Clinical Trial Protocol: THR-1442-C-448

Study Title:	A double blind placebo controlled study to evaluate the effect of bexagliflozin tablets on hemoglobin A1c in patients with type 2 diabetes mellitus and moderate renal impairment
Study Number:	THR-1442-C-448
Study Phase:	3
Product Name:	Bexagliflozin Tablets
Indication:	Type 2 Diabetes Mellitus
Investigators:	Multi-center study
Sponsor:	Theracos Sub, LLC
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	Date
Version 4.0:	25 October 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 effect of bexagliflozin tablets on hemoglobin A1c in patients with type 2 diabetes mellitus and moderate renal impairment

Study Number:THR-1442-C-448

Study Phase: 3

Primary Objective:

The primary objective of this study is to determine the efficacy of bexagliflozin on lowering HbA1c in patients with type 2 diabetes mellitus and moderate renal impairment.

Secondary Objectives:

The key secondary efficacy objectives are:

- To assess the effect of bexagliflozin on the change in body weight at week 24 in subjects with baseline BMI $\geq$ 25 kg/m^2
- To assess the effect of bexagliflozin on the change in systolic blood pressure (SBP) at week 24 in subjects with baseline SBP $\geq$ 130 mmHg
- Change in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m^2 at week 24
- Change in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m^2 at week 24

Study Design:
THR-1442-C-448 is a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral administration of bexagliflozin tablets, 20 mg compared to placebo in subjects with type 2 diabetes mellitus (T2DM), moderate renal impairment, and inadequate glycemic control.

Main eligibility criteria include: 1) male or female subjects with T2DM, 2) screening HbA1c of 7.0-10.5% (inclusive), and 3) estimated glomerular filtration rate (eGFR) based on serum creatinine at 2 different assessments $\geq$ 30 to < 60 mL/min/1.73 m^2. The eGFR will be calculated by the modification of diet in renal disease study equation (MDRD). At the time of screening, the doses and frequency of all anti-diabetic medications must have been stable for 8 weeks.

All eligible subjects will continue their pre-screening anti-diabetic medications and start a 1-week placebo run-in period. Subjects who are compliant in taking run-in medication (missing no more than one dose) will be eligible for randomization and receive study drug.

Approximately 300 subjects of 150 subjects per group will be randomly assigned to receive

bexagliflozin tablets, 20 mg or placebo, in equal ratio once daily for 24 weeks in an outpatient setting. Randomization will be stratified by screening HbA1c level (7.0 to 8.5% or 8.6 to 10.5%), screening anti-diabetic treatment regimen (insulin treated or other) and screening eGFR (30 to 44 mL/min/1.73 m^2 or 45 to 59 mL/min/1.73 m^2). A minimal of 135 subjects must be in the eGFR 30 to 44 mL/min/1.73 m^2 stratum.

Subjects with hyperglycemia based on blood glucose levels may receive approved anti-diabetic medication. In addition, adjustment by the investigator to the prescreening anti-diabetic therapies will be recommended if hypoglycemia occurs.

Study subjects will have scheduled visits at weeks 2, 6, 12, 18, and 24 for safety and efficacy evaluation. At weeks 2 and 18, the visit will be conducted a phone interviews unless clinically necessary. A final follow up visit will be conducted at week 26.

Measurement of bexagliflozin plasma concentration over time (sparsely sampled) will also be conducted from approximately 144 study subjects as part of a bexagliflozin population pharmacokinetic (PK) study.

Study Population:
The study population will consist of 300 subjects who have been diagnosed with sub-optimally controlled T2DM with moderate renal impairment. The study population will comprise:

