Clinical Trial Protocol with Statisitical Analysis Plan:
THR-1442-C-476

Study Title:	A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c in patients with type 2 diabetes and increased risk of cardiovascular adverse events
Study Number:	THR-1442-C-476
Study Phase:	3
Product Name:	Bexagliflozin Tablets
Indication:	Type 2 diabetes mellitus
NCT Number:	02558296
EudraCT Number:	2015-001760-19
Sponsor:	Theracos Sub, LLC.

	Date
Protocol Version 8.0	01 December 2016
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Sponsor:	Theracos Sub, LLC.
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	Date
Version 8.0	01 December 2016

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SYNOPSIS

Sponsor: Theracos Sub, LLC.

Name of Finished Product: Bexagliflozin Tablets

Name of Active Ingredient: Bexagliflozin

Study Title:
A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c in patients with type 2 diabetes and increased risk of cardiovascular adverse events

Study Number: THR-1442-C-476

Study Phase: 3

Primary Efficacy Objective:
The primary efficacy objective of this trial is to evaluate the placebo-adjusted change in hemoglobin A1c (HbA1c) from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects at high risk of cardiovascular adverse events.

Secondary Efficacy Objectives:
The key secondary efficacy objectives are:

- To evaluate the effect of bexagliflozin compared to placebo on the change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- To evaluate the effect of bexagliflozin on the change in body weight from baseline to week 48 in randomized subjects with a BMI $\geq$ 25 kg/m^2 compared to placebo
- To evaluate the effect of bexagliflozin on the change in systolic blood pressure (SBP) from baseline to week 24 in subjects with baseline systolic blood pressure $\geq$ 140 mmHg compared to placebo

Additional exploratory efficacy objectives are:

- To assess the effect of bexagliflozin treatment on the change in HbA1c versus placebo over time
- To evaluate the effect of bexagliflozin treatment on the change in fasting plasma glucose (FPG) versus placebo over time
- To measure the proportion of subjects requiring an intensification of anti-diabetic regimen versus placebo over time
- To measure the proportion of subjects requiring a relaxation of their anti-diabetic regimen versus placebo over time
- To measure the incidence of hospitalization for heart failure among all subjects and among subjects with a history of heart failure at baseline.

Safety Objectives:
The primary safety objective of this study is the contribution of at least 134 major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a

hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo. MACE+ is defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina.

An additional objective is the evaluation of the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population that is at elevated risk for major adverse cardiovascular events.

Other Objectives:

- Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted at 30 sites and will include approximately 240 subjects
- Measurement of cardiovascular biomarkers at baseline and week 12 in an exploratory study to increase the understanding of bexagliflozin treatment effect on the biomarkers that are relevant in the CV disease diagnosis and prognosis

Study Design:
THR-1442-C-476 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. Approximately 1650 subjects with poorly controlled T2DM and at high risk of cardiovascular (CV) adverse events will be randomized to bexagliflozin tablets, 20 mg, or placebo in a ratio of 2:1 in addition to the background anti-diabetic medications.

Potential participants with suboptimal glycemic control (HbA1c between 7.0 % and 11 %) despite treatment as recommended in local guidelines and at high risk of cardiovascular adverse events will enter a screening period of up to 3 weeks. Qualified participants will enter a single-blind, placebo run-in period to allow for diabetes education and optimization of compliance with diet and exercise recommendations. Qualified subjects will continue their pre-screening regimen for glycemic control and will be instructed to take the run-in medication once daily for 13 ± 2 days. Adjustment of treatment for hypertension or dyslipidemia will not be permitted during the screening and run-in periods although initiation of anti-coagulant therapy (if clinically indicated) will be permitted. If a change in treatment is required to improve management of hypertension or dyslipidemia, the subject may re-enter the screening after the clinical condition and treatment regimen have not changed for at least 4 weeks. Subjects who continue to qualify for the study and who have demonstrated compliance by missing no more than 1 dose of the run-in doses as instructed will be randomized to receive the investigational product.

Assignment to treatment groups will be stratified by baseline HbA1c (> or ≤ 9.5%), baseline eGFR (eGFR ≥ or < 60 mL/min/1.73m^2), baseline BMI (≥ or < 25 kg/m^2) and history of heart failure. The study subjects will visit the clinic or complete phone interviews for evaluation at 2, 6, 12, 18, 24, 36 and 48 weeks post-randomization with subsequent visits scheduled every 24 weeks and a phone interview at 12 weeks after each clinic visit. The study duration will be determined by event accumulation. The treatment period will end when all randomized subject have completed at least 52 weeks of treatment and a total of 134 subjects have experienced a MACE+. A follow-up visit will take place 4 weeks after the conclusion of

treatment.

During the first 24 weeks of the efficacy assessment period, hyperglycemia should be managed with diet and exercise counseling. Changes in the medical therapy are allowed if the investigator feels it is necessary for the well-being of the subject. After 24 weeks, changes to the medical therapy for hyperglycemia should occur at the discretion of the investigator based on SMBG, FPG, and HbA1c information using local standards of care for subjects with T2DM. During the course of the study investigators will adjust other medications to effect changes in blood pressure and serum lipid values according to national or local guidelines. At every visit participants will be queried regarding adverse events and information on all events that potentially represent a MACE endpoint will be forwarded to a Cardiovascular Endpoint Committee (CEC) for blinded adjudication. An investigator should also query the subject about symptoms that may be associated with possible diabetic ketoacidosis (DKA) at every visit. A DKA Adjudication Committee will review and adjudicate all suspected DKA cases.

In this study, the incidence of MACE+ will be recorded for subsequent meta-analysis. MACE+ is defined as CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. It is estimated that the required total of 134 patients with a MACE+ will accrue over a treatment period of 2 to 3 years.

During the trial, a Data and Safety Monitoring Board (DSMB) will review the unblinded data periodically and may recommend an early termination of the trial for safety reasons. No interim analysis will be performed for efficacy assessment and the study will not be stopped for futility or benefit of bexagliflozin treatment.

Measurement of bexagliflozin plasma concentration as a function of time (sparsely sampled) will also be conducted at 30 centers and will include approximately 240 study subjects as part of a bexagliflozin population PK study. Samples will be drawn at weeks 6 or 12.

Cardiovascular biomarkers will be measured at baseline before treatment is administered and after 12 weeks of treatment in an exploratory study to evaluate the effect of bexagliflozin treatment on biomarkers that are relevant in cardiovascular disease diagnosis and prognosis.

Study Population:
The study population will consist of approximately 1650 subjects who have been diagnosed with sub-optimally controlled T2DM and who exhibit an elevated risk of cardiovascular events. The study population will comprise:

1. Male or female adult subjects (age ≥ 40 years)
2. Subjects with a diagnosis of T2DM
3. Subjects with HbA1c values of 7.0 – 11 %, inclusive
4. Subjects with fasting plasma glucose (FPG) ≤ 300 mg/dL at screening
5. Subjects who have a regimen for treatment of T2DM that has been stable for the past 3 months. A stable regimen is defined as: no changes in dose or frequency of oral hypoglycemic agents or GLP-1 agonists, or < 20% variability in total daily insulin dose.

6. Subjects with either established cardiovascular disease or with multiple cardiovascular risk factors (if no documented cardiovascular disease) having the following attributes:

Group 1: A history of atherosclerotic vascular disease as defined by one or more of the following: a) myocardial infarction (MI) or ischemic (non-hemorrhagic) stroke > 3 months but ≤ 5 years prior to screening or b) documented history of coronary, carotid, or peripheral arterial revascularization (coronary artery bypass grafting must have occurred ≥ 5 years prior to screening)

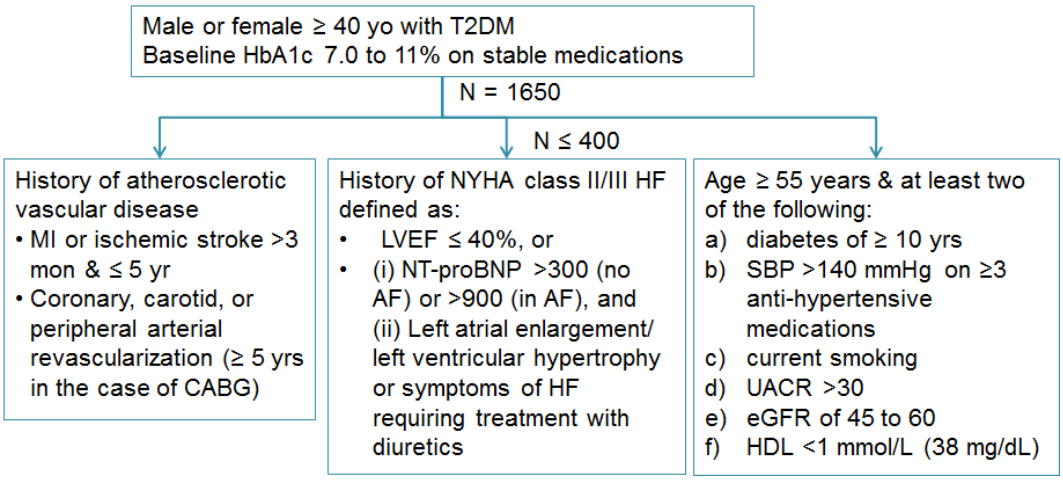
Group 2: A history of NYHA class II or class III heart failure (Appendix 4) at the time of screening. A history of heart failure is defined as:

- documented left ventricular ejection fraction (LVEF) ≤ 40% and no subsequent LVEF > 40% within 6 months of screening, or
- (i) an NT-proBNP >300 pg/mL and no evidence of atrial fibrillation/flutter (AF) at the time of the screening ECG or an NT-proBNP >900 pg/mL and evidence of AF at the time of the screening ECG and (ii) either (a) structural heart disease documented by report of left atrial enlargement or left ventricular hypertrophy, or (b) exhibiting symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening.

Group 3: Age ≥ 55 years with 2 or more of the following:

a. diabetes duration of ≥ 10 years,
b. uncontrolled hypertension defined as SBP > 140 mmHg despite 3 or more anti-hypertensive medications,
c. current smoking,
d. urine albumin:creatinine ratio (UACR) > 30 mg/g,
e. eGFR of 45 to 60 mL/min/1.73 m^2, or
f. HDL < 1 mmol/L (38 mg/dL)

To ensure that subjects with various cardiovascular risks are adequately represented, a minimum of 352 subjects (21%) from each of the three groups will be recruited and ≤ 400 subjects who have a history of heart failure will be randomized in the study. The intended population is presented in the figure below.



If a subject has a history of class II or III heart failure, the subject will be allocated to group 2, regardless of any history of atherosclerotic vascular disease or cardiovascular risk factors. If a subject does not have a heart failure history and has a history of atherosclerotic vascular disease, the subject will be allocated to group 1 regardless of having other cardiovascular risks.

Test Product, Dose, and Mode of Administration:
Bexagliflozin tablets, 20 mg, or placebo administered orally once per day

Duration of Treatment:
The study is an event-driven trial. The treatment period will end when the last randomized subject has completed at least 52 weeks of treatment and at least 134 subjects have experienced a MACE+.

Efficacy Assessments:
Primary efficacy endpoint:

- Change in HbA1c from baseline to week 24, compared to placebo

Secondary efficacy endpoints:

- Change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- Change in body weight from baseline to week 48 in subjects with a BMI ≥ 25 kg/m^2
- Change in SBP from baseline to week 24 in subjects with baseline systolic blood pressure ≥ 140 mmHg

Exploratory efficacy endpoints:

- Change in HbA1c from baseline over time
- Change in FPG from baseline over time
- Change in body weight from baseline over time
- Change in SBP over time

- Requirement of additional anti-diabetic medications, including insulin, over time
- Requirement of reduced anti-diabetic medications, including insulin, over time
- Incidence of hospitalization for heart failure among all subjects and among subjects who have a history of heart failure

Other endpoint:

Samples for population PK analysis will be collected and the plasma concentration of bexagliflozin determined. The PK parameters will be assessed separately as part of the population PK analysis. Biomarker samples will be collected. The biomarker analysis will be performed separately.

Safety Assessments:

The safety endpoints will include:

- A 5-point composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization
- A 6-point composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, coronary revascularization or hospitalization for heart failure
- Individual events including all-cause mortality, CV death, fatal and non-fatal MI, fatal and non-fatal stroke, hospitalization for unstable angina, hospitalization for CHF, or coronary revascularization. Both first events and total events, taking account of repeat events will be examined
- Change in eGFR from baseline
- Change in UACR from baseline
- Incidence of adverse events of interest. Adverse events of interest including urinary tract infections including urosepsis and pyelonephritis, genital mycotic infections, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders, renal failure events, and amputations

Other safety assessments:

- Adverse events
- Clinical laboratory events
- Physical examinations
- Vital signs including orthostatic blood pressure
- Use of concomitant medications

Statistical Methods:

The primary endpoint is the difference in the change in HbA1c from week 0 (randomization visit) to week 24 among subjects exposed to bexagliflozin, 20 mg, compared to subjects exposed to placebo. Statistical significance will be declared at a two-sided 0.05 level of significance. The intention-to-treat population that includes all randomized subjects regardless of treatment adherence or availability of follow-up data will be analyzed. A mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA) with baseline HbA1c as a covariate will be performed on the available data, incorporating all visits from

each patient at which HbA1c was measured.

Three key secondary endpoints are:

1. Change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes
2. Change in body weight from baseline to week 48 in subjects with a BMI ≥ 25 kg/m^2
3. Change in SBP from baseline to week 24 in subjects with baseline systolic blood pressure ≥ 140 mmHg

A hierarchical testing strategy in the following order will be undertaken, if the null hypothesis is excluded for the primary efficacy endpoint:

1. Effect of bexagliflozin on the change in HbA1c from baseline to week 24 in subjects who have been prescribed insulin to control diabetes at baseline, using MMRM ANCOVA adjusting for baseline HbA1c at a two-sided 0.05 level of significance; if a significant bexagliflozin effect is found, then:
2. Comparison of treatments on the change in body weight at week 48 in subjects with baseline BMI ≥ 25 kg/m^2, using MMRM ANCOVA adjusting for baseline body weight. at a two-sided 0.05 level of significance; if a significant bexagliflozin effect is found, then:
3. Comparison of treatments on the change in SBP at Week 24 in subjects with baseline systolic blood pressure ≥ 140 mmHg, using MMRM ANCOVA, adjusting for baseline SBP, at a two-sided 0.05 level of significance.

Additional effects of bexagliflozin on FPG, changes in HbA1c over time, changes in body weight over time, frequency of hospitalization for heart failure (in all subjects and in subjects with a history of heart failure), and general safety of bexagliflozin in subjects with T2DM will be analyzed as exploratory endpoint and will not be adjusted for multiplicity.

The sample size of 1650 patients is estimated based on the required number of events of MACE+ for the program-wide meta-analysis to assess bexagliflozin effect on cardiovascular safety, and provides adequate power to compare treatments on the primary endpoint of change in HbA1c from baseline to 24 weeks.

Statistical analyses and summaries will be performed using SAS® software (SAS Institute, Cary, NC).

Date of Revised Protocol Version 8.0: 01 December 2016

Protocol History	**Date**
Version 1.0:	06 May 2015
Version 2.0:	22 June 2015
Version 3.0:	07 July 2015
Version 4.0:	25 August 2015

Protocol History	Date
Version 5.0:	08 September 2015
Version 5.1 (Canada only)	26 October 2015
Version 6.0	02 February 2016
Version 7.0	12 October 2016
Version 8.0 (US)	28 October 2016
Version 8.0 (EU and AP)	01 December 2016

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CEC	cardiovascular endpoint committee
CI	confidence interval
CRF	case report form
CRO	contract research organization
CRT	cardiac resynchronization therapy
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
DPP4	dipeptidyl peptidase-4
DSMB	data and safety monitoring board
ECG	electrocardiogram
ED_{50}	dose conveying 50% of the maximal effect
FAS	full analysis set
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GEE	generalized estimating equation
GLP-1	glucagon-like peptide-1 agonist
GMI	genital mycotic infection
GFR	glomerular filtration rate
h	hour/s
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HF	heart failure
HF-REF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HUA	hospitalization for unstable angina
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRAE	immediately reportable adverse event
IRB	institutional review board
IWRS	interactive web response system
LDL	low density lipoprotein
LC- MS/MS	liquid chromatography–tandem mass spectrometry
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event

MDRD	modification of diet in renal disease
MI	myocardial infarction
min	minute/s
MMRM	mixed model repeated measures
MODY	maturity onset diabetes of the young
N	total sample size
NYHA	New York Heart Association
OHA	oral hypoglycemic agent
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetics
PP	per protocol
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose linked transporter 2
SMBG	self- monitored blood glucose
SOP	Standard Operating Procedures
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
UADR	unexpected adverse drug reaction
UACR	urine albumin to creatinine ratio
UGE	urinary glucose excretion
ULN	upper limit of normal
UPT	urinary pregnancy test
UTI	urinary tract infection
WHO-DD	World Health Organization-Drug Dictionary
WOCBP	woman of childbearing potential

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality worldwide, affecting an estimated 382 million people in 2013 (IDF, 2014). More than 95% of people with diabetes have type 2 diabetes, and more than 80% of those with T2DM are overweight or obese. In Western societies, individuals with diabetes have at least twice the risk of hypertension and major cardiovascular complications compared to individuals without diabetes (Bhatt et al., 2010; Preis et al., 2009; Sarwar et al., 2010) and the major cause of death among patients with T2DM is cardiovascular disease (Go et al., 2013). In addition, congestive heart failure is highly prevalent among men and women with T2DM, and T2DM increases the occurrence of heart failure independently of underlying coronary disease (Boudina and Abel, 2007; Domanski et al., 2003; Kannel and McGee, 1979).

Although glycemic control clearly reduces microvascular diabetic complications (ADA, 2013), it is less clear whether any specific approach to reducing blood glucose concentration, particularly among patients with long standing T2DM or established cardiovascular risk factors, confers additional risk with respect to cardiovascular events (Duckworth et al., 2009; Patel et al., 2008). As a result of this uncertainty, both FDA and European Medicines Agency (EMA) require demonstration of long-term cardiovascular safety prior to the approval of new drugs for treatment of T2DM (FDA Guidance 2008, ucm071627.pdf).

The renal Na+/glucose transport protein (SGLT2) actively transports extracellular glucose into cells using the driving energy of the transmembrane electrochemical potential for sodium ions. Individuals with disruptions in SLC5A2, the gene encoding SGLT2, exhibit prominent glucosuria in the absence of significant co-morbidities (Santer et al., 2003; van den Heuvel et al., 2002). The excretion of glucose in the urine of diabetic subjects in amounts comparable to or greater than that seen in individuals harboring loss of functions mutations in SLC5A2 has the potential to improve both fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia. Several SGLT2 inhibitors have demonstrated these clinical benefits as a mono- or combination therapy with other oral anti-diabetic medications including insulin (Nauck, 2014). Studies of the three SGLT2 inhibitors licensed in the US, dapagliflozin, canagliflozin, and empagliflozin, have demonstrated that long term use of an SGLT2 inhibitor does not increase the incidence of major adverse cardiovascular events (MACE). Because heart failure is exacerbated by fluid retention, the development of diuretic oral anti-diabetic agents is potentially attractive for the treatment of diabetic patients with comorbid heart failure and may be similarly attractive in patients with both diabetes and hypertension. The potential benefit in macrovascular disease outcome has been demonstrated in diabetic patients with increased CV risks who have been treated with empagliflozin. In a post-hoc analysis, a 30% reduction in CV mortality and hospitalization for heart failure were shown in the empagliflozin treated groups in all study subjects or in subjects with a history of heart failure (Zinman et al., 2015).

1.1 Bexagliflozin Tablets for T2DM

Bexagliflozin is a candidate oral antidiabetic agent that is a potent and highly specific inhibitor of SGLT2. It was identified following a synthetic program aimed at creating molecules with high selectivity and potency for SGLT2 (Zhang et al., 2011). Bexagliflozin has been shown to cause dose-dependent increases in urinary glucose excretion in humans, rats, dogs and monkeys and to reduce HbA1c in animal models of T2DM and in diabetic patients. The safety and efficacy of bexagliflozin capsules, 20 mg, were evaluated in a 96-week study that established efficacy in reducing hemoglobin A1c (HbA1c). Adverse event incidences, particularly for urinary tract infection (UTI) and genital mycotic infection, were similar between placebo and active agent cohorts. Details of the pharmacology, efficacy, and safety assessments are described in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Efficacy Objectives

The primary efficacy objective of this trial is to evaluate the placebo-adjusted change in HbA1c from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects with increased risk of cardiovascular adverse events.

2.2 Secondary Efficacy Objectives

The key secondary efficacy objectives are:

- To evaluate the effect of bexagliflozin compared to placebo on the change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- To evaluate the effect of bexagliflozin on the change in body weight from baseline to week 48 in randomized subjects with a BMI ≥ 25 kg/m^2 compared to placebo
- To evaluate the effect of bexagliflozin on the change in systolic blood pressure (SBP) from baseline to week 24 in subjects with baseline systolic blood pressure ≥ 140 mmHg compared to placebo

Additional exploratory efficacy objectives are:

- To assess the effect of bexagliflozin treatment on the change in HbA1c versus placebo over time
- To evaluate the effect of bexagliflozin treatment on the change in fasting plasma glucose (FPG) versus placebo over time
- To measure the proportion of subjects requiring an intensification of anti-diabetic regimen versus placebo over time
- To measure the proportion of subjects requiring a relaxation of their anti-diabetic regimen versus placebo over time
- To measure the incidence of hospitalization for heart failure among all subjects and among subjects with a history of heart failure at baseline

2.3 Safety Objectives

The primary safety objective of this study is the contribution of at least 134 major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo. MACE+ is defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina.

An additional objective is the evaluation of the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population that is at elevated risk for major adverse cardiovascular events.

2.4 Other Objectives

- Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted at 30 sites and will include approximately 240 subjects.
- Measurement of cardiovascular biomarkers from baseline and on week 12 will be performed in an exploratory study to increase the understanding of bexagliflozin treatment effect on the biomarkers that are relevant in the CV disease diagnosis and prognosis.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

THR-1442-C-476 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. Approximately 1650 subjects with sub-optimally controlled T2DM and elevated risk for cardiovascular adverse events will be randomized to bexagliflozin tablets, 20 mg, or placebo in a 2:1 ratio as an add-on therapy to background anti-diabetic medications.

3.2 Research Methods and Procedures

3.2.1 Screening Period

All participants must provide written informed consent and be willing and able to adhere to the protocol requirements. Potential participants with sub-optimal glycemic control and additional cardiovascular risk factors will enter a screening period of up to 21 days. Subjects will be eligible if they exhibit any of the following 3 characteristics: (i) a history of atherosclerotic vascular disease, (ii) a history of heart failure, or (iii) an age of ≥ 55 years plus at least two additional risk factors chosen from long diabetes duration, hypertension, smoking, renal impairment, or dyslipidemia. To ensure that subjects with diverse cardiovascular risks are adequately represented, a minimum of 352 subjects (21%) from each of the three groups will be recruited in the study and ≤ 400 subjects who have a history of heart failure will be randomized in the study. The intended population is presented below.

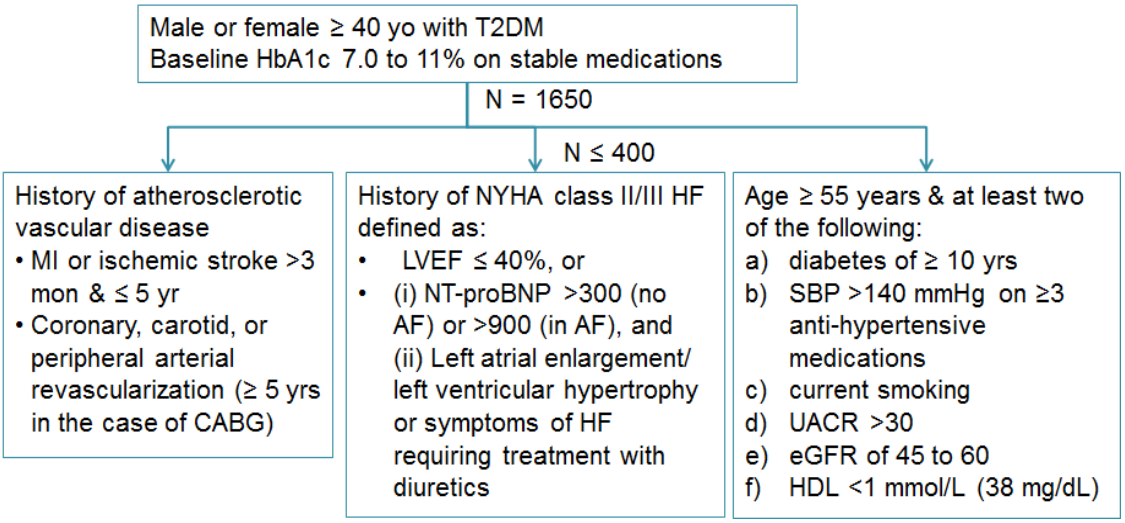


Figure 1 Eligibility Criteria for the Study Population

If a subject has a history of heart failure, the subject will be allocated to the heart failure group, regardless of any history of atherosclerotic vascular disease or additional cardiovascular risk factors. If a subject does not have a heart failure history and has a history

of atherosclerotic vascular disease, the subject will be allocated to group 1 regardless of other cardiovascular risks.

Qualified participants will start a single-blind, placebo 2-week run-in period intended to familiarize subjects with trial procedures and to identify and reject subjects at high risk for non-compliance. During the run-in period, subjects will receive diet and exercise counseling and instructions on contacting the clinic in the event of hypoglycemia or symptoms that may suggest ketoacidosis. Participants will be provided with a glucometer and instructions for its daily use. Eligible subjects will be instructed to take the run-in (placebo) dosages once daily for 13 ± 2 days. Adjustment of treatment for hypertension or dyslipidemia will not be permitted during the screening and the run- in periods. If a change in treatment is required to appropriately manage hypertension or dyslipidemia, the subject may re-enter the screening after the clinical condition and treatment regimen have not changed for at least 4 weeks.

Subjects will not be eligible for randomization if during the run-in period they: 1) have fasting blood glucose values ≥ 300 mg/dL on two or more consecutive days, 2) omit more than one dose of the run-in drug due to non-compliance, or 3) are deemed inappropriate for the study by the investigator.

