Official Title: A 52-week Randomized, Double-blind, Double-dummy, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Glimepiride or Placebo Added to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycemic Control with Metformin Monotherapy

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Lexicon Pharmaceuticals, Inc.

Sotaglifozin/ LX4211

Protocol No.: EFC14838

A 52-week Randomized, Double-blind, Double-dummy, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin compared to Glimepiride or Placebo Added to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycemic Control with Metformin Monotherapy

Covance Study ID: 000000155206

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.

Covance Approval:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
BMI:	body mass index
BP:	blood pressure
BUN:	blood urea nitrogen
CEC:	Clinical Endpoint Committee
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CPK:	creatine phosphokinase
CRO:	contract research organization
CSR:	clinical study report
CV:	cardiovascular
DBP:	diastolic blood pressure
DCCT:	diabetes control and complications trial
DILI:	drug-induced liver injury
DKA:	diabetic ketoacidosis
DMC:	Data Monitoring Committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EOSI:	event of special interest
FPG:	fasting plasma glucose
HbA1c:	hemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IFCC:	International Federation of Clinical Chemistry and Laboratory Medicine
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent-to-treat
KM:	Kaplan-Meier
LDH:	lactic acid dehydrogenase
LDL-C:	low density lipoprotein cholesterol

LLN:	lower limit of normal
LLT:	lower level term
LS:	least-squares
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
MTD:	maximal tolerable dose
NIMP:	noninvestigational medicinal product
PCSA:	potentially clinically significant abonormality
PD:	pharmacodynamics
P-gp:	P-glycoprotein
PK:	pharmacokinetic
PPG:	postprandial glucose
PQAT:	patient qualitative assessment of treatment
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SGLT:	sodium-glucose linked transporter
SMBG:	self-monitoring of blood glucose
SOC:	system organ class
T2D:	type 2 diabetes
TC:	total cholesterol
TEAE:	treatment-emergent adverse event
TG:	triglycerides
ULN:	upper limit of normal
UTI:	urinary tract infection
VTE:	venous thrombotic event
WBC:	white blood cell
WHO-DD:	World Health Organization-drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This study is a Phase 3 randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group, multicenter study that is anticipated to enroll approximately 930 patients.

The study will consist of a Screening Period comprised of an up to 2 weeks Screening Phase and a 2-week single-blind placebo Run-in Phase, a 52-week double-blind and double-dummy Treatment Period, and a 2-week post-treatment Follow-up Period (patients who prematurely discontinue the study treatment are expected to continue in the study).

In order to qualify for randomization, patients must demonstrate compliance during the Run-in Phase based upon tablet and capsule count (≥80%) and as assessed at the discretion of the Investigator. Eligible patients will be randomized centrally by an Interactive Response Technology (IRT) using a permuted-block randomization schedule with a fixed block size. Randomization will be stratified by hemoglobin A1c (HbA1c) at Screening (≤8.5%, >8.5%) and systolic blood pressure (SBP) at the screening visit (<130 mmHg, ≥130 mmHg).

Following randomization, patients will be treated in a double-blind and double-dummy manner for 52 weeks. A total of 930 patients ≥18 years of age will be randomly assigned at a 2:1:2:1 ratio to the following four treatment groups on top of open-label metformin:

- Sotagliflozin 400 mg group: sotagliflozin 400 mg, given as two 200 mg tablets, and two glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day (N = 310 patients).
- Sotagliflozin 200 mg group: sotagliflozin 200 mg, given as one 200 mg tablet and one sotagliflozin-matching placebo tablet, and two glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day (N = 155 patients).
- Glimepiride group: two sotagliflozin-matching placebo tablets, and combination of two glimepiride (or matching placebo) capsules with adequate dose strengths per dose titration (titrated up to 6 mg), taken orally once daily before the first meal of the day (N = 310 patients).
- Placebo group: two sotagliflozin-matching placebo tablets and two glimepiride-matching placebo capsules, taken orally once daily before the first meal of the day (N = 155 patients).

Fasting plasma glucose (FPG; plasma or serum) and HbA1c will be masked to study sites and patients after randomization until study end. Additionally, urinalysis by dipstick will not include the measurement of urine glucose.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the non-inferiority of sotagliflozin 400 mg compared to glimepiride on HbA1c reduction at Week 52 in patients with Type 2 diabetes (T2D) who have inadequate glycemic control with metformin.

1.2.2 Secondary objectives

- To demonstrate the superiority of sotagliflozin 400 mg compared to glimepiride on:
  - Change in body weight from Baseline to Week 52,
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg,
  - Change in SBP from Baseline to Week 12 in all patients,
  - The proportion of patients with at least one documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period.
- To demonstrate the superiority of sotagliflozin 400 mg compared to placebo on change in HbA1c from Baseline to Week 26.
- To demonstrate the superiority of sotagliflozin 200 mg compared to placebo on change in HbA1c from Baseline to Week 26.
- To demonstrate the superiority of sotagliflozin 400 mg compared to placebo on:
  - Change in body weight from Baseline to Week 26,
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg,
  - Change in SBP from Baseline to Week 12 in all patients.
- To demonstrate the non-inferiority of sotagliflozin 200 mg compared to glimepiride on change in HbA1c from Baseline to Week 52.
- To demonstrate the superiority of sotagliflozin 400 mg compared to glimepiride on change in HbA1c from Baseline to Week 52.
- To evaluate the safety of sotagliflozin compared to glimepiride and placebo over 52 weeks of treatment.

1.2.3 Other objectives

To evaluate sotagliflozin compared to glimepiride and placebo with respect to:

- Change in FPG.
- The number of hospital visits due to hypoglycemia.
- Change in estimated glomerular filtration rate (eGFR).

- Change in SBP for all patients, the subset of patients with baseline SBP <130 mmHg and the subset of patients with baseline SBP ≥130 mmHg.
- Change in diastolic blood pressure (DBP) for all patients and the subset of patients with baseline DBP ≥80 mmHg.
- The proportion of patients requiring rescue medication for hyperglycemia.
- The proportion of patients with HbA1c <6.5%, <7.0%.
- The proportion of patients with HbA1c <6.5%, <7.0% and no documented symptomatic hypoglycemic event (≤70 mg/dL).
- Patient Qualitative Assessment of Treatment (PQAT).

1.3 DETERMINATION OF SAMPLE SIZE

The sample size/power calculations were performed based on the primary endpoint of change of HbA1c from Baseline to Week 52 in the intent-to-treat (ITT) population. Assuming a common standard deviation (SD) of 1.1%, and the true difference between sotagliflozin 400 mg and glimepiride is zero, 310 patients in the sotagliflozin 400 mg and glimepiride groups will ensure that the upper bound of the 2-sided 95% confidence interval (CI) of the adjusted mean difference is below 0.3% with at least 90% power. This sample size will have 80% power to test the non-inferiority of change of HbA1c from Baseline to Week 52 in completers, with a 30% dropout rate.

A sample size of 310 patients in sotagliflozin 400 mg group and 155 patients in placebo group will have more than 99% power to detect a treatment difference of 0.6% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 400 mg and placebo (SD 1.2%; 2-sided 5% significance level).

A sample size of 155 patients in sotagliflozin 200 mg group and 155 patients in placebo group will have 95% power to detect a treatment difference of 0.5% in mean HbA1c change from Baseline to Week 26 between sotagliflozin 200 mg and placebo (SD 1.2%; 2-sided 5% significance level).

The total sample size is 930 patients to be randomized (sotagliflozin 400 mg group: 310; sotagliflozin 200 mg group: 155; glimepiride: 310; placebo: 155).

1.4 STUDY PLAN

A patient should not be randomized more than once. In case where original screen failure was due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the patient can be rescreened once prior to entering Run-in for this study.

The investigational medicinal products (IMPs) are sotagliflozin (400 and 200 mg) and glimepiride (1 mg titrated up to 6 mg). Patients will be provided with kits containing wallets of sotagliflozin or sotagliflozin-matching placebo (supplied as tablets identical to sotagliflozin 200 mg in

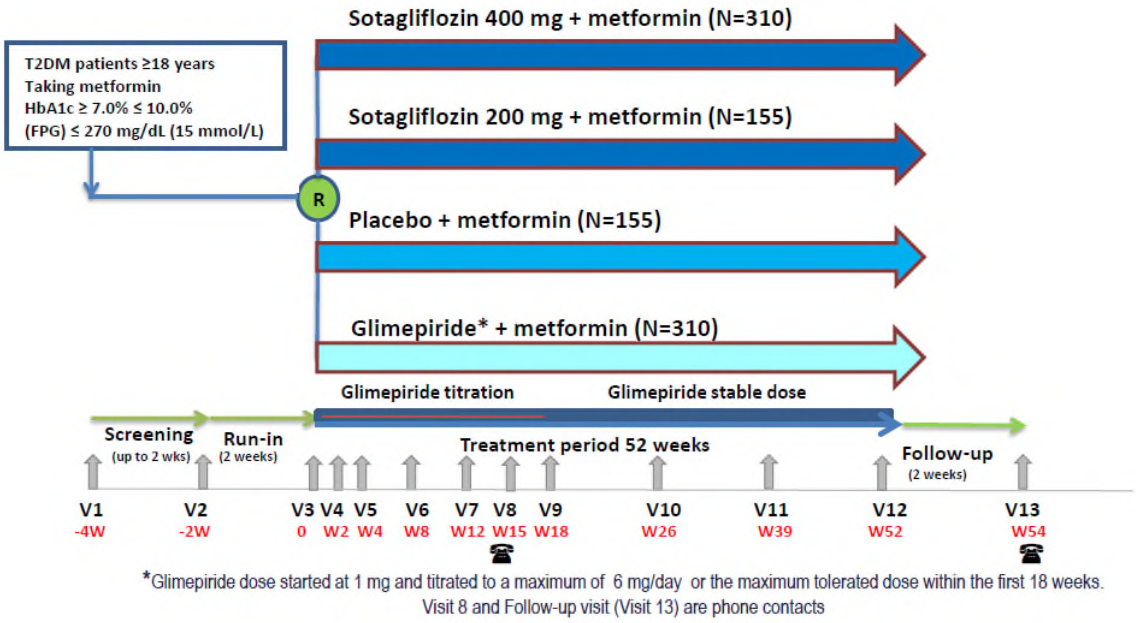
appearance) and kits containing wallets of glimepiride (supplied as 1, 2, and 4 mg capsules) or glimepiride-matching placebo (supplied as capsules). Treatment kits will be provided to the sites containing the appropriate number of IMP for the given Treatment Period (including visit windows).

All patients will receive treatment at a fixed dose of sotagliflozin (or matching placebo) as assigned at randomization throughout the 52-week study period. All patients will receive glimepiride (or glimepiride-matching placebo) on Day 1 starting from 1 mg daily. Glimepiride (or glimepiride-matching placebo) will be titrated (or mock-titrated) up to 6 mg (or maximum tolerated dose [MTD]). Titration will be possible at 5 dose levels (1, 2, 3, 4, and 6 mg) through a combination of glimepiride (or matching placebo) capsules with different dose strengths. Titration will occur during the first 18 weeks post-randomization; the glimepiride dose will have to remain stable after the first 18 weeks, unless a dose reduction is required for safety reasons.

In case of recurrent hypoglycemia, down-titration of glimepiride (or matching placebo) can be performed at any time during the study for the patients taking a daily dose higher than 2 mg of glimepiride. In the glimepiride blister delivered to the patient, the first column will correspond to the lower dose strength. If an unscheduled phone visit is prompted due to recurrent hypoglycemia, the Investigator may use discretion to advise patients to temporarily (<7 days) decrease glimepiride/matching placebo dose by omitting the capsule of lower dose until they are able to return to the site to be evaluated and receive a new treatment kit as needed. In this case, an on-site visit should occur as soon as possible within 7 days.

The study flowchart can be found in Appendix E.

Figure 1 - Graphical study design



Abbreviations FPG fasting plasma glucose HbA1c hemoglobin A1c N number of patients T2DM Type 2 diabetes mellitus R randomization V Visit W Week

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 01 December 2017. There are no planned interim analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	07-Sep-2017	Remove urgent coronary revascu ar zat ons from the events subject to the C n ca Endpo nt Comm ttees (CECs) rev ew. Urgent coronary revascu ar zat on events w not be nc uded as a card ovascu ar endpo nt and thus w not be adjud cated by the CECs.	Urgent coronary revascu ar zat on w not be nc uded n adjud cat on re ated ana yses.
1	07-Sep-2017	Rep ace Other object ve “Change n SBP for pat ents w th base ne SBP <130 mmHg” w th "Change n SBP for a pat ents, the subset w th base ne SBP <130 mmHg, and the subset w th base ne SBP ≥130 mmHg". Assessment of the change n SBP n a pat ents and subset of pat ents w th base ne SBP ≥130 mmHg after Week 12 s a so an add t ona exp oratory object ve of the study that was om tted n the protoco .	Ana yses for Other endpo nts w be based on the rev sed Other object ves.
1	07-Sep-2017	Add “Change from Base ne to Week 26 and 52 n SBP for a pat ents and the subset w th base ne SBP ≥130 mmHg to Other endpo nts. Assessment of the change n SBP from base ne to Week 26 and 52 n a pat ents and subset of pat ents w th base ne SBP ≥130 mmHg s a so an add t ona exp oratory endpo nt of the study that was om tted n the protoco	Ana yses for Other endpo nts w be conducted on the rev sed Other endpo nts.