1. Men or non-pregnant women ≥ 20 years of age. Women of childbearing potential must agree to use contraception during the entire study to avoid any possible pregnancy. Females who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible if they test negative on the urine pregnancy test.
2. Subjects with a diagnosis of T2DM with an HbA1c between 7.0 and 10.5% (inclusive) at the time of screening.
3. Subjects who are treatment naïve or are treated with a stable regimen of anti-diabetic medications that do not provide adequate glycemic control when combined with diet and exercise. At the time of screening, the doses and frequency of all anti-diabetic medications must have been stable for 8 weeks.
4. Subjects who have an estimated glomerular filtration rate (eGFR) ≥ 30 and < 60 mL/min/1.73 m^2 at 2 time points: screening (V1), and 1 additional time point between 1 and 12 months of screening (the most recent historical value may be obtained from available medical records). The eGFR will be calculated by the MDRD equation.
5. Subjects who have a body mass index (BMI) ≤ 45 kg/m^2 (inclusive)
6. Subjects who taking stable doses of medications for hypertension or hyperlipidemia for at least 30 days prior to randomization
7. Subjects who have stable eGFR between the most recent historic value and day of screening (no more than 20% change in eGFR).

Test Product, Dose, and Mode of Administration:
Bexagliflozin tablets, 20 mg or placebo, once daily by mouth

Duration of Treatment:
25 weeks: 1 week run-in, 24 weeks of treatment

Efficacy Assessments:

Primary efficacy assessment:

- Change of HbA1c from baseline to week 24

Secondary efficacy assessments:

- Change in body weight in subjects with baseline body mass index (BMI) ≥25 kg/m
- Changes in systolic blood pressure (SBP) over time in subjects with baseline SBP ≥130 mmHg
- Change in HbA1c over time in subjects with eGFR 45 to 59 mL/min/1.73 m^2
- Change in HbA1c over time in subjects with eGFR 30 to 44 mL/min/1.73 m^2

Samples for population PK analysis will be collected and the required plasma concentrations determined. The PK parameters will be assessed separately as part of the population PK analysis.

Safety Assessments:
Safety will be assessed based on an analysis of the adverse events record; of laboratory data, including hematology, serum chemistry, urinalysis, urinary electrolytes and creatinine; of electrocardiograms (ECGs), vital signs and physical examinations; and of concomitant medication use.

Statistical Methods:
In general, descriptive statistics will be presented for continuous variables, and frequency and percentage for categorical variables.

For the primary objectives, efficacy is defined as lowering of HbA1c at week 24 from baseline for bexagliflozin when compared to placebo. For the primary endpoint analysis, the primary analysis will utilize a mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA) approach, with treatment, visit, treatment-by-visit interaction and randomization stratification factors as the fixed effects terms and baseline HbA1c as a covariate on all available data, incorporating all visits from each patient at which HbA1c was measured in the intention-to-treat (ITT) analysis set. All observed data will be analyzed and data obtained after rescue will not be excluded. In addition, same analyses will be conducted in per-protocol (PP) analysis set (if it is deemed different from the ITT analysis set).

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following will be performed for the ITT analysis set:

1. Missing HbA1c data will be imputed via multiple imputation, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will not be excluded.

2. Missing HbA1c data will be imputed via last observation carried forward (LOCF), following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
3. HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be re-performed.

If the PP analysis set is different from the ITT analysis set, the same analyses as described above will be conducted in PP analysis set as well.

The effects of bexagliflozin on the secondary endpoints will be tested in a hierarchical testing strategy to preserve experiment-wide type I error at 0.05:

1. Superiority test of the change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2 in the bexagliflozin group compared to the placebo group
2. Superiority test of the change in systolic blood pressure (SBP) over time in subjects with SBP ≥ 130 mmHg in the bexagliflozin group compared to the placebo group
3. Superiority test of the change in HbA1c over time in subjects with eGFR 45 to 59 mL/min/1.73m^2 in the bexagliflozin group compared to the placebo group
4. Superiority test of the change in HbA1c over time in subjects with eGFR 30 to 44 mL/min/1.73m^2 in the bexagliflozin group compared to the placebo group

Additional effects of bexagliflozin on FPG, changes in HbA1c over time, proportion of subjects who reach an HbA1c < 7%, change in body weight over time, change in urine albumin-to-creatinine ratio (UACR) over time, and the general safety of bexagliflozin in subjects with T2DM will be analyzed. No hypothesis testing will be conducted and will not be adjusted for multiplicity.