3.2.2 Treatment Period

The treatment period for each study subject will start at randomization. Randomization will be stratified by baseline HbA1c (> or ≤ 9.5%), baseline estimated glomerular filtration rate (eGFR) (< or ≥ 60 mL/min/1.73m^2), baseline BMI (< or ≥ 25 kg/m^2) and history of heart failure. The study subjects will be in contact with the study site at 2, 6, 12, 18, 24, 36 and 48 weeks post-randomization. The interactions at week 2 and week 18 will be conducted by phone unless a clinic visit is necessary. After week 48, clinic visits will be scheduled every 24 weeks and a phone interview will be conducted at 12 weeks after each clinic visit. The treatment period will vary from subject to subject and will end for all subjects after the last randomized subject has completed at least 52 weeks of treatment and a total of 134 subjects have experienced a MACE+. It is anticipated that subjects will receive treatment for 2 to 3 years. A follow-up visit will take place 4 weeks after the conclusion of treatment.

At the start of the treatment period each subject will be provided investigational product, dosing instructions, and a glycemic control diary in which to record glucose measurements obtained through self-monitored blood glucose (SMBG) testing. Information related to the occurrence of hyperglycemic or hypoglycemic events as well as symptoms that may suggest ketoacidosis will be recorded. The subjects will be instructed to take the investigational product with water in the morning prior to eating. Additional medications for hyperglycemia and for control of other medical conditions will be allowed if deemed medically necessary by the investigator, and will be recorded (Section 5.2.5 and Section 5.6).

During the first 24 weeks of the treatment period, hyperglycemia should be managed with diet and exercise counseling and only with changes in the medical therapy if the investigator feels it is necessary for the well-being of the subject. Intensification of the antidiabetic regimen should adhere to the following guidelines upon the report by a study subject of two fasting blood glucose self-measurements exceeding the following values on consecutive

days: (i) ≥ 270 mg/dL (15 mmol/L) from week 1 to week 6; ≥ 240 mg/dL (13.3 mmol/L) between week 6 and week 12; and ≥ 200 mg/dL (11.1 mmol/L) between week 12 and week 24. After 24 weeks, changes to the medical therapy for hyperglycemia should occur at the discretion of the investigator based on SMBG, FPG, and HbA1c information using local standards of care for subjects with T2DM. During the course of the study investigators will manage blood pressure and lipid values according to accepted standards of care for the management of hypertension and dyslipidemia.

Rescue medications may include any approved anti-diabetic medication except an SGLT2 inhibitor. Adjustment by the investigator to the anti-diabetic therapies is recommended if hypoglycemia occurs.

The safety information will be drawn from review of adverse events (AEs), concomitant medications, vital signs, electrocardiograms (ECGs), and results from physical examinations and blood and urine specimen collections. On the day of the clinic visit a minimum fasting period of 10 hours (h) must be confirmed prior to blood draw. At every visit, including the phone interviews, participants will be queried regarding AEs and information on all events that potentially represent major adverse cardiovascular events will be forwarded to a cardiovascular endpoint committee (CEC) for blinded adjudication of the event. Following the exit visit, subjects will be advised to see their primary physician to undergo treatment to control their diabetes and cardiovascular conditions. The scheduled visits and procedures for each visit are provided in Appendix 1. The duration of participation for each subject is estimated to be 2 to 3 years but may vary based on the projected recruitment rate and the estimated event rate. An assessment of bexagliflozin pharmacokinetics (PK) will also be conducted at 30 centers to include approximately 240 subjects. Samples will be taken during weeks 6 and 12.

3.2.3 Interim Analyses

No interim analysis will be performed and the study will not be stopped for futility or overwhelming benefit of bexagliflozin treatment. During the trial, a Data and Safety Monitoring Board (DSMB) will review the unblinded aggregate data periodically and may recommend an early termination of the trial for safety reasons.

An estimated total of 134 MACE+ are required for the CV meta-analysis. During the study, subjects will continue to receive various OHAs and/or insulin. All AEs that potentially represent a major cardiovascular event will be submitted to the CEC for an independent and blinded adjudication.

3.3 Rationale for Study Design and Control Group

3.3.1 Rationale for the Study Design

Patients with T2DM have increased risk of developing micro- and macrovascular complications. Improved control of hyperglycemia or blood pressure reduces the risk of diabetic complications (UKPDS(1998)). Administration of bexagliflozin, a potent SGLT2 inhibitor, has been shown to be well tolerated and to decrease HbA1c in subjects with T2DM

drawn from a general population. Study THR-1442-C-476 is designed to demonstrate that bexagliflozin also improves glycemic control in patients at higher risk of CV AEs. The glucosuria and diuresis induced by bexagliflozin may additionally benefit the study subjects through caloric wasting and reduction of blood pressure. Thus, the potential for weight loss in overweight subjects and for blood pressure improvement in hypertensive subjects will be tested. This study is designed to contribute a minimum of 134 MACE+ events to an eventual meta-analysis intended to evaluate whether treatment with bexagliflozin is associated with an unacceptable increase in cardiovascular risk in a T2DM population (FDA Guidance ucm071627, 2008 and EMA CPMP/EWP/1080/00 Rev. 1, 2012). The study is also designed to permit an assessment of the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population at elevated risk of major adverse cardiovascular events.

A placebo-controlled, double-blind, parallel-arm design was chosen for this study. The inclusion of a placebo group will allow medication effects to be differentiated from influences of confounding factors. The subjects will continue to receive background glucose lowering therapies as well as other medications to manage co-morbidities throughout the study. Study subjects may receive additional approved antidiabetic medications if their hyperglycemia is not well controlled.

3.3.2 Rationale for the Dose Selection

Bexagliflozin produces a dose-dependent, saturable increase in UGE in healthy volunteers and diabetic subjects. Near-maximal UGE is produced by 20 mg of bexagliflozin, whether delivered as an immediate release or an extended release formulation. A single dose of 20 mg produces a significant reduction in fasting plasma glucose (FPG) and a modest diuretic effect. Population pharmacodynamic modeling has indicated that bexagliflozin doses of 20 mg would result in 90% of the maximal UGE, respectively. In a long term treatment study, daily administration of 20 mg bexagliflozin in an immediate release formulation was found to reduce HbA1c by 0.79% compared to placebo at week 24. The treatment benefit was observed to improve to 1.02% at week 96. FPG reduction, weight loss, and decreased systolic and diastolic blood pressure were also observed following 96 weeks of treatment. In addition, AEs, particularly those involving UTI and genital mycotic infections (GMI), were found to be similar between placebo and active agent cohorts. To evaluate the safety and efficacy of bexagliflozin for the treatment of patients with T2DM and increased CV risk, bexagliflozin tablets, 20 mg, will be administered in this trial.

The PK and pharmacodynamic (PD) effects of bexagliflozin administration have been determined in patients with T2DM and renal impairment. Absorption of bexagliflozin was not affected by diminished renal function. Reduced clearance due to renal impairment was associated with a 34 % higher systemic exposure in subjects with GFR between 30 and 60 mL/min/1.73/m^2. Mean glucosuria decreased to 40 g/d in patients with moderate renal impairment compared to 99.6 g/d in patients with normal renal function. The decreased glucosuria is consistent with a reduced renal filtration rate. However, an improvement in glycemic control can be predicted by the UGE of nearly 40 g of glucose per day. Given the modest increase in drug exposure, dose adjustment in patients with mild to moderate renal impairment is not expected to be necessary. A thorough QT study has demonstrated that

100 mg of bexagliflozin administered in an immediate release formulation did not prolong the QT interval or produce adverse changes in any other parameters measured by ECG.

3.3.3 Rationale for the Selection of Patient Population

Study THR-1442-C-476 will include patients with increased CV risk factors including older age, hypertension, smoking, renal impairment, dyslipidemia, and history of cardiovascular disease. Among patients with T2DM, approximately 12% have been reported to exhibit heart failure (HF) (Nichols et al., 2001); the prevalence of HF increases to 39% among elderly diabetic patients (Aronow and Ahn, 1999). A study population that includes subjects with additional CV risks will allow an efficacy assessment of bexagliflozin in this vulnerable population and will permit any potential benefits of weight reduction or blood pressure lowering to be recorded. While reduction of HbA1c has not been shown to alter the course of HF, weight reduction has been found to lower the risk for hospitalization.

To ensure that subjects with various cardiovascular risks will be adequately represented, a minimum of 352 subjects (21%) from each of the three groups will be recruited in the study. In a 2 year cardiovascular outcomes study in patients with T2DM the event rate for CV death was 0.0365 or 0.0115 per subject per year for subjects with or without a heart failure history, respectively (Scirica et al., 2013; Scirica et al., 2014b). Because the CV mortality rate is higher among subjects with a HF history, the number of subjects with HF will be limited to 400 in this trial. The projected number of CV deaths from subjects with HF history is anticipated to be < 50% of the total CV deaths. Because a subject may be qualified in one or all of the groups based on the risk factors at baseline, subjects will be allocated to whichever group represents the highest projected event rate. For example, if a subject has a history of class II or III heart failure, the subject will be allocated to group 2, regardless of any history of atherosclerotic vascular disease or additional cardiovascular risk factors. If a subject does not have a heart failure history and does have a history of atherosclerotic vascular disease, the subject will be allocated to group 1 regardless of other cardiovascular risks.

Identification of heart failure in the setting of preserved ejection fraction will rely on symptomatic evidence of heart failure together with specific criteria for N-terminal pro-BNP levels. An NT-proBNP > 300 pg/mL with no evidence of atrial fibrillation/flutter (AF) at the time of the screening ECG or an NT-proBNP > 900 pg/mL with evidence of AF at the time of the screening ECG will be considered sufficient to exclude prospective subjects without heart failure. These limits are conservative. NT-proBNP levels increase with age and age-dependent cutpoints provide superior decision value; in one study cutpoints ranging from 50 ng/mL for males < 50 years to 250 ng/mL for males > 75 years were shown to provide higher sensitivity than an age-independent measure (Hildebrandt et al., 2010). For individuals in chronic heart failure the age-independent cutpoint to exclude non-failure etiologies is considered to be 125 pg/mL, whereas in an acute presentation the appropriate age-independent cutpoint is considered to be 300 pg/mL (Januzzi et al., 2006; McMurray et al., 2012; Ponikowski et al., 2016). Atrial fibrillation is associated with elevated NT-proBNP and hence higher cutpoints are required. Although there has yet to be a practice guideline recommendation, in the Biomarkers in ACute Heart Failure (BACH) study, comorbid atrial fibrillation decreased test specificity and in general eroded the diagnostic power of NT-

proBNP measurement (Richards et al., 2013). From this study an age-independent cutpoint of 1075 pg/mL for subjects with atrial fibrillation had the highest accuracy of three cutpoints or cutpoint algorithms (Richards et al., 2013). The sponsor's subject matter experts have advised that to discriminate HF in the presence of preserved ejection fraction and AF, it is common in clinical trials to use an NT-proBNP cutpoint of 2 – 4 times that of the cutpoint in the absence of AF (J.J. McMurray, personal communication: S. Solomon, personal communication). The specific cutpoint chosen here reflects the midpoint, 3 times the cutpoint for subjects in sinus rhythm.

3.3.4 Treatment Duration

The mean treatment duration is expected to fall between two and three years, depending on the accrual of MACE+. A minimum treatment duration of 52 weeks is planned to ensure sufficient bexagliflozin exposure to allow meaningful safety evaluation.

3.3.5 Rationale for the Overall Analysis

The primary safety objective of this study is to contribute MACE+ to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater. The study population planned in this protocol is enriched for CV risk and the anticipated event rate is based on a recently published CV outcomes study (Scirica et al., 2013; Scirica et al., 2014b). There will be no interim analysis.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 1650 subjects diagnosed with sub-optimally controlled T2DM who have a history of cardiovascular disease or who present with CV risk factors. Eligible subjects who consent to participate in the study will be enrolled in clinical investigational sites in multiple countries.

At selected sites, plasma samples will be collected for population PK analysis. Study subjects will be informed of the purpose of the PK study and requested to consent to the additional procedures and blood collection.

4.2 Inclusion Criteria

The study population will include:

1. Male or female adult subjects with an age ≥40 years
2. Subjects with a diagnosis of T2DM
3. Subjects with HbA1c values of 7.0 – 11%, inclusive
4. Subjects with fasting plasma glucose (FPG) ≤300 mg/dL at screening
5. Subjects who have a regimen for treatment of T2DM that has been stable for the past 3 months. A stable regimen is defined as: no changes in dose or frequency of OHAs or GLP-1 agonists, or < 20% variability in total daily insulin dose.
6. Subjects who present with at least one of the following 3 histories:

Group 1: A history of atherosclerotic vascular disease as defined by one or more of the following: a) myocardial infarction (MI) or ischemic (non-hemorrhagic) stroke > 3 months but ≤ 5 years prior to screening or b) documented history of coronary, carotid, or peripheral arterial revascularization (coronary artery bypass grafting must have occurred ≥ 5 years prior to screening)

Group 2: A history of NYHA class II or class III heart failure (Appendix 4) at the time of screening. History of heart failure is defined as:

- a documented left ventricular ejection fraction (LVEF) ≤ 40% and no subsequent LVEF > 40% documented within 6 months of screening, or
- (i) an NT-proBNP >300 pg/mL and no evidence of atrial fibrillation/flutter (AF) at the time of the screening ECG or an NT-proBNP >900 pg/mL and evidence of AF at the time of the screening ECG and (ii) either (a) structural heart disease documented by report of left atrial enlargement or left ventricular hypertrophy, or (b) exhibiting symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening.

Group 3: Age ≥ 55 years with 2 or more of the following:

a. diabetes duration of ≥ 10 years,
b. uncontrolled hypertension defined as SBP > 140 mmHg despite 3 or more anti-hypertensive medications,
c. current smoking,
d. urine albumin:creatinine ratio (UACR) > 30 mg/g,
e. eGFR of 45 to 60 mL/min/1.73 m^2, or
f. HDL < 1 mmol/L (38 mg/dL)

7. Female subjects of childbearing potential who are willing to use an adequate method of contraception and to not become pregnant for the duration of the study. Adequate contraceptive measures include, but are not limited to, oral contraceptives, intrauterine devices, Depo-Provera, Norplant, hormonal contraceptive implants, bilateral tubal ligation, partner with vasectomy, condom or diaphragm plus contraceptive sponge, foam, or jelly, and abstinence
8. Subjects who are willing and able to return for all clinic visits and to complete all study-required procedures, including self-monitored blood glucose (SMBG) measurement, and take run-in medication, missing no more than one dose due to non-compliance
9. Subjects who receive anti-hypertensive medications at a stable dosage for ≥ 2 weeks prior to randomization
10. Subjects who receive lipid modifying therapy on a stable regimen for 6 weeks prior to randomization
11. Subjects who have seated SBP < 170 mmHg and DBP < 110 mmHg at screening.

4.3 Exclusion Criteria

Patients who exhibit any of the following characteristics will be excluded from the study.

1. Diagnosis of type 1 diabetes mellitus or maturity–onset/diabetes of the young (MODY)
2. Hemoglobinopathy that affects HbA1c measurement
3. Frequent symptomatic hypoglycemia (greater than one episode per week on average)
4. Genitourinary tract infection within 6 weeks of screening or history of ≥ 3 genitourinary infections requiring treatment within the last 6 months
5. Cancer, active or in remission for < 3 years (Non-melanoma skin cancer or basal cell carcinoma or carcinoma *in situ* of the cervix will not be grounds for exclusion)
6. History of alcohol or illicit drug abuse in the past 2 years
7. Evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase > 1.5 x upper limit of normal (ULN) with the exception of isolated Gilbert's syndrome); or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x ULN
8. History of MI, stroke or hospitalization for heart failure in the prior 3 months
9. Evidence of NYHA class IV heart failure at screening or randomization
10. Presently scheduled for percutaneous coronary intervention, coronary artery bypass grafting or any surgical procedure
11. Previous treatment with bexagliflozin or EGT0001474

12. Currently or within 3 months of taking any SGLT2 inhibitors (Appendix 3)
13. Any condition, disease, disorder, or clinically relevant laboratory abnormality that, in the opinion of the PI, would jeopardize the subject's appropriate participation in this study or obscure the effects of treatment
14. Prior renal transplantation or evidence of nephrotic syndrome, defined as a urine albumin: creatinine ratio (UACR) > 2000 mg/g, at screening
15. Implantation of a cardiac resynchronization therapy device within 3 months prior to screening or intent to implant a cardiac resynchronization therapy (CRT) within 6 months following screening
16. Diagnosis of peripartum or chemotherapy-induced cardiomyopathy within 12 months prior to screening
17. Symptomatic bradycardia or second or third degree atrioventricular block without a pacemaker
18. eGFR, as calculated by the modification of diet in renal disease study equation (MDRD), < 45 mL/min/1.73 m^2 or requiring dialysis
19. Pregnant or nursing
20. Currently participating in another interventional trial.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Investigational Product

Bexagliflozin tablets, 20 mg or placebo, are blue caplet-shaped, film-coated tablets that are intended for use in investigational studies in humans. The tablets contain excipients designed to promote extended release through a gastroretentive mechanism. The active tablets exhibit a greater than 75% release of drug substance by 8 h in simulated gastric fluid *in vitro*. The following investigational products will be used for oral administration:

- Bexagliflozin tablets, 20 mg: tablets containing 20 mg of bexagliflozin
- Bexagliflozin tablets, placebo: tablets containing no bexagliflozin

5.2 Treatments Administered

5.2.1 Investigational Product

Bexagliflozin tablets, 20 mg or placebo, should be taken in the morning prior to eating or drinking. The tablets should be taken with 250 mL of water.

5.2.2 Background Oral Hypoglycemic Agents (OHAs)

Subjects will continue OHAs that were prescribed prior to screening. The dose, frequency, and time of administration of these medications should remain stable throughout the study unless the investigator deems adjustment necessary for the medical well-being of the subject. Changes to the dose or frequency of oral anti-diabetic medications will be recorded in the concomitant medications log.

5.2.3 Background Insulin Therapy

Subjects who are prescribed insulin prior to screening will continue the dose, frequency, and time of insulin administration throughout the study. The dose, frequency, and time of insulin injections should remain stable unless the investigator deems adjustment (decrease or increase) necessary for the medical well-being of the subject. Changes to the dose, frequency, or time of administration of insulin will be recorded in the concomitant medications log.

5.2.4 Anti-hypertensive Medications Including Diuretics

Subjects who are prescribed anti-hypertensive medications will continue the current dose, frequency, and time of administration of these medications throughout the study. Adjustment of treatment for hypertension or dyslipidemia will not be permitted during the screening and run-in periods although initiation of anti-coagulant therapy (if clinically indicated) will be permitted. If a change in treatment is required to improve management of hypertension or dyslipidemia, the subject may re-enter screening after the clinical condition and treatment regimen have not changed for at least 4 weeks. Anti-hypertensive and diuretic medications

can be reduced to mitigate symptomatic hypotension at the discretion of the investigator at any time. Changes to the dose or frequency of anti-hypertensive and diuretic medications will be recorded in the concomitant medications log.

5.2.5 Rescue Medications for Hyperglycemia

During the treatment period subjects will be advised to conduct daily fasting SMBG measurements. Blood glucose values collected via SMBG will be evaluated at study visits by the investigator. In addition, hyperglycemia will be monitored by FPG measurement at each study visit. HbA1c values will also be available to the investigator for decision-making regarding the need for rescue medication.

If hyperglycemia is identified through SMBG or FPG measurements, the investigator will determine whether the subject has fasted for a minimum of 10 h prior to the morning blood draw to ensure that the FPG value is truly a fasting sample. If proper fasting has not occurred, the subject will be asked to return for a repeat blood test within a week.

During the first 24 weeks of the treatment period, hyperglycemia should be managed with diet and exercise counseling and only with changes in the medical therapy if the investigator feels it is necessary for the well-being of the subject. Intensification of the antidiabetic regimen should adhere to the following guidelines upon the report by a study subject of two fasting blood glucose self-measurements exceeding the following values on consecutive days: (i) ≥ 270 mg/dL (15 mmol/L) from week 1 to week 6; ≥ 240 mg/dL (13.3 mmol/L) between week 6 and week 12; and ≥ 200 mg/dL (11.1 mmol/L) between week 12 and week 24. After 24 weeks changes to the medical therapy for hyperglycemia should occur at the discretion of the investigator based on SMBG, FPG, and HbA1c information using local standards of care for subjects with T2DM. If a rescue medication for hyperglycemia is to be prescribed, a blood sample must be drawn prior to the administration of the rescue medication so that a final HbA1c value can be determined for the HbA1c efficacy analyses.

The investigator may provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated, with the exception of an SGLT2 inhibitor. Dose or frequency increases in OHA or insulin regimens prescribed prior to screening will be considered rescue medication. During the treatment period, increments or decrements in the doses of OHA or insulin must be documented in the concomitant medications CRF.

Subjects who receive rescue medication due to poor glycemic control will continue to receive investigational product and standard care according to current treatment guidelines. Following the exit visit subjects will be advised to see their primary care physician to undergo treatment to control their diabetes.

5.3 Selection and Timing of Dose for Each Patient

Dosing with bexagliflozin tablets, 20 mg or placebo, will be based on randomized assignment. All study subjects will be instructed to self-administer tablets once daily in the morning prior to eating or drinking; the medication should be taken with water. There will be no change of dose during the treatment period.

On the day of each scheduled clinic visit, subjects must fast for a minimum of 10 h prior to the collection of blood samples. During the fasting period, only water will be permitted. The investigational product should be administered at the clinic under supervision on the day of visit V2 when the run-in drug is dispensed and on the day of visit V3 when the double-blind study drug is dispensed. Only one tablet per day should be administered.

5.4 Method of Assigning Patients to Treatment Groups

The study will be conducted at investigative sites in multiple countries and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but each site will be capped at 48 subjects per site. Activation of investigational sites in each country will be centrally controlled by a centrally managed Interactive Web Response system (IWRS).

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized in a 2:1 ratio to receive investigational product. Subjects will be assigned to treatment groups in sequential order as they qualify for the study, using IWRS. Randomization will be stratified according to baseline HbA1c ($\leq$ 9.5% or > 9.5% at screening visit), baseline eGFR (eGFR < 60 or $\geq$ 60 mL/min/1.73 m^2 at screening), BMI (< 25 kg/m^2 or $\geq$ 25 kg/m^2, and history of heart failure.

Among the 3 groups of subjects based on the baseline CV risks, a minimum of 352 subjects (21%) from each of the three groups will be recruited and $\leq$ 400 subjects who have a history of heart failure can be randomized in the study. If a subject has a history of class II or III heart failure, the subject will be allocated to group 2, regardless of any history of atherosclerotic vascular disease or additional cardiovascular risk factors. If a subject does not have a heart failure history and has a history of atherosclerotic vascular disease, the subject will be allocated to group 1 regardless of other cardiovascular risks.

5.5 Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the CEC and DKA adjudication committee members will be blinded to the composition of the investigational product. Upon randomization, each subject will receive a subject randomization number and a drug kit assigned to the subject. To maintain blinding of the individual treatment assignments, central laboratory glucose urinalysis data will not be made available to any study personnel or subjects.

If knowledge of the investigational product ingredients is needed to manage the subject's condition, the investigator will contact the IWRS to obtain the treatment assignment. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded on the case report form (CRF) and the sponsor must be notified within 24 h.

A designated statistician who is not involved in the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse

reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies.

The treatment assignment will continue to be withheld from the CEC members until all investigational studies contributing to the MACE+ meta-analysis are completed and the meta-analysis has been conducted.

5.6 Concomitant Therapy

During the course of the study investigators will manage glucose, blood pressure and lipid levels according to local or regional standard of care guidance documents for the management of T2DM and cardiovascular risk factors/disease as issued by the relevant professional bodies (e.g. ADA, AHA, ESC, etc.). Subjects should be provided access to all additional therapies and interventions during the course of the study (including appropriate anti-platelet and anti-thrombotic therapies, PCI, etc.) if these are clinically indicated and approved by local competent authorities.

Subjects will be allowed to take medications or medicinal supplements prescribed to manage non-diabetic medical conditions during the study. Any concurrent medication or supplemental treatment of other, non-diabetes medical conditions should be continued at a stable dose and frequency for the entire study duration unless there is clinical reason to change the dose or frequency.

Blood pressure medications should not be altered during the screening period and the first 12 weeks of the main treatment period unless it is medically necessary to do so. If a change in treatment is required to appropriately manage hypertension or dyslipidemia during the run-in period, the subject may re-enter the screening after the clinical condition and treatment regimen have not changed for at least 4 weeks. If it is medically necessary to alter blood pressure medications during the first 12 weeks of the treatment period, new diuretic medications should not be initiated and the dose and frequency of existing diuretic medications should not be increased.

Subjects who do not meet protocol-specified glycemic targets at specified time points during the study will review diet and exercise counseling and/or receive rescue medication at the discretion of the investigator during the study. Anti-diabetic therapies prescribed to subjects for the purpose of treating hyperglycemia for more than 2 weeks will be considered rescue medications (see Prescribing Rescue Medication, above). Concomitant use of other SGLT2 inhibitors will not be permitted. A blood sample will be collected to measure the last HbA1c value prior to administration of any rescue medications. The rescue medications must be recorded as concomitant medications in the CRF.

Subjects may receive any medications for AEs that are necessary in the investigators' judgments. Concomitant medications prescribed at the time of the run-in period and during the study are to be recorded on the CRF. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. This documentation should continue through the treatment and follow up periods.

Any medication prescribed to a subject after enrollment and prior to randomization, including contraceptives, must be recorded in the CRF.

5.7 Restrictions

5.7.1 Prior Therapy

All subjects will continue regimens for medical conditions other than diabetes during the study as indicated above. No subject shall have been treated with an SGLT2 inhibitor within 3 months of screening.

5.7.2 Fluid and Food Intake

During the study, subjects will be counseled to remain adequately hydrated at all times. In addition, subjects will receive counseling regarding an appropriate diet to achieve glycemic control based on standards of medical care in diabetes. Subjects will fast for a minimum of 10 h prior to the scheduled blood sample draws. During fasting, only water will be permitted.

5.7.3 Patient Activity Restrictions

Throughout the study period, subjects will be counseled and encouraged to engage in a level of physical activity that is appropriate for their physical condition. For those without specific restrictions or limitations, at least 150 min/week of moderate activity is advised by the American Diabetes Association (American Diabetes, 2014). Alternatively, local guidelines may be used.