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	07-Sep-2017	The current on-Treatment Per od has a 5-day nterva , from the f rst dose of doub e-b nd IMP up to 5 days (1 day for hypog ycem a) after the ast dose of doub e-b nd IMP. In order to assess the s de effects of sotag f oz n n pat ents w th moderate rena dysfunct on, n whom the ha f- fe of the IMP s potent a y ncreased, the on-Treatment Per od s extended to 10 days after the ast dose of doub e-b nd IMP.	Observat on per od of safety endpo nts, treatment-emergent adverse event (TEAE) per od, w be updated accord ng y.
1	07-Sep-2017	In a Jo nt Pos t on Statement of the Amer can D abetes Assoc at on and the European Assoc at on (Internat ona Hypog ycaem a Study Group. G ucose Concentrat ons of Less Than 3.0 mmo /L (54 mg/dL) Shou d Be Reported n C n ca Tr a s: A Jo nt Pos t on Statement of the Amer can D abetes Assoc at on and the European Assoc at on for the Study of D abetes. D abetes Care. 2017;40(1):155-7), the Internat ona Hypog ycaem a Study Group recommends that the frequency of detect on of a g ucose concentrat on <3.0 mmo /L (<54 mg/dL), wh ch t cons ders to be c n ca y s gn f cant b ochem ca hypog ycem a, be nc uded n reports of c n ca tr a s of g ucose- ower ng drugs eva uated for the treatment of d abetes me tus.	Hypog ycem a ep sodes w th a p asma g ucose of ≤70 mg/dL (≤3.9 mmo /L) and <54 mg/dL (<3.0 mmo /L) w be ana yzed separate y.
1	07-Sep-2017	AE ead ng to study d scont nuat on s ess c n ca y re evant than AE ead ng to treatment d scont nuat on. De ete AEs ead ng to d scont nuat on from the study from safety endpo nts to be cons stent w th other stud es of sotag f oz n c n ca deve opment program.	AE ead ng to study d scont nuat on w not be summar zed n the same way as other AEs, e, by system organ c ass (SOC), h gh- eve group term (HLGT), h gh- eve term (HLT) and preferred term (PT) sorted n a phabet ca order for each treatment group, the number (N) and percentage (%) of pat ents exper enc ng an AE.
2	09-Apr-18	Base ne eGFR def ned as recommended by CDISC Therapeut c Area Data Standards User Gu de for D abet c K dney D sease.	For serum creat n ne and eGFR, the base ne va ue s def ned as the average of a va ues before the f rst dose of doub e-b nd IMP for those random zed and exposed or before random zat on for those who were random zed but never exposed to IMP.

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	09-Apr-18	A AEs that occurred dur ng treatment shou d be fo owed for at east 2 weeks fo ow ng the ast dose of IMP, or unt the event has reso ved, the cond t on has stab zed, or the pat ent s ost to fo ow-up, wh chever comes the atest.	The fo ow ng erroneous anguage was removed from the protoco : "A AEs that occurred dur ng treatment shou d be fo owed for at east 4 weeks fo ow ng the ast dose of IMP, or unt the event has reso ved, the cond t on has stab zed, or the pat ent s ost to fo ow-up, wh chever comes ear er."
2	09-Apr-18	C ar fy "as-treated" ana ys s on Safety popu at on.	The fo ow ng text s added: "When a pat ent s exposed to both g mep r de and p acebo, the pat ent w be ana yzed n the g mep r de group."
2	09-Apr-18	Add t ona subgroup ana yses for pr mary eff cacy endpo nt ana ys s.	The fo ow ng text s added: "Assessment of treatment effect by subgroup • Base ne eGFR (≥30 to <60 mL/m n/1.73 m^2 [Moderate decrease n GFR], ≥60 to <90 mL/m n/1.73 m^2 [M d decrease n GFR], and ≥90 mL/m n/1.73 m^2 [Norma]). • Durat on of d abetes (<10, ≥10 years)".

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

In this section summarize major changes in statistical analysis features made in approved statistical analysis plan (SAP) versions, and there are no changes after study start (after the first patient was enrolled).

The SAP history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the SAP. 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	26-Ju -2018	Remove urgent coronary revascu ar zat ons from the events subject to the C n ca Endpo nt Comm ttees (CECs) rev ew. Urgent coronary revascu ar zat on events w not be nc uded as a card ovascu ar	Urgent coronary revascu ar zat on w not be nc uded n adjud cat on re ated ana yses[a].

SAP version number	Date approved	Rationale	Description of statistical changes
		endpo nt and thus w not be adjud cated by the CECs.	
1	26-Ju -2018	Rep ace Other object ve "Change n SBP for pat ents w th base ne SBP <130 mmHg" w th "Change n SBP for a pat ents, the subset w th base ne SBP <130 mmHg, and the subset w th base ne SBP ≥130 mmHg". Assessment of the change n SBP n a pat ents and subset of pat ents w th base ne SBP ≥130 mmHg after Week 12 s a so an add t ona exp oratory object ve of the study that was om tted n the protoco .	Ana yses for Other endpo nts w be based on the rev sed Other object ves[a].
1	26-Ju -2018	Add "Change from Base ne to Week 26 and 52 n SBP for a pat ents and the subset w th base ne SBP ≥130 mmHg to Other endpo nts. Assessment of the change n SBP from base ne to Week 26 and 52 n a pat ents and subset of pat ents w th base ne SBP ≥130 mmHg s a so an add t ona exp oratory endpo nt of the study that was om tted n the protoco	Ana yses for Other endpo nts w be conducted on the rev sed Other endpo nts[a].
1	26-Ju -2018	The current on-Treatment Per od has a 5-day nterva , from the f rst dose of doub e-b nd IMP up to 5 days (1 day for hypog ycem a) after the ast dose of doub e-b nd IMP. In order to assess the s de effects of sotag f oz n n pat ents w th moderate rena dysfunct on, n whom the ha f- fe of the IMP s potent a y ncreased, the on-Treatment Per od s extended to 10 days after the ast dose of doub e-b nd IMP.	Observat on per od of safety endpo nts, treatment-emergent adverse event (TEAE) per od, w be updated accord ng y[a].
1	26-Ju -2018	In a Jo nt Pos t on Statement of the Amer can D abetes Assoc at on and the European Assoc at on (Internat ona Hypog ycaem a Study Group. G ucose Concentrat ons of Less Than 3.0 mmo /L (54 mg/dL) Shou d Be Reported n C n ca Tr a s: A Jo nt Pos t on Statement of the Amer can D abetes Assoc at on and the European Assoc at on for the Study of D abetes. D abetes Care. 2017;40(1):155-7), the Internat ona Hypog ycaem a Study Group recommends that the frequency of detect on of a g ucose concentrat on <3.0 mmo /L (<54 mg/dL), wh ch t cons ders to be c n ca y s gn f cant b ochem ca hypog ycem a, be nc uded n reports of c n ca tr a s of g ucose- ower ng	Hypog ycem a ep sodes w th a p asma g ucose of ≤70 mg/dL (≤3.9 mmo /L) and <54 mg/dL (<3.0 mmo /L) w be ana yzed separate y[a].

SAP version number	Date approved	Rationale	Description of statistical changes
		drugs eva uated for the treatment of d abetes me tus.	
1	26-Ju -2018	AE ead ng to study d scont nuat on s ess c n ca y re evant than AE ead ng to treatment d scont nuat on. De ete AEs ead ng to d scont nuat on from the study from safety endpo nts to be cons stent w th other stud es of sotag f oz n c n ca deve opment program.	AE ead ng to study d scont nuat on w not be summar zed n the same way as other AEs, e, by system organ c ass (SOC), h gh- eve group term (HLGT), h gh- eve term (HLT) and preferred term (PT) sorted n a phabet ca order for each treatment group, the number (N) and percentage (%) of pat ents exper enc ng an AE[a].
1	26-Ju -2018	Base ne eGFR def ned as recommended by CDISC Therapeut c Area Data Standards User Gu de for D abet c K dney D sease	For serum creat n ne and eGFR, the base ne va ue s def ned as the average of a va ues before the f rst dose of doub e-b nd IMP for those random zed and exposed or before random zat on for those who were random zed but never exposed to IMP[b].
1	26-Ju -2018	A AEs that occurred dur ng treatment shou d be fo owed for at east 2 weeks fo ow ng the ast dose of IMP, or unt the event has reso ved, the cond t on has stab zed, or the pat ent s ost to fo ow-up, wh chever comes the atest.	The fo ow ng erroneous anguage was removed from the protoco : "A AEs that occurred dur ng treatment shou d be fo owed for at east 4 weeks fo ow ng the ast dose of IMP, or unt the event has reso ved, the cond t on has stab zed, or the pat ent s ost to fo ow-up, wh chever comes ear er."[b]
1	26-Ju -2018	C ar fy "as-treated" ana ys s on Safety popu at on.	The fo ow ng text s added: "When a pat ent s exposed to both g mep r de and p acebo, the pat ent w be ana yzed n the g mep r de group."[b]
1	26-Ju -2018	Add t ona subgroup ana yses for pr mary eff cacy endpo nt ana ys s.	The fo ow ng text s added: "Assessment of treatment effect by subgroup • Base ne eGFR (≥30 to <60 mL/m n/1.73 m^2 [Moderate decrease n GFR], ≥60 to <90 mL/m n/1.73 m^2 [M d decrease n GFR], and ≥90 mL/m n/1.73 m^2 [Norma]). • Durat on of d abetes (<10, ≥10 years)".[b]
1	26-Ju -2018	C ar f cat on on EOSI rena events.	Deta s spec f ed on rena events to be cons stent w th outcome stud es n Sect on 2.1.4.2.
1	26-Ju -2018	[redacted]	[redacted]
1	26-Ju -2018	[redacted]	[redacted]

SAP version number	Date approved	Rationale	Description of statistical changes
2	18-Ju -2019	[redacted]	[redacted]

SAP version number	Date approved	Rationale	Description of statistical changes
2	18-Ju -2019	To preserve pat ent pr vacy, UGT data to be hand ed outs de of the c n ca database, as spec f ed n protoco .	Summary or st ng w NOT be prov ded for pharmacogenet cs data upon ava ab ty.
2	18-Ju -2019	Word ng change to be cons stent w th CEC charter.	"Heart fa ure ead ng to hosp ta zat on" changed to "Heart fa ure requ r ng hosp ta zat on".
2	18-Ju -2019	MedDRA vers on and d ct onary updated.	MedDRA vers on was updated to V22 and st of PTs for se ected EOSI were updated.
2	18-Ju -2019	C ar f cat on of mputat on methods.	C ar f cat on of mputat on of pat ents on G mep r de group added n Sect on 2.4.4.1.
2	18-Ju -2019	Number of terat ons for mu t p e mputat on was changed.	Number of terat ons for mu t p e mputat on was changed from 10000 to 2000.
3	Th s vers on	[redacted]	[redacted]
3	Th s vers on	[redacted]	[redacted]
3	Th s vers on	[redacted]	[redacted]
3	Th s vers on	[redacted]	[redacted]
3	Th s vers on	Assess robustness on the ITT-based ana yses	Ident fy poss b e need to conduct sens t v ty ana yses
3	Th s vers on	Summary stat st cs of SBP	Descr pt ve stat st cs of SBP n pat ents w th base ne SBP≥140 mmHg

a Change made in Protocol Amendment 1 dated 07-Sep-2017
b Change made in Protocol Amendment 2 dated 09-Apr-2018

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 generally 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.

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

Demographic characteristics

Demographic characteristics to be summarized are:

- Age (years) derived as: (Year of informed consent - Year of birth).
- Age categories (<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 (based on IRT data).
- SBP at screening visit.
- Randomization strata of SBP (<130 mmHg, ≥130 mmHg) at screening visit (based on IRT data).
- 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.
- Duration of metformin treatment (years): (date of informed consent - date of first intake of metformin + 1)/365.25.
- Daily dose of metformin (mg) at baseline.
- Categorized daily dose of metformin at baseline (<1500, ≥1500 to <2500, ≥2500 mg).
- Baseline diabetic microvascular complications (Yes, No) (ie, diabetic retinopathy, diabetic neuropathy, diabetic peripheral neuropathy [sensory or motor], diabetic autonomic neuropathy, diabetic nephropathy, and diabetic foot infection).
- eGFR at screening (mL/min/1.73 m^2).
- eGFR categories at screening (<15 mL/min/1.73 m^2 [End stage renal disease], ≥15 to <30 mL/min/1.73 m^2 [Severe decrease in GFR], ≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73 m^2 [Normal]).
- Prior antihypertensive medication identified by therapeutic class as agents acting on the renin-angiotensin system, beta blocking agents, diuretics (a sub-category: loop diuretics identified by pharmacological class as high-ceiling diuretics), calcium channel blockers, and antihypertensives according to World Health Organization-Drug Dictionary (WHO-DD).

Medical or surgical history

Medical history and medical findings include:

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

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

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

2.1.2 Prior or concomitant medications

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

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

- Prior medications are those the patient used prior to first administration of double-blind IMP. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the 1st administration of double-blind IMP to the date of last administration + 10 days. A given medication can be classified both as a prior medication and as a concomitant medication.
- Posttreatment medications are those the patient took in the period running from the 11th day after the last administration of double-blind IMP up to the end of the study.

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

2.1.2.1 Rescue therapy

Except for SGLT2 inhibitors and sulfonylurea, any approved medication(s) including oral antidiabetic drugs or insulin can be prescribed to treat the hyperglycemia at the discretion of the investigator. Rescue therapy is considered a noninvestigational medicinal product (NIMP).

2.1.2.2 Prohibited, prior and concomitant medications

During the study Treatment Period, the following medications are prohibited:

- Initiation of any antidiabetic agents, including oral or injectable antihyperglycemic agents other than the IMP and metformin are not allowed before the rescue therapy. The existing background medication (NIMP) should not be modified before the rescue.
- SGLT2 inhibitors (eg, canagliflozin, dapagliflozin, or empagliflozin), and sulfonylurea are not allowed for rescue.
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, ophthalmic, intra-articular, nasal spray or inhaled applications are allowed).
- IMPs in any other clinical trial.

- Modification of antihypertensive medication before Week 12 is not allowed unless for safety reasons.
- Initiation of any weight loss drugs (eg, phentermine, orlistat).

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

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

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 and 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).

Hemoglobin A1c (HbA1c), FPG, serum creatinine, and eGFR are measured/calculated in a central laboratory (see study flowchart in Appendix E). Body weight, SBP and DBP (see Section 2.1.4.5) are measured at on-site visits by the investigator. Patients requiring rescue are identified as those with the reason for treatment ticked “rescue therapy” in e-CRF “Medication” page.

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

2.1.3.1 Primary efficacy endpoint(s)

Comparison of sotagliflozin 400 mg versus glimepiride in change from Baseline to Week 52 in HbA1c (%).

2.1.3.2 Secondary efficacy endpoint(s)

Secondary endpoints (sotagliflozin 400 mg dose):

- Change from Baseline to Week 26 in HbA1c.
- Change from Baseline to Weeks 26 and 52 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 at least one documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period.