For the primary efficacy endpoint, sample size calculation is based on a two-sided significance at the 5% level. Assuming 1.0% as the standard deviation for difference in mean changes from baseline in HbA1c between bexagliflozin and placebo, an estimated sample size of 133 in each arm will have 90% power to detect a difference in mean HbA1c changes of 0.40% between bexagliflozin and placebo. To account for an estimated dropout rate of 12%, we propose randomizing 150 subjects in each study arm.

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	angiotensin-converting enzyme
ADA	American Diabetic Association
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
CRF	case report form
CRO	contract research organization
CV	cardiovascular
DPP4	dipeptidyl peptidase 4
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FPG	fasting plasma glucose
γ-GTP	gamma-glutamyl transferase
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
h	hour
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HDPE	high density polyethylene
HF	heart failure
Hgb	hemoglobin
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
IC_{50}	inhibitory concentration 50%
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IND	Investigational New Drug
IRAE	immediately reportable adverse event
IRB	Institutional Review Board
ITT	Intention-to-treat
IWRS	Interactive Web Response System
KDOQI	Kidney Disease Outcomes Qualify Initiative
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
LDH	lactic dehydrogenase
MACE	major adverse cardiovascular event
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MODY	maturity–onset diabetes of the young
NYHA	New York Heart Association
OHA	oral hypoglycemia agent
PD	pharmacodynamics
PK	pharmacokinetics
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium glucose cotransporter 2
SMBG	self-monitored blood glucose
SOP	standard operating procedure
T2DM	Type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
UACR	urine albumin-to-creatinine ratio
UGE	urinary glucose excretion
ULN	upper limit of normal
UPT	urine pregnancy test
UTI	urinary tract infection
WOCBP	woman of child bearing potential
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality worldwide, affecting an estimated 387 million people in 2014 and reaching epidemic proportions in nearly all countries in the world. Approximately 179 million of those affected are estimated to be unaware of their condition and over 80% reside in low- and middle-income countries (International Diabetes Foundation, 2014). T2DM accounts for at least 90% of all diabetes cases. Despite the availability of several classes of therapeutics, the number of people with T2DM is projected to increase by 55% to over 590 million adults by 2035.

Chronic glycemic control is necessary to prevent the microvascular complications of T2DM, including nephropathy. Up to one-third of patients with T2DM have renal impairment (Coll-de-Tuero et al., 2012). While the progressive nature of T2D ultimately requires most patients with T2DM to require multiple therapies to maintain normal glucose levels (Inzucchi et al., 2012; Turner et al., 1999), many of these therapies are restricted in the context of renal impairment (Inzucchi et al., 2012). In addition, oral hypoglycemic agents (OHAs) commonly used, such as sulfonylureas, are associated with increased risks of hypoglycemia and weight gain particularly in patients with renal impairment (Cavanaugh, 2007), (Inzucchi et al., 2012), (1998a). Thus, novel effective therapies that can be used safely in patients with T2DM and renal impairment are needed.

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 been approved as a single agent or in combination with other hypoglycemic agents for the treatment of patients with T2DM (Vivian, 2015; Whalen et al., 2015). Although the effectiveness of SGLT2 inhibitors, measured by glucosuria, is reduced as the glomerular filtration rate (GFR) decreases, the drugs have been well tolerated in general and substantial amount of urinary glucose is disposed in diabetic patients with chronic kidney disease. The effectiveness of SGLT2 inhibitors for HbA1c reduction in patients with moderate renal impairment has been demonstrated in clinical trials of canagliflozin (Gilbert, 2014; Kohan et al., 2014), dapagliflozin (Yale et al., 2013), and empagliflozin (FDA Medical review empagliflozin, reference ID: 3402257, page 102/319). Although the efficacy varied, all SGLT2 inhibitors produced HbA1c reductions in patients with GFR between 45 and 60. The clinical efficacy in patients with GFR between 30 and 45 varied among different SGLT2 inhibitors (Scheen, 2015).

In a trial assessing the cardiovascular hazards of administration of empagliflozin (EMPA-REG), diabetic patients with increased cardiovascular risk were treated with empagliflozin or placebo in combination with standard of care for approximately 3 years. The primary

composite outcome of death, MI, and stroke (MACE) occurred in 10.5% of patients in the empagliflozin groups and in 12.1% of the patients in the placebo group. The MACE hazard ratio for patients with eGFR < 60 was 0.78 favoring empagliflozin and there was no statistically significant difference between patients with normal and impaired renal function (Zinman et al., 2015).