5.8 Treatment Compliance

Subjects will be provided with dosing instructions each time that study medication is dispensed. Subjects will also be instructed to bring their medication with them at every visit. Subjects will be excluded from randomization if more than one dose of the run-in medication has been missed.

At each visit the study staff will review the SMBG diary and medication use with the subject and record the drug consumption in the CRF. Reasons for non-adherence will also be recorded in the protocol deviation log if applicable.

5.9 Packaging and Labeling

Investigational product will be provided to the pharmacist or designated site personnel in bottles of 90 tablets enclosed with a child-resistant cap. Bottles of 15 placebo tablets will be provided for the 2-week run-in portion of the study. All investigational product supplies will be prepared and labeled according to the requirements of local laws and regulations and will be kept in a secure storage facility at controlled room temperature, 15 to 30°C (59 to 86°F). The pharmacist or designated site personnel will dispense the investigational products for each subject according to randomization assignment made in the Interactive Web Response System (IWRS). During the treatment period, subjects will be provided with a new bottle

every 12 weeks in the first 48 weeks and two bottles every 24 weeks after week 48. There will be no intra-subject dose escalation or back-titration.

Subjects who require rescue medication due to hyperglycemia will receive standard care for T2DM in addition to the investigational product.

There are two types of investigational product kits.

5.9.1 Run-in Kit

Each kit contains one bottle of 15 tablets of bexagliflozin tablets, placebo.

The labels attached to each run-in kit will contain the protocol number, product identification, lot number, subject number, storage condition, the sponsor's name and address, expiration date, and the investigational drug caution statement.

5.9.2 Investigational Product Kit

Each kit contains 1 bottle of 90 tablets of bexagliflozin tablets, 20 mg or placebo.

The labels attached to each study kit will contain some or all of the following information: the kit number, protocol number, product identification, blinded batch number, subject number, storage conditions, sponsor's name, manufacturer's name and address, investigator's name, expiration date, and the investigational drug caution statement.

5.10 Storage and Accountability

Bexagliflozin tablets will be stored at controlled room temperatures of 15 °C to 30 °C (59 °F to 86 °F). The rescue medications will be stored in conditions specified in the manufacturers' prescription information. The sponsor will notify the sites of the process for returning unused drug.

5.11 Investigational Product Retention at Study Site

The investigational products will be stored in a secure area with limited access. The drug storage facility must comply with the medication storage instructions. Bexagliflozin or placebo should be stored at controlled room temperature until ready for dispensing to study subjects. The trial staff must record the amount of investigational product dispensed to each subject in the dosing record. To ensure adequate recordkeeping, subjects must bring all investigational products to each visit. The remaining tablets will be accounted for in the CRF and drug consumption forms. The procedures for obtaining drug resupply will be provided by the sponsor. All unused drug must be returned to a sponsor-designated depot after drug accounting is verified by the sponsor or its designee.

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects will be informed of the nature and purpose of the study and their written informed consent will be obtained during the pre-study screening procedures. A copy of the informed consent forms, including subject information, will be provided to each subject.

6.2 Medical History

The following information will be collected at the screening visit:

6.2.1 General Demographics and Characteristics

1. Date of birth, age, sex, and race, and whether of childbearing potential if female
2. Significant medical and surgical history, including dates of diagnoses and procedures and whether the condition is ongoing, if applicable.

6.2.2 Diabetes History

1. History of all medications used to treat diabetes (to be recorded in the concomitant medication form), including start date, duration of use, and stop date, if applicable.
2. History of complications due to diabetes, including nephropathy, retinopathy, neuropathy, non-traumatic amputations, and diabetic ketoacidosis, including date of diagnosis
3. Frequency of hypoglycemic events (per week) that are symptomatic or require assistance.

6.2.3 Cardiovascular Disease History

History of cardiovascular disease including presence of angina, congestive heart failure (classification), known atherosclerotic cardiovascular disease, prior myocardial infarction, transient ischemic attack (TIA) or stroke, and prior cardiac or peripheral re-vascularization procedures. History should include date of diagnosis and current status of diagnosis (resolved or ongoing).

6.2.4 Medication History

1. Use of prescribed or non-prescribed medications, including name of medication, indications for usage, start and stop dates, dose, and frequency
2. Use of supplements, including over the counter drugs, vitamins, herbal preparations, and dietary supplements within the past 30 days prior to screening. Each medication history will include the agent used, indication for usage, start and stop dates, dose, and frequency.

6.3 Physical Examination

A complete physical examination will be performed by the investigator at visit V3 prior to randomization and at the last study visit. The examination will include measurement of body weight, general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, and extremities.

An abbreviated physical examination will include body weight and general assessment of the skin, heart, lungs and abdomen. Abbreviated physical examinations will be performed by the investigator at all other time points as defined in the schedule of events, unless clinically indicated.

The body weight must be determined using a scale that is calibrated. The same scale should be used throughout the study duration. Height will be measured only at screening.

6.4 Vital Signs

Vital signs will be measured as indicated in the Schedule of Events (Appendix 1) and will include supine, sitting and standing blood pressure (BP) measurements, and heart rate.

Devices designed to measure BP from the finger or wrist may not be used. The left arm and same cuff sizes should be used for each measurement at all visits. If the left arm cannot be used for BP measurements, the reason should be documented, and the right arm should be used for BP measurements at all study visits.

At each visit, BP measurements will be obtained using a calibrated sphygmomanometer while the subject is in sitting, supine, and standing positions. A single heart rate measurement should be taken just prior to the BP evaluation in the sitting, supine, and standing positions.

All readings are to be entered into the source document and CRF for all subjects. The date and time of BP measurements should be captured in the source document and CRF. BP will be assessed first in the sitting position. Sitting BP and heart rate will be measured after the subject has been sitting for at least 5 minutes with feet on the floor and arm supported at heart level.

After sitting BP measurement has been completed, supine and standing BP will be measured to evaluate orthostatic vital signs. Supine and standing blood pressure measures will not be used to determine eligibility for the study. First, the subject will lie flat for 5 minutes and have heart rate and supine blood pressure measured using the same equipment and arm as described for sitting BP. Once the supine BP measurement is complete, the subject will stand. Standing BP and heart rate will be measured after 2 minutes of standing. For standing BP measurements, the arm should be supported and extended such that the cuff is at heart level.

6.5 Electrocardiography

A 12-lead electrocardiogram (ECG) will be recorded as listed in Schedule of Events in Appendix 1 and whenever clinically indicated. This procedure should be performed in the supine position after at least 10 minutes of rest. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities or arrhythmia.

It is the investigator's responsibility to review the results of the ECG as they become available. For each abnormal ECG result, the investigator shall ascertain if the observation represents a clinically significant change from the screening ECG for that individual subject (this determination, however, does not necessarily need to be made the first time an abnormal result is observed. The investigator may repeat the ECG to verify the results of the original result). If the ECG result is determined to be a clinically significant and abnormal change from baseline for that subject, it is considered to reflect an AE.

6.6 Diet and Exercise Counseling

Subjects will receive counseling regarding an appropriate diet and exercise to aid in glycemic control based on standards of medical care in diabetes throughout the study. In addition, all subjects are encouraged to consume enough liquid to maintain adequate hydration.

6.7 Clinical Laboratory Tests

6.7.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. A schedule of each laboratory test is outlined in Appendix 1. Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Test Name		Blood or urine Vol. (mL)	Shipment
Hematology[1]		2 (blood)	Ambient
Hematocrit (Hct)	Mean corpuscular volume (MCV)		
Hemoglobin (Hgb)	Red cell distribution width (RDW)		
Mean corpuscular hemoglobin (MCH)	Red blood cell (RBC) count		
Mean corpuscular hemoglobin concentration (MCHC)	White blood cell (WBC) count with differential		
Platelet count			
Serum Chemistry and Electrolytes[1]		5 (serum)	Ambient
Albumin (ALB)	Total protein		
Alanine aminotransferase (ALT)	Calcium (Ca)		
Aspartate aminotransferase (AST)	Magnesium		
Alkaline phosphatase (ALK)	Phosphorus		
Blood urea nitrogen (BUN)	Potassium (K)		
Glucose	Sodium (Na)		
Bicarbonate (HCO_3)	Total bilirubin		
Creatinine	Direct bilirubin		
Chloride (Cl)	Uric acid		
Glycemic Control[1]			Ambient
Fasting plasma glucose (FPG)		2 (plasma)	
Hemoglobin A1c (HbA1c)		2 (blood)	
Serum Lipids [1, 2]		6 (serum)	Ambient
Total cholesterol (TC)	Low-density lipoprotein cholesterol (LDL-C), calculated		
High-density lipoprotein cholesterol (HDL-C)	LDL-C, direct		
Triglycerides (TG)			
Urinalysis[3]		10 (urine)	Ambient
Appearance	Nitrite		
Bilirubin	Occult blood		
Color	pH		
Glucose	Protein		
Ketones	Specific gravity		
Microscopic examination of sediment	Urobilinogen		
UACR	Leukocyte esterase		
Infectious Disease Testing[4]		9 (serum)	Ambient
HBsAg	HCV		
HIV (Canada only)			
Urine pregnancy test (WOCBP)[5]		2 (urine)	Local
Population PK Sampling[6]		2 (plasma)	Frozen
Bexagliflozin plasma level			
Biomarker evaluation[7]		5 (serum)	Ambient
NT-proBNP evaluation (select Group 2 subjects)[8]		5 (serum)	Ambient

[1] *Blood for clinical chemistry and hematology will be drawn after 10 h of fasting prior to breakfast (i.e. only water is allowed, no caloric intake).*

[2] *LDL-C will be calculated by the Friedewald equation. If triglycerides are > 400 mg/dL, the calculated LDL-C value is invalid by this equation and will be set as missing. Direct LDL-C will be determined in subjects whose baseline triglycerides are > 350 mg/dL. All subsequent LDL-C of these subjects will be*

determined by the same direct LDL-C measurements only.

[3] *Urinalysis will be collected routinely at designated clinic visits from a clean catch sample. Glucose in the urinalysis results must be suppressed from the central laboratory report so the dosing blind can be maintained. UACR will be determined at screening (V1), at randomization (V3), and every 24 weeks until study ends. Testing strips measuring only leucocyte esterase and nitrite will be provided for immediate assessment at the clinical sites.*

[4] *Infectious disease testing will be conducted at screening only. HIV testing at screening will be conducted in Canada.*

[5] *Urine pregnancy test (UPT) will be performed for WOCBP at all clinic visits. For surgically sterile or post- menopausal women, it will only be done at visit V1.*

[6] *Blood samples for the population PK analysis will be drawn at weeks 6 and/or 12 from 240 randomly selected subjects in participating trial centers.*

[7] *Serum samples for biomarker evaluation will be drawn at baseline and at week 12 post-randomization*

[8] *Serum samples for NT-proBNP evaluation will be drawn within 1 h of the ECG measurement during the screening (V1) visit for Group 2 subjects with undocumented ejection fraction or documented left ventricular ejection fraction (LVEF) > 40%.*

6.7.2 Sample Collection, Storage, and Shipping

6.7.2.1 Hematology, Blood Chemistry, Serum Lipids, and Glycemic Control Assessments

Blood samples for hematology, chemistry, serum lipids and glycemic control assessments will be collected. Timing of collection is described in Section 7 and the schedule of events in Appendix 1 and Appendix 2.

The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of proper fasting practice. A subject must be queried to assess compliance with a minimum 10 h fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for 10 h, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting.

6.7.3 Urinalysis

Urine samples will be collected per the schedule outlined in Section 7.

Investigator or staff should document if pre-menopausal female subjects are menstruating and note it in the source documents since hematuria is likely to be identified on dipstick urinalysis.

Urine samples will be transported to the central laboratory for urinalysis. In addition, strips for assessing leukocyte esterase and nitrite but not glucose will be provided for immediate assessment at the clinical sites. Urine culture may be performed if more than a trace amount of positive leukocyte esterase or nitrite testing is shown or if subjects report symptoms that may suggest a UTI.

Microscopy will be conducted by the central laboratory if the subject has a positive result on the leukocyte esterase or nitrite dipstick tests that requires microscopic follow-up to clarify the significance of the finding.

Results of glucose measurement in the urinalysis must be suppressed from the laboratory reports so the sponsor, investigators, study coordinators, pharmacists, study subjects, and the adjudication committee members will remain blinded to the dosing assignment.

6.7.4 Population PK Sampling

Blood samples for the population PK analysis will be drawn when the subjects return to the clinic during week 6 and/or week 12 from 240 subjects who consent to participating in the PK study in selected trial centers. One blood sample will be drawn at each of the 3 time points from each subject for a total of 3 post-dose samples per subject. Approximately 120 subjects will be sampled at 0.25 to1 h, 7 to 10 h, and 20 to 24 h post dose (routine 1). Another 120 subjects will be sampled at 1.5 to 3 h, 3.5 to 6.5 h and 7 to 10 h post-dose (routine 2). The sampling time should take into consideration the study subject availability and can be on any of the days during the week of the specified clinical visits. The precise dosing time and sample draw time must be recorded.

Two mL (2 mL) of whole venous blood will be collected from a peripheral vein. Samples will be placed in tubes containing K_2EDTA, stored on ice, and centrifuged under refrigeration for at least ten minutes at 3,000 rpm. After centrifugation, plasma will be removed and stored frozen in 3 aliquots of 200 µL at or below -20° C. Processed frozen plasma samples will be transferred on dry ice to the analytical laboratory and will be stored at or below -20^{o} C until analysis.

Plasma concentrations of bexagliflozin will be determined by a validated LC-MS/MS method. Approximately 480 measurements of bexagliflozin plasma concentrations will be collected from an estimated 160 subjects who will have received active drug in this study.

6.7.5 Biomarker Sampling

Samples for the exploratory biomarker study will be collected in a serum separation tube. The blood (5 mL) will be thoroughly mixed and allowed to clot for 30-60 minutes. After the clot has formed, the tube will be centrifuged at 1500 to 2000 x g for 15 min to separate clot and serum. The serum will be transferred to 2 cryovials and transported under ambient conditions to the central laboratory in which the samples will be stored at or below -70 °C until analysis is performed.

6.7.6 NT-proBNP Sampling

Serum samples for NT-proBNP measurement will be drawn from Group 2 subjects with undocumented left ventricular ejection fraction (LVEF) or with LVEF > 40% (i.e. Group 2 subjects who have a history of heart failure that require NT-proBNP evaluation for eligibility confirmation) within 1 h of the ECG evaluation during the V1 screening visit.

Samples for the NT-proBNP evaluation will be collected in a serum separation tube. The 5 mL blood sample will be thoroughly mixed and allowed to clot for 30-60 minutes. After the clot has formed, the tube will be centrifuged at 1500 to 2000 × g for 15 min to separate the clot from serum. The serum will be transferred to a tube and transported under ambient conditions to the central laboratory for evaluation.

6.7.7 Laboratory Testing in Unscheduled Visits

An investigator can perform additional laboratory testing to diagnose or to follow up an adverse event progression or resolution. Clinical samples should be analyzed in a local laboratory if a fast turn-around time is necessary to determine treatment plan.

6.8 Dispensing Investigational Product

Each study subject will receive one bottle of run-in drug on visit V2 and one bottle of investigational product every 12 weeks between week 1 and 48. Each subject will receive two bottles of investigational product every 24 weeks after week 48.

6.9 Efficacy Assessments

6.9.1 HbA1c Determination

The HbA1c values will be determined in a central laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay.

6.9.2 Body Weight

Total body weight will be determined in every clinical visit as described in Section 6.3.

6.9.3 Blood Pressure

Systolic and diastolic blood pressure will be determined as described in the vital signs section (Section 6.4).

6.9.4 Hospitalization for Heart Failure

Hospitalization for heart failure is defined as an unplanned presentation to an acute care facility (i.e., hospital, emergency room, observation unit) for an exacerbation of heart failure requiring an overnight stay (change in calendar day) which meets the criteria described in Appendix 4.

6.10 Adverse Events Assessments

6.10.1 Definition of Adverse Events

Adverse event (AE*):* Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event (SAE): A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
- is an important medical event. An important medical event is an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.* Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Adverse Reaction: An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

Unexpected Adverse Drug Reaction (UADR): An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

Serious and Unexpected Suspected Adverse Reaction (SUSAR): The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

Severity: AEs will be graded on a 3-point scale and reported as indicated on the CRF. The intensity of an adverse experience is defined as follows:

1 = Mild: event is medically significant but produces no disruption to daily activity;

2 = Moderate: event is medically significant and reduces or affects normal daily activity;

3 = Severe: event is medically significant and results in inability to work or perform normal daily activity.

Investigational Product Causality: An assignment made by the investigator based on the circumstances of the event and its analysis. Cases with causal relationship classified as possible, probable or definite are defined as related. Cases with causal relationship categorized as not likely or unrelated are defined as not related. Relationship of an AE to dosing will be assessed as follows:

Definite: The event responds to withdrawal of the investigational product (dechallenge), and recurs with rechallenge by administration of the investigational product.

Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Possible: There is a reasonable causal relationship between the investigational product and the AE. Dechallenge is lacking or dechallenge response is unclear.

Not Likely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the event.

Unrelated: There is not a temporal or causal relationship to investigational product administration.

6.10.2 Eliciting and Reporting AEs

The investigator will periodically assess subjects for the occurrence of AEs after a subject consents to participation in the study. To avoid bias in collecting information about AEs, the investigator should ask subjects the following question: "How have you felt since you were last checked?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor.

It is the investigator’s responsibility to review the results of all laboratory tests as they become available. For each abnormal laboratory test result the investigator should ascertain if this is a clinically significant change from baseline for that individual subject (this

determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests). If the laboratory value is determined to be a clinically significant and abnormal change from baseline for that subject, this is considered a laboratory AE.

Hypoglycemia is defined as any FPG or SMBG value ≤ 70 mg/dL and documented as described in Section 6.10.10.

Any increase in liver function tests (AST, ALT, or bilirubin) greater than 3 times the ULN for the laboratory utilized will be considered a laboratory AE.

In addition, the sponsor's Medical Monitor or its designated personnel must be notified immediately by telephone, email, or fax of any immediately reportable AEs (IRAE) according to the procedure outlined below. Special attention should be paid to recording hospitalization and concomitant medications.

6.10.3 Immediately Reportable AEs

The investigator must report any SAE to the sponsor or its representative immediately after the investigator becomes aware of the event. An SAE form should be completed and sent to the sponsor within 24 h of knowledge of the event.

Non-serious events that require discontinuation of investigational product (including laboratory abnormalities) should be reported to the sponsor within 3 working days in the CRF AE form.

Subjects experiencing an SAE should be followed clinically until their health has returned to baseline status or no further improvement in condition can be expected with further care. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

6.10.4 Pregnancy

Women of childbearing potential (WOCBP) who are sexually active must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about study participation for WOCBP. The topics should generally include:

1. General information
2. Informed consent form
3. Pregnancy prevention information
4. Drug interactions with hormonal contraceptives
5. Contraceptives in current use

6. Guidelines for the follow-up of a reported pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating the above-mentioned risk factors and that the consequences were discussed with her.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual cycle).

If a subject or investigator suspects that the subject may be pregnant prior to investigational product administration, the investigational product administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the investigational product and must not remain in or be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the investigational product must be withheld immediately until the result of the pregnancy is known. If pregnancy is confirmed, the investigational product will be permanently discontinued and the subject will be withdrawn from the trial. (Exceptions to study discontinuation may be considered for life-threatening conditions only after consultations with the Medical Monitor or the sponsor's designated personnel.) The investigator must notify the Medical Monitor within 3 working days of the receipt of information that any female subject has become pregnant. This reporting requirement will continue until 4 weeks after the last investigational product exposure.

The investigator must record the event on the Pregnancy Surveillance form and forward it to the sponsor's clinical or designated personnel.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (*e.g.*, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the appropriate Pregnancy Surveillance form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of six months.

6.10.5 Procedure for Breaking the Blind

As indicated in Section 5.5 above, the sponsor, medical monitor, study coordinators, pharmacists, study subjects, and the CEC members will be blinded to the treatment assignment during the study period. The investigator should also remain blinded to the subject treatment during the entire study unless knowledge of the subject's treatment is required for clinical care and safety. The Emergency Code Break module in the IWRS is used for such situations. The investigator must confirm the intention to unblind the subject's treatment to obtain the dose information from the IWRS. Upon completion of the unblinding, the system will send an alert to designated study team members that an unblinding event has occurred. Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken, and the names of the personnel

requesting and authorizing unblinding. The treatment assignment will continue to be withheld from the CEC members until all phase 3 studies are completed.

6.10.6 Follow-up of AEs

6.10.6.1 Follow-up of Non-Serious AEs

Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE CRF with the current status noted. All non-serious events that are ongoing at the time will be recorded as ongoing on the CRF.

6.10.6.2 Follow-up of Post-Study SAEs

SAEs that are identified on the last scheduled contact must be recorded on the AE CRF page and reported to Sponsor according to the reporting procedures outlined in Section 6.10.2. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these subjects until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved.

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the Medical Monitor or the sponsor's designated personnel. These may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined study period (i.e., up to last scheduled contact). The investigator should follow subjects with SAEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved. This study requires that subjects be actively monitored for SAEs for at least 4 weeks after the last treatment.

6.10.7 Urinary Tract Infections (UTIs)

Events potentially representing UTIs, cystitis, urethritis, pyelonephritis, or urosepsis should be carefully evaluated and documentation of signs, symptoms, culture results for infectious agent, and treatment should be undertaken when appropriate.

The investigator should query the subject at every clinical visit for symptoms that may be related to a UTI and, if appropriate, document these events as symptomatic UTIs in the CRF unless an alternative diagnosis is present. In addition, a clean catch urine sample will be obtained at all clinical visits and a urinalysis will be performed on that sample at every clinical visit. A positive urinalysis will be defined as one with detectable leukocyte esterase and/or nitrites. If the subject reports symptoms consistent with a UTI or the urinalysis at the clinical site is positive, a urine culture test will be performed at the central laboratory. A

positive urine culture will be defined as one with ≥ 10^5 CFU of any species. The investigator may also perform a urine culture using local resources if necessary for clinical care.

6.10.8 Genital Mycotic Infections (GMIs)

The investigator will query the subjects for signs or symptoms that may represent a GMI at all clinic visits. GMIs will be diagnosed based on symptoms and, if appropriate, physical exam and laboratory findings. Investigators must exclude the possibility of sexually transmitted infections before diagnosing GMI. Diagnosis of GMIs must be documented in the CRF.

6.10.9 Hepatotoxicity

If plasma AST and/or ALT concentrations > 3 x ULN are detected, the investigator will record in the source documents the date corresponding to the date of the laboratory abnormality; the type, frequency, and dose of any concurrent medications or supplements taken by the subject within the 14 days of the detected abnormality; and any symptoms or change in physical exam that have occurred since the prior assessment. The investigator should perform additional laboratory and imaging tests to attempt to establish the cause of the AST and ALT elevations, including ruling out any potential contribution from bone or muscle etiologies.

Any clinically significant increase in hepatic enzymes and specifically any ALT or AST > 3 x ULN requires immediate repeat test within 48 to 72 h to confirm the hepatic enzyme elevation and should be repeated based on the clinical situation at least every 96 h (4 days) until ALT and AST return to < 2.5 x ULN. Study medication should be stopped and the event should be reported as a laboratory AE within the CRF if the enzyme elevation is confirmed or worsening.

Hepatotoxicity will be diagnosed and entered as an AE should any of the following occur:

- ALT or AST > 8 x ULN;
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5 (INR will not be measured as a routine laboratory but should be assessed when needed for medical decision making in the appropriate clinical scenario).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

In the event of hepatotoxicity, investigational product should be permanently discontinued. The investigator is encouraged to consult with the Medical Monitor regarding diagnostic evaluation for the hepatic enzyme elevations. Consultation with a hepatologist may also be appropriate in some circumstances.

6.10.10 Hypoglycemia

Events of hypoglycemia or potentially representing hypoglycemia should be carefully evaluated.

All subjects will be provided with a glucometer and diary for recording blood glucose measurements and signs and symptoms that may be related to hypoglycemia, hyperglycemia, or potential diabetic ketoacidosis. During the study the subject is expected to perform daily fasting blood glucose readings and record all signs and symptoms. In the event of possible signs or symptoms of hypoglycemia, the subject is expected to check the blood glucose if it is reasonably safe to do so, and consume carbohydrates, if appropriate, to treat hypoglycemia.

The subject will be expected to record in the glycemic control diary the following information:

1. SMBG reading at the time of the signs and symptoms attributed to hypoglycemia
2. Time elapsed from the most recent food to the onset of signs and symptoms
3. Type of treatment used (e.g., juice, crackers) for the signs and symptoms and whether assistance was required from another person to administer the treatment
4. SMBG reading 15 minutes after treatment
5. Signs and symptoms attributed to hypoglycemia, hyperglycemia, or potential symptoms that may suggest ketoacidosis

Subjects will be encouraged to call the study clinic should signs and symptoms be potentially related to hypoglycemia or ketoacidosis.

At each study visit, the investigator is expected to review the glucometer recordings and glycemic control diary with particular attention to any SMBG value ≤ 70 mg/dL and any recorded signs or symptoms potentially related to hypoglycemia. In addition, the investigator should query the subject with regard to the occurrence of signs and symptoms potentially related to hypoglycemia even if none are recorded in the diary.

In the event of a blood glucose value ≤ 70 mg/dL or signs and symptoms potentially related to hypoglycemia, the investigator should complete the supplemental CRF which will include data from the glycemic control diary and action items to reduce future hypoglycemia episodes.

Hypoglycemia events will be recorded in the hypoglycemia log under 5 categories:

1. Severe hypoglycemia: an event requiring assistance by another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, 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. All such events should be recorded as SAEs in the CRF.
2. Documented symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).

3. Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured blood glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
4. Probable symptomatic hypoglycemia: an event during which symptoms of hypoglycemia are not accompanied by a blood glucose determination but that is presumably caused by a blood glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
5. Relative hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg/dL (3.9 mmol/L).

While each event meeting the criteria above will be entered into the hypoglycemia log, only severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia will be entered as AEs.

In the event of asymptomatic hypoglycemia, the investigator should review the signs and symptoms of hypoglycemia with the subject to elicit a complete description and should review proper glucometer technique to ensure that the low glucose value is not due to improper use of the glucometer.