Secondary endpoints (sotagliflozin 200 mg dose):

- Change from Baseline to Weeks 26 and 52 in HbA1c.

2.1.3.3 Other efficacy endpoint(s)

Other efficacy endpoints (sotagliflozin 400 mg and 200 mg doses):

- Change from Baseline to Weeks 26 and 52 in FPG.
- Number of hospital visits due to hypoglycemia during the 52-week Treatment Period.
- Change from Baseline in eGFR.
- Change from Baseline to Weeks 26 and 52 in SBP for all patients and the subset with baseline SBP ≥130 mmHg.
- Change from Baseline to Weeks 12, 26, and 52 in SBP for patients with baseline SBP <130 mmHg.
- Change from Baseline to Weeks 12, 26, and 52 in DBP for all patients and the subset with baseline DBP ≥80 mmHg.
- Proportion of patients requiring rescue treatment for hyperglycemia during the 52-week Treatment Period.
- The proportion of patients with HbA1c <6.5%, <7.0% at Week 52.
- The proportion of patients with HbA1c <6.5%, <7.0% at Week 52 and no documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period.
- PQAT at Weeks 26 and 52.

2.1.4 Safety endpoints

Assessments for safety include adverse events (AEs), self-monitoring of blood glucose (SMBG), clinical laboratory assessments, physical examination, electrocardiogram (ECG), weight, and vital signs. The following safety endpoints will be assessed:

- Adverse events, AEs leading to discontinuation from the IMP, AEs of special interest (AESIs), events of special interest (EOSIs), serious adverse events (SAEs), and deaths.
- Hypoglycemia (all, severe and/or documented symptomatic).
- Safety laboratory results (including amylase, lipase, and fasting lipids).
- Vital signs and ECG results.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the first administration of the double-blind IMP.
- The **treatment** epoch is defined as the time from the first administration of the double-bind IMP to the last administration of the double-blind IMP.
- The **residual treatment** epoch is defined as the time from the last administration of the double-blind IMP up to 10 days (1 day for hypoglycemia) after the last administration of the double-bind IMP.

The treatment-emergent adverse event (TEAE) period will include both **treatment** and **residual treatment** epochs.

- The **posttreatment** epoch is defined as the period of time starting the day after the end of the TEAE period up to the last protocol-planned visit or the resolution/stabilization of all SAEs, AESIs and EOSIs, whichever is the latest.

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 SAEs, AESIs and EOSIs if applicable.

2.1.4.1 Hypoglycemia

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

Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Self-monitored plasma glucose values may not be available, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

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

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

   And

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

Documented symptomatic hypoglycemia

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

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

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

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

   And

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

   And

3. With a plasma glucose value before countermeasure ≤3.9 mmol/L (≤70 mg/dL).

Asymptomatic hypoglycemia

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

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

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

   And

2. To the question "Were Symptoms Present", ticked "No".

   And

3. With a plasma glucose value before countermeasure ≤3.9 mmol/L (≤70 mg/dL).

Probable symptomatic hypoglycemia

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

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

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

   And

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

   And

3. With no plasma glucose value before countermeasure.

   And

4. To the question "Did this countermeasure lead a significant improvement or prompt recovery?", ticked "Yes".

Relative hypoglycemia

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

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

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

   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).

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 AEs that developed or worsened or became serious from the signed informed consent date up to first administration of double-bind IMP.
- Treatment-emergent adverse events (TEAEs) are AEs that developed or worsened or became serious during the TEAE period.
- Posttreatment adverse events are AEs that developed or worsened or became serious during the posttreatment period.

All AEs (including SAE, AESI and EOSI) will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the version of MedDRA currently in effect at Covance at the time of database lock.

The occurrence of AEs (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 CV events (eg, heart failure requiring hospitalization).
- Severe hypoglycemia.
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candida balanitis in males).
- Urinary tract infections (UTIs).
- Clinically relevant volume depletion and events related/possibly related to volume depletion.
- Diarrhea.
- Pancreatitis.
- Bone fractures.
- Venous thrombotic events (VTEs) to include deep venous thrombosis and thromboembolism (to include pulmonary embolism).
- Diabetic ketoacidosis (DKA).
- Renal events, to include 50% decline in eGFR, end stage kidney disease, renal death.
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid cancer).
- Adverse events leading to an amputation.

The Clinical Endpoint Committees (CECs) will, in a blinded manner, review and adjudicate all deaths, MACE/selected CV events (myocardial infarction, stroke, unstable angina requiring hospitalization, and heart failure requiring hospitalization), selected renal events, bone fracture, and DKA.

Two independent committees will review safety events that require ongoing monitoring in 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 assessments to the Data Monitoring Committee (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	e-CRF "Pregnancy".
Symptomat c overdose w th IMP/NIMP	"Overdose of Tab et", "Overdose of Capsu e" or "Overdose of NIMP" checked and "Symptomat c overdose" checked n e-CRF "Overdose".
A an ne am notransferase (ALT) ncrease >3X upper m t of norma (ULN)	e-CRF "ALT ncrease".
EOSI adjudicated	
Card ovascu ar death	Pos t ve y adjud cated by CEC: "Card ovascu ar" or "Undeterm ned" as the pr mary cause of death.
Myocard a nfarct on, unstab e ang na requ r ng hosp ta zat on	Pos t ve y adjud cated by CEC: Yes to the quest on "Does the event meet the def n t on of an MI for th s study?", or Yes to the quest on "If event s not an MI, does the event meet the def n t on of an UA Requ r ng adm ss on to hosp ta or emergency room, for th s study?"
Stroke	Pos t ve y adjud cated by CEC: Yes to the quest on "Does the event meet the def n t on of a Stroke for th s study?"
Heart fa ure requ r ng hosp ta zat on	Pos t ve y adjud cated by CEC: Yes to the quest on "Does the event meet the def n t on of a Heart Fa ure Event for th s study?"
Bone fractures	Pos t ve y adjud cated by CEC: Yes to the quest on "D d the Fracture occur?"
D abet c ketoac dos s	Pos t ve y adjud cated by CEC: Yes to the quest on "Does th s event meet the cr ter a to be a DKA event?"
EOSI Renal events where select events adjudicated	
Susta ned ≥50% decrease n eGFR	1. For ≥50% decrease n eGFR from base ne, (1a) Conf rmed ≥50% decrease n GFR for ≥30 days w th no revers b e cause as recorded n e-CRF "eGFR decrease", OR (1b) Pos t ve y adjud cated by CEC: Yes to the quest on "Does the subject meet the cr ter a of CKD progress on" for ≥50% decrease n eGFR.
Susta ned eGFR <15 mL/m n/1.73 m^2	2. For eGFR <15 mL/m n/1.73 m^2, (2a) Conf rmed eGFR <15 mL/m n/1.73 m^2 for ≥30 days w th no revers b e cause as recorded n e-CRF "eGFR decrease", OR (2b) Pos t ve y adjud cated by CEC: Yes to the quest on "Does the subject meet the cr ter a of CKD progress on".

AE Grouping	Criteria
Chron c d a ys s	3. For d a ys s, (3a) D a ys s asted for ≥90 days (e, end date - start date + 1 ≥90) as recorded n e-CRF "Rena Event - D a ys s", OR (3b) Pos t ve y adjud cated by CEC: Yes to the quest on "Does the subject meet the cr ter a for ESRD".
Rena transp ant[a]	4. "Rena transp ant" captured n e-CRF "Other procedure form", where adjud cat on s not requ red. PTs of Rena transp ant (10038533), Rena and pancreas transp ant (10052278), Rena and ver transp ant (10052279) based on MedDRA V22.
Rena death	5. Rena death as pos t ve y adjud cated by CEC: "Death - Non-Card ovascu ar (Rena)" as the pr mary cause of death.
EOSI not adjudicated[a]	
Severe hypog ycem a	A gor thm spec f ed n Sect on 2.1.4.1 based on e-CRF "Hypog ycem c Event".
Gen ta mycot c nfect ons	PTs n Append x C.
Ur nary tract nfect ons	PTs n Append x C.
C n ca y re evant vo ume dep et on and events re ated/poss b y re ated to vo ume dep et on	PTs n Append x C.
D arrhea	Narrow search on "Non nfect ous d arrhoea (SMQ)" [20000218] p us the fo ow ng PTs (MedDRA V22): Gastroenter t s (10017888), Ant d arrhoea support ve care (10055660), Enter t s (10014866), Enter t s eukopen c (10014877), Enteroco t s (10014893), Enteroco t s haemorrhag c (10014896).
Pancreat t s	PTs n Append x C.
Venous thrombot c events	PTs n Append x C.
Ma gnanc es of spec a nterest	Breast cancer: Narrow search on "Breast cancer: Narrow search on "Breast neop asms, ma gnant and unspec f ed (SMQ)" [20000149]. Prostate cancer: Narrow search on "Prostate neop asms, ma gnant and unspec f ed (SMQ)" [20000152]. Leyd g-ce cancer: PTs of Leyd g ce tumour of the test s (10024407) and Ovar an Serto -Leyd g ce tumour (10073270) based on MedDRA V22. Thyro d cancer: PTs n Append x C. Rena ce cancer: PTs n Append x C. Pancreat c cancer: PTs n Append x C. B adder cancer: PTs n Append x C.
EOSI AE leading to an amputation	
AE ead ng to amputat on	"AE Correct on" as the reason for amputat on n e-CRF form "Other Procedures re ated to Amputat on".
AE potent a y ead ng to an amputat on[b]	PTs n Append x C.

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

b AE potentially leading to an amputation not belong to the EOS list defined in protocol the item is included and analyzed due to its relevance in regards to lower limb complications and amputations

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

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

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

- Clinical chemistry
  - **Metabolism:** glucose (serum), creatine phosphokinase (CPK),
  - **Electrolytes and minerals**: sodium, potassium, chloride, bicarbonate (ie, carbon dioxide), calcium, phosphorus, magnesium,
  - **Renal function**: blood urea nitrogen (BUN), creatinine, uric acid,
  - **Liver function**: total protein, albumin, ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, Lactic acid dehydrogenase (LDH).
- Lipid parameters (fasting): total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) (calculated by Friedwald equation, see Section 2.5.1), Non-HDL-C (calculated as the difference between TC and HDL-C), triglycerides (TG).
- Pancreatic enzymes: lipase, amylase.

Urine samples will be collected at designated visits (see study flowchart in Appendix E). The central urinalysis includes:

- 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.

For creatinine and calculated eGFR, potentially clinically significant abnormality (PCSA) summaries will be presented in the safety section while descriptive summaries in the efficacy section.

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include: heart rate (HR), sitting systolic and diastolic blood pressure (SBP and DBP), 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 five minutes. Blood pressure (BP) and HR will be assessed three times with at least one minute between each measurement following the 5-minute rest period, and prior to phlebotomy. The mean of the three 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 10 (Week 26) and Visit 12 (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

The 12-lead ECGs will be performed at Visit 1 (Screening), Visit 10 (Week 26) and Visit 12 (Week 52). ECG status of "normal" or "abnormal" will be reported in the e-CRF as determined by the investigator.

2.1.5 Quality-of-life endpoints

The PQAT includes a 7-point Likert Scale for the patient to evaluate his/her subjective response to the treatment (-3 to +3 including 0 for a neutral response) and two free-text response questions to describe key advantages and disadvantages.

The PQAT will be administered to English-speaking patients at sites in English-speaking countries.

The patients will be asked to complete it electronically from home just before the on-site visits planned at Weeks 26 (Visit 10) and 52 (Visit 12). They will be asked to do it by themselves without any help from friends or relatives.

At the beginning of the Weeks 26 (Visit 10) and 52 (Visit 12) patient visits, Investigators will have to review patient answers (accessible on a web platform) in order to identify any potential AEs reported by patients within the open-ended questions.

All patients' answers will be analyzed qualitatively and quantitatively, as relevant, using appropriate data analysis software.

The analysis method for this exploratory analysis will be provided in a separate SAP and the analyses results will be documented in a separate report.

If a patient discontinues treatment with IMP during the Treatment Period, the patient will be asked to complete this qualitative assessment of treatment at time of discontinuation.

2.2 DISPOSITION OF PATIENTS

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

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

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

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

- Screened patients.
- Run-in patients: patients who had a run-in record in IRT.

- Screen failure patients (including failures during run-in) and reasons for screen failure (see Appendix A for details on the mapping of inclusion and exclusion criteria under the original protocol and Amendment).
- Nonrandomized but treated patients.
- Randomized patients.
- Randomized but not treated patients.
- Randomized and treated patients.
- Patients who have completed the 52-week double-blind Treatment Period as scheduled.
- Patients who did not complete the 52-week double-blind Treatment Period as scheduled and the reasons for permanent treatment discontinuation.
- Patients who have completed the study as scheduled.
- Patients who did not complete the study as scheduled and the reasons for study discontinuation.
- Patients' end of study status (completed, not completed) and corresponding end of treatment status (completed, not completed).
- Status at last study contact.

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

A summary of the distribution of patients by country and center will also be provided (overall number of patients screened, run-in, randomized, and treated, as well as number of patients randomized, discontinued from study treatment, and discontinued from study for each treatment group).

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

The randomization strata (HbA1c at Screening [≤8.5%, >8.5%] and 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 discontinuations due to any reason and due to AEs will be provided for the double-blind Treatment Period separately

(see Section 2.5.4). A listing of these patients, along with the reason for discontinuation of treatment, study completion status and the reason for discontinuation of study, will be provided.

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

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

- Efficacy population: ITT population.
- Safety population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

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

   OR

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

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

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized but 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 populations

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

2.3.1.1 Intent-to-treat population

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

2.3.1.2 Completers population

The completers population is a subset of the ITT population who complete the 52-week Treatment Period and do not start rescue therapy. Sensitivity and subgroup analyses for the primary endpoint of change from Baseline to Week 52 HbA1c comparisons will be conducted on this population.