1.1 Bexagliflozin for the Treatment of Type 2 Diabetes Mellitus

Bexagliflozin is a potent and highly specific inhibitor of the SGLT2 with an *in vitro* IC_{50} of 2 nM or 0.9 ng/mL and a 2435-fold selectivity for human SGLT2 compared with SGLT1. Bexagliflozin elicits a prominent and predictable glucosuria in laboratory animals and human subjects.

1.1.1 Summary of Non-clinical Data with Bexagliflozin

The potential adverse effects of bexagliflozin have been evaluated in studies of non-clinical safety pharmacology, acute and chronic general toxicology, genotoxicity, acute and chronic reproductive toxicity and two-year carcinogenicity. Repeat dose toxicity studies have found exacerbation of chronic progressive nephropathy and gastric irritation, including sporadic ulceration, at the lowest observable dose level in male rats, as well as signs of reversible cardiac inflammation and abdominal distension at a dose level of 200 mg/kg in monkeys. Details of the adverse findings are provided in the Investigator's Brochure.

1.1.2 Summary of Clinical Data with Bexagliflozin

Theracos has completed eight phase 1 studies to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and drug metabolism in healthy subjects, subjects with T2DM, and diabetic subjects with renal impairment. Bexagliflozin was well tolerated by patients with normal and impaired renal function and produced clinically significant urinary glucose excretion (UGE), in patients with normal renal function and in patients with mild and moderate renal impairment. Patients with renal impairment experienced smaller increases in UGE versus patients with normal renal function. However, the amount of glucosuria experience by patients with mild and moderate renal impairment is anticipated to provide therapeutic benefit. Details of the pharmacology, efficacy, and safety assessments are described in the Investigator's Brochure and summarized in the following sections.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to determine the efficacy of bexagliflozin on lowering HbA1c in patients with T2DM and moderate renal impairment after 24 weeks of treatment.

2.2 Key Secondary Objectives

The key secondary objectives are:

- To assess the effect of bexagliflozin on the change in body weight at week 24 in subjects with baseline BMI ≥25 kg/m^2
- To assess the effect of bexagliflozin on the change in systolic blood pressure (SBP) at week 24 in subjects with baseline SBP ≥130 mmHg
- Change in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m^2 at week 24
- Change in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m^2 at week 24

Additional exploratory objectives are:

- Change in HbA1c over time in all subjects
- Proportion of subjects who reach target HbA1c of < 7% over time
- Changes in fasting plasma glucose (FPG) over time
- Proportion of ≥ 5% reduction of body weight in subjects with baseline BMI ≥ 25 kg/m^2 at week 24
- Change in body weight in all subjects over time
- Changes in SBP and diastolic BP over time in all subjects
- Change in albuminuria (urine albumin creatinine ratio or UACR) from baseline to week 24 in all subjects and in subjects with baseline macroalbuminuria (UACR ≥ 300)

2.3 Safety Objectives

The safety objective is the evaluation of the safety of exposure to bexagliflozin for 24 weeks.

An additional safety objective of this study is the contribution major adverse cardiovascular events (MACE) to an eventual meta-analysis that is intended to exclude excessive cardiovascular risks for subjects exposed to bexagliflozin compared to subjects exposed to placebo during the investigational phase of bexagliflozin.

2.4 Other Objective

Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted and will include approximately 144 subjects.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

THR-1442-C-448 is a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral administration of bexagliflozin at 20 mg versus placebo in subjects with T2DM, moderate renal impairment, and inadequate glycemic control.

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 suboptimal glycemic control despite diet and exercise or combination of diet and exercise and treatment as recommended in local guidelines and with moderate renal impairment will enter a screening period of between 3 and 21 days. The main eligibility criteria include: 1) male or female subjects with T2DM, 2) screening HbA1c of 7.0 to 10.5% (inclusive), and 3) estimate glomerular filtration rate (eGFR) $\geq$ 30 to < 60 mL/min/1.73 m^2 based on the serum creatinine at the screening visit and one additional time point between 1 and 12 months prior to screening (may be obtained from available medical records). The eGFR will be calculated by the modification of diet in renal disease study equation (MDRD). At the time of screening, the doses and frequency of all anti-diabetic medications must have been stable for 8 weeks.