The investigator should be alerted to the likelihood of improper glucose measurement technique if a study subject reports an SMBG value < 55 mg/dL (3.1 mmol/L) that is not associated with any signs or symptoms of hypoglycemia and is not treated by some form of glucose administration.

In the event of probable symptomatic hypoglycemia, the investigator should encourage the subject to obtain glucose values, when possible, in the context of signs and symptoms of hypoglycemia, even if the glucose value is measured after treatment for the symptoms is administered.

If hypoglycemia occurs in any subject prescribed rescue medication for hyperglycemia during the study, the total daily dose of the rescue medication should be reduced 50% or more at the discretion of the investigator.

6.10.11 Diabetic Ketoacidosis (DKA)

DKA is a serious, acute complication of diabetes and can be life-threatening. Subjects will be educated on the signs and symptoms of DKA and are required to call the study site and seek treatment should such signs or symptoms occur.

During the clinical trial period, potential DKA events will be monitored by the routine measurement of urinary ketones and assessment for signs or symptoms of acidosis at each clinic visit. Clinical presentations, such as difficulty breathing, abdominal pain, nausea, vomiting, lethargy, or a fruity smell on the breath, or laboratory values that suggest clinically-significant acidosis should be documented; treatment of DKA should be provided as appropriate.

If ongoing symptoms or signs suggest a possible DKA, the investigator should perform relevant laboratory testing while directing appropriate medical care for the subject. If DKA is suspected, regardless of the blood glucose level, the following assessments should be done immediately: physical exam and serum glucose, bicarbonate, electrolytes, and serum ketones measured STAT at a local laboratory. If ketoacidosis is likely, investigational product administration should be discontinued and immediate appropriate medical therapy, including insulin and volume repletion, should be initiated. A glucose infusion may be provided if necessary to avoid hypoglycemia during insulin therapy. Insulin treatment should continue until resolution of the ketoacidosis and stabilization of the subject's clinical condition. Investigational product administration may be resumed following stabilization of the subject's condition. Investigator should collect the data necessary for the completion of the DKA CRF.

If symptoms suggestive of DKA may have occurred but are not ongoing, the investigator should review available data in order to complete the DKA CRF. The investigator may also perform laboratory assessment using local resources if necessary for clinical care.

6.10.12 Major Adverse Cardiovascular Event (MACE)

Evaluation of MACE will be undertaken across the development program for bexagliflozin. All MACE reports should also be captured as SAEs and every effort will be made to ensure that events recorded as MACE are coded in a similar manner within the safety database. The SAE listing will also be reviewed periodically by the CEC members to identify potential MACE that may not have been reported by the site investigators. All subjects will be followed by investigators for MACE for the duration of the study even if study medication has been permanently withdrawn.

The independent CEC will receive and adjudicate the following events.

- All Deaths
- Suspected non-fatal myocardial infarction (MI)
- Suspected hospitalization for unstable angina (HUA)
- Suspected transient ischemic attack (TIA) and stroke
- Suspected hospitalization for HF (HF)
- Reported coronary revascularization procedure

The CDISC Draft Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials will be applied by the CEC (Hicks KA, 2014).

6.10.13 Amputation

Investigators should request that subjects provide information about any amputation or related adverse event or procedures during each study visit. A case report form for adverse events that require amputations will be completed to capture the date and type of procedure, anatomic location, and causes.

Investigators are reminded to counsel appropriate foot care to avoid cuts or sores and to treat even minor cuts or sores to prevent infection and ulceration. Patients who have had a previous amputation should be closely monitored. Special attention may be appropriate for patients who are also receiving thiazide diuretics as these have been shown to increase the risk of amputation in diabetics.

6.11 Concomitant Medication Assessments

A concomitant medication is any medication that the subject has been taking prior to enrollment and that the subject is expected to continue to take for some portion of the trial, as well as any medication other than the investigational product that the subject takes during the course of the trial.

The medications or treatment for controlling hypoglycemia must be recorded as concomitant medications in the CRF. Any medication given to treat hyperglycemia is considered a rescue therapy and should be recorded in the concomitant medication log.

Changes from baseline anti-hypertensive therapy and their rationale must be recorded in the CRF.

All prescription and over-the-counter medications, including vitamins and herbal supplements, that subjects receive during the trial must be documented in the CRF. This documentation should continue until the subjects complete the study.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A table of concomitant medications based on the anatomic therapeutic chemical classification (ATC) and preferred name will be produced. A listing of concomitant medications will include all medications taken by any subjects during the course of the study.

6.12 End of Treatment Procedure

The treatment period will end when (i) all randomized subjects have either completed at least 52 weeks of treatment or withdrawn from the study, and (ii) at least 134 subjects have an adjudicated MACE+ event confirmed by the CEC.

The sponsor or its designee will complete the following tasks within 7 days:

1. Notify all investigational sites, IRB/EC, and DSMB that the treatment period has ended
2. Inactivate the IWRS function for assigning investigational product

The investigators will complete the following procedures upon the notification that the treatment period has ended:

1. Contact all study subjects and schedule the end of treatment visit promptly
2. Schedule the follow up visit (FU) to occur 4 weeks after the end of treatment visit

6.13 Removal of Patients from the Trial or Discontinuation of Investigational Product Administration

The investigator must emphasize to potential subjects the importance of continued participation for the full duration of the trial during the informed consent process. Potential subjects should be informed that the trial procedures will allow additional medications to control hyperglycemia or other adverse conditions. It is also important to emphasize that missing data and missed visits could affect the entire trial. If subjects are dissatisfied with the conduct of the trial but have not withdrawn, the investigators should make an effort to address their concerns and retain them in the trial if possible. In doing so, investigators must be careful that the efforts do not cross over into coercion**.** Investigators should encourage a subject to remain in the study even if the investigational product administration is stopped so that safety information can be collected. If a patient is unwilling to return for study visits/assessments the investigator should ask the patient whether follow-up by telephone, through medical or other records or by contact with the patient's primary care physician is possible. The investigator should emphasize the importance for regulatory and public health/safety reasons of being able to obtain patient vital status at the end of the trial.

Participation in a clinical trial is voluntary. A subject can withdraw from the study at any time. The sponsor may terminate the study for medical or administrative reasons. An investigator may decline to participate in the conduct of the study if either the investigator or the IRB/EC determines that, based on good medical judgment, immediate cessation is appropriate for subject safety. If a decision is made to withdraw a subject from the study, no further investigational product should be administered. Even if the subject discontinues study medication, every attempt should be made to complete all required study evaluations and procedures. Reasons for all withdrawals should be recorded on the CRF. Examples of reasons for withdrawal include:

1. A protocol violation has occurred,
2. A serious or intolerable AE has occurred,
3. A clinically significant change in a laboratory parameter has occurred,
4. The sponsor terminates the study, or
5. The patient requests to be withdrawn from the study.

Subjects who do not complete the study but who have received investigational product should have a follow-up examination, including a physical examination, vital signs, ECG and clinical laboratory tests according to Section 7.

Subjects who withdraw from the study will not be replaced.

6.14 Appropriateness of Measurements

The percentage of HbA1c is a widely used measure of chronic glycemia, reflecting average blood glucose levels over a 2- to 3-month period of time. It is an accepted surrogate marker for risk of microvascular complications and is widely used as a measurement for the

adequacy of glycemic management. Other study procedures and measurements in this protocol are widely used and generally recognized as reliable, accurate, and relevant for subjects with T2DM.

7 STUDY ACTIVITIES

The study activities at each clinic visit listed below are presented in Appendix 1. The required laboratory tests scheduled at each visit are listed in Appendix 2. Detailed study procedures are described in Section 6.

A visit window of ± 3 days is allowed for all visits except visit V3. Visit 3 is the day of randomization and the basis for the visit window.

7.1 Screening Visit V1 (up to 3 weeks before run-in period)

The screening can be performed from 3 weeks to 3 days before the start of the run-in period for subjects. At the screening visit the staff at the investigational site will:

- Explain the content of the informed consent materials to the subject and collect signed informed consent
- Evaluate inclusion and exclusion criteria based on the information collected at the screening visit. Verify compliant fasting status as described in Section 6.7.2.1.
- Obtain medical history and demographic information
- Perform a brief physical examination
- Measure vital signs, including blood pressures and heart rate
- Measure body weight and height
- Perform a 12-lead ECG measurement
- Draw serum sample for NT-proBNP evaluation within 1 h of the ECG measurement from Group 2 subjects with undocumented left ventricular ejection fraction (LVEF) or LVEF > 40%
- Draw blood if a minimum 10-h fast has been completed by the subject as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2.
- Collect clean-catch, mid-stream urine sample for urinalysis, and pregnancy test for all females

7.2 Run-in Period

7.2.1 Visit V2 (two weeks prior to randomization)

- Counsel subject on appropriate diet and exercise
- Dispense glucometer and instruct subject in SMBG determination and recording
- Measure body weight
- Dispense run-in kit for run-in period
- Assess pre-treatment signs and symptoms and potential DKA and record pre-treatment concomitant medications

7.3 Treatment Period

At the end of the run-in period, subjects who have successfully completed run-in period and continue to meet inclusion/exclusion criteria will be randomized and enter the treatment period. At the following visits staff at the investigational site will:

7.3.1 Visit V3 (day 1 of week 1)

- Confirm inclusion/exclusion criteria for eligibility and review run-in drug compliance
- Perform a complete physical examination
- Review glycemic control and SMBG. Dispense glycemic control diary.
- Measure vital signs, including blood pressures and heart rate
- Measure body weight
- Perform 12-lead ECG
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample for urinalysis and UPT for women of child bearing potential.
- Dispense investigational product based on randomization
- Assess pre-treatment signs and symptoms and potential DKA and record pre-treatment concomitant medications.

7.3.2 Visit V4 (week 2, a phone interview)

- Review SMBG and glycemic control record
- Assess AEs and potential DKA and record concomitant medications
- Schedule an unscheduled clinic visit if clinically indicated

7.3.3 Visit V5 (week 6)

- Review SMBG and glycemic control record
- Measure vital signs, including blood pressures and heart rate
- Measure body weight
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Assess AEs and potential DKA and record concomitant medications.
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers

7.3.4 Visit V6 (week 12)

- Perform an abbreviated physical examination
- Review SMBG and glycemic control record
- Measure vital signs, including blood pressures and heart rate
- Measure body weight
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Dispense study medication
- Assess AEs and potential DKA, and record concomitant medications.
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers

7.3.5 Visit V7 (week 18, a phone interview)

- Review daily SMBG and glycemic control record
- Assess AEs, potential DKA, and record concomitant medications
- Schedule an ad hoc visit if clinically indicated

7.3.6 Visit V8 (week 24)

- Review SMBG and glycemic control record
- Perform an abbreviated physical examination
- Measure vital signs, including blood pressures and heart rate
- Measure body weight
- Perform 12-lead ECG
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential;
- Dispense investigational product
- Assess AEs, potential DKA, and record concomitant medications

7.3.7 Visit V9 (week 36)

- Review SMBG and glycemic control record
- Perform an abbreviated physical examination
- Measure vital signs, including blood pressures and heart rate
- Measure body weight

- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential;
- Dispense investigational product
- Assess AEs, potential DKA, and record concomitant medications

7.3.8 Visit V10 (week 48)

- Review SMBG and glycemic control record
- Perform an abbreviated physical examination
- Measure vital signs, including blood pressures and heart rate
- Measure body weight
- Perform 12-lead ECG
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential;
- Dispense investigational product
- Assess AEs, potential DKA, and record concomitant medications

7.3.9 Visit V11, V13, V15, V17, etc. (week 60 to end of treatment; phone interviews)

- Review daily SMBG and glycemic control record
- Assess AEs, potential DKA, and record concomitant medications
- Schedule an ad hoc visit if clinically indicated

7.3.10 Visits V12, V14, V16, V18, etc. (week 72 to end of treatment, clinic visits)

- Review SMBG and glycemic control record
- Perform an abbreviated physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Perform 12-lead ECG
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Dispense study medication
- Assess AEs, potential DKA, and record concomitant medications

7.3.11 Visit EV (end of treatment, a clinic visit)

An End of Treatment Visit should be scheduled within 2 weeks after the end of treatment is declared or as soon as scheduling allows.

- Review SMBG and glycemic control record
- Perform an abbreviated physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Perform 12-lead ECG
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean catch mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Perform the drug accountability procedure and record the last day of dose administration
- Assess AEs, potential DKA, and record concomitant medications

7.4 Exit Visit

7.4.1 Visit FU (4 weeks after the last dose of investigational product is administered or if a subject withdraws consent)

- Review SMBG and glycemic control record
- Perform a complete physical examination
- Measure vital signs, including blood pressures and heart rate
- Measure body weight
- Perform 12-lead ECG if clinically indicated
- Draw blood from subjects who have completed a compliant fast as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Assess AEs, potential DKA, and record concomitant medications: If a subject has an ongoing SAE, the subject will be followed until the AE has resolved or no meaningful further improvement can be expected. Every possible attempt should be made to document resolution of acute and chronic toxicities.

7.5 Discontinuation of Investigational Product Administration

Subjects who discontinue the investigational product administration early but are willing to remain in the study to allow safety information to be collected should complete the End of Treatment visit procedures. Safety data may be documented following the scheduled clinic visit and/or phone interview procedures as much as possible without the study drug

dispensation and accountability procedures. Alternative follow up methods to allow safety assessment to be recorded may be implemented as unscheduled visits.

7.6 Early Termination Procedures

Subjects who withdraw consent and have received investigational product should have a follow-up examination, including a complete physical examination, vital signs, ECG, and clinical laboratory tests (hematology, serum chemistry, and glycemic control). The sponsor must be notified in the event that a subject withdraws or has been withdrawn from the study.

8 QUALITY CONTROL AND ASSURANCE

The clinical research facility will be monitored by the study monitor to ensure correct performance of the study procedures and to ensure that the study is conducted according to the protocol and relevant regulatory requirements. CRF entries will be verified with the source documentation.

Quality control principles will be applied throughout the performance of this study by following the Standard Operating Procedures (SOP) of the CRO and the sponsor. Review procedures will be implemented at the CRO for all documents that are generated in relation to the study.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The following sections provide a summary of the planned analysis of the trial but a full analysis plan will be developed as a separate document and will become the final plan. All statistical analyses will be performed using SAS Version 9.4 or higher.

Data summaries will use descriptive statistics (number of subjects [N], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage of subjects for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage.

Unless otherwise specified, all tests will be two-tailed using a 0.05 level of significance. All confidence intervals (CIs) will be two-sided 95% confidence intervals.

9.2 Determination of Sample Size

The sample size is determined based on the required number of MACE+ for the program-wide meta-analysis of bexagliflozin cardiovascular safety assessment, where non-inferiority of bexagliflozin to control will be formally assessed from a hazard ratio perspective. There will be no formal non-inferiority statistical testing of MACE+ rate within THR-1442-C-476; the only primary endpoint is the change in HbA1c from baseline to Week 24.

The following are the assumptions for protocol THR-1442-C-476 to have an adequate number of events to appropriately power the meta-analysis:

1. Enrollment will take 1 year.
2. Every subject is followed for a minimum of 1 years and a maximum of 3 years, except for premature withdrawals.
3. The annual premature withdrawal rate is 6.5%
4. The randomization ratio is 2:1 (bexagliflozin vs. placebo)
5. The primary analysis is non-inferiority of treatment vs. placebo from a hazard ratio perspective over a 3 year period, using a non-inferiority margin of 1.8 for MACE+.
6. A one-sided 0.025 level of significance will be used to assess non-inferiority
7. Non-inferiority to placebo for MACE + will be assessed by comparing the upper limit of a one-sided 97.5% CI of the hazard ratio (treatment vs. placebo) to a margin of 1.8; the hazard ratio will be calculated from Cox proportional hazards regression.
8. The actual hazard ratio is an equivalence hazard ratio of 1.00 and the reference group monthly hazard rate is 0.00308.

Under the above assumptions, 134 events across 1650 randomized patients (1100 vs. 550 placebo) yields 87% power to detect non-inferiority of experimental treatment to placebo with respect to MACE+. Thus, protocol C-476 will continue until at least 134 events have occurred. If the study accrues 134 MACE+ events before every subject has either been exposed to investigational product for at least 52 weeks or withdrawn from the study, the

study will continue until all subjects either complete the minimum 52 week course of exposure or withdraw.

If the true hazard ratio is 0.9, the power to claim non-inferiority increases to 93%. This should yield sufficient power for the meta-analysis (where all experimental dose groups are pooled and considered as one treatment group), since the number of patients with events in the meta-analysis will be at least the same as that in protocol THR-1442-C-476 and since the treatment to placebo ratio will remain approximately 2:1 across the meta-analysis.

To determine the sample size of THR-1442-C-476 study, the event rates were estimated based on published cardiovascular outcome study SAVOR (Scirica et al., 2013; Scirica et al., 2014a). In the study, subjects with T2DM with a baseline HbA1c of 6.5% to 12.0%, and either a history of established cardiovascular disease or multiple risk factors for vascular disease were included. The estimated 2 year event rate of the placebo group was 7.2%. Assuming a similar event rate in the THR-1442-C-476 study, a sample size of 1650 is planned so that 134 study subjects with an adjudicated MACE+ will occur with a treatment duration between 2 and 3 years. The estimated numbers of MACE+ based on the heart failure background were shown in Table 2. The projected number of CV deaths from subjects with HF history is anticipated to be ≤50% of the total CV deaths.

Table 2. Estimated Event Rates in Patients with Cardiovascular Risks[1]

Event rate in 2 years	No prior HF (%)	Prior HF (%)	From 1250 non-HF	From 400 HF	Total of 1650 subjects
Mortality	3.5%	8.8%	44	35	79
CV death	2.3%	7.3%	29	29	58
MI	3.2%	4.5%	40	18	58
Stroke	1.0%		16		16
Hospital. for HF	1.7%	10.2%	21	41	62
Hospital. for unstable angina	1.0%		16		16

[1] *Event rate is based on the outcome of the placebo group in the SAVER study (Scirica et al., 2013; Scirica et al., 2014a)*

The estimated sample size of 1650 in a 2:1 active to placebo ratio will yield 90% power to detect a treatment effect of 0.22% in HbA1c reduction assuming the SD is 1.1% and HbA1c values from all subjects will be used for the primary efficacy analysis.

9.3 Analysis Populations

9.3.1 Intention-to-Treat Analysis Set

All subjects who are randomized regardless of treatment adherence or availability of follow-up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized assigned treatment.

9.3.2 Safety Analysis Set

All subjects who are randomized and take at least one dose of double-blind study medication will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually dispensed to each subject. This is the primary analysis set for safety. If a randomization error causes a subject in the placebo arm to receive active drug inadvertently, the subject will be considered exposed to active drug and will be analyzed accordingly in the SAS population. If a subject in the active arm receives placebo inadvertently but receives active drug subsequently, the subject will be considered exposed to active drug and will be analyzed accordingly.

9.3.3 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will include all subjects in the FAS who meet the study eligibility requirements and have no major protocol deviations that will affect the validity of the efficacy measurements. Protocol deviations that may result in subject exclusion from the PP Analysis Set will be detailed in the Statistical Analysis Plan. The subject assignment to the PP Analysis Set will be determined prior to database lock.

9.4 Demographics and Baseline Characteristics

Demographic characteristics include age, gender, race, ethnicity, country, and CV history. Baseline characteristics include baseline HbA1c value, blood pressure (systolic and diastolic), body weight, fasting plasma glucose level, and stratification factors determined at screening visit, including HbA1c ($< 9.5\%$ or $\geq 9.5\%$), eGFR (< 60 or ≥ 60 mL/min/1.73 m^2), body mass index (BMI < 25 kg/m^2 or ≥ 25 kg/m^2) and history of heart failure (yes or no). Summary statistics by treatment group will include counts and percentages for discrete variables, and means, SD, Q1, medians, Q3, minimum and maximum for continuous variables and counts and percentage of patients for categorical variables. A further descriptive summaries will be provided separately for subjects who enrolled prior to and subjects who enrolled post the modification of inclusion criteria.

9.5 Primary Endpoints

9.5.1 Primary Efficacy Endpoint

The primary efficacy hypothesis is that bexagliflozin reduces HbA1c after 24 weeks of treatment when compared to placebo. The primary efficacy analysis on change in HbA1c at week 24 is based on the ITT using all observed data. Missing data will be handled using a mixed model repeated measures (MMRM) approach and will include terms for visit, treatment, treatment-by-visit interaction and randomization stratification factors as fixed effects and the corresponding baseline HbA1c value as a fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the placebo group will be estimated from the model at week 24 with the corresponding p-values and their two-sided 95% CIs presented. An unstructured covariance will be used to model the within-subject correlation. In the unlikely event the model with the unstructured covariance structure does

not converge, an autoregressive (1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from the analysis.

As a secondary sensitivity analysis, the multiple imputation method will be used to impute missing observations (including observations obtained after rescue medication) prior to carrying out the MMRM analysis. To further examine the sensitivity of the analysis, a last observation carried forward (LOCF) method will then be used to impute the missing observations prior to carrying out the MMRM model.

For supportive analyses, the primary efficacy endpoint will be analyzed with observed available data using the PP analysis sets in a similar manner as above.

9.5.2 Handling Dropouts, and Missing Data

Discontinuation criteria are explained in Section 6.13. Subjects who withdraw consent to participate in the study will not be replaced.

The early termination rate is estimated to be 6.5% annually. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. But if data are missing for the primary endpoint and the first key secondary endpoint (ie, change of HbA1c for subjects who have been prescribed insulin), they will be handled as follows:

1. All observed data will be analyzed and data obtained after rescue will not be excluded and considered as missing. This will be considered the primary analysis.
2. Missing primary efficacy endpoint information will be imputed via multiple imputation linear regression approach. A total of 10 imputed datasets will be generated, and the corresponding primary analyses will be carried out on each imputed dataset for each endpoint; the analyses results will be combined across the 10 datasets using the standard techniques for multiply imputed data sets in order to yield overall treatment comparison results on the imputed data for each endpoint.

The number, timing, pattern, reason for and possible implications of missing values in efficacy assessments will be investigated. The dropout patterns will be assessed by Kaplan-Meier plots if applicable to assess whether they differ between treatment groups.

The handling of missing safety endpoint (MACE+) data is described below in section 9.6.3; however, analyses on MACE+, while being collected in C-476, will only be formally analyzed in the meta-analysis.

For all other endpoints, the missing data will not be imputed and only the observed data will be used in the analyses.

9.5.3 Multiple Comparisons / Multiplicity

A sequential testing procedure will be applied to the testing of the treatment differences of the primary and key secondary efficacy endpoints, to control the familywise error rate at a two-sided 5% level. Each comparison will be done based on the pre-specified testing hierarchy, so multiplicity adjustment will not be performed.

9.6 Secondary Endpoints

9.6.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints include:

- Change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- Change in body weight from baseline to week 48 in subjects with a BMI $\geq$ 25 kg/m^2
- Change in SBP from baseline to week 24 in subjects with baseline systolic blood pressure $\geq$ 140 mmHg

It is anticipated that approximately 50% of the randomized subjects will have been prescribed insulin to manage their disease. The sample size for the key secondary efficacy end point to evaluate the treatment effect of bexagliflozin compared to placebo on the change in HbA1c from baseline to week 24 in subjects who have been prescribed insulin to control their diabetes is estimated to be 800. For this key secondary endpoint, the estimated sample size will yield >90% power to detect a treatment effect of 0.3% assuming the SD is 1.1% for a two-sided superiority testing.

It is also anticipated that a high proportion of the randomized subjects would have a baseline BMI $\geq$ 25 kg/m^2 and baseline SBP $\geq$140 mmHg in this cardiovascular risk enriched population for the analysis in change in body weight and change in SBP.

A hierarchical testing procedure will be applied to these endpoints in the sequence provided above. These key secondary endpoints will only be tested sequentially when significant treatment differences are established for the primary efficacy endpoint in the comparisons between bexagliflozin and placebo.

The comparison between treatment populations at week 24 (HbA1c and SBP) or 48 (body weight) will be carried out using an MMRM ANCOVA model with unstructured covariance assumption. The model will include terms for treatment, randomization stratification factors, visit, and treatment-by-visit interaction as fixed effects and the corresponding baseline value as an additional fixed effect covariate. Treatment comparison p-values and the difference at week 24 (HbA1c and SBP) or 48 (body weight) will be estimated from the model, with the two-sided 95 % CIs of the difference also presented. If the model does not converge with the unstructured correlation assumption, an autoregressive (1) covariance structure will be used.

9.6.2 Exploratory Efficacy Endpoints

The exploratory secondary efficacy endpoints include:

- Change from baseline in HbA1c over time
- Change from baseline in FPG over time
- Change from baseline in body weight over time
- Change from baseline in SBP over time
- Requirement of additional anti-diabetic medications, including insulin; and time to first use of additional anti-diabetic medication
- Requirement of reduced anti-diabetic medications, including insulin dose over time
- Hospitalization for heart failure in all subjects and in subjects with a history of heart failure
- time to hospitalization for heart failure in subjects in all subjects and in subjects with a history of heart failure

For changes from baseline in HbA1c, FPG, body weight, and SBP over time, a similar MMRM ANCOVA model will be used as for the key secondary efficacy endpoints. Of interest in the MMRM ANCOVA model is the difference between treatments on these endpoints across all post-baseline time points. Also, changes from baseline for each endpoint will be estimated and analyzed at each study visit using this MMRM model. Specifically, for each endpoint, treatment difference in least squares means will be estimated by visit from the model with the corresponding p-values and the two-sided 95% CIs of the difference between treatments.

Endpoints measuring proportions over time will be analyzed using generalized estimating equation (GEE) logistic regression using similar independent variables as the MMRM ANCOVA models above (the treatment-by-visit interaction term will be removed if not significant), and using an unstructured correlation structure (or autoregressive(1) if the model with the unstructured structure does not converge). Of interest is the difference between treatments across all post-baseline time points. Also, odds ratios will be estimated from the model with the corresponding p-values and their two-sided 95% CIs presented at each visit. For time-to-event endpoints, Cox proportional hazards models with treatment and randomization stratification factors as the covariates will be used to estimate the hazard ratio of the endpoint, p-value and its two-sided 95% confidence interval comparing bexagliflozin to placebo. Subjects who withdraw from the trial and for whom no follow up event data are collected (i.e., lost to follow-up subjects) will be censored at the last known follow-up.