2.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least one dose of double-blind IMP (regardless of the amount of treatment administered). Patients will be analyzed for safety analyses 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.
- For patient receiving both sotagliflozin and placebo during the trial, the treatment group allocation for as-treated analysis will be sotagliflozin group (depending on the treatment kits taken [400 mg or 200 mg]).
- For patients receiving both sotagliflozin 400 mg (treatment kits) and 200 mg (treatment kits) during the trial, the treatment group allocation for as-treated analysis will be sotagliflozin 200 mg group.
- For patients receiving both sotagliflozin and glimepiride during the trial, the treatment group allocation for as-treated analysis will be sotagliflozin group (depending on the treatment kits taken [400 mg or 200 mg]).
- For patients receiving both glimepiride and placebo during the trial, the treatment group allocation for as-treated analysis will be glimepiride 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 medication. If a patient is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, SD, median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number 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 (ie, randomized patients) for any treatment group.

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

P-values on demographic and baseline characteristic data will not be calculated.

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.

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 of patients. Statistical tests for the between-group differences will not be performed.

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

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

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

Antihypertensive 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) unless otherwise specified.

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, and actual dose information.

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

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

- 1 to 28 days.
- 29 to 56 days.
- 57 to 84 days.
- 85 to 126 days.
- 127 to 182 days.
- 183 to 364 days.
- >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 percentage of patients by final dose at the end of the treatment will also be presented by each active treatment group.

Glimepiride (matching placebo) dose information will be assessed using ITT population by the following variables for each treatment group according to the treatment group to which they are randomized:

- The final dose at the end of the titration period, recorded at Visit 9 (Week 18).
- The final dose at the end of the treatment.
- Maximal tolerable dose: the MTD recorded at Visit 9 (Week 18) if MTD is checked in e-CRF.

Dose information variables will be summarized descriptively (number, mean, SD, median, minimum, and maximum).

Number and percentage of patients by final dose of glimepiride (matching placebo), MTD status and MTD at the end of the titration period (recorded at Visit 9), and by final dose of glimepiride (matching placebo) 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. Treatment compliance will be calculated and presented for glimepiride or matching placebo (Capsule) and sotagliflozin or matching placebo (Tablet) separately by treatment group.

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

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

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

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

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

2.4.4 Analyses of efficacy endpoints

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

Missing data for efficacy analyses are identified through steps described in Section 2.5.3.

2.4.4.1 Analysis of primary efficacy endpoint(s)

For the primary efficacy endpoint, the following null and alternative hypotheses will be tested:

- H_0: $\mu_T - \mu_C \geq 0.3\%$.
- H_1: $\mu_T - \mu_C < 0.3\%$.

Where μ_T and μ_C are the mean changes from Baseline in HbA1c at Week 52 for sotagliflozin and glimepiride groups, respectively.

The null hypothesis will be tested at a 1-sided alpha level of 0.025 using a non-inferiority margin of 0.3% of HbA1c change by comparing the upper bound of the 2-sided 95% CI for the adjusted mean treatment difference between sotagliflozin and glimepiride with 0.3%.

Primary analysis

The primary efficacy endpoint of change in HbA1c from Baseline to Week 52 will be analyzed by an Analysis of Covariance (ANCOVA) model using HbA1c values measured at baseline and Week 52 (observed or imputed). The missing data at endpoint will be imputed by multiple imputation (MI) methods as detailed below. To be concise, the following texts related to imputation are generalized to accommodate primary as well as continuous secondary efficacy endpoints.

Missing endpoint data at Week 52 or 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 52 or Week 26 (or Week 12 for SBP) visit but have measurements for the endpoint (ie, retrieved dropouts). The imputation model will include the randomization strata and the corresponding baseline value. In cases of non-convergence during the imputations, the offending stratum will be identified and then will be dropped from the model. Considering that the number of retrieved dropout patients in each treatment group is expected to be small, a simple imputation model based on regression will be used with baseline measurement included as the predictor. This will serve as the primary model of imputation for missing data should sampling criteria be satisfied (see below).

An alternative (back-up) imputation method will be used if the number of patients who prematurely discontinue the IMP before the Week 52 or Week 26 (or Week 12 for SBP) visit but have measurements for the endpoint is less than five (< 5) in any treatment groups (ie, 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 separately.

In the back-up imputation method, missing post-baseline endpoint values at Week 52 or 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 52 or Week 26 (or Week 12 for SBP) in all treatment groups (sotagliflozin 200 mg and 400 mg, glimepiride 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, sotagliflozin 200 mg and glimepiride groups with missing data at Week 52 or 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 52 or 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 52 or Week 26 (or Week 12 for SBP) endpoint values will be subsequently imputed from the multiple copies of the original dataset where each copy will have a monotone missing pattern.

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

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

Using either imputation method, missing endpoint data will be imputed 2000 times to generate multiple datasets with complete data. Other details of the imputation procedures such as the seed number and sort ordering are specified in the SAS programs. The change from baseline to Week 52 (or Week 12 for SBP) will be derived from observed and imputed HbA1c values at Week 52 (or Week 12 for SBP). Each of the complete datasets after the imputation will be analyzed using the ANCOVA model with treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo groups), randomization stratum of HbA1c at Screening (≤8.5%, >8.5%), randomization stratum of SBP at Screening (<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 52 (or Week 12 for SBP) for each treatment group, as well as the between-group differences and their associated 95% CIs. If the upper bound of the 2-sided 95% CI for the adjusted mean difference (sotagliflozin 400 mg versus glimepiride) in HbA1c change from Baseline to Week 52 is <0.3%, then non-inferiority will be declared.

Sensitivity analyses

A sensitivity analysis will be conducted with the 52-week treatment completers (ie, all patients who complete the 52-week Treatment Period and do not start rescue therapy) using the Week 52 values and the same missing data imputation method (washout imputation method) and ANCOVA model described above.

Tipping-point analysis based on the same MI method as applied to the primary analysis will be performed to examine the robustness of the results from the primary analysis. Patients who were randomized to sotagliflozin 400 mg group and had no HbA1c data at Week 52 will be given a penalty. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of statistically non-inferior to glimepiride is changed. The tipping point is the penalty level, at which the magnitude of efficacy reduction in patients without HbA1c data at Week 52 creates a shift in the treatment effect of sotagliflozin 400 mg from being statistically non-inferior to glimepiride to statistically inferior to glimepiride. Least-squares (LS) mean difference between sotagliflozin and glimepiride and its associated 95% CI will be provided for each penalty level. The steps to perform the tipping point analysis are as follows:

1. Missing data will be imputed using the same MI method as applied to the primary analysis.
2. The imputed HbA1c value at Week 52 in the sotagliflozin 400 mg group will be penalized by adding a penalty δ (eg, δ 0.1%) in each complete dataset.
3. Change from Baseline at Week 52 in HbA1c will be analyzed using the same ANCOVA model as specified in the primary analysis in each complete dataset.
4. Results will be combined across complete datasets using Rubin's formula.
5. For noninferiority of sotaglifozin 400 mg versus glimepiride on HbA1c reduction, Steps 2 to 4 will be repeated with incremental penalty at δ (ie, δ, 2δ, 3δ, …) until the upper bound of the 2-sided 95% CI for the adjusted mean difference is ≥0.3%. The range of penalty values will include the non-inferiority margin of 0.3% to evaluate bias toward the null.
6. For superiority of sotaglifozin 400 mg versus placebo on HbA1c reduction, steps 2 to 4 will be repeated with incremental penalty at δ (ie, δ, 2δ, 3δ, …) until the p-value for treatment effect of sotaglifozin 400 mg compared to placebo estimated in Steps 2 to 4 is ≥0.05.

The tipping point analysis will be performed on the ITT population and completer's population. Similarly, the tipping point analysis will be conducted for the sotaglifozin 400 mg versus glimepiride non-inferiority endpoint only if the primary efficacy endpoint analysis yields a statistically significant finding and the upper bound of the 2-sided 95% CI associated with the non-inferiority test is < 0.3%.

In addition to the tipping point analyses, if the retrieved dropout imputation is applied to the primary analysis, the analysis based on the washout imputation (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 years, ≥50 to <65 years, ≥65 years) (any category with fewer than five 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 SBP (<130 mmHg, ≥130 mmHg).

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

The treatment effects (sotagliflozin 400 mg versus glimepiride) across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 52 in HbA1c in the ITT population, and using the retrieved dropouts method if there are at least 5 patients in each study treatment group who discontinued but have the endpoint. Otherwise, the washout imputation method will be used. The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo), randomization stratum of HbA1c at Screening (≤8.5%, >8.5%), randomization stratum of SBP at Screening (<130 mmHg, ≥130 mmHg), subgroup factor, treatment-by-subgroup factor and country as fixed factors, and baseline HbA1c value as a covariate. The adjusted estimates of treatment mean differences (sotagliflozin 400 mg versus glimepiride) with standard error (SE) and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided.

In the event that the subgroup factor is identical or similar to a randomization strata factor (eg, Baseline HbA1c category or Baseline SBP category) or country, 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 or country will not be included in the model.

Summary statistics at scheduled visits

Summary statistics (for screening value, baseline value, observed postbaseline 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 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 Screening HbA1c (≤8.5%, >8.5%), randomization stratum of Screening SBP (<130, ≥130 mmHg), and baseline value in the imputation model.
Each continuous secondary efficacy endpoint (Section 2.1.3) will be analyzed using a similar ANCOVA model including the measurements at baseline and endpoint (observed or imputed).

The missing data at endpoint will be imputed by the retrieved dropouts if there are at least 5 patients in each study treatment group who discontinued but have the endpoint. Otherwise, the washout imputation method will be used. After the imputation, each of the complete datasets will be analyzed by an ANCOVA model.
The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo), randomization stratum of HbA1c (≤8.5%, >8.5%), randomization stratum of SBP (<130 mmHg, ≥130 mmHg), and country as fixed effects, and the corresponding baseline secondary endpoint value as a covariate. For the analysis of SBP in patients with baseline SBP ≥130 mmHg, the randomization stratum of SBP will not be included. Results from each complete dataset will be combined using Rubin's formula to provide the adjusted mean change from Baseline to Week 52 (or Week 12 for SBP) for each treatment group, as well as the between-group differences and the 95% CIs for the differences.

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 ≥130 mmHg. Same analyses will also be described for patients with baseline SBP≥140 mmHg.

The categorical secondary efficacy variables of HbA1c <6.5%, <7% at Week 52 will be analyzed respectively using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of HbA1c (≤8.5%, >8.5%), and randomization stratum of SBP (<130 mmHg, ≥130 mmHg). The proportion in each treatment group will be provided, as well as the difference of proportions between sotagliflozin 400 mg and placebo with associated 2-sided 95% CI. For HbA1c responders at Week 52 (<6.5%, <7% respectively), all values at Week 52 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.

The categorical secondary endpoint, the proportion of patients with at least one documented symptomatic hypoglycemic event (≤3.9 mmol/L [≤70 mg/dL]) during the 52-week Treatment Period, will be analyzed respectively using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization stratum of Screening HbA1c (≤8.5%, >8.5%) and randomization stratum of Screening SBP (<130 mmHg, ≥130 mmHg). The proportion in each treatment group will be provided, as well as the difference of proportions between sotagliflozin 400 mg group and glimepiride group with its associated 2-sided 95% CI. Summary tables and graphs will also be provided by treatment group at scheduled visits.

Sensitivity analyses

Tipping-point analysis similar to that is described in Section 2.4.4.1 will be performed to evaluate the robustness of the treatment effect on HbA1c data for the following comparisons, using the same MI method and similar ANCOVA model for the primary endpoint analysis:

- Superiority comparison of sotagliflozin 400 mg and placebo on change from Baseline to Week 26.
- Superiority comparison of sotagliflozin 200 mg and placebo on change from Baseline to Week 26.
- Non-inferiority comparison of sotagliflozin 200 mg and glimepiride on change from Baseline to Week 52.
- Superiority comparison of sotagliflozin 400 mg and glimepiride on change from Baseline to Week 52.

Missing data will be imputed at Week 26 or Week 52 as appropriate. The sotagliflozin groups will be penalized incrementally by a penalty, and repeated until the upper bound of the 2-sided 95% CI is ≥0.3% for the non-inferiority comparison or until the p-value for treatment effect between the two treatment groups is >0.05 for the superiority comparison, respectively.

The tipping-point analysis will be performed only if the respective secondary endpoint comparison is statistically significant at a two-sided $\alpha = 0.05$.

A sensitivity analysis will also be conducted with the treatment completers (ie, all patients who complete the 26-week double-blind treatment period and do not start rescue therapy) for noninferiority of sotagliflozin 400 mg versus glimepiride on HbA1c reduction using the same ANCOVA model described in Section 2.4.4.1. The washout imputation method will be used, where missing endpoint data in all treatment groups are imputed from a model estimated from patients in the placebo group who 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.

Assessment of treatment effect by subgroup

Similar to that is described in Section 2.4.4.1, the treatment effects for the following treatment group comparisons across subgroups will be estimated for the change from Baseline in HbA1c in the ITT population, and using the same MI method for the primary endpoint analysis:

- Sotagliflozin 400 mg group vs. placebo group at Week 26.
- Sotagliflozin 200 mg group vs. placebo group at Week 26.
- Sotagliflozin 200 mg group vs. glimepiride group at Week 52.

The ANCOVA model will include treatment groups (sotagliflozin 400 mg, sotagliflozin 200 mg, glimepiride, and placebo groups), randomization stratum of Screening HbA1c (≤8.5%, >8.5%), randomization stratum of Screening SBP (<130 mmHg, ≥130 mmHg), subgroup factor, treatment-by-subgroup factor, and country as fixed factors and using baseline HbA1c value as a

covariate. The adjusted estimates of treatment mean differences with SE and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided.

2.4.4.3 Analysis of other efficacy endpoints

The analysis of other endpoints (see Section 2.1.3.3) will be descriptive with no formal testing. Summary statistics at scheduled visits based on observed value will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time as appropriate.

Hospital visits due to hypoglycemia includes emergency room visit, outpatient visit and any hospitalization due to hypoglycemia. It is identified in e-CRF "Hypoglycemic Event" page as those documented as ticked "Yes" to the question "As a result of this hypoglycemia event, did a hospital visit occur?" The number (%) of patients with hospital visits due to hypoglycemia will be provided by each treatment group during the TEAE period defined for hypoglycemia, as well as the incidence rate in patient years if any patients have multiple hospital visits due to hypoglycemia. The number (%) of patients who used rescue therapy and a KM curve for the time-to-first rescue therapy will be provided by treatment group. A list of patients who used rescue therapy will also be provided (see Section 2.5.4).