3.2.2 Run-in Period

All eligible subjects will enter a one-week 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 (including OHAs and/or insulin) and will be instructed to take the run-in medication once daily for 7 and up to 9 days 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, hyperglycemia, or symptoms that may suggest ketoacidosis. Subjects will be trained to use the glucometer and record any events in the glycemic control diary. Adjustment of treatment for hypertension or dyslipidemia will not be permitted during the run-in period. If a change in treatment is required to appropriately manage dyslipidemia during the screening period, the subject may re-enter the screening as a new subject after the clinical condition and treatment regimen have not changed for at least 30 days. When re-screening, a new subject number will be assigned and all screening activities and assessments will be performed. Adjustment for anti-diabetic medication during the screening and run-in period is not permitted. Re-screening after adjustment for anti-diabetic medication is not recommended as it takes 12 weeks to establish an HbA1c stable baseline.

3.2.3 Treatment Period

Subjects who are compliant in taking run-in medication (missing no more than one dose), have screening eGFR ≥ 30 and < 60 mL/min/1.73 m^2, and have stable GFR (no more than 20% change in eGFR between a historical value and the value determined at the screening visit V1) will be eligible for randomization and receive double blind study drugs.

The treatment period for each study subject will start at randomization. Approximately 300 eligible subjects will be randomized at the end of the run-in period in a 1:1 ratio to receive once daily bexagliflozin tablets for 24 weeks. Randomization will be stratified by HbA1c level (value on screening visit V1 to be 7.0 to 8.5% or 8.6 to 10.5%), screening anti-diabetic treatment regimen (insulin treated or not) and eGFR (value on screening visit V1 to be 30-44 or 45-59 mL/min/1.73 m^2). At least 135 subjects in each of the eGFR groups must be enrolled.

The study subjects will be in contact with the study site at 2, 6, 12, 18, and 24 weeks post-randomization. The interactions at week 2 and week 18 will be conducted by phone unless a clinic visit is necessary.

At the start of the treatment period each subject will be provided with a bottle of double blind investigational product, dosing instructions, and a glycemic control diary in which to record information related to the occurrence of hyperglycemic or hypoglycemic events as well as symptoms that may suggest ketoacidosis. The subjects will be instructed to take the investigational product with water in the morning prior to eating. Additional medications for hyperglycemia (see Section 3.2.4) and for control of other medical conditions will be allowed if deemed medically necessary by the investigator, and will be recorded.

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 8 hours 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 diabetic ketoacidosis (DKA) or 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.

An assessment of bexagliflozin population pharmacokinetics (PK) will also be conducted to include approximately 144 subjects. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

Subjects will return to the clinic for a follow-up exit visit at Week 26 or two weeks after last dose of study drug if the subject terminates prior to Week 24. Following the exit visit, subjects will be advised to see their primary physician and resume standard treatment to

control their diabetes. The duration of the overall study is estimated to be approximately 30 weeks.

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.

3.2.4 Glycemic Control Monitoring

Subjects with hyperglycemia based on blood glucose levels during the treatment period may receive approved anti-diabetic medication. In addition, adjustment by the investigator to the pre-screening anti-diabetic therapies will be recommended if hypoglycemia occurs.

PLACEBO RUN-IN PERIOD

During the placebo run-in period subjects will be instructed to determine the SMBG daily after fasting overnight for a minimum of 8 h. If the fasting blood glucose is ≥ 250 mg/dL (13.9 mmol/L) the subject should contact the clinic and the investigator will determine whether the participant should attempt to improve diet and exercise to maintain glycemic control or if the participant must discontinue from the study and initiate a more intense pharmacological regimen for glucose control. Subjects with SMBG readings ≥ 250 mg/dL (13.9 mmol/L) and severe clinical signs or symptoms of hyperglycemia during the screening or run-in periods, including weight loss, blurred vision, increased thirst, increased urination, or fatigue should be excluded. Patients with symptomatic hypoglycemia should be withdrawn from the study if symptoms are severe.