9.6.3 Safety Endpoint

The safety endpoint of the program-wide meta-analysis is the hazard ratio for the time to first occurrence of adjudicated MACE+ which is defined as the composite of CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina. All these events will be adjudicated by an independent CEC, blinded to treatment assignments. A Cox proportional hazards model with treatment and randomization stratification factors as the covariates will

be used to estimate the hazard ratio of the composite endpoint and its two-sided 95 % confidence interval comparing bexagliflozin to placebo. The analysis set is the Safety Analysis Set. Subjects who withdraw from the study early and subjects who did not prematurely terminate but who did not experience a MACE+ event by the end of the study will be censored at the last known follow-up.

As a sensitivity analysis, the incidence of MACE+ will be compared between treatments following multiple-imputation of the MACE+ endpoint. The methodology for sensitivity analyses of time-to-event data to be used will be that described in *Zhao, Yue, et al (Zhao et al., 2014).* The dropout patterns will be assessed by Kaplan-Meier plots if applicable to assess whether they differ between treatment groups.

In addition, a sensitivity analysis will be conducted separately for subjects who enrolled prior to inclusion criteria modification and subjects who enrolled post inclusion criteria modification.

9.6.4 Other Safety Endpoints

The other safety endpoints include

- Time to a 5-point composite adjudicated endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization
- Time-to a 6-point composite adjudicated endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization; and time to onset of event
- Time to individual events including all-cause mortality, CV death, non-fatal MI, non-fatal stroke, transient ischemic attack, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization; and time to onset of each event
- Incidence of treatment emergent AEs (TEAEs) of interest
- Incidence of amputations
- Change from baseline in eGFR by study visit
- Change from baseline in UACR by study visit

AEs of special interest include the following categories:

- Genital mycotic infections
- Urinary tract infections including urosepsis and pyelonephritis
- Diuretic effects including hypovolemia
- Hypotension episodes
- Hepatotoxicity
- Hypoglycemia
- Falls and fractures
- Malignancies

- Hypersensitivity reactions
- Acid-base disorders including DKA
- Renal failure events

AEs of special interest will be defined programmatically based on MedDRA system organ class and preferred terms which will be predefined by a blinded medical reviewer and will be specified in the Statistical Analysis Plan.

Event terms, signs, and symptoms will be documented in the listings. The number and percentage of subjects who have experienced treatment emergent adverse events (TEAEs) of special interest will be summarized for each treatment group by type of AE. A TEAE is an AE that started or worsened in severity at or after start of randomized treatment.

A case report form for adverse events that require amputation will be completed to capture the date and type of procedure, anatomic location, and causes. The number and percentage of subjects experienced any TEAE that requires amputation will be summarized for each treatment group by type of events. The incidence of lower extremity amputation per 100 patient years will also be summarized. Additional analyses will be specified in the statistical analysis plan to evaluate potential risks in subpopulations based on age, gender, or other baseline characteristics (if sample size allows).

MMRM ANCOVA will be used for the analyses of changes from baseline in eGFR in a similar manner as for the secondary endpoints. Least squares mean treatment differences between each bexagliflozin group and placebo will be estimated from the model with the two-sided 95% CIs presented.

The time to event onset will be analyzed using the Cox proportional hazards model with treatment and randomization stratification factors as the covariates. For each endpoint, the hazard ratio and its 95% confidence interval comparing bexagliflozin to placebo will be presented. Subjects who dropped out of the trial and for whom no follow up event data were collected (i.e., lost to follow-up subjects) will be censored at the last known follow-up.

Additional sensitivity analyses may also be conducted for subjects who enrolled prior to inclusion criteria modification separately from subjects who enrolled post inclusion criteria modification to assess a potential impact of subject population differences within the study due to inclusion criteria adjustment.

Additional safety endpoints will also include:

- Incidence of all TEAEs
- Change from baseline as well as shift in clinical laboratory findings
- Change from baseline in vital signs measurements including orthostatic blood pressure
- Incidence of abnormal physical examination findings by body system
- Incidence of concomitant medication use

AEs that begin after the first administration of double-blind study medication or existing AEs that worsen after the first dose of double-blind study medication will be considered TEAEs. The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred term, then by severity, and by relationship to study treatment. Drug-related AEs will be considered those to be at least possibly related to investigational product based on the investigator's assessment. The number and percentage of subjects reporting SAEs, and the number and percentage of subjects reporting AEs leading to treatment discontinuation will also be summarized for each treatment group by MedDRA system organ class and preferred term. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory data, vital signs data, and ECG interval data, presented as both actual values and changes from baseline relative to each study visit. For each continuous laboratory parameter, results will be categorized as low, normal or high based on the laboratory normal ranges. Frequencies and percentages will be presented for subjects who had a shift to low and for patients who had a shift to high from baseline to any post-dosing assessment. Baseline values for all safety analyses will be defined as the last observation prior to dosing. All out-of-range and clinically significant laboratory results will be identified in patient data listings.

Abnormal physical examination findings will be tabulated by treatment and presented in a by-patient data listing.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A by-subject listing of concomitant medications will include all medications taken during the study regardless of the timing for the start of the medication. All medications started prior to the administration of the investigational product will be included in the data but will be flagged as prior in the listing. Only the concomitant medication use will be summarized in terms of frequency and percentages by body system and medication name.

In addition, safety profile for subjects who were prescribed with insulin will be separately analyzed, eg, adverse events of special interest, incidences of TEAEs, laboratory abnormalities, vital signs, physical exams, and concomitant medication usages.

9.7 Other Assessments or Analyses

Blood samples will be collected at selected sites for pharmacokinetic analysis. The sampling times will be presented in a by-subject listing only. A population PK analysis will be performed based on a separate analysis plan after samples from all phase 3 studies are collected and bexagliflozin plasma concentrations determined.

Biomarker samples will be collected. A biomarker analysis will be performed separately. The results will not be included in the THR-1442-C-476 study report.

9.8 Interim Analysis

No interim analysis will be performed for efficacy assessment and the study will not be stopped for futility or overwhelming benefit of bexagliflozin treatment.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Information regarding key personnel involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, and technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the investigational site.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The study protocol, informed consent document, relevant supporting information, and all types of subject recruitment or advertisement information will be submitted to the IRB/IEC for review and must be approved by the sponsor and the IRB/IEC before the study is initiated. Any amendments or addenda to the protocol must also be approved by the IRB/IEC prior to implementing changes in the study. The investigator is responsible for keeping the IRB/IEC informed of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once a year. The investigator must also keep the IRB/IEC informed of any SAEs occurring to subjects under their supervision.

10.3 Ethical Conduct of the Study

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor and investigator follow Good Clinical Practice (GCP) Guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. An inspection by the sponsor representatives and/or their designee and/or other authorized regulatory authorities representatives may occur at any time. The investigator must agree to the inspection of study-related records by the regulatory authority/sponsor representatives, and must allow direct access to source documents to the regulatory authority/sponsor representatives.

The investigator is responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from or a change of the protocol to eliminate any immediate hazards to the trial subjects without prior IRB/IEC or sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment should be submitted to the IRB/IEC and sponsor.

Any deviations from the protocol must be fully explained and documented by the investigator. The circumstances, action taken, and impact of the deviation on the trial must be communicated by the principal investigator to the designated medical monitor. Any subsequent actions will be assessed by the designated medical monitor and documented.

10.4 Subject Information and Consent

Prior to the beginning of the study, the investigator must have received from the IEC or IRB the written approval or favorable opinion of the informed-consent form and any other written information to be provided to subjects. The written approval of the IRB/IEC together with the approved subject information/ informed consent forms must be filed. The informed consent form must contain all elements required by authorized regulatory authorities and the ICH GCP Guidelines (E6), in addition to, any other elements required by regulations or institutional policy.

Written informed consent must be obtained before any study-specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files. A copy of the signed informed consent form must be provided to the subject. If applicable, it will be provided in a certified translation in the language understood by the subject, if not English. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

10.5 Subject Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be used by the sponsor in connection with the development of the investigational product. The study investigator is obliged to provide the sponsor with complete test results and all data developed in this study. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission. To ensure compliance with current ICH guidelines, data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the sponsor, and the IRB/IEC for each study site. Study information from this protocol will be posted on clinicaltrials.gov and any local regulatory registry websites, as required by regulation.

Subject names and other identifiers, such as photographs, audio, or videotapes, may not be disclosed in any publication without prior written authorization from the subject.

10.6 Study Monitoring

An authorized sponsor representative will conduct site visits to inspect study data, subjects' medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective national and local government regulations and guidelines.

The investigator will permit authorized representatives of the sponsor and the respective national or local health authorities, other authorized regulatory authorities, and IRB/IEC to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

For each subject consented, a case report form (CRF) in electronic format will be supplied and maintained by the sponsor or designated CRO staff and signed by the investigator or authorized designee to indicate that he/she has reviewed and agrees with the entered data. This also applies to those subjects who fail to complete the trial. The reason a subject has withdrawn must be recorded in the case report form.

Entries made in the CRF must be verifiable against source documents. Source documents are original documents, data, and records, such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medical/analytical facilities engaged in the course of the clinical trial.

All CRFs and source documents should be completed following GCP and the Sponsor or its designee's standard operating procedures.

10.8 Data Monitoring Committee

An independent DSMB will monitor overall safety information during the bexagliflozin development program. The safety review activity and potential risk benefit assessments utilized by the DSMB are defined in its charter.

For protocol THR-1442-C-476, the DSMB will review the unblinded aggregate data periodically and may recommend an early termination of the trial for safety reasons. No interim analysis will be performed for efficacy assessment and the study will not be stopped for futility or overwhelming benefit of bexagliflozin treatment.

10.9 Cardiovascular Endpoint Committee

An independent CEC has been established to prospectively adjudicate, in a blinded fashion, major cardiovascular events. These events will include CV mortality, MI, stroke, hospitalization for HF, acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints. The CEC will have access to relevant CRFs, site data, hospital records, imaging studies, ECG records, or other laboratory testing results but will remain blinded to the subject treatment assignment throughout the entire development program. The end point definition is described in a separate CEC Manual of Operation.

The protocol specific safety and efficacy analyses will be conducted based on the adjudicated CV events documented by the CEC. A separate meta-analysis will be performed after all controlled phase 2/3 clinical trials are completed and will include all CEC adjudicated end

points for the analyses that will be prospectively defined in a meta-analysis plan. The event terms determined by the CEC will not be reconciled with the Investigators' assessment in each phase 2/3 study protocol.

10.10 Protocol Violations/Deviations

Protocol violations include deviations from the inclusion and exclusion criteria, concomitant medication restrictions, and any other protocol requirement that results in a significant added risk to the patient or has an impact on the quality of the data collected or the outcome of the study. A deviation occurs when there is non-adherence to study procedures or schedules, as specified by the protocol, which does not involve inclusion/exclusion criteria or the primary endpoint and which does not place the patient at any added risk or affect the data quality or study outcome. Examples of deviations may include common out-of-window visits, a missed procedure, etc. Protocol violations will reported in the final clinical study report, whereas protocol deviations may be mentioned but are not required to be reported.

It is important to conduct the study according to the protocol. Protocol deviation waivers will not be prospectively granted by the sponsor. If minor protocol deviations occur, the investigator must decide the most appropriate way to proceed with study activities and should consult the study representative for assistance. If major protocol deviations occur, the sponsor's medical monitor must be notified immediately so that a decision about whether to keep the subject in the study can be made.

Only when an emergency occurs that requires a departure from the protocol for an individual subject can there be a departure without the sponsor's pre-approval. The nature and reasons for the protocol deviation will be recorded in the subject's CRF, and the principal investigator must notify the Sponsor.

10.11 Access to Source Documentation

Authorized sponsor representatives will conduct site visits to inspect study data, subjects' medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective local and national government regulations and guidelines.

The investigator will permit authorized representatives of the sponsor and the respective national or local health authorities, other authorized regulatory authorities, and IRB/IEC to inspect facilities and records relevant to this study.

Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP, and legal aspects. This will include on-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

All CRF data will be entered into a clinical database. Following the correction of any errors, the clinical database will be locked.

10.12 Retention of Data

The study file and all source data should be retained until notification is given by the sponsor for destruction.

If the investigator withdraws from the trial and relinquishes his/her responsibility for the maintenance and retention of records, he/she must notify the sponsor in writing so that arrangements can be made to properly store the trial materials.

10.13 Publication and Disclosure Policy

All data and results and all intellectual-property rights in the data and results derived from the study will be the property of Sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

No publication or disclosure of study results will be permitted except as specified in a separate, written agreement between Sponsor, Inc. and the investigator. If results of this study are reported in medical journals or at meetings, all subjects' identities will remain confidential.

The outcome of the study will not be published prior to completion of all pre-market phase 2/3 clinical trials of bexagliflozin and the completion of the meta-analysis of CV risk assessment.

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Appendix 1 Schedule of Events

A. SCHEDULE OF EVENTS FROM SCREENING TO WEEK 48

Procedure	**Screening**	**Run-in**	**Treatment Period**							
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Time to Randomization Visit (weeks)[1]	-2 to -5	-2	0	2	6	12	18	24	36	48
Type of visit[2]	C	C	C	P	C	C	P	C	C	C
Informed Consent	X									
Screening for I/E criteria	X		X							
Demographics and medical history	X									
Diet & exercise counseling[3]		X								
Physical exam[4]	X		X			X		X	X	X
Weight and height[5]	X	X	X		X	X		X	X	X
Diary & glucometer record review[6]		X	X	X	X	X	X	X	X	X
Dispense Run-in Medication		X								
Randomization			X							
Vital signs	X		X		X	X		X	X	X
ECG	X		X					X		X
Dispense study medication[7]			X			X		X	X	X
Blood draw for clinical lab test[8]	X		X		X	X		X	X	X
Population PK sampling[9]					X	X				
Urine collection[10]	X		X		X	X		X	X	X
AE and potential DKA		X	X	X	X	X	X	X	X	X
Con Med		X	X	X	X	X	X	X	X	X

B. SCHEDULE OF EVENTS AFTER WEEK 48 TO END OF STUDY

Procedure	**Treatment Period**			**Follow Up**
Visit number	V 11, 13, 15, 17, etc.	V 12, 14, 16, 18, etc.	EV	FU
Time to Randomization Visit (weeks)[1]	60, 84, 108, 132, 156, etc.	72, 96, 120, 144, 168, etc.	End of treatment visit	4 weeks after EV
Type of Visit[2]	P	C	C	C
Informed Consent				
Screening for I/E criteria				
Demographics and medical history				
Diet & exercise counseling[3]				
Physical exam[4]		X	X	X
Weight and height[5]		X	X	X
Diary & glucometer record review[6]	X	X	X	X
Dispense Run-in Medication				
Randomization				
Vital signs		X	X	X
ECG		X	X	X
Dispense study medication[7]		X		
Blood draw for clinical lab test[8]		X	X	X
Population PK sampling[9]				
Urine collection[10]		X	X	X
AE and potential DKA	X	X	X	X
Con Med	X	X	X	X

Footnotes for the Schedules of Events:

[1] *Screening period may last up to 3 weeks (V1 to V2); run-in period is to be 2 weeks (V2); the efficacy assessment period (V3 to V8) will be 24 weeks; the total treatment period will be 104 to 156 weeks. A visit window of ± 3 days is allowed for all visits except visit V3. Visit V3 is to be scheduled between 13 and 15 days after visit V2 is complete. Visits V4 and V7 will be phone interviews.*

[2] *Visits will be conducted as phone interviews (P) or clinic visits (C).*

[3] *Diet and exercise counseling will be performed at V2.*

[4] *A complete physical examination will be performed by the investigator at V3 prior to randomization and at the follow up visit (FU). Abbreviated physical examinations will be performed by the investigator at all other time points, unless clinically indicated. During the abbreviated physical examinations, general assessment of the skin, heart, lungs and abdomen will be performed.*

[5] *Weight will be determined at all clinic visits and height will be determined at screening visit only (V1).*

[6] *Glucometer will be dispensed to each enrolled subject at visit V2. Glycemic control diary will be dispensed at visit V3. Subjects will be trained on using glucometer and SMBG recording. SMBG record will be reviewed by the investigator at all subsequent visits including both phone interview and clinic visits.*

[7] *One bottle of the investigational product will be dispensed between V3 and V9. Two bottles of the investigational product will be dispensed between V10 and end of treatment visit EV.*

[8] *Blood sample collection and laboratory tests at designated visits are listed in Appendix 2. A minimum fasting time of 10 h must be confirmed prior to blood draw.*

[9] *PK samples will be drawn in selected subjects in participating trial centers only. The samples will be drawn during the weeks 6, and 12.*

[10] *Urine pregnancy test (UPT) is scheduled for all women at screening and just for WOCBP thereafter.*

Appendix 2 Schedule of Laboratory Tests

Procedure	Screening	Treatment						Follow up
Visit Number	**V1**	**V3**	**V5**	**V6**	**V8, 9, 10**	**V 12, 14, 16, 18, etc.**	**EV**	**FU**
Time to Randomization Visit (weeks)		**0**	**6**	**12**	**24, 36, 48**	**every 24 weeks**	**End of treatment**	
Hematology[1]	X	X		X	X	X	X	X
Serum chemistry electrolytes[1]	X	X		X	X	X	X	X
Fasting Plasma Glucose[1]	X	X	X	X	X	X	X	X
HbA1c[1]	X	X	X	X	X	X	X	X
Lipids[1, 2]	X	X		X	X	X	X	X
Urinalysis[3]	X	X	X	X	X	X	X	X
UACR[4]	X	X			X	X	X	
Infectious disease testing[5]	X							
Urine pregnancy test (UPT) [6]	X	X	X	X	X	X	X	X
PK sampling[7]			X	X				
Biomarker sampling		X		X				
NT-proBNP sampling[8]	X							

[1] *Blood for clinical chemistry and hematology will be drawn after 10 h of fasting prior to breakfast (i.e. only water is allowed).*

[2] *LDL-C will be calculated by the Friedewald equation. At screening, the calculated LDL-C value is invalid by this equation and will be set as missing if triglycerides are > 400 mg/dL. Direct LDL-C will be determined in subjects whose baseline triglycerides are > 350 mg/dL. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only.*

[3] *Urine samples will be collected at all clinic visits. Glucose in the urinalysis results must be suppressed from the laboratory report so the dosing blind can be maintained. Testing strips with only the leucocytes and nitrate will be provided for immediate assessment at the sites.*

[4] *UACR will be determined at screening V1, V3, and every 24 weeks until the end of treatment visit is conducted.*

[5] *Infectious disease testing will be conducted at screening only. HIV testing will be conducted at screening in Canada.*

[6] *UPT will be performed for WOCBP at all clinic visits. For surgically sterile or post- menopausal women, it will only be done at Visit V1.*

[7] *Samples for the PK analysis will be drawn at weeks 6 and/or 12 from 240 subjects who consent to the PK study in participating trial centers.*

[8] *Samples for NT-proBNP evaluation will be drawn within 1 h of the ECG measurement during the screening (V1) visit for Group 2 subjects with undocumented ejection fraction or documented left ventricular ejection fraction (LVEF) > 40%.*

Appendix 3 Examples of SGLT2 Inhibitors

The following medications are prohibited during the study. Other SGLT2 inhibitors that may be approved for the treatment of T2DM during the THR1442-C-476 study will also be prohibited as a concomitant medication in this protocol.

Generic Name	**Trade Name**
canagliflozin	Invokana™
canagliflozin plus metformin	Invokamet™
dapagliflozin	Farxiga™ or Forxiga™
empagliflozin	Jardiance®
empagliflozin plus linagliptin	Glyxambi®

Appendix 4 Congestive Heart Failure Classes

The New York Heart Association (NYHA) Functional Classification classifies the heart failure based on how much the patients are limited during physical activity.

Table 3. NYHA Classification of Heart Failure

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix 5 Sponsor Signatures

Study Title: A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c in patients with type 2 diabetes and increased risk of cardiovascular adverse events

Study Number: THR-1442-C-476

Protocol V8.0 Date: 01 December 2016

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 01 Dec 2016

Yuan-Di C. Halvorsen, Ph.D.
Protocol Originator
Massachusetts General Hospital
Consultant for Theracos Sub, LLC.

Signed: _____ Date: 02 Dec 2016

Joseph Massaro, Ph.D.
Study Statistician
Boston University
Consultant for Theracos Sub, LLC.

Signed: J. Paul Lock, MD Date: 02 Dec 2016

J. Paul Lock, M.D.
Medical Monitor
Consultant for Theracos Sub, LLC.

Appendix 6 Investigator's Agreement

Study Title: A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c in patients with type 2 diabetes and increased risk of cardiovascular adverse events

Study Number: THR-1442-C-476

Protocol V8.0 Date: 01 December 2016

I have read the protocol described above. I agree to comply with the International Conference on Harmonisation (ICH) Tripartite guideline on Good Clinical Practice (GCP) and all applicable regulations and to conduct the study as described in the protocol.

I agree to ensure that Financial Disclosure Statements will be completed by myself and my subinvestigators at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Theracos Sub, LLC.

Signed:_____ Date:_____
Clinical Investigator

Statistical Analysis Plan

Sponsor Name:	Theracos Sub, LLC
Protocol Number and Title:	THR-1442-C-476 A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A_{1c} in patients with type 2 diabetes and increased risk of cardiovascular adverse events
Protocol Version and Date:	Version 8.0, 28 October 2016
INC Research Project Code:	1010225
Author(s):	Fang Zhu, Principal Biostatistician
SAP Version:	Version 2.0
SAP Version Date:	20-Nov-2019

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
Version 0.1	02-Oct-2017	Fang Zhu	Initial Release Version
Version 0.2	20-Nov-2017	Fang Zhu	Update per sponsor comments
Version 0.3	15-Dec-2017	Fang Zhu	Update per sponsor comments
Version 1.0	15-Dec-2017	Fang Zhu	Same as above, just update version
Version 1.1	30-Aug-2018	Fang Zhu	• Include additional analysis or summaries for subjects who have been prescribed insulin or sulfonylurea to control their diabetes. • Update primary analysis for primary endpoint using retrieval dropouts • Change sensitivity analysis of primary analysis from jump to reference multiple imputations to tipping point analysis. • Change baseline definition for efficacy endpoints to be based on first dose of study medication to be consistent with safety endpoints. Randomization date is only used if first dose date is missing.
Version 1.2	28-Mar-2019	Fang Zhu	• Minor correction per comments, e.g. model covariates, and other changes to make text and shell consistent; • Removing intensification and relaxation adjudication process. Adding definition for intensification/relaxation. Unify wording of intensification, rescue medication; • Update censoring rule in section 8.2.2.5; • Update sensitivity analyses for key secondary endpoints. • Update compliance computation for unreturned kit. • Update AE of interest list. • Adding ECG values inclusion rule.

Version #	**Date** (dd-mmm-yyyy)	**Document Owner**	**Revision Summary**
Version 1.3	25-Sep-2019	Fang Zhu	• Add exploratory endpoints of time to hospitalization for a heart failure or a cardiovascular death event. • Add definitions to subsets of subjects who have been prescribed insulin and subjects who have been prescribed sulfonylurea. • Remove adjudication of rescue medication and remove reviewing of short course hypoglycemic agent. • Add rules of intensification of hypoglycemic agent related to PRN and intensification after relaxation. • Remove statements that visits after Week 48 will not be mapped. • Remove covariates in multiple imputation models based on retrieval dropouts due to insufficient number of subjects.
Verion 1.4	09-Oct-2019	Fang Zhu	• Update overtime analysis to include all post-baseline visits. • For overtime analysis on HbA_{1c} and FPG, use of other hypoglycemic agent is added as a covariate. • Minor updates to wordings and formats. Missing abbreviations are added to glossary table.
Version 2.0	20-Nov-19	Fang Zhu	Update DKA analysis to include adjudication results.

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
INC Research	
Lead Biostatistician Fang Zhu Principal Biostatistician	20-Nov-2019 **Date** (dd-Mmm-yyyy)
Senior Reviewing Biostatistician Mike Ou Senior Director, Biostatistics	20-Nov-2019 **Date** (dd-Mmm-yyyy)
Theracos Sub, LLC	
Sponsor Contact Yuan-Di Halvorsen Program Manager for Theracos Sub, LLC	20-Nov-2019 **Date** (dd-Mmm-yyyy)

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADA	American Diabetes Association
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CEC	Cardiovascular Endpoint Committee
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimating Glomerular Filtration Rate
FAS	Full Analysis Set
FMI	Fraction of Missing Information
FPG	Fasting Plasma Glucose
GLP-1	Glucagon-like Peptide-1
GMI	Genital Mycotic Infection
GGT	Gamma Glutamyl Transferase
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
Hct	Hematocrit
HDL-C	High Density Lipoprotein Cholesterol
Hgb	Hemoglobin

Abbreviation	Description
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IP	Investigational Product
ITT	Intention to Treat
IVRS	Interactive Voice Randomization System
IWRS	Interactive Web Randomization System
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
LVEF	Left ventricular ejection fraction
MACE	Major Adverse Cardiovascular Event
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hematocrit
MCV	Mean Cell Volume
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Multiple Imputation
Min	Minimum
mL	Milliliter
MMRM	Mixed Model Repeated Measures
N/A	Not Applicable
Na	Sodium
OHA	Oral Hypoglycemic Agent
PP	Per Protocol
PR	Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
PRN	pro re nata
PT	Preferred Term

Abbreviation	Description
QRS	Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram
QTc	Time between the start of the Q wave and the end of the T wave in the ECG, corrected for heart rate
RBC	Red Blood Cell
RR	Time between the start of one R wave and the start of the next R wave in the ECG
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGLT2	Sodium Glucose Linked Transporter 2
SI	Standard International System of Units
SMBG	Self-Monitored Blood Glucose
SOC	System Organ Class
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TLF	Table, Listing And Figure
UACR	Urine Albumin To Creatinine Ratio
UGE	Urine Glucose Excretion
UPT	Urine Pregnancy Test
UTI	Urinary Tract Infection
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. The current SAP is based on protocol version 8.0.

2.1. RESPONSIBILITIES

Theracos has designed the study protocol and is responsible for the conduct of the study. Covance is responsible for the development and validation of a clinical database using the MediData RAVE platform.