For the categorical endpoints of HbA1c responders (<6.5% and <7%, respectively) and HbA1c responders with no hypoglycemic event, summary tables and graphs will be provided by each treatment group at scheduled visits. All values will be used to determine whether a patient is a responder or not at each visit, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no HbA1c measurement at each scheduled visit will be treated as non-responders. For the composite endpoint of HbA1c responders and no documented symptomatic hypoglycemic event, a patient will be treated as a responder only if the criterion is met for each component.

2.4.4.4 Multiplicity issues

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

- The primary endpoint of the HbA1c change from Baseline to Week 52 comparing sotagliflozin 400 mg versus glimepiride will be tested at $\alpha = 0.025$ (1-sided) using a non-inferiority margin of 0.3% of HbA1c change. Once the non-inferiority is declared (the upper bound of the 2-sided 95% CI of the adjusted mean difference between sotagliflozin 400 mg and glimepiride is <0.3%), the following secondary hypothesis based on change from Baseline scores will be tested in the following prioritized order :The superiority of sotagliflozin 400 mg compared to glimepiride on:
  - Change in body weight from Baseline to Week 52,
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg,
  - Change in SBP from Baseline to Week 12 in all patients,

  - The proportion of patients with at least one documented symptomatic hypoglycemic event (≤70 mg/dL) during the 52-week Treatment Period.

- The superiority of sotagliflozin 400 mg compared to placebo on the change in HbA1c from Baseline to Week 26.
- The superiority of sotagliflozin 200 mg compared to placebo on the change in HbA1c from Baseline to Week 26.
- The superiority of sotagliflozin 400 mg compared to placebo on:
  - Change in body weight from Baseline to Week 26,
  - Change in SBP from Baseline to Week 12 in patients with baseline SBP ≥130 mmHg,
  - Change in SBP from Baseline to Week 12 in all patients.
- The non-inferiority of sotagliflozin 200 mg compared to glimepiride on the change in HbA1c from Baseline to Week 52.
- The superiority of sotagliflozin 400 mg compared to glimepiride on the change in HbA1c from Baseline to Week 52.

If any hypothesis is found to be not statistically significant, the testing procedure will be stopped and the following hypotheses will not be tested. The non-inferiority hypothesis will be declared significant if the upper bound of the 2-sided 95% CI for the adjusted mean difference is <0.3. The superiority hypothesis will be declared statistically significant at α 0.05 (2-sided).

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

2.4.5 Analyses of safety data

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

The "observation period" defined in Section 2.1.4 is applicable to 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.

- The 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 one PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE 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 creatinine and eGFR, PCSA summaries will be presented in safety Section 2.4.5 while descriptive summaries in efficacy Section 2.4.4.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from Baseline values by visit and treatment group. Summaries will include the last on-treatment value. The last on-treatment value is commonly defined as the value collected at the same day/time of the last administration of IMP. If this value is missing, this last on-treatment value will be the closest value prior to the last dose administration.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus comparator (glimepiride or placebo) and their 95% CIs may be provided, if relevant.
- Selected safety analyses will be summarized by age, gender, racial subgroups, and any pertinent subgroups (see details in Section 2.4.5.1 and Section 2.4.5.2).

2.4.5.1 Analyses of hypoglycemia

Analyses of hypoglycemia will be performed on the TEAE period as defined in Section 2.1.4. Hypoglycemia will be classified as severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia or relative hypoglycemia (see Section 2.1.4.1).

The number (%) of patients with any hypoglycemia, severe hypoglycemia and documented symptomatic hypoglycemia will be summarized respectively by treatment group during the TEAE period, as well as the incidence rate in patient years. Two types of incidence rate 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 that exposure (in days) here is the duration of TEAE period, ie, duration of IMP treatment in days + 1 (see Section 2.1.4).

The summary of frequency and incidence rate in patient years for severe hypoglycemia or documented symptomatic hypoglycemia will be provided as appropriate by gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years), race (White, Black or African American, Asian, Other).

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

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

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

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on TEAEs. Pretreatment and posttreatment AEs will be described separately.

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

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

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other 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 TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE,
  - Serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, showing number (%) of patients with at least one TEAE, sorted by internationally agreed order of primary SOC.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT in the sotagliflozin 400 mg group.
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least one TEAE, 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 tables, unless otherwise specified.
- All TEAEs regardless of relationship and related to IMP, by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least one TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least one TEAE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.
- Common TEAEs (PTs with an incidence ≥2% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.
- Common TEAEs (PTs with an incidence ≥2% in any treatment group) will be provided as appropriate by primary SOC and PT and by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years of age), race (White, Black or African American, Asian, other), baseline SBP category (<130 mmHg, ≥130 mmHg), and baseline eGFR category (≥30 to <60 mL/min/1.73 m^2 [Moderate decrease in GFR], ≥60 to

<90 mL/min/1.73 m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73 m^2 [Normal]). SOC will be sorted by internationally agreed order and the PT level by decreasing incidence within each SOC in the sotagliflozin 400 mg group, as described above.

- TEAEs (PTs with an incidence ≥5% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.

Analysis of all treatment emergent serious adverse event(s)

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

Analyses of adverse events of special interest

Pregnancy and overdose will be included in overall AE summaries if any are reported. ALT increase >3 x ULN is included in laboratory PCSA summary if any.

In addition, the number (%) of patients with an AESI will be summarized by PT and by treatment group. Corresponding listings will be provided as appropriately.

Analyses of events of special interest

CV events, bone fracture and DKA

For EOSIs that are adjudicated (ie, deaths, myocardial infarction, stroke, and unstable angina requiring hospitalization, heart failure requiring hospitalization, bone fractures, and DKA), 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,

A) Recorded in e-CRF "GFR decrease",

B) Recorded in e-CRF "Renal Event - Dialysis",

C) Identified as "Renal transplant" in e-CRF "Other procedure".

Renal death will be part of all deaths specified above.

Other EOSIs

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

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

Adverse event (AE) leading to an amputation is described in the section below.

Analysis of Amputation

The number (%) of patients with amputation will be summarized by treatment group and by PT and LLT during the study (ie, regardless of on- or post-treatment). Amputation is a procedure recorded in e-CRF "Other Procedures related to Amputation". Patients who had a procedure related to amputation will be listed.

The number (%) of patients with an "AE leading to an amputation" will be summarized by treatment group and by PT. The "AE leading to an amputation" is determined by the AE identifier recorded in e-CRF "Other Procedures related to Amputation" when "AE correction" is chosen as the reason for the amputation procedure.

In addition, the number (%) of patients with an "AE potentially leading to an amputation" will be summarized by treatment group and by PT (as identified in Table 3 in Section 2.1.4.2). These PTs in Table 3 were requested by the European Medicines Agency (EMA)/ Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report, 9 February 2017). The associated list will be provided as well, with patients who had an amputation procedure flagged. "AE potentially leading to an amputation" represents the condition that commonly precedes the amputation procedure, but not in all cases an amputation has occurred.

Analysis of pretreatment and posttreatment adverse events

- All pretreatment AEs by primary SOC and PT, showing the number (%) of patients with at least one pretreatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the sotagliflozin 400 mg group.
- All posttreatment AEs by primary SOC and PT, showing the number (%) of patients with at least one posttreatment AE, 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 IMP), AE duration, duration of exposure, intensity, corrective treatment, action taken with IMP, date of treatment discontinuation (if relevant), relationship to IMP (Capsule and Tablet) or NIMP, outcome, date of death (if any), seriousness, seriousness criteria, and AE status ("E" for a TEAE; and "P" for an on-study posttreatment 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, poststudy).
- Deaths in nonrandomized patients or randomized but not treated patients.
- TEAEs leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.

2.4.5.4 Analyses of laboratory variables

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

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

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

- Normal/missing.

- Abnormal according to PCSA criterion or criteria.

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

All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. These summaries will include patients in the safety population who have at least one 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 one postbaseline 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 white blood cell (WBC) and differential counts will be determined using data expressed in international units.

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

Drug-induced liver injury

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

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

2.4.5.5 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, SD, 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, each postbaseline time point, last on-treatment) by treatment group.

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

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

2.4.6 Analyses of quality of life variables

The analysis method for this exploratory analysis will be provided in a separate SAP and the analyses results will be documented in a separate report.

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).

Calculation of LDL-C

When triglycerides (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 MImethod (if there are at least 5 patients in each study treatment group who discontinued but have the endpoint) or washout MI method according to the criterion described in Section 2.4.4.1.

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

2.5.3 Missing data

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

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

Incomplete date of first administration of double-blind IMP

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

For patients who are randomized and dispensed a double-blind treatment kit but who are lost to follow-up just after Visit 3 (eg, only the treatment kit number is reported in the e-CRF "Exposure - Treatment Period (Capsule)" or "Exposure - Treatment Period (Tablet)" 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 for both Capsule and Tablet in the e-CRF "First dose IMP" module.

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

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

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

Handling of medication missing/partial dates

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

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

Missing or partial adverse event/hypoglycemia onset dates and times will be imputed so that if the partial adverse event/hypoglycemia onset date/time information does not indicate that the adverse event/hypoglycemia started prior to treatment or after the TEAE period, the adverse event/hypoglycemia will be classified as treatment-emergent. No imputation of adverse event/hypoglycemia 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/hypoglycemia resolution.

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

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

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

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

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

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

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

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

Handling of missing assessment of relationship of adverse events to IMP (Capsule or Tablet)

If the assessment of the relationship to glimepiride or matching placebo (Capsule) is missing, then the relationship to Capsule has to be assumed and the AE considered as such in the frequency tables of possibly Capsule-related AEs. If the assessment of the relationship to sotagliflozin or matching placebo (Tablet) is missing, then the relationship to Tablet has to be assumed and the AE considered as such in the frequency tables of possibly Tablet-related AEs. No imputation should be done at the data level.

Handling of missing severity/grades of adverse events

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

Handling of potentially clinically significant abnormalities

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

For PCSAs with two 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 is still no measurement for a given parameter at a scheduled visit, the analysis window below (Table 4) will be applied to re-allocate a postbaseline unscheduled measurement to a scheduled measurement.

Table 4 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 2 (V s t 4)	14	2 to 20
Week 4 (V s t 5)	28	21 to 41
Week 8 (V s t 6)	56	42 to 69
Week 12 (V s t 7)	84	70 to 104
Week 18 (V s t 9)	126	105 to 153

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 26 (V s t 10)	182	154 to 227
Week 39 (V s t 11)	273	228 to 318
Week 52 (V s t 12)	364	≥319

Study days are calculated from the day of first administration of double-blind MP the day of first administration of MP (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 is still no measurement for a given parameter at a scheduled visit, data are considered missing for efficacy analyses, where MI 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, local results will only be used in the PCSA summary if they are accompanied by a local laboratory normal range.

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

Time-to-event analysis

For time-to-event analysis/KM plot, time-to-event (eg, treatment discontinuation, rescue therapy, hypoglycemia, etc) is defined as the number of days from the date of the first administration of double-blind IMP (or the date of randomization if not exposed) to the start date of the first occurrence of the event during the 52-week double-blind treatment period.

Patients who did not experience any event during the 52-week double-blind Treatment Period are considered censored observations. For time-to-treatment discontinuation/rescue therapy, censoring date is the date of EOT. For time-to-severe or documented hypoglycemia, censoring date is date of EOT + 1 or date of EOS, whichever is the earliest. Date of EOS will be used if date of EOT is not available. Last contact date will be used if date of EOS is not available.

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

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

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

There are no formal interim analyses for efficacy planned for this study. The study will not be terminated early for excellent efficacy.

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

4 DATABASE LOCK

The database lock was on the 12Sep2019.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

Not Applicable.

7 LIST OF APPENDICES

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

Order	Original Protocol	Amendment 1	CSR Display
1	I01		I01
2	I02		I02
3	E01		E01
4	E02		E02
5	E03		E03
6	E04		E04
7	E05		E05
8	E06		E06
9	E07		E07
10	E08		E08
11	E09		E09
12	E10		E10
13	E11		E11
14	E12		E12
15	E13		E13
16	E14		E14
17	E15		E15
18	E16		E16
19	E17		E17
20	E18		E18
21	E19		E19
22	E20		E20
23	E21		E21
24	E22		E22
25	E23		E23
26	E24		E24
27	E25		E25
28	E26		E26
29	E27		E27
30	E28		E28
31	E29		E29
32	E30		E30
33	E31		E31
34	E32		E32
35	E33		E33
36	E34		E34
37	E35		E35
38	E36		E36
39	E37		E37
40	E38		E38