MAIN TREATMENT PERIOD

During the main treatment period subjects will be advised to continue daily fasting SMBG measurements. Intensification of the anti-diabetic regimen should adhere to the guidelines described in Section 5.2.4 for "*Prescription of Rescue Medication*".

Study subjects should contact the clinic if any fasting SMBG is ≥ 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, or ≥ 200 mg/dL (11.1 mmol/L) between week 12 and week 24. Blood glucose values collected via SMBG will be reviewed at study visits by the investigator. In addition, hyperglycemia will be monitored by fasting plasma glucose (FPG) at each clinical visit except visit V2.

If hyperglycemia is identified through SMBG or FPG measurements, the investigator will determine whether the subject had fasted for a minimum of 8 hours prior to the morning blood draw to ensure that the glucose value is truly from a fasting sample. If proper fasting had not occurred, the subject will be asked to return for a repeat blood test within a week.

If a concomitant medication for hyperglycemia is to be prescribed, a sample must be drawn prior to the administration of the rescue medication so that an HbA1c value can be assessed. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not

recommended. The investigator should assess the benefits and risks of continuing metformin treatment for patients who have been taking metformin and whose eGFR falls below 45 mL/minute/1.73 m^2. Metformin therapy should be discontinued if the patient's eGFR falls below 30 mL/minute/1.73 m^2.

Subjects will be instructed to contact the clinic staff for hypoglycemia, defined as: 1) any SMBG value < 70 mg/dL (3.9 mmol/L); or 2) any symptoms of hypoglycemia that resolve with food intake, with or without an accompanying SMBG value. Hypoglycemia may also be detected by FPG values, measured by central laboratory at every clinic visit, except V2, using the same criteria as for SMBG values.

If recurring hypoglycemia (*i.e.*, clinically significant hypoglycemia occurring on multiple different days) is identified during the main treatment period, the dose and frequency of background (pre-screening) medical therapy for diabetes should be reduced at the discretion of the investigator. If the subject is taking insulin and OHA, the dose of insulin should be reduced first, and, if necessary to prevent further hypoglycemia, insulin should be discontinued before oral hypoglycemic agents are reduced. If the subject is taking only OHAs or GLP-1 agonist, the dose or frequency of these background medications can be reduced at the discretion of the investigator.

3.2.5 OTHER SAFETY MONITORING ACTIVITIES

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.

3.2.5.1 Renal Function

Evaluation and management of subjects with and at risk for acute kidney injury (AKI) should be performed during the study period based on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline in 2012 (KDIGO Clinical Practice Guideline for AKI, 2012). The classification/staging System for AKI is described in Appendix 3.

If serum creatinine increases suggesting a possible stage 1 AKI, the investigator should confirm the increase in serum creatinine within 48 h of learning the result and enter an AE into the CRF if the serum creatinine does not spontaneously returns to < 0.3 mg/dL from baseline. The investigator should encourage the subjects to maintain hydration and pursue any additional clinically relevant investigations to elucidate the cause or potential consequences of the decline in renal function. Study drug administration may be suspended if clinically indicated until the creatinine value returns to < 0.3 mg/dL from baseline. Serum creatinine should be monitored based on the investigator's judgment until creatinine returns to baseline level, within 0.3 mg/dL difference.

If serum creatinine increases or other signs suggesting a possible stage 2 or 3 AKI, the subject should be monitored daily and nephrology consultation or hospitalization within 24 h should be considered. Study drug administration should be stopped until the creatinine value returns to < 0.3 mg/dL from baseline. If potentially life-threatening conditions (*i.e.*, uremia,

pulmonary edema, arrhythmia, disseminated intravascular coagulation, hyperkalemia, metabolic acidosis) are present occurring in the setting of a possible stage 2 or 3 AKI event, the administration of study drug must be stopped and the medical monitor should be informed. The medical monitor will advise on whether the study drug can be restarted after the resolution of the potentially life-threatening condition. Local laboratory testing will be acceptable when immediate lab results are necessary for clinical assessment.