INC Research will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

Adverse events that have met the seriousness criteria defined in the protocol are reported on the serious adverse event (SAE) forms using the MediData RAVE platform. An SAE case report, consisting of the information reported in the SAE forms, subject characteristics documented in the case report forms, and additional source data such as a hospital discharge summary, is recorded in a validated ARGUS database which is managed by Covance. Any discrepancies in critical data fields of each SAE report will be reconciled between the AUGUS and THR-1442-C-476 clinical databases prior to database lock. The SAE coding, analyses and summaries will be based on the final study data recorded in the clinical database. Theracos will perform a review of all tables, figures and listings before final acceptance.

An independent Cardiovascular Endpoint Committee (CEC) has been established to prospectively adjudicate, in a blinded fashion, suspected cardiovascular events. All suspected major adverse cardiovascular events (MACE) reports should also be captured as SAEs and every effort will be made to ensure that events recorded as suspected MACE are coded in a similar manner within the safety database. The SAE listing will also be reviewed periodically by the CEC members to identify potential MACE that may not have been reported by the study investigators.

The independent CEC will receive and adjudicate the following types of events:

- All deaths
- Suspected non-fatal myocardial infarction
- Suspected hospitalization for unstable angina (HUA)
- Suspected transient ischemic attack (TIA) and stroke
- Suspected hospitalization for HF (HF)
- Reported coronary revascularization procedures

For study THR-1442-C-476, MACE+ is defined as adjudicated cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina.

An independent DKA adjudicator is to review, in a blinded fashion, all suspected cases of acidosis to identify confirmed or probable diabetic ketoacidosis (DKA) according to prespecified DKA case definitions.

2.2. TIMINGS OF ANALYSES

The final analysis of safety and efficacy is planned to be conducted when (i) all randomized subjects have either completed at least 52 weeks of treatment or withdrawn from the study, and (ii) at least 134 subjects have an adjudicated MACE+ event confirmed by the CEC.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

To evaluate the placebo-adjusted change in hemoglobin A_{1c} (HbA_{1c}) from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects with increased risk of cardiovascular adverse events.

3.2. SECONDARY OBJECTIVES

The key secondary efficacy objectives of this study are:

- To evaluate the effect of bexagliflozin compared to placebo on the change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes;
- To evaluate the effect of bexagliflozin on the change in body weight from baseline to week 48 in randomized subjects with a BMI ≥ 25 kg m^{-2} compared to placebo;
- To evaluate the effect of bexagliflozin on the change in systolic blood pressure (SBP) from baseline to week 24 in subjects with baseline systolic blood pressure ≥ 140 mm Hg compared to placebo.

The other exploratory secondary efficacy objectives are:

- To assess the effect of bexagliflozin treatment on the change in HbA_{1c} versus placebo over time;
- To evaluate the effect of bexagliflozin treatment on the change in fasting plasma glucose (FPG) versus placebo over time;
- To measure the proportion of subjects requiring an intensification of anti-diabetic regimen versus placebo over time;
- To measure the proportion of subjects requiring a relaxation of their anti-diabetic regimen versus placebo over time;
- To measure the incidence of hospitalization for heart failure among all subjects and among subjects with a history of heart failure at baseline;
- To compare the time to hospitalization for a heart failure event or a cardiovascular death;

- To assess the effect of bexagliflozin compared to placebo on the change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed sulfonylurea without insulin to control their diabetes.

3.3. SAFETY OBJECTIVES

- To contribute at least 134 subjects who have experienced at least one adjudicated major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo/comparator. MACE+ is defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina.

- To evaluate the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population that is at elevated risk for major adverse cardiovascular events.

3.4. OTHER OBJECTIVES

- Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted at 30 sites and will include approximately 240 subjects.

- Measurement of cardiovascular biomarkers at baseline and at week 12 will be performed in an exploratory study of the bexagliflozin treatment effect on biomarkers that are relevant to cardiovascular (CV) disease diagnosis and prognosis.

3.5. BRIEF DESCRIPTION

THR-1442-C-476 is a multi-center, randomized, double-blind, placebo-controlled, parallel group study. Approximately 1650 subjects with sub-optimally controlled type 2 diabetes mellitus (T2DM) and at high risk of CV adverse events will be randomized to bexagliflozin tablets, 20 mg, or placebo in a ratio of 2:1 in addition to the background anti-diabetic medications.

Potential participants with suboptimal glycemic control (HbA_{1c} between 7.0 % and 11 %) despite treatment as recommended in local guidelines and at high risk of cardiovascular adverse events will enter a screening period of up to 3 weeks. Qualified participants will enter a single-blind, placebo run-in period to allow for diabetes education and optimization of compliance with diet and exercise recommendations. Qualified subjects will continue their pre-screening regimen for glycemic control and will be instructed to take the run-in medication once daily for 13 ± 2 days. Adjustment of treatment for hypertension or dyslipidemia will not be permitted during the screening and run-in periods

although initiation of anti-coagulant therapy (if clinically indicated) will be permitted. If a change in treatment is required to improve management of hypertension or dyslipidemia, the subject may re-enter the screening after the clinical condition and treatment regimen have not changed for at least 4 weeks. Subjects who continue to qualify for the study and who have demonstrated compliance by missing no more than 1 dose of the run-in doses as instructed will be randomized to receive the investigational product.

Assignment to treatment arms will be stratified by baseline HbA_{1c} (> or ≤ 9.5%), baseline eGFR (eGFR ≥ or < 60 mL min^{-1} per 1.73 m^2), baseline BMI (≥ or < 25 kg m^{-2}) and history of heart failure. The study subjects will visit the clinic or complete phone interviews for evaluation at 2, 6, 12, 18, 24, 36 and 48 weeks post-randomization with subsequent visits scheduled every 24 weeks and a phone interview at 12 weeks after each clinic visit. The study duration will be determined by event accumulation. The treatment period will end when all randomized subjects have completed at least 52 weeks of treatment and a total of 134 subjects have experienced a MACE+. A follow-up visit will take place 4 weeks after the conclusion of treatment.

3.6. SUBJECT SELECTION

The study population will include subjects who have been diagnosed with sub-optimally controlled T2DM and who exhibit an elevated risk of cardiovascular events. Subjects with either established cardiovascular disease or with multiple cardiovascular risk factors (but no documented cardiovascular disease) and having the following attributes will be included:

Group 1: A history of atherosclerotic vascular disease as defined by one or more of the following: a) myocardial infarction or ischemic (non-hemorrhagic) stroke > 3 months but ≤ 5 years prior to screening or b) documented history of coronary, carotid, or peripheral arterial revascularization (coronary artery bypass grafting must have occurred ≥ 5 years prior to screening)

Group 2: A history of NYHA class II or class III heart failure (Appendix 4 of the protocol) at the time of screening. A history of heart failure is defined as:

- documented left ventricular ejection fraction (LVEF) ≤ 40% and no subsequent LVEF > 40% within 6 months of screening, or
- (i) an NT-proBNP >300 pg mL^{-1} and no evidence of atrial fibrillation/flutter (AF) at the time of the screening ECG or an NT-proBNP >900 pg mL^{-1} and evidence of AF at the time of the screening ECG and (ii) either (a) structural heart disease documented by report of left atrial enlargement or left ventricular hypertrophy, or (b) exhibiting symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening.

Group 3: Age ≥ 55 years with 2 or more of the following:

a. diabetes duration of ≥ 10 years,
b. uncontrolled hypertension defined as SBP > 140 mm Hg despite 3 or more anti-hypertensive medications,
c. current smoking,
d. urine albumin: creatinine ratio (UACR) > 30 mg g^{-1},
e. eGFR of 45 to 60 mL min^{-1} per 1.73 m^2, or
f. HDL < 1 mmol L^{-1} (38 mg dL^{-1})

To ensure that subjects with various cardiovascular risks are adequately represented, a minimum of 352 subjects (21%) from each of the three groups will be recruited and ≤ 400 subjects who have a history of heart failure will be randomized in the study.

3.6.1. Inclusion Criteria

Refer to protocol section 4.2 for inclusion criteria.

3.6.2. Exclusion Criteria

Refer to protocol section 4.3 for exclusion criteria.

3.7. DETERMINATION OF SAMPLE SIZE

The sample size is based on the required number of MACE+ for the program wide meta-analysis of bexagliflozin cardiovascular safety assessment, in which non-inferiority of bexagliflozin to control will be formally assessed by a hazard ratio analysis. There will be no formal non-inferiority statistical testing of MACE+ rate; the only primary endpoint is the change in HbA_{1c} from baseline to Week 24.

The following are the assumptions to have an adequate number of events to appropriately power the meta-analysis:

1. Enrollment will take 1 year.

2. Every subject is followed for a minimum of 1 years and a maximum of 3 years, except for premature withdrawals.

3. The annual premature withdrawal rate is 6.5%.

4. The randomization ratio is 2:1 (bexagliflozin vs. placebo).

5. The primary analysis is non-inferiority of treatment vs. placebo from a hazard ratio perspective over a 3 year period, using a non-inferiority margin of 1.8 for MACE+.

6. A one-sided 0.025 level of significance will be used to assess non-inferiority.

7. Non-inferiority to placebo for MACE + will be assessed by comparing the upper limit of

a one-sided 97.5% CI of the hazard ratio (treatment vs. placebo) to a margin of 1.8; the hazard ratio will be calculated from Cox proportional hazards regression.

8. The actual hazard ratio is an equivalence hazard ratio of 1.00 and the reference group monthly hazard rate is 0.00308.

Under the above assumptions, the observation of 134 events across 1650 randomized patients (1100 active and 550 placebo) yields 87% power to detect non-inferiority of experimental treatment compared to placebo with respect to MACE+. If the study accrues 134 MACE+ events before every subject has either been exposed to investigational product for at least 52 weeks or withdrawn from the study, the study will continue until all subjects either complete the minimum 52 week course of exposure or withdraw.

If the true hazard ratio is 0.9, the power to claim non-inferiority increases to 93%. This should yield sufficient power for the program-wide meta-analysis (in which all experimental dose groups will be pooled and considered as one treatment arm), since the number of program-wide events will be greater than the number in study THR-1442-C-476, and since the ratio of the treatment population size to the placebo population size will remain approximately 2:1 across the meta-analysis.

To determine the sample size of THR-1442-C-476 study, the event rates were estimated based on a published cardiovascular outcome study (SAVOR; Scirica et al., 2013; Scirica et al., 2014a). In the SAVOR study, subjects with T2DM with a baseline HbA_{1c} of 6.5% to 12.0%, and either a history of established cardiovascular disease or multiple risk factors for vascular disease were included. The estimated 2 year event rate of the placebo group was 7.2%. Assuming a similar event rate in the THR-1442-C-476 study, a sample size of 1650 is anticipated to provide 134 MACE+ within a treatment duration of between 2 and 3 years. The estimated numbers of MACE+ based on the heart failure background are shown in **Table 1**. The projected number of CV deaths from subjects with an HF history is anticipated to be ≤50% of the total CV deaths.

Table 1 Estimated Event Rates in Patients with Cardiovascular Risks[1]

Event rate in 2 years	No prior HF (%)	Prior HF (%)	From 1250 non-HF	From 400 HF	Total of 1650 subjects
Mortality	3.5%	8.8%	44	35	79
CV death	2.3%	7.3%	29	29	58
Myocardial infarction	3.2%	4.5%	40	18	58
Stroke	1.0%		16		16
Hospital. for HF	1.7%	10.2%	21	41	62
Hospital. for unstable angina	1.0%		16		16

1 Event rate is based on the rate observed for the placebo group in the SAVOR study (Scirica et al., 2013; Scirica etal., 2014a)

The estimated sample size of 1650 in a 2:1 active to placebo ratio yields 90% power to detect a treatment effect of 0.22% in HbA_{1c} reduction assuming the SD is 1.1% and HbA_{1c} values from all subjects will be used for the primary efficacy analysis.

For the key secondary objective to measure change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes, it is anticipated that approximately 50% of the randomized subjects will have been prescribed insulin to manage their disease. For this key secondary endpoint, a sample size of 800 subjects will yield >90% power to detect a treatment effect of 0.3% assuming the SD is 1.1% for a superiority testing at one sided significance level of 0.025.

3.8. TREATMENT ASSIGNMENT & BLINDING

3.8.1. Treatment Assignment

Potential study subjects will be screened and assigned a subject number. Once all screening procedures are completed and the study eligibility is confirmed by the investigator, the randomization numbers will be allocated to subjects within the appropriate treatment arm by the randomization system. Once a screening or randomization number has been assigned, it will never be re-used. No subjects will be randomized into the study more than once. If a randomization number has been allocated incorrectly, no attempt will be made to remedy the error once study medication has been dispensed. The subject will continue with the randomization number and study medication. The study staff will notify the Sponsor Contact as soon as the error is discovered without disclosing the study medication administered. Admission of subsequent eligible subjects will continue using the next unallocated number in the sequence.

The study will be conducted at investigative sites in multiple countries and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but each site will be capped at 48 subjects per site. Activation of investigational sites in each country will be centrally controlled by a centrally managed Interactive Web Response system (IWRS).

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized in a 2:1 ratio to receive investigational product. Subjects will be assigned to treatment arms in sequential order as they qualify for the study, using the IWRS. Randomization will be stratified according to baseline HbA_{1c} ($\leq$ 9.5% or > 9.5% at screening visit), baseline eGFR (eGFR < 60 or $\geq$ 60 mL min^{-1} per 1.73 m^2at screening), BMI (<25 kg m^{-2} or $\geq$ 25 kg m^{-2}) and history of heart failure (yes or no).

Among the 3 groups of subjects based on the baseline CV risks, a minimum of 352 subjects (21%) from each of the three groups will be recruited and $\leq$ 400 subjects who have a history of heart failure can be randomized in the study. If a subject has a history of class

II or III heart failure, the subject will be allocated to group 2, regardless of any history of atherosclerotic vascular disease or additional cardiovascular risk factors. If a subject does not have a heart failure history and has a history of atherosclerotic vascular disease, the subject will be allocated to group 1 regardless of other cardiovascular risks. Subject status with respect to group assignment criteria will be recorded on the CRF and group assignment will be stored in the IWRS. The final group assignment used in the summary or analysis will be primarily based on data captured in the IWRS. Subjects will be considered as CV risk group 2 if subject is assigned to group 2 on IWRS or satisfied group 2 criteria on CRF. Otherwise, CV risk group will be determined based on the assignment by IWRS.

3.8.2. Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the CEC and DKA adjudication committee members will be blinded to the composition of the investigational product. Upon randomization, each subject will receive a subject randomization number and a drug kit assigned to the subject. To maintain blinding of the individual treatment assignments, central laboratory glucose urinalysis data will not be made available to any study personnel or subjects.

If knowledge of the investigational product ingredients is needed to manage the subject's condition, the investigator will contact the IWRS to obtain the treatment assignment. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded on the case report form (CRF) and the sponsor must be notified within 24 h.

A designated statistician who is not involved in the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies.

The treatment assignment will continue to be withheld from the cardiovascular endpoint committee (CEC) members until all investigational studies contributing to the MACE+ meta-analysis are completed and the meta-analysis has been conducted.

3.9. ADMINISTRATION OF STUDY MEDICATION

The following investigational products (IP) will be used for oral administration:

- Bexagliflozin tablets, 20 mg: tablets containing 20 mg of bexagliflozin
- Bexagliflozin tablets, placebo: tablets containing no bexagliflozin

Bexagliflozin tablets, 20 mg or placebo, should be taken in the morning prior to eating or drinking. The tablets should be taken with 250 mL of water.

Dosing with bexagliflozin tablets, 20 mg or placebo, will be based on randomized assignment. All study subjects will be instructed to self-administer tablets once daily in the morning prior to eating or drinking; the medication should be taken with water. There will be no change of dose during the treatment period.

On the day of each scheduled clinic visit, subjects must fast for a minimum of 10 hours prior to the collection of blood samples. During the fasting period, only water will be permitted. The investigational product should be administered at the clinic under supervision on the day of visit V2 when the run-in drug is dispensed and on the day of visit V3 when the double-blind study drug is dispensed. Only one tablet per day should be administered.

3.10. STUDY PROCEDURES AND FLOWCHART

The study activities at each clinic visit are presented in Table 2 and Table 3. The schedule of laboratory tests is presented in Table 4.

A visit window of ± 3 days is allowed for all visits except Visit 3. Visit 3 is the day of randomization and the basis for the visit window.

The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of proper fasting practice. A subject must be queried to assess compliance with a minimum 10 hours fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for 10 hours, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting. Urine samples will be transported to the central lab for urinalysis.

Table 2 Schedule of Events from Screening to Week 48

Procedure	Screening	Run-in	Treatment Period							
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Time to Randomization Visit (weeks)[1]	-2 to -5	-2	0	2	6	12	18	24	36	48
Type of visit[2]	C	C	C	P	C	C	P	C	C	C
Informed Consent	X									
Screening for I/E criteria	X		X							
Demographics and medical history	X									
Diet & exercise counseling[3]		X								
Physical exam[4]	X		X			X		X	X	X
Weight and height[5]	X	X	X		X	X		X	X	X
Diary & glucometer record review[6]		X	X	X	X	X	X	X	X	X
Dispense Run-in Medication		X								
Randomization			X							
Vital signs	X		X		X	X		X	X	X
ECG	X		X					X		X
Dispense study medication[7]			X			X		X	X	X
Blood draw for clinical lab test[8]	X		X		X	X		X	X	X
Population PK sampling[9]					X	X				
Urine collection[10]	X		X		X	X		X	X	X
AE and potential DKA		X	X	X	X	X	X	X	X	X
Con Med		X	X	X	X	X	X	X	X	X

Table 3 Schedule of Events after Week 48 to End of Study

Procedure	Treatment Period			Follow Up
Visit number	V 11, 13, 15, 17, etc.	V 12, 14, 16, 18, etc.	EV	FU
Time to Randomization Visit (weeks)[1]	60, 84, 108, 132, 156, etc.	72, 96, 120, 144, 168, etc.	End of treatment visit	4 weeks after EV
Type of Visit[2]	P	C	C	C
Informed Consent				
Screening for I/E criteria				
Demographics and medical history				
Diet & exercise counseling[3]				
Physical exam[4]		X	X	X
Weight and height[5]		X	X	X
Diary & glucometer record review[6]	X	X	X	X
Dispense Run-in Medication				
Randomization				
Vital signs		X	X	X
ECG		X	X	X
Dispense study medication[7]		X		
Blood draw for clinical lab test[8]		X	X	X
Population PK sampling[9]				
Urine collection[10]		X	X	X
AE and potential DKA	X	X	X	X
Con Med	X	X	X	X

Footnotes for the Schedules of Events:

1 Screening period may last up to 3 weeks (V1 to V2); run-in period is to be 2 weeks (V2); the efficacy assessment period (V3 to V8) will be 24 weeks; the total treatment period will be 104 to 156 weeks. A visit window of ± 3 days is allowed for all visits except visit V3. Visit V3 is to be scheduled between 13 and 15 days after visit V2 is complete. Visits V4 and V7 will be phone interviews.

2 Visits will be conducted as phone interviews (P) or clinic visits (C).

3 Diet and exercise counseling will be performed at V2.

4 A complete physical examination will be performed by the investigator at V3 prior to randomization and at the follow up visit (FU). Abbreviated physical examinations will be performed by the investigator at all other time points, unless clinically indicated. During the abbreviated physical examinations, general assessment of the skin, heart, lungs and abdomen will be performed.

5 Weight will be determined at all clinic visits and height will be determined at screening visit only (V1).

6 Glucometer will be dispensed to each enrolled subject at visit V2. Glycemic control diary will be dispensed at visit V3. Subjects will be trained on using glucometer and SMBG recording. SMBG record will be reviewed by the investigator at all subsequent visits including both phone interview and clinic visits.

7 One bottle of the investigational product will be dispensed between V3 and V8. Two bottles of the investigational product will be dispensed between V12 and end of treatment visit EV.

8 Blood sample collection and laboratory tests at designated visits are listed in Appendix 2 of the protocol. A minimum fasting time of 10 h must be confirmed prior to blood draw.

9 PK samples will be drawn in selected subjects in participating trial centers only. The samples will be drawn during the weeks 6, and 12.

10 Urine pregnancy test (UPT) is scheduled for all women at screening and just for WOCBP thereafter.

Table 4 Schedule of Laboratory Tests

Procedure	Screening	Treatment						Follow up
Visit Number	**V1**	**V3**	**V5**	**V6**	**V8, 9, 10**	**V 12, 14, 16, 18, etc.**	**EV**	**FU**
Time to Randomization Visit (weeks)		**0**	**6**	**12**	**24, 36, 48**	**every 24 weeks**	**End of treatment**	
Hematology1	X	X		X	X	X	X	X
Serum chemistry electrolytes1	X	X		X	X	X	X	X
Fasting Plasma Glucose1	X	X	X	X	X	X	X	X
HbA_{1c}1	X	X	X	X	X	X	X	X
Lipids1, 2	X	X		X	X	X	X	X
Urinalysis3	X	X	X	X	X	X	X	X
UACR4	X	X			X	X	X	
Infectious disease testing5	X							
Urine pregnancy test (UPT) 6	X	X	X	X	X	X	X	X
PK sampling7			X	X				
Biomarker sampling		X		X				
NT-proBNP sampling8	X							

1 Blood for clinical chemistry and hematology will be drawn after 10 h of fasting prior to breakfast (i.e. only water is allowed).

2 LDL-C will be calculated by the Friedewald equation. At screening, the calculated LDL-C value is invalid by this equation and will be set as missing if triglycerides are > 400 mg dL^{-1}. Direct LDL-C will be determined in subjects whose baseline triglycerides are > 350 mg dL^{-1}. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only.

3 Urine samples will be collected at all clinic visits. Glucose in the urinalysis results must be suppressed from the laboratory report so the dosing blind can be maintained. Testing strips with only the leucocytes and nitrate will be provided for immediate assessment at the sites.

4 UACR will be determined at screening V1, V3, and every 24 weeks until the end of treatment visit is conducted.

5 Infectious disease testing will be conducted at screening only. HIV testing will be conducted at screening in Canada.

6 UPT will be performed for WOCBP at all clinic visits. For surgically sterile or post- menopausal women, it will only be done at Visit V1.

7 Samples for the PK analysis will be drawn at weeks 6 and/or 12 from 240 subjects who consent to the PK study in participating trial centers.

8 Samples for NT-proBNP evaluation will be drawn within 1 h of the ECG measurement during the screening (V1) visit for Group 2 subjects with undocumented ejection fraction or documented left ventricular ejection fraction (LVEF) > 40%.

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

- Change in HbA_{1c} from baseline to week 24, compared to placebo

4.2. SECONDARY EFFICACY ENDPOINTS

The key secondary efficacy endpoints include:

- Change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- Change in body weight from baseline to week 48 in subjects with a BMI ≥ 25 kg m^{-2}
- Change in SBP from baseline to week 24 in subjects with baseline systolic blood pressure $\geq$ 140 mm Hg

The exploratory secondary efficacy endpoints include:

- Change from baseline in HbA_{1c} over time
- Change from baseline in FPG over time
- Change from baseline in body weight over time
- Change from baseline in SBP over time
- Requirement of additional anti-diabetic medications, including insulin; and time to first use of additional anti-diabetic medication
- Requirement of reduced anti-diabetic medications, including insulin dose over time; and time to first reduced anti-diabetic medications
- Hospitalization for heart failure in all subjects and in subjects with a history of heart failure
- Time to hospitalization for heart failure in subjects in all subjects and in subjects with a history of heart failure
- Time to hospitalization for heart failure or cardiovascular death in all subjects and in subjects with a history of heart failure
- Change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed sulfonylurea without insulin to control their diabetes

4.3. SAFETY ENDPOINTS

The key safety endpoints include:

- A 5-point composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization
- A 6-point composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, coronary revascularization or hospitalization for heart failure
- Individual events including all-cause mortality, CV death, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for unstable angina, hospitalization for CHF, or coronary revascularization. Both first events and total events, taking account of repeat events will be examined
- Change in eGFR from baseline
- Change in UACR from baseline
- Incidence of adverse events of interest. Adverse events of interest including urinary tract infections (UTI), pyelonephritis urosepsis, genital mycotic infections (GMI), diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis, rash, renal failure events, and amputations

Other safety endpoints include:

- Adverse events
- Clinical laboratory events
- Physical examinations
- Vital signs including orthostatic blood pressure
- Use of concomitant medications

4.4. OTHER ENDPOINTS

Samples for population PK analysis will be collected and the plasma concentration of bexagliflozin determined. The PK parameters will be assessed separately as part of the population PK analysis. Biomarker samples will be collected. The biomarker analysis will be performed separately. These analyses will not be discussed in this SAP.

5. ANALYSIS SETS

5.1. SCREENED ANALYSIS SET

The screened analysis set will include all subjects who have signed the informed consent forms and completed the eligibility screening prior to randomization. The screened population will consist of both enrolled subjects and subjects who do not meet the eligibility criteria. Unless specified otherwise, this population will be used for summaries of subject disposition.

5.2. SAFETY ANALYSIS SET

All subjects who are randomized and take at least one dose of the double-blind IPs will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually dispensed to each subject. This is the primary analysis set for safety. If a randomization error causes a subject in the placebo arm to receive active drug inadvertently, the subject will be considered exposed to active drug and will be analyzed accordingly in the Safety Analysis Set. If a subject in the active arm receives placebo inadvertently but receives active drug subsequently, the subject will be considered exposed to active drug and will be analyzed accordingly.

5.3. INTENTION-TO-TREAT ANALYSIS SET

All subjects who are randomized regardless of treatment adherence or availability of follow up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized assigned treatment by the IWRS.

5.4. PER PROTOCOL ANALYSIS SET

The Per Protocol (PP) Analysis Set will include all subjects in the ITT who meet the study eligibility requirements and have no major protocol deviations that will affect the validity of the efficacy measurements. Detailed protocol deviations that may result in subject or visit exclusion from the PP Analysis Set are described in Section 5.5. The subject assignment to the PP analysis set will be determined prior to database lock. The PP Analysis Set will serve as the secondary set for efficacy assessment.

5.5. PROTOCOL DEVIATIONS

Protocol deviations will be captured during monitoring visits. Major protocol deviations that could affect the primary and secondary variables, in the opinion of the medical monitor, will be considered when determining a subject's eligibility for the PP population. Table 5 describes some possible types of major protocol deviations. All protocol deviations will be reviewed and determined as major or minor before database lock.

