopy)[o]		X	X	X	X	X	X	X	X	X	X	X	X	
Collection of home urine for albumin, protein, creatinine, calcium, phosphorus, magnesium, glucose and albumine-creatinine ratio[p]			X	X	X	X	X		X		X		X	
[redacted]														
Evaluate for glycemic rescue			To be assessed and reported throughout the treatment period											
Evaluate for 50% increase in creatinine [s]			To be assessed and reported throughout the treatment period											
Hypoglycemia	To be assessed and reported throughout the study													
AEs/SAEs/EOSIs/AESIs	To be assessed and reported throughout the study[t]													

a All visits' dates will be scheduled based on the date of randomization within visit window allowed as per flowchart. If a patient discontinues treatment with investigational medicinal product (IMP) early during the Treatment Period, the patient will have a Premature EOT Visit (similar to Visit 13, see Section 10.1.3.2 in protocol and a Follow-up Visit 4 weeks after the last dose of IMP (similar to Visit 14. See Section 10.1.14.1 in protocol). However, every effort will be made to have the patients return to the site for all scheduled visits, in particular the Week 26 and Week 52 Visits. 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 for both premature EOT after the last dose of IMP.

b Height to be measured only at screening.

c Vital sign measurements (sitting blood pressure [BP], heart rate temperature, and respiratory rate): 3 separate seated BP and heart rate measurements should be taken with at least 1 minute between readings, following a 5-minute rest period and prior to phlebotomy (see Section 9.2.1.5 in protocol and detailed instructions in Appendix C in protocol).

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

e Additional visit (recheck creatinine) from visit 8 every 2 weeks, contact IRT for treatment allocation if applicable.

f Self-monitored blood glucose (SMBG) is to be performed fasting, at least 3 times per week from start of Run-in until end of Treatment Period including on day of each on-site study visit except Visits 4 and 5. Patients will also be requested to self-assess blood glucose levels whenever they experience symptoms of hypoglycemia. SMPG ≤70 mg/dL (3.9 mmol/L) will be documented on the hypoglycemia e-CRF. The SMBG will be presented as equivalent self-monitoring plasma glucose (SMPG).

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

h All laboratory assessments occur prior to dose of double-blind IMP. All visit dates will be scheduled based on the date of randomization with a ±5 days visit window allowed during the treatment period.

i Safety laboratory will include hematology and clinical chemistry, please see the list in Table 2 in protocol. Other clinical chemistry tests will include amylase and lipase.

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

k Plasma concentration samples for sotagliflozin and sotagliflozin-3-O-glucuronide collected on Weeks 4, 18, 26, 39, and 52 may be drawn with the other laboratory assessments but MUST be collected before administration of IMP. The 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, neither at all subsequent visits.

l An additional blood sample will be drawn at Weeks 26 and 52 Visits at 3 hours after administering the dose of IMP for creatinine (for eGFR) and for assessing plasma concentration of sotagliflozin and sotagliflozin-3-O-glucuronide.

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

n Markers of bone and calcium metabolism :serum calcium , serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum phosphorus , serum magnesium, serum parathyroid hormone (iPTH), markers of bone resorption (serum NTX, serum β-CTX-1), bone formation (serum P1NP and osteocalcin) and serum alkaline phosphatase.

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

p Patients will collect overnight urine on Weeks 0, 2, 4, 12, 26, and 52. In the night prior to the visits, the urine before sleep will be discarded and the urine during sleep and the first morning urine (after getting up) will be collected. The visits should be rescheduled to allow for urine collection in case a patient missed it. Urinary albumin, total protein, creatinine, calcium (adjusted for creatinine), phosphorus (adjusted for serum phosphorus and creatinine), magnesium (adjusted for serum magnesium and urinary creatinine), and glucose will be assessed.

[redacted]

s The 50% increase will be from baseline value (to Week 8) or from the arithmetic mean of creatinine values from last 2 visits (after Week 8) only at visits having a measurement of creatinine.

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