Order	Original Protocol	Amendment 1	CSR Display
41		E39	E39

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 d str but on ana ys s : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes act v t es must be expressed n ULN, not n IU/L. Concept paper on DILI - FDA draft Gu dance Oct 2007. Interna DILI WG Oct 2008. Categor es are cumu at ve. F rst row s mandatory. Rows fo ow ng one ment on ng zero can be de eted.
AST	By d str but on ana ys s : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes act v t es must be expressed n ULN, not n IU/L. Concept paper on DILI - FDA draft Gu dance Oct 2007. Interna DILI WG Oct 2008. Categor es are cumu at ve. F rst row s mandatory. Rows fo ow ng one ment on ng zero can be de eted.
A ka ne Phosphatase	>1.5 ULN	Enzymes act v t es must be expressed n ULN, not n IU/L. Concept paper on DILI - FDA draft Gu dance Oct 2007. Interna DILI WG Oct 2008.
Tota B rub n	>1.5 ULN >2 ULN	Must be expressed n ULN, not n µmo /L or mg/L. Categor es are cumu at ve. Concept paper on DILI - FDA draft Gu dance Oct 2007. Interna DILI WG Oct 2008.
Conjugated B rub n	>35% Tota B rub n and TBILI>1.5 ULN	Conjugated b rub n dosed on a case-by-case bas s.
ALT and Tota B rub n	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI - FDA draft Gu dance Oct 2007. Interna DILI WG Oct 2008. To be counted w th n a same treatment phase, whatever the nterva 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 Card o Apr 2006. Categor es are cumu at ve. F rst row s mandatory. Rows fo ow ng one ment on ng zero can be de eted.
CLcr (mL/m n) (Est mated creat n ne c earance based on the Cokcroft-Gau t equat on)	<15 (end stage rena d sease) ≥15 - <30 (severe decrease n GFR) ≥30 - <60 (moderate decrease n GFR) ≥60 - <90 (m d decrease n GFR) ≥90 (norma GFR)	FDA draft Gu dance 2010. Pharmacok net cs n pat ents w th mpa red rena funct on-study des gn, data ana ys s, and mpact on dos ng and abe ng.
eGFR (mL/m n/1.73 m^2) (Est mate of GFR based on an MDRD equat on)	<15 (end stage rena d sease) ≥15 - <30 (severe decrease n GFR) ≥30 - <60 (moderate decrease n GFR) ≥60 - <90 (m d decrease n GFR) ≥90 (norma GFR)	FDA draft Gu dance 2010. Pharmacok net cs n pat ents w th mpa red rena funct on-study des gn, data ana ys s, and mpact on dos ng and abe ng.
Creat n ne	≥150 µmo /L (Adu ts) ≥30% change from base ne ≥100% change from base ne	Ben chou C, 1994.
Ur c Ac d Hyperur cem a Hypour cem a	 >408 µmo /L <120 µmo /L	Harr son- Pr nc p es of nterna Med c ne 17th Ed, 2008.
B ood Urea N trogen	≥17 mmo /L	
Ch or de	<80 mmo /L >115 mmo /L	
Sod um	≤129 mmo /L ≥160 mmo /L	
Potass um	<3 mmo /L ≥5.5 mmo /L	FDA Feb 2005.
Tota Cho estero	≥7.74 mmo /L	Thresho d for therapeut c ntervent on.
Tr g ycer des	≥4.6 mmo /L	Thresho d for therapeut c ntervent on.
L pasem a	≥3 ULN	
Amy asem a	≥3 ULN	

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

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
G ucose		
Hypog ycaem a	≤3.9 mmo /L and <LLN	ADA May 2005.
Hyperg ycaem a	≥11.1 mmo /L (unfasted); ≥7 mmo /L (fasted)	ADA Jan 2008.
HbA1c	>8%	
A bum n	≤25 g/L	
CRP	>2 ULN or >10 mg/L (f ULN not prov ded)	FDA Sept 2005.
Hematology		
WBC	<3.0 G ga/L (Non-B ack); <2.0 G ga/L (B ack) ≥16.0 G ga/L	Increase n WBC: not re evant. To be nterpreted on y f no d fferent a count ava ab e.
Lymphocytes	>4.0 G ga/L	
Neutroph s	<1.5 G ga/L (Non-B ack);<1.0 G ga/L (B ack)	Internat ona Consensus meet ng on drug- nduced b ood cytopen as, 1991. FDA cr ter a.
Monocytes	>0.7 G ga/L	
Basoph s	>0.1 G ga/L	
Eos noph s	>0.5 G ga/L or >ULN (f ULN≥0.5 G ga/L)	Harr son- Pr nc p es of nterna Med c ne 17th Ed, 2008.
Hemog ob n	≤115 g/L (Ma e); ≤95 g/L (Fema e) ≥185 g/L (Ma e); ≥165 g/L (Fema e) Decrease from Base ne ≥20 g/L	Cr ter a based upon decrease from base ne are more re evant than based on abso ute va ue. Other categor es for decrease from base ne can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocr t	≤0.37 v/v (Ma e) ; ≤0.32 v/v (Fema e) ≥0.55 v/v (Ma e) ; ≥0.5 v/v (Fema e)	
RBC	≥6 Tera/L	Un ess spec f ca y requ red for part cu ar drug deve opment, the ana ys s s redundant w th that of Hb. Otherw se, cons der FDA cr ter a.
P ate ets	<100 G ga/L ≥700 G ga/L	Internat ona Consensus meet ng on drug- nduced b ood cytopen as, 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 base ne ≥20 bpm ≥120 bpm and ncrease from base ne≥20 bpm	To be app ed for a pos t ons (nc ud ng m ss ng) except STANDING.
SBP	≤95 mmHg and decrease from base ne ≥20mmHg ≥160 mmHg and ncrease from base ne ≥20 mmHg	To be app ed for a pos t ons (nc ud ng m ss ng) except STANDING.
DBP	≤45 mmHg and decrease from base ne ≥10 mmHg ≥110 mmHg and ncrease from base ne ≥10 mmHg	To be app ed for a pos t ons (nc ud ng m ss ng) except STANDING.
Orthostat c Hypotens on		
Orthostat c SDB	≤-20 mmHg	
Orthostat c DBP	≤-10 mmHg	
We ght	≥5% ncrease from base ne ≥5% decrease from base ne	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 gu dance (2005) and E14 Q&A (2012), and Card ac Safety Research Consort um Wh te Paper on PR and QRS (Nada et a . Am Heart J. 2013;165(4):489-500).
HR	<50 bpm	Categor es are cumu at ve.
	<50 bpm and decrease from base ne ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from base ne ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from base ne ≥20 bpm	
	>90 bpm	Categor es are cumu at ve.
	>90 bpm and ncrease from base ne ≥20bpm	
	>100 bpm	
	>100 bpm and ncrease from base ne ≥20bpm	
	>120 bpm	
	>120 bpm and ncrease from base ne ≥20 bpm	
PR	>200 ms	Categor es are cumu at ve.
	>200 ms and ncrease from base ne ≥25%	
	>220 ms	
	>220 ms and ncrease from base ne ≥25%	
	>240 ms	
	>240 ms and ncrease from base ne ≥25%	
QRS	>110 ms	Categor es are cumu at ve.
	>110 msec and ncrease from base ne ≥25%	
	>120 ms	
	>120 ms and ncrease from base ne ≥25%	
QT	>500 ms	
QTc	Abso ute va ues (ms)	To be app ed to any k nd of QT correct on formu a. Abso ute va ues categor es are cumu at ve.
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc >60 ms are the 2 PCSA categor es to be dent f ed n nd v dua pat ents st ngs.
	>500 ms	
	Increase from base ne	
	Increase from base ne]30-60] ms	
	Increase from base ne >60 ms	

Appendix C List of PTs for select EOSIs (MedDRA V22)

EOSI	Preferred Term Code	Preferred Term
Gen ta Mycot c Infect ons	10004074	Ba an t s cand da
Gen ta Mycot c Infect ons	10071209	Cand da cerv c t s
Gen ta Mycot c Infect ons	10079521	Funga ba an t s
Gen ta Mycot c Infect ons	10018143	Gen ta cand d as s
Gen ta Mycot c Infect ons	10061180	Gen ta nfect on funga
Gen ta Mycot c Infect ons	10065582	Urogen ta nfect on funga
Gen ta Mycot c Infect ons	10047784	Vu vovag na cand d as s
Gen ta Mycot c Infect ons	10064899	Vu vovag na mycot c nfect on
Ur nary tract nfect ons	10059517	Bacter a pye onephr t s
Ur nary tract nfect ons	10078665	Bacter a urethr t s
Ur nary tract nfect ons	10058523	B adder cand d as s
Ur nary tract nfect ons	10081262	Cand da urethr t s
Ur nary tract nfect ons	10011781	Cyst t s
Ur nary tract nfect ons	10065198	Cyst t s bacter a
Ur nary tract nfect ons	10011790	Cyst t s escher ch a
Ur nary tract nfect ons	10048837	Cyst t s g andu ar s
Ur nary tract nfect ons	10065199	Cyst t s he m nth c
Ur nary tract nfect ons	10011797	Cyst t s k ebs e a
Ur nary tract nfect ons	10011799	Cyst t s pseudomona
Ur nary tract nfect ons	10065197	Cyst t s v ra
Ur nary tract nfect ons	10051350	Cytomega ov rus ur nary tract nfect on
Ur nary tract nfect ons	10056351	Emphysematous cyst t s
Ur nary tract nfect ons	10068822	Emphysematous pye onephr t s
Ur nary tract nfect ons	10074409	Escher ch a pye onephr t s
Ur nary tract nfect ons	10052238	Escher ch a ur nary tract nfect on
Ur nary tract nfect ons	10017525	Funga cyst t s
Ur nary tract nfect ons	10081163	Funga urethr t s
Ur nary tract nfect ons	10018185	Gen tour nary ch amyd a nfect on
Ur nary tract nfect ons	10061181	Gen tour nary tract gonococca nfect on
Ur nary tract nfect ons	10061182	Gen tour nary tract nfect on
Ur nary tract nfect ons	10023424	K dney nfect on

EOSI	Preferred Term Code	Preferred Term
Ur nary tract nfect ons	10082040	Nephr t s bacter a
Ur nary tract nfect ons	10037584	Pye t s
Ur nary tract nfect ons	10049100	Pye ocyst t s
Ur nary tract nfect ons	10037596	Pye onephr t s
Ur nary tract nfect ons	10037597	Pye onephr t s acute
Ur nary tract nfect ons	10037601	Pye onephr t s chron c
Ur nary tract nfect ons	10065214	Pye onephr t s funga
Ur nary tract nfect ons	10037603	Pye onephr t s mycop asma
Ur nary tract nfect ons	10065213	Pye onephr t s v ra
Ur nary tract nfect ons	10037653	Pyonephros s
Ur nary tract nfect ons	10038351	Rena abscess
Ur nary tract nfect ons	10058596	Rena cyst nfect on
Ur nary tract nfect ons	10070300	Streptococca ur nary tract nfect on
Ur nary tract nfect ons	10044828	Tubercu os s of gen tour nary system
Ur nary tract nfect ons	10048302	Tubu o nterst t a nephr t s
Ur nary tract nfect ons	10061395	Ureter abscess
Ur nary tract nfect ons	10051250	Ureter t s
Ur nary tract nfect ons	10046424	Urethra abscess
Ur nary tract nfect ons	10046480	Urethr t s
Ur nary tract nfect ons	10046482	Urethr t s ch amyd a
Ur nary tract nfect ons	10046483	Urethr t s gonococca
Ur nary tract nfect ons	10075063	Urethr t s mycop asma
Ur nary tract nfect ons	10046490	Urethr t s ureap asma
Ur nary tract nfect ons	10051959	Ur nary b adder abscess
Ur nary tract nfect ons	10066757	Ur nary tract abscess
Ur nary tract nfect ons	10046571	Ur nary tract nfect on
Ur nary tract nfect ons	10054088	Ur nary tract nfect on bacter a
Ur nary tract nfect ons	10046572	Ur nary tract nfect on enterococca
Ur nary tract nfect ons	10049059	Ur nary tract nfect on funga
Ur nary tract nfect ons	10062279	Ur nary tract nfect on pseudomona
Ur nary tract nfect ons	10062280	Ur nary tract nfect on staphy ococca
Ur nary tract nfect ons	10064825	Ur nary tract nfect on v ra
Ur nary tract nfect ons	10064921	Ur nary tract nf ammat on
Ur nary tract nfect ons	10065583	Urogen ta nfect on bacter a

EOSI	Preferred Term Code	Preferred Term
Ur nary tract nfect ons	10065582	Urogen ta nfect on funga
Ur nary tract nfect ons	10046704	Urogen ta tr chomon as s
Ur nary tract nfect ons	10048709	Uroseps s
Vo ume dep et on	10005697	B ood osmo ar ty ncreased
Vo ume dep et on	10005731	B ood pressure ambu atory decreased
Vo ume dep et on	10005734	B ood pressure decreased
Vo ume dep et on	10005737	B ood pressure d asto c decreased
Vo ume dep et on	10005748	B ood pressure mmeasurab e
Vo ume dep et on	10053356	B ood pressure orthostat c decreased
Vo ume dep et on	10005758	B ood pressure systo c decreased
Vo ume dep et on	10005761	B ood pressure systo c nsp ratory decreased
Vo ume dep et on	10050760	B ood urea n trogen/creat n ne rat o ncreased
Vo ume dep et on	10007979	Centra venous pressure decreased
Vo ume dep et on	10009192	C rcu atory co apse
Vo ume dep et on	10050905	Decreased ventr cu ar pre oad
Vo ume dep et on	10012174	Dehydrat on
Vo ume dep et on	10066077	D asto c hypotens on
Vo ume dep et on	10013578	D zz ness postura
Vo ume dep et on	10021097	Hypotens on
Vo ume dep et on	10021137	Hypovo aem a
Vo ume dep et on	10021138	Hypovo aem c shock
Vo ume dep et on	10060089	Left ventr cu ar end-d asto c pressure decreased
Vo ume dep et on	10026983	Mean arter a pressure decreased
Vo ume dep et on	10069431	Orthostat c heart rate response ncreased
Vo ume dep et on	10031127	Orthostat c hypotens on
Vo ume dep et on	10063927	Orthostat c nto erance
Vo ume dep et on	10063080	Postura orthostat c tachycard a syndrome
Vo ume dep et on	10072370	Prerena fa ure
Vo ume dep et on	10036653	Presyncope
Vo ume dep et on	10060231	Pu monary arter a pressure decreased
Vo ume dep et on	10037327	Pu monary arter a wedge pressure decreased
Vo ume dep et on	10069583	Pu se vo ume decreased
Vo ume dep et on	10042772	Syncope
Vo ume dep et on	10046640	Ur ne f ow decreased