Table 5 Some Possible Types of Major Protocol Deviations

Category	Criteria	Exclusion
Inclusion/Exclusion Criteria		
Ineligible subject is enrolled	- Subjects not satisfying HbA_{1c} inclusion criteria - Treated with SGLT2 within 3 months of screening	Subject exclusion
Prior or Concomitant Medication Restrictions		
Use of another SGLT2 inhibitor	Use of an SGLT2 inhibitor as the rescue medication for hyperglycemia	Visit exclusion [exclude data post SGLT2 starts]
Dosing Non-Compliance		
Dosing Non-Compliance	-Subject missed more than 50% of the investigational product doses between week 12 and week 24	Subject exclusion

5.6. SUBSETS

Subsets below will be repeated for selected analyses:

- Subjects who have been prescribed insulin: This subset includes all subjects who are taking insulin (ATC class 3 is A10A - INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING) on the day that the subject took the first dose of the study medication. This subset will be used in the baseline demographics, analyses of primary and key secondary efficacy endpoints, adverse event, clinical lab, and vital signs in addition to all subjects.

- Subjects who have been prescribed sulfonylurea: This subset includes all subjects who are taking sulfonylurea (ATC class 4 is A10BB – SULFONYLUREAS) and not taking insulin on the day that the subject took the first dose of the study medication. This subset will be used in the analysis for primary and key secondary efficacy endpoints, adverse event, clinical lab, and vital signs in addition to all subjects.

- Subjects with a history of heart failure: This subset includes all subjects who indicate they had a history of congestive heart failure at screening on CRF cardiovascular disease history page. This subset is primarily used in the analyses on heart failure related exploratory endpoints.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

The proposed statistical methodology and analyses are in accordance with the principles outlined by the ICH E9 guidelines. All statistical analyses will be conducted using SAS statistical software version 9.3 or higher.

Tables, listings and figures (TLFs) will be produced in accordance with the principles outlined by the ICH E3 guidelines. For most summary statistics, data will be analyzed by the following treatment arms: Bexagliflozin 20 mg and Placebo. All available data from subjects who signed an informed consent will be presented in the subject listings.

Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum and maximum) for continuous variables, and frequency and percentage of subjects for categorical and ordinal variables, unless otherwise specified.

Unless otherwise specified, all statistical tests will be one-tailed using a 0.025 level of significance. All confidence intervals (CIs) will be two-sided 95% CIs.

The analysis visit window will be assigned to data collection. One selected data point per visit will appear in summary tables and figures. Refer to section 6.4 for details. All visit assessment data will be included in shift tables and will appear in the subject listings.

No data imputation will be applied for missing values, unless otherwise specified.

6.2. KEY DEFINITIONS

6.2.1. Baseline Values

Baseline is defined as the last non-missing value on or prior to the day of the first dose of double-blind study medication. If the first dose date is missing, the last non-missing value on or prior to the randomization date will be used.

6.2.2. First Dose Date

Two “first dose dates” will be required – one for the Run-In period and one for the double-blind treatment period. The first dose date for the Run-In period will be the date of administration of the first dose of single-blind placebo tablets during the Run-In period. The first dose date for the double-blind treatment period will be the date that the first dose of randomized, double-blind study drug is administered. Both first dose

dates will be obtained from the eCRF. Study analyses will use the double-blind treatment period first dose date.

6.2.3. Study Day

Study Day is the number of days starting from the first administration of double-blind study drug, which is counted as Study Day 1. If the assessment date is after the date of the first double-blind study drug, the study day is calculated as date of assessment - date of the first dose administration+1. If the assessment date is prior to the date of the first double-blind study drug, the study day is calculated as date of assessment - date of the first dose administration.

6.2.4. Duration

Duration of double-blind treatment will be determined as Double-Blind Duration = Double-Blind Last Dose Date minus Double-Blind First Dose Date plus 1. Duration of Run-In period will be determined as Duration = Last Dose Date in the run-in period minus First Dose Date in the run-in period plus 1.

6.2.5. End of Study

The end of study is defined as the date of final contact as entered on the End of Study page of the eCRF. Any missing date of last contact on the End-of-Study eCRF will be imputed as the date of last contact recorded in the database.

6.2.6. Patient Years

Patient years are calculated as sum of the duration from first dose of double-blind treatment to the end of study / 365.25 of all subjects in the specified analysis set and treatment arm. This is used as the denominator of the computation of incidence rate.

6.2.7. Intensification of Hypoglycemic Agent Use

Intensification of hypoglycemic therapies should be considered if one or more of the following:

1. A new oral hypoglycemic therapy is added to the prior medication.
2. An increase of dose in any of the prior oral therapies.
3. A new injectable non-insulin hypoglycemic therapy is added to the prior medication.
4. An insulin therapy is initiated in addition or in place of oral hypoglycemic therapy (ies).
5. An increase of ≥ 5 units total daily dose of insulin any time during the treatment period

The following scenarios are NOT considered intensification:

1. A replacement of a sulfonylurea or insulin with an injectable GLP-1 agonist;

2. An increase of < 5 unit of insulin total daily dose;
3. Any increase of the therapy use after the last day of investigational product administration;
4. Insulin dose usage as needed or pro re nata (PRN) will be considered the same dose;
5. A short course treatment of insulin or other therapies to manage an acute illness.
6. An intensification after relaxation will not be considered as intensification.

6.2.8. Relaxation of Hypoglycemic Agent Use

Relaxation of hypoglycemic therapies should be considered if one or more of the following:
1. Stop or decrease dose of one or more oral hypoglycemic therapies occur during the double-blind treatment period;
2. A decrease of ≥ 5 unit total daily dose of insulin any time during the treatment period.

The following scenarios are NOT considered relaxation:
1. A decrease of hypoglycemic therapies after an intensification of hypoglycemic therapy use.
2. Stopping of a short course of hypoglycemic therapy use.

6.3. MISSING DATA

The handling of missing or incomplete data is described for each endpoint and data type (as needed) in Section 7 to 8.2.2.6.

6.4. ANALYSIS VISIT WINDOWS

Table 6 shows how data will be mapped to visit number prior to selection of records for analysis. All post-baseline visits, including unscheduled and early termination visits, will be mapped.

After mapping the data to the visits, the following rules will apply unless other handling is specified for a particular analysis.

- If multiple records are available within a single visit window, the record closest to the planned assessment day will be selected for analysis.
- If 2 records are equidistant from the target day, then the later record will be selected.
- If a subject has no record in an analysis window, the data will be considered missing at that visit.

Table 6 Analysis Visit Windows

Study Day Window	Scheduled day	Scheduled Visit/Week
Day 1 - 63	Day 42	Visit 5/Week 6
Day 64 – 105	Day 84	Visit 6/Week 12
Day 106 - 147	Day 126	Visit 7/Week 18
Day 148 - 210	Day 168	Visit 8/Week 24
Day 211 - 294	Day 252	Visit 9/Week 36
Day 295 - 420	Day 336	Visit 10/Week 48
Day (xx*7-83) – minimum (xx*7+84, End of Treatment Visit date)	Day (xx*7)	Visit /Week xx, where xx is every 24 weeks.
> End of Treatment Visit date + 7	End of Treatment Visit + 28	Follow-up Visit

If there are multiple end of treatment visits, the one closest to the last dose date will be used. If multiple records are equidistant from the last dose date, the later one will be used. Analysis visit windows will be used for all lab, vital sign, and ECG data.

6.5. POOLING OF CENTERS

Subjects will not be pooled based on site size, but rather by region, to ensure a sufficient number of subjects per treatment arm in both ITT and PP populations for analysis that contain region as a model effect. The table below shows which countries comprise each of the regions to be used in analysis.

Region	Country
Europe	Czech Republic
	Denmark
	Netherlands
	Poland
	Russian Federation
North America	United States
	Canada
	Mexico
Asia Pacific	Republic of Korea
	Taiwan, Province of China

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition data will be listed. A disposition table will present, by treatment arm and overall, the number and/or percentage of subjects who signed the informed consent and entered the study (i.e., were screened, screen failed prior to Run-in, screen failed during the Run-in, and randomized), completed study drug through week 24, completed the study drug, withdrew from the study, completed the study, and discontinued treatment after randomization. The reasons for early withdrawal after randomization will be summarized.

Attempts will be made to collect vital status information that is allowed by local guidelines in subjects who discontinued participation in the study after randomization. The number of subjects for whom vital status has been determined will be presented.

Assignment to the analysis sets (safety, ITT, and PP) will be summarized.

All dispositions will be summarized for all subjects, subjects who has been prescribed insulin or sulfonylurea, and by subgroups: CV risk groups.

7.2. SUBJECT ELIGIBILITY AND PROTOCOL DEVIATIONS

All subjects, including screen failure subjects, who do not meet the Inclusion/exclusion criteria, will be listed. Reasons for screen failure will be summarized.

Deviations that could affect the primary and secondary variables will be considered when determining a subject's eligibility for the PP population. The number and percent of subjects who had any major deviation and each type of major protocol deviation will be tabulated for the ITT Analysis Set.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics include age, gender, race, ethnicity, country of investigational site and CV history. Baseline characteristics will include baseline HbA_{1c}, baseline HbA_{1c} categories (< 9.5% or ≥ 9.5%), baseline eGFR, baseline eGFR categories (< 60 or ≥ 60 mL min^{-1} per 1.73 m^2), blood pressure (systolic and diastolic), body weight, FPG, stratification factors recorded at screening visit in IWRS: including HbA_{1c} (< 9.5% or ≥ 9.5%), eGFR (< 60 or ≥ 60 mL min^{-1} per 1.73 m^2), body mass index (BMI < 25 kg m^{-2} or BMI ≥ 25 kg m^{-2}) and history of heart failure (yes or no), cardiovascular risk factors and subcategories, and type of hypertensive medication and hypoglycemic agents used by ATC class 4. Hypertensive medication includes any medication in ATC level 2 class of C02, C07, C08, C09, and C03. For Group 2 subjects, NT-proBNP values will be

determined at the screening visit in subjects who consent to participate in the study under protocol amendment 8. Ejection fraction is reported for Group 2 subjects. Ejection fraction will be summarized for Group 2 subjects.

Summary descriptive statistics by treatment will include counts and percentages for discrete variables and means, standard deviations, medians, inter-quartile range (Q1, Q3), minimum, and maximum for continuous variables. Subjects' baseline demographic and personal baseline characteristics will be summarized by treatment arm and overall for subjects in the safety, ITT, and PP analysis set. Subject age will be the age at date of informed consent collected from CRF. Summary for demographics will be repeated for region, CV groups, and tables based on safety and ITT analysis set will be repeated for insulin use and sulfonylurea use subgroups.

7.4. MEDICAL HISTORY

Significant medical and surgical history, including dates of diagnoses and procedures and whether the condition is ongoing, if applicable, will be collected. Each condition will be recorded as a verbatim term, date of onset, date resolved, and a checkbox that indicates ongoing conditions. Significant surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Medical and surgical history will be summarized for the Safety Analysis Set by treatment arm, system organ class (SOC), and MedDRA preferred term (PT), overall.

Subject diabetes and cardiovascular diseases history will be summarized for statistical treatment as categorical variables by frequency and percentage, for all subjects and by insulin use, sulfonylurea use.

7.5. MEDICATION

All prescription and over-the-counter medications, including vitamins and herbal supplements, that subjects receive during the trial must be documented on the CRF. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. This documentation should continue through the treatment period and the follow up period. Changes from baseline anti-hypertensive therapy and their rationale must be recorded in the CRF.

All medication will be coded using the World Health Organization Drug Dictionary (WHO-DD) version B2Enhanced March 2016. The preferred drug name and Anatomical/Therapeutic/ Chemical (ATC) class will be reported for inclusion in the database.

Medication summaries based on ATC level 2, and the preferred drug names will be produced for the Safety Analysis Set. The summaries will present, by treatment arm, the frequency and percentage of subjects who used any medication in an ATC class, or any medication based on a single preferred drug name. Medication summaries will be sorted by descending total frequency of ATC class and by PT within ATC class. Subjects will be counted only once for each medication class and each preferred drug name.

For subject listings, medications will be reported based on ATC class and PT; multiple medications for an individual subject will be listed by start date and then by stop date, from earliest to latest medications.

7.5.1. Prior Medication

Any medication with a start date and an end date prior to or on the first dose date for the double-blind treatment period will be considered a prior medication.

Prior and concomitant medications will be presented together on a single listing. The listing will be ordered by subject number, and medication start/end dates. Prior medication will be identified in the listing.

7.5.2. Concomitant Medication

A concomitant medication is any medication that the subject has taken in any time during the study treatment period. In the case of a missing stop date, medication will be assumed to be concomitant.

All medications must be recorded in the CRF medication log.

Concomitant medications will be presented in a summary table as well as in a subject listing.

8. EFFICACY

Efficacy data include HbA_{1c}, FPG, body weight, and blood pressure. All changes from baseline will be calculated as the post-treatment value minus the baseline value. All continuous efficacy data will be summarized for observed and change values by treatment and visit. The proportion of subjects requiring an intensification of anti-diabetic regimen, proportion of subjects requiring a relaxation of anti-diabetic regimen, incidence of and time to hospitalization for heart failure will be summarized by frequency, and the proportion by treatment and visit.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy hypothesis is that bexagliflozin reduces HbA_{1c} after 24 weeks of treatment when compared to placebo.

8.1.1. Primary Efficacy Analysis

Let $\mu_{Bexagliflozon}$ and μ_{PBO} represent the mean changes from baseline in HbA_{1c} at Week 24 for bexagliflozin and placebo arms, respectively. The following hypotheses will be tested:

$$H0: \mu \text{ bexagliflozin} - \mu \text{ placebo} \geq 0$$

$$Ha: \mu \text{ bexagliflozin} - \mu \text{ placebo} < 0$$

Missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputations techniques; HbA_{1c} values collected after the start of intensification of hypoglycemic agent will not be excluded. A pattern-mixture model will be used to explore the impact of the missing data. Imputation will be conducted within each treatment arm and subgroup (treatment completer vs. treatment terminated early) under the assumption that non-adherent subjects with missing data will follow the same trajectory of non-adherent subjects with values observed. All efforts will be made to retain subjects in the study. If treatment is discontinued, subjects are encouraged to remain in the study and complete all scheduled visits, including final follow-up visit. However, with all efforts, insufficient values may be available for reliable imputation. This analysis will be performed only if at least 5 subjects in each treatment arm completed scheduled week 24 visit after treatment is stopped. This number is chosen to allow sufficient data to establish a regression model for imputation. For this analysis, the following three-step approach outlined below will be used:

a. Non-monotone (intermediate visits) missing data will be imputed first using the Monte Carlo Markov Chain (MCMC) method under the MAR assumption in all treatment arms (using the MCMC statement in PROC MI). Multiple chains option

(CHAIN=MULTIPLE option in the MCMC statement of PROC MI) will be used. For the non-monotone imputation of the HbA_{1c} missing data, a multivariate normal model will be used including variables for the HbA_{1c} at baseline and all post-baseline visits within each treatment group. Five hundred imputed datasets will be generated.

b. After the non-monotone missing data have been imputed, the remaining monotone missing data will be imputed within each treatment arm and subgroup, defined by whether subject completed 24 week of study treatment, using regression approach. The predictors for the regression imputation model at any time point will be HbA_{1c} at all previous time points, including baseline. Imputations will be performed using a sequence of regression-based imputations (using PROC MI statement MONOTONE REG) at each post-baseline time point.

c. Imputed data in each of the multiple imputed datasets will be analyzed using a mixed model repeated measures (MMRM) approach. The MMRM model will include treatment, visit, treatment-by-visit interaction, region, visit, treatment, treatment-by-visit interaction, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not, as fixed effects and the corresponding baseline HbA_{1c} as a fixed effect covariate. The analysis will evaluate the mean change from baseline in HbA_{1c} over the 24 week double blind treatment period. An unstructured covariance will be used to model the within subject correlation. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. If the model with the unstructured covariance structure does not converge, an autoregressive(1) covariance structure will be used. HbA_{1c} values obtained after the start of intensification of hypoglycemic agent will not be excluded from the analysis. The treatment and treatment by visit interaction terms allow for comparisons of the treatment groups at each visit, and over week 6 to week 24. Least squares (LS) mean treatment differences between the bexagliflozin group and the placebo group at week 24 will be estimated from the model. The LS mean results from all imputed datasets will be combined using the Rubin's combination rule (PROC MIANALYZE).

If no sufficient week 24 values from treatment discontinued subjects are available for imputation, MMRM analysis will be performed using all available data. Method described in above step c will be utilized.

Descriptive statistics (n, mean, Q1, median, Q3, SD, minimum, and maximum) will be reported by treatment arm and all observed visits. The least squares means, differences between LS means, a 2-sided 95% confidence interval for each difference, and p-values from the model effects up to week 24 visit will be presented. In addition, the observed change from baseline for all available visits with standard errors, LS means with

standard errors of the change from baseline over time and difference between treatment arms with 95% will be presented graphically for the ITT population.

For supportive analyses, the primary efficacy endpoint will be analyzed with observed available data using the PP analysis set in a similar manner as above.

8.1.2. Sensitivity Analyses

Randomized subjects who withdraw consent to participate in the study will not be replaced. The early termination rate is estimated to be 6.5% annually. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct, but if data are missing for the primary endpoints and the first key secondary endpoint (change in HbA_{1c} for subjects who have been prescribed insulin), the number, timing, pattern, and reason for the missing value will be summarized. The reason for missing values will be evaluated to investigate possible implications of missing values for efficacy assessments. The dropout patterns will be assessed by Kaplan-Meier plots, if applicable, to assess whether they differ between treatment arms. If there are missing values for the primary and key secondary analysis, all observed data will be analyzed and data obtained after rescue will not be excluded.

To evaluate the impact from missing data and intensification of hypoglycemic agent, the following sensitivity analyses will be conducted:

1) Tipping point analysis will be conducted. Data after intensification of hypoglycemic agent will be considered as missing. Following steps will be followed:

    a. Create monotone missing data as step a in section 8.1.1;

        b. Regression approach under MAR will be used to generate complete datasets. The predictors for the regression imputation model at any time point will be region, baseline eGFR categories (<60 or ≥60 mL min^{-1}per 1.73 m^2), baseline BMI category (< 25 kg m^{-2} or ≥ 25 kg m^{-2}), history of heart failure (yes or no), insulin use or not, and HbA_{1c} at all previous time points, including baseline. The first imputed values will be penalized or rewarded based on the treatment subject received:

    - Subjects in the bexagliflozin group: missing value will be analyzed assuming the treatment effect is worsened by $\delta 1$ (where δ = 0.1 to 0.5, in step of 0.1) compared to the subjects who have no missing value in the reduction of HbA_{1c} value;

- Subjects in the placebo group: missing value will be analyzed assuming the treatment effect is better by $\delta 2$ (where δ = 0 to 0.5, in step of 0.1) compared to the subjects who have no missing value in the reduction of HbA_{1c} value;

The penalty or reward will not be applied to the values from later time points as these values are penalized or rewarded through regression on previous time points.

c. Imputed datasets will be analyzed and results combined as step c in section 8.1.1.

For each combination of ($\delta 1$, $\delta 2$), 100 imputed datasets will be obtained. These 25 combinations will be separately analyzed to explore under which condition where the null hypothesis can no longer having evidence to be rejected.

2) Furthermore, data that are missing or after intensification of hypoglycemic agent will be imputed using LOCF. All observed data and the imputed values will be analyzed using MMRM model. Model as specified in the primary analysis will be used.

8.1.3. Subgroups

The primary efficacy endpoint will be summarized and analyzed by the following subgroups:

- Age (<65 years or ≥65 years)
- Gender (male or female)
- Race (White or Caucasian; Black or African-American; American Indian or Alaska native; Asian; Other)
- Baseline HbA_{1c} (>8.5% or ≤ 8.5%)
- Baseline eGFR (<60 or ≥60 mL min^{-1} per 1.73 m^2)
- Subject cardiovascular disease history or risk factors groups (Group 1; Group 2; or Group 3)
- Region (Europe, North America, or Asia Pacific)

8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

The key secondary efficacy endpoints include:

- Change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes.

- Change in body weight from baseline to week 48 in subjects with BMI ≥ 25 kg m^{-2}
- Change in SBP from baseline to week 24 in subjects with baseline systolic blood pressure ≥ 140 mm Hg

The exploratory efficacy endpoints include:

- Change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed sulfonylurea to control their diabetes
- Change from baseline in HbA_{1c} over time
- Change from baseline in FPG over time
- Change from baseline in body weight over time
- Change from baseline in SBP over time
- Requirement of additional anti-diabetic medications, including insulin; and time to first use of additional anti-diabetic medication
- Requirement of reduced anti-diabetic medications, including insulin dose over time
- Hospitalization for heart failure in all subjects and in subjects with a history of heart failure, identified on cardiovascular history CRF page.
- Time to hospitalization for heart failure in all subjects and in subjects with a history of heart failure
- Time to hospitalization for heart failure or cardiovascular death in all subjects and in subjects with a history of heart failure

8.2.1. Key secondary efficacy endpoints and analyses

A hierarchical testing procedure will be applied to these endpoints in the sequence of key secondary endpoints provided above. These key secondary endpoints will only be tested sequentially when significant treatment differences are established for the primary efficacy endpoint in the comparisons between the bexagliflozin and placebo groups.

Analysis for key secondary endpoints will be based on the ITT analysis set and repeated for the PP analysis set.

8.2.1.1. Change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed insulin to control their diabetes

This will be tested if the primary efficacy endpoint is significant. Change from baseline in HbA_{1c} at week 24 will be analyzed using the MMRM ANCOVA model with unstructured

covariance assumption. The model will include terms for treatment, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), visit, treatment-by-visit interaction, and region as fixed effects and the corresponding baseline HbA_{1c} value as an additional fixed effect covariate. Data up to week 24 for subjects who have been prescribed insulin to control their diabetes will be used. Treatment comparison p-values and difference at week 24 will be estimated from the model, with the two-sided 95% CIs of the treatment difference also presented. If the model does not converge with the unstructured correlation assumption, an autoregressive AR(1) model will be used. If AR(1) does not converge, a compound symmetry model will be used.

Subgroup analysis will be conducted by baseline HbA_{1c} category and baseline eGFR categories.

8.2.1.2. Change in body weight from baseline to week 48 in subjects with BMI≥ 25 kg m^{-2}

This will be tested if the primary efficacy endpoint and the key secondary endpoint-change from baseline HbA_{1c}, overall and in subjects prescribed with insulin, are significantly different between bexagliflozin and placebo groups based on ITT analysis set. Change from baseline in body weight at week 48 will be analyzed using the MMRM ANCOVA model with unstructured covariance assumption. The model will include terms for treatment, visit, treatment-by-visit interaction, baseline HbA_{1c}, region, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not as fixed effects and the corresponding baseline body weight value as an additional fixed effect covariate. Treatment comparison p-values and difference at week 48 will be estimated from the model, with the two-sided 95% CIs of the treatment difference also presented. If the model does not converge with the unstructured correlation assumption, an autoregressive AR(1) model will be used. If the primary hypothesis or treatment effect on HbA_{1c} for subjects prescribed with insulin is not significant, the nominal p-value will not be used for inferential purposes. Analysis will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

8.2.1.3. Change in SBP from baseline to week 24 in subjects with baseline SBP ≥ 140 mm Hg

This will be tested if the primary efficacy endpoint and the key secondary endpoints – change from baseline HbA_{1c} for subjects prescribed with insulin, and change from baseline body weight are significant. Change from baseline in sitting SBP at week 24 will be analyzed using the MMRM ANCOVA model with unstructured covariance assumption. The model will include terms for treatment, region, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not, visit, treatment-by-visit interaction, baseline HbA_{1c} as

fixed effects and the baseline SBP value as an additional fixed effect covariate. Data used for this analysis includes change from baseline in SBP for all visits up to week 24 and for all subjects with baseline SBP ≥ 140 mm Hg. Treatment comparison p-values and difference at week 24 will be estimated from the model, with the two-sided 95% CIs of the treatment difference also presented. If the model does not converge with the unstructured correlation assumption, an autoregressive AR(1) model will be used. If the primary hypothesis on change of HbA_{1c}, treatment effect on HbA_{1c} for subjects prescribed with insulin, or change of weight from baseline to week 48 is not significant, the nominal p-value will not be used for inferential purposes. Analysis will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

8.2.1.4. Sensitivity analysis

Same sensitivity analysis as described in section 8.1.2 for HbA_{1c} in randomized subjects will be used for subjects who have been prescribed insulin to control their diabetes. For other secondary analyses of body weight and SBP, missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputations techniques. Imputation steps include:

a. Create monotone missing data as step a of section 8.1.1 with 100 imputed datasets;

b. Regression approach under MAR will be used to generate complete datasets. The predictors for the regression imputation model at any time point will be region, baseline eGRF (≥ 60 or < 60 mL min^{-1} $[1.73m]^{-2}$), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not, baseline HbA_{1c}, treatment, and values at all previous time points, including baseline. Values at each visit will be imputed sequentially. The first imputed values for subjects in bexagliflozin arm will be penalized by the mean improvement of bexagliflozin on SBP at week 24 (i.e. the mean change from baseline at week 24) or on body weight at week 48 (i.e. the mean change from baseline at week 48). Imputed values for subjects in placebo will not be penalized. Imputed values after the first missing value will be penalized through regression on first penalized value.

c. Imputed datasets will be analyzed and results combined as in step c in section 8.1.1.

8.2.2. Exploratory secondary efficacy endpoints and analyses

All endpoints in this section are exploratory. No sensitivity analyses and adjustment for multiple comparisons will be conducted. Nominal p-values will be used to examine any trends in these endpoints.

8.2.2.1. Change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed sulfonylurea to control their diabetes

Same MMRM ANCOVA model as in section 8.1.1 will be used for this analysis. Analysis will be conducted based on ITT and PP analysis set. Same sensitivity analysis as in section 8.1.2 will be repeated. Subgroup analysis will be conducted by baseline HbA_{1c} category and baseline eGFR categories.

8.2.2.2. Changes from baseline in HbA_{1c} and FPG over time

Of interest is the difference between treatments on these two endpoints across all post-baseline time points with sufficient number of values. If for any treatment arm, less than 20 subjects completed the assessment in the analysis visit window, the visit will not be included in the analysis. Both endpoints will be analyzed using MMRM model with the change from baseline values across all post-baseline visits used as dependent variable. The fixed effect will include baseline eGRF (≥ 60 or < 60 mL min^{-1} $[1.73m]^{-2}$), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not, treatment, visit, treatment and visit interaction, other hypoglycemic agent use (no change, after relaxation, or after intensification), treatment and other hypoglycemic agent use interaction, and baseline value. For each endpoint, treatment difference in least squares means will be estimated by visit from the model with the corresponding p-values and the two-sided 95% CIs of the difference between treatments.