EOSI	Preferred Term Code	Preferred Term
Vo ume dep et on	10059895	Ur ne output decreased
Vo ume dep et on	10047235	Venous pressure decreased
Vo ume dep et on	10047239	Venous pressure jugu ar decreased
Vo ume dep et on	10047689	Vo ume b ood decreased
Pancreat t s	10056977	A coho c pancreat t s
Pancreat t s	10069002	Auto mmune pancreat t s
Pancreat t s	10076058	Haemorrhag c necrot c pancreat t s
Pancreat t s	10056976	Hered tary pancreat t s
Pancreat t s	10066127	Ischaem c pancreat t s
Pancreat t s	10052400	Oedematous pancreat t s
Pancreat t s	10048984	Pancreat c abscess
Pancreat t s	10033625	Pancreat c haemorrhage
Pancreat t s	10058096	Pancreat c necros s
Pancreat t s	10056975	Pancreat c ph egmon
Pancreat t s	10033635	Pancreat c pseudocyst
Pancreat t s	10033636	Pancreat c pseudocyst dra nage
Pancreat t s	10033645	Pancreat t s
Pancreat t s	10033647	Pancreat t s acute
Pancreat t s	10033649	Pancreat t s chron c
Pancreat t s	10033650	Pancreat t s haemorrhag c
Pancreat t s	10065189	Pancreat t s he m nth c
Pancreat t s	10033654	Pancreat t s necrot z ng
Pancreat t s	10033657	Pancreat t s re aps ng
Pancreat t s	10056277	Pancreatorena syndrome
Pancreat t s	10074894	Traumat c pancreat t s
Venous thrombot c events	10003192	Arter ovenous f stu a thrombos s
Venous thrombot c events	10053182	Arter ovenous graft thrombos s
Venous thrombot c events	10003880	Ax ary ve n thrombos s
Venous thrombot c events	10063363	Brach ocepha c ve n thrombos s
Venous thrombot c events	10006537	Budd-Ch ar syndrome
Venous thrombot c events	10007830	Cavernous s nus thrombos s
Venous thrombot c events	10008138	Cerebra venous thrombos s
Venous thrombot c events	10051055	Deep ve n thrombos s
Venous thrombot c events	10066881	Deep ve n thrombos s postoperat ve

EOSI	Preferred Term Code	Preferred Term
Venous thrombot c events	10014522	Embo sm venous
Venous thrombot c events	10078810	Hepat c ve n embo sm
Venous thrombot c events	10019713	Hepat c ve n thrombos s
Venous thrombot c events	10061251	Intracran a venous s nus thrombos s
Venous thrombot c events	10023237	Jugu ar ve n thrombos s
Venous thrombot c events	10027402	Mesenter c ve n thrombos s
Venous thrombot c events	10069909	Metastat c pu monary embo sm
Venous thrombot c events	10074349	Ophtha m c ve n thrombos s
Venous thrombot c events	10072059	Ovar an ve n thrombos s
Venous thrombot c events	10050216	Paget-Schroetter syndrome
Venous thrombot c events	10034272	Pe v c venous thrombos s
Venous thrombot c events	10034324	Pen e ve n thrombos s
Venous thrombot c events	10036206	Porta ve n thrombos s
Venous thrombot c events	10077623	Portosp enomesenter c venous thrombos s
Venous thrombot c events	10063909	Post procedura pu monary embo sm
Venous thrombot c events	10048591	Post thrombot c syndrome
Venous thrombot c events	10050902	Postoperat ve thrombos s
Venous thrombot c events	10037377	Pu monary embo sm
Venous thrombot c events	10037421	Pu monary m croembo
Venous thrombot c events	10037437	Pu monary thrombos s
Venous thrombot c events	10037459	Pu monary venous thrombos s
Venous thrombot c events	10038547	Rena ve n embo sm
Venous thrombot c events	10038548	Rena ve n thrombos s
Venous thrombot c events	10038908	Ret na ve n thrombos s
Venous thrombot c events	10041659	Sp en c ve n thrombos s
Venous thrombot c events	10049446	Subc av an ve n thrombos s
Venous thrombot c events	10042567	Super or sag tta s nus thrombos s
Venous thrombot c events	10043570	Thromboph eb t s
Venous thrombot c events	10043581	Thromboph eb t s m grans
Venous thrombot c events	10043595	Thromboph eb t s superf c a
Venous thrombot c events	10043605	Thrombosed var cose ve n
Venous thrombot c events	10067270	Thrombos s corpora cavernosa
Venous thrombot c events	10044457	Transverse s nus thrombos s
Venous thrombot c events	10047193	Vena cava embo sm

EOSI	Preferred Term Code	Preferred Term
Venous thrombot c events	10047195	Vena cava thrombos s
Venous thrombot c events	10047249	Venous thrombos s
Venous thrombot c events	10061408	Venous thrombos s mb
Venous thrombot c events	10077829	V scera venous thrombos s
Thyro d cancer	10002240	Anap ast c thyro d cancer
Thyro d cancer	10073153	Fam a medu ary thyro d cancer
Thyro d cancer	10016935	Fo cu ar thyro d cancer
Thyro d cancer	10066136	Huerth e ce carc noma
Thyro d cancer	10027105	Medu ary thyro d cancer
Thyro d cancer	10033701	Pap ary thyro d cancer
Thyro d cancer	10076603	Poor y d fferent ated thyro d carc noma
Thyro d cancer	10072613	Thyro d B-ce ymphoma
Thyro d cancer	10066474	Thyro d cancer
Thyro d cancer	10055107	Thyro d cancer metastat c
Thyro d cancer	10072162	Thyro d cancer recurrent
Thyro d cancer	10070567	Thyro d cancer stage 0
Thyro d cancer	10071027	Thyro d cancer stage I
Thyro d cancer	10071028	Thyro d cancer stage II
Thyro d cancer	10071029	Thyro d cancer stage III
Thyro d cancer	10071030	Thyro d cancer stage IV
Thyro d cancer	10043744	Thyro d neop asm
Rena ce cancer	10073251	C ear ce rena ce carc noma
Rena ce cancer	10067944	Hered tary e omyomatos s rena ce carc noma
Rena ce cancer	10050513	Metastat c rena ce carc noma
Rena ce cancer	10078493	Pap ary rena ce carc noma
Rena ce cancer	10038389	Rena cancer
Rena ce cancer	10050018	Rena cancer metastat c
Rena ce cancer	10038390	Rena cancer recurrent
Rena ce cancer	10038391	Rena cancer stage I
Rena ce cancer	10038392	Rena cancer stage II
Rena ce cancer	10038393	Rena cancer stage III
Rena ce cancer	10038394	Rena cancer stage IV
Rena ce cancer	10067946	Rena ce carc noma
Rena ce cancer	10038410	Rena ce carc noma recurrent

EOSI	Preferred Term Code	Preferred Term
Rena ce cancer	10038411	Rena ce carc noma stage I
Rena ce cancer	10038412	Rena ce carc noma stage II
Rena ce cancer	10038413	Rena ce carc noma stage III
Rena ce cancer	10038414	Rena ce carc noma stage IV
Rena ce cancer	10061482	Rena neop asm
Pancreat c cancer	10073363	Ac nar ce carc noma of pancreas
Pancreat c cancer	10052747	Adenocarc noma pancreas
Pancreat c cancer	10055007	Carc no d tumour of the pancreas
Pancreat c cancer	10073364	Ducta adenocarc noma of pancreas
Pancreat c cancer	10051709	Gastr noma ma gnant
Pancreat c cancer	10018404	G ucagonoma
Pancreat c cancer	10022498	Insu noma
Pancreat c cancer	10073365	Intraducta pap ary-muc nous carc noma of pancreas
Pancreat c cancer	10025997	Ma gnant neop asm of s ets of Langerhans
Pancreat c cancer	10029341	Neurotens noma
Pancreat c cancer	10033609	Pancreat c carc noma
Pancreat c cancer	10033610	Pancreat c carc noma metastat c
Pancreat c cancer	10033613	Pancreat c carc noma recurrent
Pancreat c cancer	10059320	Pancreat c carc noma stage 0
Pancreat c cancer	10059321	Pancreat c carc noma stage I
Pancreat c cancer	10059322	Pancreat c carc noma stage II
Pancreat c cancer	10059323	Pancreat c carc noma stage III
Pancreat c cancer	10059326	Pancreat c carc noma stage IV
Pancreat c cancer	10061902	Pancreat c neop asm
Pancreat c cancer	10067517	Pancreat c neuroendocr ne tumour
Pancreat c cancer	10068909	Pancreat c neuroendocr ne tumour metastat c
Pancreat c cancer	10055006	Pancreat c sarcoma
Pancreat c cancer	10073367	Pancreatob astoma
Pancreat c cancer	10069345	So d pseudopap ary tumor of the pancreas
Pancreat c cancer	10041329	Somatostat noma
Pancreat c cancer	10047430	V poma
B adder cancer	10004986	B adder adenocarc noma recurrent
B adder cancer	10004987	B adder adenocarc noma stage 0
B adder cancer	10004988	B adder adenocarc noma stage I

EOSI	Preferred Term Code	Preferred Term
B adder cancer	10004989	B adder adenocarc noma stage II
B adder cancer	10004990	B adder adenocarc noma stage III
B adder cancer	10004991	B adder adenocarc noma stage IV
B adder cancer	10004992	B adder adenocarc noma stage unspec f ed
B adder cancer	10005003	B adder cancer
B adder cancer	10005005	B adder cancer recurrent
B adder cancer	10005006	B adder cancer stage 0, w th cancer n s tu
B adder cancer	10005007	B adder cancer stage 0, w thout cancer n s tu
B adder cancer	10005008	B adder cancer stage I, w th cancer n s tu
B adder cancer	10005009	B adder cancer stage I, w thout cancer n s tu
B adder cancer	10005010	B adder cancer stage II
B adder cancer	10005011	B adder cancer stage III
B adder cancer	10005012	B adder cancer stage IV
B adder cancer	10005056	B adder neop asm
B adder cancer	10005075	B adder squamous ce carc noma recurrent
B adder cancer	10005076	B adder squamous ce carc noma stage 0
B adder cancer	10005077	B adder squamous ce carc noma stage I
B adder cancer	10005078	B adder squamous ce carc noma stage II
B adder cancer	10005079	B adder squamous ce carc noma stage III
B adder cancer	10005080	B adder squamous ce carc noma stage IV
B adder cancer	10005081	B adder squamous ce carc noma stage unspec f ed
B adder cancer	10005084	B adder trans t ona ce carc noma
B adder cancer	10071664	B adder trans t ona ce carc noma metastat c
B adder cancer	10066750	B adder trans t ona ce carc noma recurrent
B adder cancer	10066749	B adder trans t ona ce carc noma stage 0
B adder cancer	10066751	B adder trans t ona ce carc noma stage I
B adder cancer	10066753	B adder trans t ona ce carc noma stage II
B adder cancer	10066754	B adder trans t ona ce carc noma stage III
B adder cancer	10066752	B adder trans t ona ce carc noma stage IV
B adder cancer	10057352	Metastat c carc noma of the b adder
B adder cancer	10078341	Neuroendocr ne carc noma of the b adder
B adder cancer	10051690	Ur nary b adder sarcoma
Potent a y ead ng to amputat on	10050473	Abscess mb
Potent a y ead ng to amputat on	10061627	Amputat on

EOSI	Preferred Term Code	Preferred Term
Potent a y ead ng to amputat on	10059245	Ang opathy
Potent a y ead ng to amputat on	10003084	Aref ex a
Potent a y ead ng to amputat on	10056418	Arter a bypass operat on
Potent a y ead ng to amputat on	10060963	Arter a d sorder
Potent a y ead ng to amputat on	10061655	Arter a graft
Potent a y ead ng to amputat on	10062599	Arter a occ us ve d sease
Potent a y ead ng to amputat on	10060965	Arter a stenos s
Potent a y ead ng to amputat on	10061657	Arter a stent nsert on
Potent a y ead ng to amputat on	10052949	Arter a therapeut c procedure
Potent a y ead ng to amputat on	10003178	Arter a thrombos s
Potent a y ead ng to amputat on	10003210	Arter osc eros s
Potent a y ead ng to amputat on	10003222	Arter osc erot c gangrene
Potent a y ead ng to amputat on	10061666	Autonom c neuropathy
Potent a y ead ng to amputat on	10068653	Bone abscess
Potent a y ead ng to amputat on	10051548	Burn nfect on
Potent a y ead ng to amputat on	10006784	Burn ng sensat on
Potent a y ead ng to amputat on	10007904	Ce u t s enterococca
Potent a y ead ng to amputat on	10007905	Ce u t s gangrenous
Potent a y ead ng to amputat on	10007921	Ce u t s staphy ococca
Potent a y ead ng to amputat on	10007922	Ce u t s streptococca
Potent a y ead ng to amputat on	10012174	Dehydrat on
Potent a y ead ng to amputat on	10060734	D abet c foot
Potent a y ead ng to amputat on	10060803	D abet c foot nfect on
Potent a y ead ng to amputat on	10012665	D abet c gangrene
Potent a y ead ng to amputat on	10054044	D abet c m croang opathy
Potent a y ead ng to amputat on	10012679	D abet c neuropath c u cer
Potent a y ead ng to amputat on	10012680	D abet c neuropathy
Potent a y ead ng to amputat on	10056340	D abet c u cer
Potent a y ead ng to amputat on	10061815	D abet c vascu ar d sorder
Potent a y ead ng to amputat on	10049927	Dry gangrene
Potent a y ead ng to amputat on	10059385	Extrem ty necros s
Potent a y ead ng to amputat on	10017711	Gangrene
Potent a y ead ng to amputat on	10020937	Hypoaesthes a
Potent a y ead ng to amputat on	10021137	Hypovo aem a

EOSI	Preferred Term Code	Preferred Term
Potent a y ead ng to amputat on	10064601	I ac artery occ us on
Potent a y ead ng to amputat on	10021519	Impa red hea ng
Potent a y ead ng to amputat on	10021784	Infected sk n u cer
Potent a y ead ng to amputat on	10022562	Interm ttent c aud cat on
Potent a y ead ng to amputat on	10062610	Ischaem c mb pa n
Potent a y ead ng to amputat on	10024774	Loca sed nfect on
Potent a y ead ng to amputat on	10062198	M croang opathy
Potent a y ead ng to amputat on	10028862	Necros s schaem c
Potent a y ead ng to amputat on	10050502	Neuropath c u cer
Potent a y ead ng to amputat on	10029331	Neuropathy per phera
Potent a y ead ng to amputat on	10031149	Oste t s
Potent a y ead ng to amputat on	10031252	Osteomye t s
Potent a y ead ng to amputat on	10031253	Osteomye t s acute
Potent a y ead ng to amputat on	10065237	Osteomye t s bacter a
Potent a y ead ng to amputat on	10031256	Osteomye t s chron c
Potent a y ead ng to amputat on	10065239	Osteomye t s funga
Potent a y ead ng to amputat on	10031262	Osteomye t s sa mone a
Potent a y ead ng to amputat on	10031264	Osteonecros s
Potent a y ead ng to amputat on	10033775	Paraesthes a
Potent a y ead ng to amputat on	10074396	Penetrat ng atherosc erot c u cer
Potent a y ead ng to amputat on	10062585	Per phera arter a occ us ve d sease
Potent a y ead ng to amputat on	10069379	Per phera arter a reocc us on
Potent a y ead ng to amputat on	10057518	Per phera artery ang op asty
Potent a y ead ng to amputat on	10072561	Per phera artery bypass
Potent a y ead ng to amputat on	10057525	Per phera artery occ us on
Potent a y ead ng to amputat on	10072557	Per phera artery restenos s
Potent a y ead ng to amputat on	10072563	Per phera artery stenos s
Potent a y ead ng to amputat on	10072562	Per phera artery stent nsert on
Potent a y ead ng to amputat on	10072564	Per phera artery thrombos s
Potent a y ead ng to amputat on	10034568	Per phera co dness
Potent a y ead ng to amputat on	10072560	Per phera endarterectomy
Potent a y ead ng to amputat on	10034576	Per phera schaem a
Potent a y ead ng to amputat on	10056673	Per phera sensor motor neuropathy
Potent a y ead ng to amputat on	10034620	Per phera sensory neuropathy