Analysis of HbA_{1c} over time will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

8.2.2.3. Changes from baseline in SBP and weight over time

Both endpoints will be analyzed using MMRM model with the change from baseline values across all post-baseline visits used as dependent variable. The fixed effect will include baseline eGRF (≥ 60 or < 60 mL min^{-1} $[1.73m]^{-2}$), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not, treatment, visit, treatment and visit interaction, and baseline value. For each endpoint, treatment difference in least squares means will be estimated by visit from the model with the corresponding p-values and the two-sided 95% CIs of the difference between treatments.

8.2.2.4. Proportions of subjects with intensification and relaxation of hypoglycemic agent (i.e. requirement of additional anti-diabetic medications and with requirement of reduced anti-diabetic medications)

These endpoints will be analyzed using logistic regression. The model will include terms for treatment, region, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), and history of heart failure (yes or no), insulin use or not,

and baseline HbA_{1c}. The LS mean proportions and the two-sided 95% CI for each treatment will be presented. Also, odds ratio of treatment difference of bexagliflozin group over the placebo group will be estimated from the model with the corresponding p-values and their two-sided 95% CIs presented. Analysis will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

8.2.2.5. Proportions of subjects with hospitalization of heart failure in all subjects, with hospitalization of heart failure in subjects with a history of heart failure

These endpoints will be analyzed using logistic regression. The model will include terms for treatment, region, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), history of heart failure (yes or no), insulin use or not, and baseline HbA_{1c}. Odds ratios will be estimated from the model with the corresponding p-values and their two-sided 95% CIs. The odds ratios of bexagliflozin group over the placebo group will be estimated from LS means based on the model with the corresponding p-values and their two-sided 95 % CIs presented.

8.2.2.6. Time to first use of intensification or relaxation of hypoglycemic agent

Kaplan-Meier plots will be prepared for these endpoints by treatment. These endpoints will be analyzed using Cox proportional hazards models with treatment, region, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), history of heart failure (yes or no), insulin use or not, and baseline HbA_{1c} as the covariates. Maximum likelihood with ties method of Breslow will be used. The hazard ratio of the endpoint, p-value with its two-sided 95% CIs presented. Subjects who withdraw from the trial and have post-baseline assessments will be censored at the last contact date. Subjects who have no follow-up event data will be censored at the date of randomization + 1 day. Analysis will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes. Time to first intensification of hypoglycemic agent will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

8.2.2.7. Time to hospitalization for heart failure and time to cardiovascular death or hospitalization for a heart failure event in all subjects and in subjects with a history of heart failure

Same analyses in Section 8.2.2.6 will be conducted. History of heart failure will not be used in the analysis model in subjects with a history of heart failure.

9. SAFETY

The safety endpoint of the program-wide meta-analysis is the hazard ratio for the time to first occurrence of adjusted MACE+. The analysis of this endpoint will not be discussed in this SAP.

The other safety endpoints include:

- Time to a 5-point composite adjudicated endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization
- Time to a 6-point composite adjudicated endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization; and time to onset of event
- Time to individual events including all-cause mortality, CV death, non-fatal MI, non-fatal stroke, transient ischemic attack, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization; and time to onset of each event
- Incidence of treatment emergent AEs (TEAEs) of interest
- Incidence of amputations
- Change from baseline in eGFR by study visit
- Change from baseline in UACR by study visit

Note that analysis for time to event endpoints (ie, first 3 bullets as listed above) will be included in a meta analysis plan, and not be included in this SAP.

Additional safety endpoints will also include:

- Incidence of all TEAEs
- Change from baseline as well as shift in clinical laboratory findings
- Change from baseline in vital signs measurements including orthostatic blood pressure
- Incidence of abnormal physical examination findings by body system
- Incidence of concomitant medication use

The analysis population used for safety analyses will be the Safety Analysis Set.

9.1. EXTENT OF EXPOSURE

Study drug exposure will include:

- Treatment duration by treatment arm
- Total dose received by treatment arm

Treatment duration (in weeks) is calculated as (the date of the last dose of study drug – the date of the first dose of study drug + 1) / 7 and rounded to 1 decimal place.

Total dose taken will be calculated as number of tablets/capsules dispensed – number of tablets/capsules, including all doses for glimepiride, returned. For unreturned bottles, if subject has completed the study, all study medications are considered as completely taken. If a subject withdrew early, and it is not the last kit dispensed, or if 2 kits are dispensed and only one is not returned, all medications will be considered as completely taken. If a subject withdrew early, and all kits dispensed are the last visit are not returned, the number taken is considered as what expected from date of dispense to the date of last dose date. Summary statistics for total dose taken will be provided by treatment group for the double-blind treatment period.

Summary statistics for treatment duration (in weeks) and total dose received, as well as a frequency summary of treatment duration categories (e.g., < 1, 1 - < 6 weeks), will be provided. Summary will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

9.2. TREATMENT COMPLIANCE

Subjects will be provided with dosing instructions each time study medication is dispensed. Subjects will also be instructed to bring their medication with them to every visit. During the run-in period, subjects will be considered compliant in investigational product administration by missing no more than one dose of run-in medication. Subjects who are not compliant during the run-in period will be excluded from randomization.

At each visit the study staff will review the self-monitored blood glucose (SMBG) diary and medication use with the subject and record the drug consumption in the CRF. Reasons for non-adherence will also be recorded in the protocol deviation log if applicable.

Compliance in the double-blind phase is calculated for as follows:

- Percent compliance = (number of tablets taken / number of tablets that should have been taken) x 100.
- Number of tablets taken = number of tablets dispensed – number of tablets returned.

- Number of tablets that should have been taken = number of exposure days.
- Number of exposure days = last dose date – first dose date + 1.

Summary statistics for tablet compliance (%) will be provided by treatment arm for the double-blind treatment period. A frequency summary of compliance will also be presented with the following categories: < 75%, 75-<100%, 100-120%, and > 120%. Summary will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

9.3. ADVERSE EVENTS

Adverse events will be collected and recorded from the time a subject signs the informed consent form (ICF) to the last scheduled contact. Any new serious adverse event (SAE) reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the sponsor or designated personnel. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined study period (i.e., up to last scheduled contact). The investigator should follow SAEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved. This study requires that subjects be actively monitored for SAEs for at least 4 weeks after the last treatment.

For all AEs, preferred AE terms and system organ class (SOC) will be coded using terminology from the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins after the first administration of double-blind study medication or an existing AE that worsens after the first dose of double-blind study medication. All reported AEs will be listed, but only TEAEs will be summarized in tables.

Drug-related AEs will be considered those to be possibly, probably and definitely related to bexagliflozin administration based on the investigators' assessment.

Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs and PTs within SOCs presented in descending order of subject incidence.

9.3.1. Derived Data

AE onset day is calculated as (date of AE start – date of double-blind first dose + 1). The onset day will be missing if the start date is missing or partially missing.

9.3.2. Data Summarization

AE summary tables are listed below:

- An overall summary of the number and percentage of subjects reporting any TEAEs, serious TEAEs, treatment-related TEAEs, serious treatment-related TEAE, any TEAEs leading to treatment discontinuation, any TEAEs leading to subject discontinuation and TEAEs leading to death.
- TEAEs overall and by SOC and PT
- TEAEs by severity, overall and by SOC and PT
- Serious TEAEs, overall and by system organ class and preferred term
- TEAEs by relationship to study treatment, overall and by system organ class and preferred term
- TEAEs leading to treatment discontinuation, overall and by SOC and PT
- TEAEs leading to study discontinuation, overall and by SOC and PT
- Most common TEAEs. Most common TEAEs are defined as TEAEs that occur in > 3% of the subjects in either of the treatment arms.

For summary tables, subjects having more than 1 event with the same PT will be counted once for that term. Subjects having more than 1 event with the same SOC will be counted once for each event and once for that SOC. For tabulations by severity, only a subject's most severe event within the category (e.g. overall, SOC, PT) will be counted; similarly, for tabulations by relationship, only a subject's most related event within a category will be counted. The denominator for percentages will be the number of subjects in the Safety Analysis Set for the given treatment arm (i.e., the N's for the columns).

Table below will also be presented for subjects who have been prescribed insulin or sulfonylurea to control their diabetes:

- An overall summary of the number and percentage of subjects reporting any TEAEs, serious TEAEs, treatment-related TEAEs, serious treatment-related TEAE, any TEAEs leading to treatment discontinuation, any TEAEs leading to subject discontinuation and TEAEs leading to death.
- TEAEs overall and by SOC and PT
- Serious TEAEs, overall and by system organ class and preferred term
- TEAEs leading to treatment discontinuation, overall and by SOC and PT
- TEAEs leading to study discontinuation, overall and by SOC and PT.

Listings will be provided for all AEs and the following subsets:

- Serious AEs
- AEs leading to treatment discontinuation
- AEs leading to death.

AE leading to treatment discontinuation and death will be presented for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

9.3.3. AE of Special Interest

AEs of special interest include UTI, pyelonephritis urosepsis, GMI, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, cardiovascular events, fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis (DKA), rash, and renal failure events. These AEs of special interest, except for DKA, cardiovascular events and amputations, will be prospectively identified based on the MedDRA PTs in the AEs log by a medical expert prior to the data base lock and unblinding of the individual subject treatment assignment. The list of AEs of special interest will be confirmed in a peer review process. Cardiovascular events and DKA will be adjudicated and the confirmed MACE events (See Section 9.3.3.3), and confirmed or possible DKA events (See Section 9.3.3.5) will be summarized in the same AE of special interest table. The hypoglycemia events by severity, and amputations will be summarized separately.

9.3.3.1. AE of special interest identified by PTs

The number and percentage of subjects experiencing TEAEs of special interest will be summarized for each treatment arm by type of event. The incidence rate of AE of special interest per 100 patient years will also be summarized. It will be calculated as the total number of AEs / total patient years in specific treatment arm (or total) * 100. Each category of events will be displayed in a separate listing. Summary will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes

9.3.3.2. Hypoglycemic Events

Hypoglycemic event categories include:

Category	Description
Severe	Assistance required and blood glucose ≤70 mg dL^{-1} or no value available but responded to glucose treatment
Documented Symptomatic	Blood glucose ≤70 mg dL^{-1} and typical symptoms of hypoglycemia
Asymptomatic	Blood glucose ≤70 mg dL^{-1} and no typical symptoms of hypoglycemia

Category	Description
Probable Symptomatic	Typical symptoms of hypoglycemia and no value available but responded to glucose treatment
Relative	Typical symptoms of hypoglycemia and blood glucose >70 mg dL^{-1}

Although each event meeting the criteria above will be entered into the hypoglycemia log, only critical (severe) hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia will be entered as AEs.

The number and percentage will be summarized by treatment for:

- Each category of hypoglycemic event;
- Severe or documented hypoglycemic events.

Summary will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes

9.3.3.3. Cardiovascular Events

The events of interest include any protocol defined MACE event of cardiovascular mortality, non-fatal MI, non-fatal stroke, transient ischemic attack, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization. Cardiovascular events considered as any events under protocol defined MACE event by the investigator will be submitted to an independent CEC for adjudication. The number, percentage and incidence rate per 100 patient years of the adjudicated MACE will be summarized for each treatment arm. Adjudicated MACE will be further summarized by PTs. MACE will be summarized in the same table of AE of special interest.

9.3.3.4. Revascularization and Amputations

Revascularization and amputation information is collected in a separate form. Frequency and percentage will be summarized for:

- Type of procedures – cardiovascular-related or amputation
- Subjects with any amputation
- Condition that resulted in amputation
- Location of amputation

Only procedures performed after the first dose of double-blind study drug will be summarized. Summary will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

9.3.3.5. Diabetic Ketoacidosis

During the clinical trial period, potential DKA will be monitored by the measurement of urinary ketones and assessment for signs or symptoms of acidosis at each clinic visit. Clinical presentations or laboratory values that suggest acidosis are to be documented in the DKA CRF. A data package of a suspected DKA case will be provided to the blinded DKA adjudicator. A DKA adjudication form will be completed and event assigned to one of the 5 categories by the independent DKA adjudicator based on clinical data and specified case definitions as outlined below.

Table 7. DKA Case Definitions

Case Term	Case Definitions
Confirmed DKA	• an episode consisting of symptoms of DKA with ketonuria or ketonemia, AND • with one or more biochemical findings of acidosis, which responds to fluid replenishment and, if needed, insulin
Probable DKA	• an episode consisting of moderate or severe symptoms of DKA, which responds to fluid replenishment and, if needed, insulin OR • an episode consisting of moderate or severe symptoms of DKA, moderate or large ketonuria and/or ketonemia without one or more biochemical findings of acidosis, which responds to fluid replenishment and/or insulin
Possible DKA	• an episode consisting of mild to moderate symptoms of DKA, ketosis not measured or ketonuria moderate or less, condition self-managed, resolves with or without change in diabetic medications; OR • an episode of 4+ or greater (40 mg/dL or greater) ketonuria with mild symptoms of DKA; OR • an episode of 5+ or greater (80 mg/dL or greater) ketonuria without symptoms of DKA
Unlikely DKA	• an episode consisting of mild symptoms of DKA with urine ketones measured small or negative; or a measurement of moderate (2+) or less ketonuria without symptoms
Indeterminate DKA	• mild to moderate symptoms of DKA without measurement of ketosis; self-managed and/or self-resolving

Additional potential DKA cases may be identified by the adjudicator when reviewing serious adverse event listing or programmatically based on AEs of special interest preferred term list which includes relevant acidosis terms in the MedDRA dictionary. A data package will be generated and submitted to the DKA adjudicator prior to study completion and treatment assignment unblinded. All suspected DKA will be presented in a by-subject listing. Events adjudicated to be "Confirmed DKA" and "Probable DKA" will be summarized in the AEs of special interest table.

9.4. LABORATORY EVALUATIONS

Laboratory tests will include hematology panel, chemistry panel, serum lipids, and urinalysis testing. Hematology, chemistry, serum lipids, and urinalysis will be performed at the following time points: at the screening visit (Week –2 to -5), at week 0, 6, 12, 24, 36, 48 from screening to week 48, at every 24 weeks after week 48 to end of study, at end of treatment visit and follow up (4 weeks after end of treatment visit) visit. Renal functional testing by UACR will be determined at screening visit (Week –2 to -5), at week 0, 24, 36, 48 from screening to week 48, at every 24 weeks after week 48 to end of study and end of treatment visit. The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of proper fasting practice. A subject must be queried to assess compliance with an approximately 10-hour fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for approximately 10 hours, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting. A list of laboratory tests is included in Table 8.

Low density lipoprotein cholesterol (LDL-C) will be calculated by the Friedewald equation. Direct LDL-C will be determined in subjects whose triglycerides are > 350 mg dL^{-1} at the screening visit. All subsequent LDL-C of these subjects will be determined by direct LDL-C measurements only. The following algorithm will be used to obtain LDL-C values for the analyses:

1. Select subjects (based on the SI unit) who have screening triglycerides >3.4 mM or >350 mg dL^{-1} based on the laboratory value reported
2. Take the LDL – direct measurement values only, throughout the study visits for those subjects
3. If screening triglycerides > 350 and no direct LDL-C values have been determined, take the calculated.

Among those subjects who have screening triglycerides >350 and have both calculated and direct LDL values, only take the direct LDL.

Urinalysis microscopy will be conducted if the subject has a positive result on the leukocyte esterase or nitrite dipstick tests to clarify the significance of the finding. Results of glucose measurement in the urinalysis must be suppressed from the

laboratory reports so the sponsor, investigators, study coordinators, pharmacists, study subjects, and the adjudication committee members will remain blinded to the dosing assignment.

The baseline value for all laboratory tests will be the latest value obtained on or prior to Day 1. Change from baseline for all continuous parameters will be calculated as the post-baseline value minus the baseline value. All continues variables will be summarized by number of subjects [n], mean, SD, Q1, median, Q3, minimum and maximum and categorical variables will be summarized by frequency and percentage.

Observed values (in SI units) and change from baseline over time will be summarized by treatment arm. Laboratory data will be classified as low, normal, or high relative to the parameter's reference range. Laboratory abnormalities for each treatment will also be summarized with shift tables for selected parameters.

For hematology, chemistry, and serum lipids, columns will be included for normal ranges and individual abnormal laboratory values will be flagged and clinical significance will be indicated.

Urine albumin/creatinine ratio (UACR) will be summarized and analyzed separately. Descriptive statistics for geometric mean, geometric coefficient of variation (gCV), median, Q1, Q3, minimum, and maximum of UACR values will be presented at screening, baseline, and all post-baseline scheduled visits for all subjects and for baseline macroalbuminuria subjects (>300 mg g^{-1}). UACR data is left-skewed and will be natural log transformed first. Change in log transformed UACR from baseline to week 24 will be analyzed by ANCOVA model. The fixed effect will include region, baseline HbA_{1c} level as continuous variable, region, baseline eGFR categories (<60 or ≥60 mL min^{-1} per 1.73 m^2), baseline BMI (< or ≥25 kg m^{-2}), history of heart failure (yes or no), insulin use or not, and treatment. The log transformed baseline values will be used as covariate. Analysis will be repeated for baseline macroalbuminuria subjects. LS means for each treatment will be estimated at week 24. The adjusted geometric mean ratio of relative change from baseline in UACR (the ratio of the week 24 geometric mean and baseline geometric mean) and the corresponding two sided 95% CI by treatment arm will be calculated as the antilog of the LS mean and 95% CI of log transformed values, converted to percentage.

Biomarker evaluation is an exploratory study that will be analyzed and reported in a separate report. The biomarker results will not be included in the subject listing or summarized in the THR-1442-C-476 study report. Summary and shift table of hematology, summary of urinalysis, and analysis table of UACR will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

Table 8 List of Laboratory Tests

Test Name		Blood or urine Vol. (mL)	Shipment
Hematology[1]		2 (blood)	Ambient
Hematocrit (Hct)	Mean corpuscular volume (MCV)		
Hemoglobin (Hgb)	Red cell distribution width (RDW)		
Mean corpuscular hemoglobin (MCH)	Red blood cell (RBC) count		
Mean corpuscular hemoglobin concentration (MCHC)	White blood cell (WBC) count with differential		
Platelet count			
Serum Chemistry and Electrolytes		5 (serum)	Ambient
Albumin (ALB)	Total protein		
Alanine aminotransferase (ALT)	Calcium (Ca)		
Aspartate aminotransferase (AST)	Magnesium		
Alkaline phosphatase (ALK)	Phosphorus		
Blood urea nitrogen (BUN)	Potassium (K)		
Glucose	Sodium (Na)		
Bicarbonate (HCO_3)	Total bilirubin		
Creatinine	Direct bilirubin		
Chloride (Cl)	Uric acid		
Glycemic Control			Ambient
Fasting plasma glucose (FPG)		2 (plasma)	
Hemoglobin A_{1c} (HbA_{1c})		2 (blood)	
Serum Lipids [1, 2]		6 (serum)	Ambient
Total cholesterol (TC)	Low-density lipoprotein cholesterol (LDL-C), calculated		
High-density lipoprotein cholesterol (HDL-C)	LDL-C, direct		
Triglycerides (TG)			
Urinalysis[3]		10 (urine)	Ambient
Appearance	Nitrite		
Bilirubin	Occult blood		
Color	pH		
Glucose	Protein		
Ketones	Specific gravity		
Microscopic examination of sediment	Urobilinogen		
UACR	Leukocyte esterase		
Infectious Disease Testing		9 (serum)	Ambient
HBsAg	HCV		
HIV (Canada only)			
Urine pregnancy test (WOCBP)		2 (urine)	Local
Population PK Sampling Bexagliflozin plasma level		2 (plasma)	Frozen
Biomarker evaluation		5 (serum)	Ambient
NT-proBNP evaluation (select Group 2 subjects)		5 (serum)	Ambient

9.5. VITAL SIGNS

Vital signs will be measured at the screening visit (Week –2 to -5), at week 0, 6, 12, 24, 36, 48 from screening to week 48, at every 24 weeks after week 48 to end of study, at end of treatment visit and follow up (4 weeks after end of treatment visit) visit. Measurements of vital signs will include measurement of supine, sitting and standing blood pressure (BP) measurements, and heart rate. Only the BP measured in the sitting position will be used to determine eligibility. Orthostatic systolic and diastolic BP will be calculated as supine measurement – standing measurement.

For BP, pulse rate, and respiration rate, observed values and change from baseline will be summarized by treatment arm and nominal visit using descriptive statistics (n, mean and median, standard deviation, Q1, and Q3, minimum and maximum). For BP, supine, sitting, standing, and orthostatic BP will be summarized. Summary will also be conducted for subjects who have been prescribed insulin or sulfonylurea to control their diabetes.

9.6. ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) will be conducted at the screening visit (Week –2 to -5), at week 0, 6, 12, 24, 36, 48 from screening to week 48, at every 24 weeks after week 48 to end of study, at end of treatment visit and follow up (4 weeks after end of treatment visit) visit. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT interval. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities or arrhythmia.

If a subject's ECG parameters cannot be determined due to pacemaker placement or atrial fibrillation, the ECG parameters will be considered missing. Any machine generated values such as negative values, 0, or 9999 will be excluded from the analyses.

For each abnormal ECG result, the investigator shall ascertain if the observation represents a clinically significant change from the screening ECG for that individual subject (this determination, however, does not necessarily need to be made the first time an abnormal result is observed. The investigator may repeat the ECG to verify the results of the original result). If the ECG result is determined to be a clinically significant and abnormal change from baseline for that subject, it is considered an AE.

For the ECG parameters, observed values and change from baseline from scheduled visits will be summarized with descriptive statistics by treatment arm and overall at each visit. The maximum change from baseline from scheduled visits will also be provided for ECG parameters.

For the ECG overall assessment, the number and percentage of subjects in each overall assessment category (normal, abnormal but not clinically significant, abnormal and

clinically significant, missing) will be presented by treatment arm and overall at each visit.

10. INTERIM ANALYSES

No interim analyses are planned.

11. DATA AND SAFETY MONITORING BOARD

An independent data and safety monitoring board (DSMB) will review descriptive summaries of accumulating safety, subject disposition and limited efficacy data every 6 months, or a frequency recommended by the DSMB.

A designated statistician who is not involved with the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies. The data outputs for this review will be created by an unblinded team. Personnel involved in the conduct of the study will not participate in the preparation of these outputs, receive the data, or participate in the unblinded portions of the DSMB meetings. More details will be provided for DSMB charter and DSMB SAP.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

In protocol, per protocol Analysis Set will include all subjects in the Full Analysis Set (FAS) who meet the study eligibility requirements and have no major protocol deviations that will affect the validity of the efficacy measurements. FAS is changed to ITT.

In all analysis models, randomization stratification factors are used as covariates in the protocol. In SAP, baseline eGFR group and continuous baseline HbA_{1c} are used, instead of screening eGFR groups and screening HbA_{1c} groups.

In protocol, primary analysis of the primary endpoint is MMRM using all available data. This has been updated to use imputed data based on retrieval dropout subjects.

Exploratory object below is added:

- To compare the time to hospitalization for a heart failure event or a cardiovascular death.
- To assess the effect of bexagliflozin compared to placebo on the change in HbA_{1c} from baseline to week 24 in randomized subjects who have been prescribed sulfonylurea without insulin to control their diabetes.

Exploratory endpoint below is added:

- Time to hospitalization for heart failure or cardiovascular death in subjects in all subjects and in subjects with a history of heart failure.
- Change in HbA1c from baseline to week 24 in randomized subjects who have been prescribed sulfonylurea without insulin to control their diabetes.

13. REFERENCE LIST

Scirica, B.M., Bhatt, D.L., Braunwald, E., Steg, P.G., Davidson, J., Hirshberg, B., Ohman, P., Frederich, R., Wiviott, S.D., Hoffman, E.B., et al. (2013). Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. The New England journal of medicine 369, 1317-1326.

14. PROGRAMMING CONSIDERATIONS

The following conventions will hold for programming of outputs:

- SAS® Version 9.4 or higher will be used for programming and production

- The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

- Patients in this study will be identified as “Subjects.”

- Descriptive statistics will be displayed in the following order:

n
Mean
Standard deviation (SD)
Q1
Median
Q3
Minimum
Maximum

- Decimal places: For summary statistics, the minimum and maximum will be reported with the same number of decimal places as the collected measure, the mean, LS mean (if applicable) and median will have 1 more decimal place than the measure collected, and the SD and confidence interval (CI) will have 2 more decimal places than the collected measure. For frequency distributions, percentages will be reported to 1 decimal place. For p-values, 4 decimal places will be reported or the SAS® p-value format of “< 0.0001” or “> 0.9999” will be reported.

- Unless otherwise noted, the denominator for percentages is the number of subjects in the applicable analysis population and treatment arm.

- If the frequency for a particular table cell is zero, then “0”, properly aligned, will be displayed (i.e. “0 (0.0%)” will not be displayed.)

- Non-numeric values: Where variables are recorded using <, > (e.g., “< 10” or “≤ 10”, “> 10” or “≥ 10”) the numeric portion of the result will be used for summary; the actual recorded results, (e.g. “< 10” or “> 10”) will appear in listings.

14.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 9
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 9.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:
  Theracos Sub, LLC
  Protocol Number: THR-1442-C-476
- Draft or Final in top right corner.
- All output should have Page n of N at the top of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment arm columns and total column (if applicable). P-values will be presented in a separate comparison column (if applicable).
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment arm in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be active treatment first, then placebo, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment arms in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
SD	X.XX
Q1	XXX.X
Median	XXX.X
Q3	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If the rounded percentage is 0.0, display as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment arm who have an observation will be the denominator. Percentages after zero counts should not be

displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for concomitant and intensification of hypoglycemic agent should be presented by treatment class with the highest occurrence in the total column in decreasing order. Tabular display of data for medical history and adverse event data should be presented by the SOC using descending order. Within the drug class and SOC, medical history (by preferred term), drugs (by ATC2 code), and adverse events (by preferred term) should be displayed in decreasing order in the total column. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment arm (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment arms as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

15. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.