EOSI	Preferred Term Code	Preferred Term
Potent a y ead ng to amputat on	10034636	Per phera vascu ar d sorder
Potent a y ead ng to amputat on	10036155	Poor per phera c rcu at on
Potent a y ead ng to amputat on	10036410	Postoperat ve wound nfect on
Potent a y ead ng to amputat on	10040026	Sensory d sturbance
Potent a y ead ng to amputat on	10040840	Sk n eros on
Potent a y ead ng to amputat on	10040872	Sk n nfect on
Potent a y ead ng to amputat on	10040943	Sk n u cer
Potent a y ead ng to amputat on	10072170	Sk n wound
Potent a y ead ng to amputat on	10062255	Soft t ssue nfect on
Potent a y ead ng to amputat on	10076246	Spontaneous amputat on
Potent a y ead ng to amputat on	10064250	Staphy ococca osteomye t s
Potent a y ead ng to amputat on	10042343	Subcutaneous abscess
Potent a y ead ng to amputat on	10075118	Subper ostea abscess
Potent a y ead ng to amputat on	10043607	Thrombos s
Potent a y ead ng to amputat on	10075714	Vascu t c u cer
Potent a y ead ng to amputat on	10052428	Wound
Potent a y ead ng to amputat on	10058042	Wound abscess
Potent a y ead ng to amputat on	10053692	Wound comp cat on
Potent a y ead ng to amputat on	10048031	Wound deh scence
Potent a y ead ng to amputat on	10048038	Wound nfect on
Potent a y ead ng to amputat on	10065240	Wound nfect on bacter a
Potent a y ead ng to amputat on	10065242	Wound nfect on funga
Potent a y ead ng to amputat on	10059444	Wound nfect on pseudomonas
Potent a y ead ng to amputat on	10059442	Wound nfect on staphy ococca
Potent a y ead ng to amputat on	10053716	Wound necros s
Potent a y ead ng to amputat on	10058041	Wound seps s
Potent a y ead ng to amputat on	10062932	Wound treatment

Appendix D Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA1c: Change from Base ne at Week 52, (sotag f oz n 400 mg vs g mep r de)	ITT and Comp eters	ANCOVA (w th m ss ng va ues mputed by the retr eved dropouts method or by washout mputat on MI method under MNAR framework): treatment, random zat on strata (HbA1c / SBP at Screen ng), and country as f xed factors, and base ne HbA1c va ue as a covar ate.	T pp ng po nt ana ys s	Subgroups: race, ethn c ty, age group, gender, base ne BMI, base ne HbA1c, base ne SBP, base ne eGFR and country.	Summary stat st cs for observed va ues and changes from base ne by v s t. Graph ca presentat ons for mean changes from base ne (±SE) and mean va ues (±SE) by v s t. By-v s t summary and graph exc ud ng measurements after rescue therapy.
Secondary endpoints					
HbA1c, body we ght, FPG: Change from Base ne to Week 26 and 52; SBP (for pat ents w th base ne SBP ≥130 mmHg and a pat ents): Change from Base ne to Week 12	ITT and Comp eters (for HbA1c change from Base ne to Week 52)	ANCOVA (w th m ss ng va ues mputed by the retr eved dropouts method or by washout mputat on MI Method under MNAR framework): treatment, random zat on strata (HbA1c/SBP at Screen ng), and country as f xed factors, and base ne va ue as a covar ate.	For HbA1c: T pp ng po nt ana ys s	Subgroups on HbA1c: race, ethn c ty, age group, gender, base ne BMI, base ne HbA1c, base ne SBP, base ne eGFR and country.	Summary stat st cs for observed va ues and changes from base ne by v s t. Graph ca presentat ons for mean changes from base ne (±SE) and mean va ues (±SE) by v s t.
Proport on of pat ents w th at east one documented symptomat c hypog ycem c event	ITT	CMH method strat f ed on random zat on strata (HbA1c / SBP at Screen ng).	No	No	By-v s t frequency summary and graphs.

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Other endpoints					
FPG, eGFR, SBP (for pat ents w th base ne SBP ≥130 mmHg, w th base ne SBP <130 mmHg and a pat ents), DBP (for a pat ents and pat ents w th base ne ≥80 mmHg): change from base ne to Week 12, 26 and 52	ITT	Summary stat st cs for observed va ues and changes from base ne by v s t.	No	No	Graph ca presentat ons for mean changes from base ne (±SE) and mean va ues (±SE) by v s t as appropr ate.
Number of hosp ta v s ts due to hypog ycem a	ITT	Number (%) of pat ents w th hosp ta v s ts due to hypog ycem a.	No	No	Inc dence rate as appropr ate.
Proport on of pat ents requ r ng rescue for hyperg ycem a	ITT	Summary stat st cs.	No	No	KM p ot; L st of pat ents rescued.
Proport on of pat ents w th HbA1c <6.5%, <7.0%, proport on of pat ents w th HbA1c <6.5%, <7.0% and no documented symptomat c hypog ycem c event	ITT	By-v s t summary and graphs.	No	No	No

SAFETY ANALYSES

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Hypog ycem a	Safety	Fo ow safety gu de nes Number (%) of pat ents w th any hypog ycem a, severe hypog ycem a, documented symptomat c hypog ycem a dur ng TEAE per od, and nc dence rates n 100 pat ent-years.	No	Severe hypog ycem a or documented symptomat c hypog ycem a by subgroups: race, age, gender	KM p ot t me-to-f rst event of severe hypog ycem a or documented symptomat c hypog ycem a. Documented symptomat c hypog ycem a maybe presented by <54 mg/dL (3.0 mmo /L) as appropr ate.
Adverse events	Safety	Fo ow safety gu de nes	No	Common TEAEs by subgroups: race, age group, gender, base ne SBP, base ne eGFR	No
C n ca aboratory data	Safety	Fo ow safety gu de nes	Descr pt ve	No	No
V ta s gns	Safety	Fo ow safety gu de nes	Descr pt ve	No	No
ECG, phys ca exam nat on	Safety	Fo ow safety gu de nes	Frequency summary	No	No

Appendix E Study flow chart

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	1	2	3 (Randomiza -tion)	4	5	6	7	8 ☎	9	10	11	12	13 [b] ☎
Week	-4	-2	0 Baseline	2	4	8	12	15	18	26	39	52	54
Day (window [days])		(-14/+3)	1	14 (±3)	28 (±3)	56 (±3)	84 (±3)	105 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±3)	378 (±3)
nformed consent	X												
nclusion criteria	X												
Exclusion criteria	X	X	X										
Demographics	X												
Medical/Surgical History	X												
Medication History	X												
Body weight height [c]	X	X	X	X	X	X	X		X	X	X	X	
Vital signs [d]	X	X	X	X	X	X	X		X	X	X	X	
Physical Examination													
Complete	X									X		X	
Abbreviated		X	X	X	X	X	X		X		X		
Diet & exercise instruction		X	X							X		X	
nstruction on basic genitourinary hygiene & hydration		X	X		X	X	X		X	X	X	X	

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	**1**	**2**	**3 (Randomiza -tion)**	**4**	**5**	**6**	**7**	**8** ☎	**9**	**10**	**11**	12	**13** [b] ☎
Week	**-4**	**-2**	**0 Baseline**	**2**	**4**	**8**	**12**	**15**	**18**	**26**	**39**	**52**	**54**
Day (window [days])		**(-14/+3)**	**1**	**14 (±3)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**105 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±3)**	**378 (±3)**
nteractive response technology (RT) contact	X	X	X	X	X	X	X		X	X	X	X	X
Randomization			X										
Dispense glucose meter for self-monitoring of blood glucose		X											
Dispense diary	X	X	X	X	X	X	X		X	X	X		
Collect/review diary		X	X	X	X	X	X		X	X	X	X	
nstruction on diabetic ketoacidosis symptoms glucose testing		X	X	X	X	X	X		X	X	X	X	
Dispense single-blind placebo		X											
Dispense double-blind MP			X	X	X	X	X		X	X	X		
Study drug accountability & compliance assessment			X	X	X	X	X		X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-monitoring of blood glucose [e]		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [f]	X									X		X	

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	**1**	**2**	**3 (Randomiza -tion)**	**4**	**5**	**6**	**7**	**8** ☎	**9**	**10**	**11**	12	**13** [b] ☎
Week	**-4**	**-2**	**0 Baseline**	**2**	**4**	**8**	**12**	**15**	**18**	**26**	**39**	**52**	**54**
Day (window [days])		**(-14/+3)**	**1**	**14 (±3)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**105 (±3)**	**126 (±3)**	**182 (±3)**	**273 (±7)**	**364 (±3)**	**378 (±3)**
Laboratory testing [g]													
FPG	X		X		X	X	X		X	X	X	X	
HbA1c	X		X				X			X	X	X	
Chemistry & Hematology	X		X				X			X	X	X	
Fasting lipids	X		X							X		X	
Pregnancy test (WOCBP) [h]	X		X	X	X	X	X		X	X	X	X	
Serum follicle-stimulating hormone and estradiol (menopausal women only) [h]	X												
Urinalysis (dipstick and microscopy) [i]	X		X							X		X	
[redacted]													
PQAT [l]										X		X	
Evaluate for glycemic rescue				To be assessed and reported throughout the Treatment Period									
Hypoglycemia	To be assessed and reported throughout the study												

	Screening Period			Double-Blind Treatment Period [a]									Follow-up
	Screening	Run-in											
VISIT	1	2	3 (Randomiza -tion)	4	5	6	7	8 ☎	9	10	11	12	13 [b] ☎
Week	-4	-2	0 Baseline	2	4	8	12	15	18	26	39	52	54
Day (window [days])		(-14/+3)	1	14 (±3)	28 (±3)	56 (±3)	84 (±3)	105 (±3)	126 (±3)	182 (±3)	273 (±7)	364 (±3)	378 (±3)
AE/SAEs/AES /EOS [m]	To be assessed and reported throughout the study												

Abbreviations AE = adverse event AES = adverse event of special interest BP = blood pressure ECG = electrocardiogram eGFR = estimated glomerular filtration rate EOS = events of special interest EOT = end of treatment EW = early withdrawal FPG = fasting plasma glucose FSH = follicle-stimulating hormone HbA1c = hemoglobin A1c MP = investigational medicinal product RT = nteractive Response Technology N MP = non-investigational medicinal product PRO = patient-reported outcome PQAT = Patient Qualitative Assessment of Treatment SAE = serious adverse event SMBG = self-monitoring blood glucose UT = urinary tract infection WOCBP = women of childbearing potential

a All visits' dates will be scheduled based on the date of randomization within visit window allowed as per flowchart f a patient discontinues treatment with investigational medicinal product (MP) during the Treatment Period the patient will have a visit as soon as possible to complete the assessments normally planned for the last dosing day with the MP [End of Treatment/Early Withdrawal [EOT/EW] Visit) and a Follow-up Visit 2 weeks after the last dose of MP n addition every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits particularly the Week 26 and Week 52 visits f the patient does not agree to a site visit they will be contacted by telephone to inquire about safety status

b All patients will have a phone call Follow-up Visit 2 weeks after the last dose of the MP to collect safety information

c Height to be measured only at Screening

d Vital sign measurements (sitting 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 4 in the protocol and detailed instructions in Appendix C in the protocol)

e Patients will measure their fasting glucose levels via SMBG and discuss results with site personnel at clinic or phone visits or unscheduled phone contacts The SMBG measurements obtained with glucose meters are displayed as plasma glucose concentration From randomization through Week 18 glimepiride or glimepiride-matching placebo dose adjustments will be made based on algorithm provided in protocol Note Changes in blinded glimepiride dose can be made only at on-site visits (except for decreases for safety reasons related to hypoglycemia) Patients will also be requested to self-assess blood glucose levels whenever they experience any illnesses (eg cold flu) or symptoms of hyperglycemia or hypoglycemia Any SMBG values ≤70 mg/dL (≤3 9 mmol/L) should be documented in the diary and collected in the hypoglycemia event case report form (CRF)

f The 12-lead ECG recordings should be obtained prior to MP administration The ECG will be evaluated as "normal" or "abnormal"

g All laboratory assessments occur under fasting condition and prior to MP and N MP administration on the day of the visit (please see the list in Table 3 in the protocol)

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

i Urinalysis includes urine dipstick and microscopy Dipstick includes assessment of specific gravity pH protein blood ketones bilirubin urobilinogen nitrite 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 n the event of abnormal urinalysis findings suspicious of urinary tract infection (UT) urine culture should be performed Positive urine culture determination will be based upon the criteria of the reporting laboratory Additionally urine culture should be performed if at any point the Principal nvestigator suspects the presence of a UT

[redacted]

l Patient Reported Outcomes (PROs) Patient Qualitative Assessment of Treatment (PQAT) to be administered to English-speaking patients at Weeks 26 and 52

m All serious adverse events (SAEs) adverse events (AEs) AEs of special interest (AES s) and events of special interest (EOS s) will be collected starting from signing informed consent and continue until the end of the study (Note for patients who discontinue treatment before Week 52 safety data will be collected until scheduled study end) All AEs that occur during treatment should be followed until study completion (or until patients leave the study) or until the event has resolved the condition has stabilized or the patient is lost to follow-up All patients will have a Follow-up visit 2 weeks after the last dose of MP to collect safety information