If interrupted, study drug may be reinitiated when serum creatinine returns to within 0.3 mg/dL of the randomization value or if renal function remains 0.5 mg/dL above the randomization value but an alternative cause of the worsened renal function has been identified. Dosing of study drug will be permanently discontinued if the subject is to start dialysis or other renal replacement therapies.

The renal function monitoring plan is summarized in Figure 1.

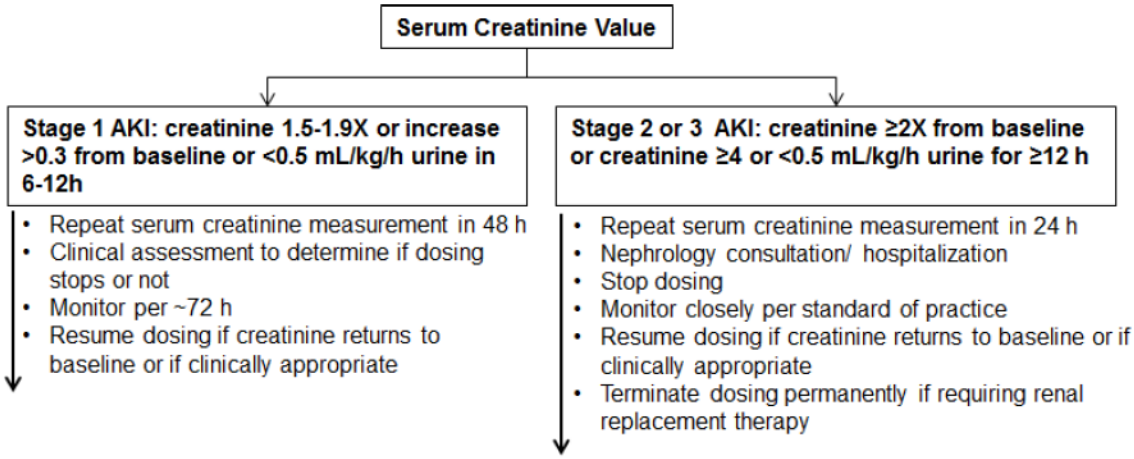


Figure 1. Renal Function Monitoring Plan

3.2.5.2 Diabetic Ketoacidosis

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 clinic and seek treatment should such signs and symptoms occur.

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

3.2.5.3 Major Adverse Cardiovascular Event (MACE)

An independent cardiovascular adjudication committee has been established to review, under blind, all potential cardiovascular events occurring during the study. The events of interest include cardiovascular mortality, myocardial infarction, stroke, hospitalization for acute coronary syndromes, hospitalization for heart failure, urgent revascularization procedures, and other possible serious cardiovascular events. The adjudicated events will be documented and archived to allow a meta-analysis to be performed at a later time.

3.2.5.4 Other General Safety Monitoring

The safety monitoring activities will include assessment of vital signs, physical examinations, urinalysis, blood chemistry, hematology, adverse events, and concomitant medication use. The occurrence of blood, liver, renal, or skin disorders will be monitored through laboratory testing and evaluation of adverse event documentation.

Adverse events of special interest as defined in the statistical analysis plan will include any clinical signs and symptoms that indicate adverse experience in the categories listed below. All such events must be appropriately documented within source documentation.

- Genital mycotic infections
- Urinary tract infections including urosepsis and pyelonephritis
- Diuretic effects including hypovolemia
- Hypotension episodes
- Hepatotoxicity
- MACE
- Hypoglycemia
- Falls and fractures
- Malignancies
- Hypersensitivity reactions
- Acid-base disorders
- Renal failure events
- Amputation

3.2.6 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent Data and Safety Monitoring Board (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.

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 (1998b)). 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. THR-1442-C-448 is designed to evaluate the safety and efficacy of bexagliflozin in the treatment of patients with T2DM and moderate renal impairment.

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 anti-diabetic medications if their hyperglycemia is not controlled.

The primary endpoint of reduction in HbA1c directly reflects improvement in glycemic control and is considered a well-validated surrogate for the long-term microvascular complications of diabetes mellitus. Results from previous clinical studies demonstrate a reduction in HbA1c in patients treated with bexagliflozin as compared with placebo.

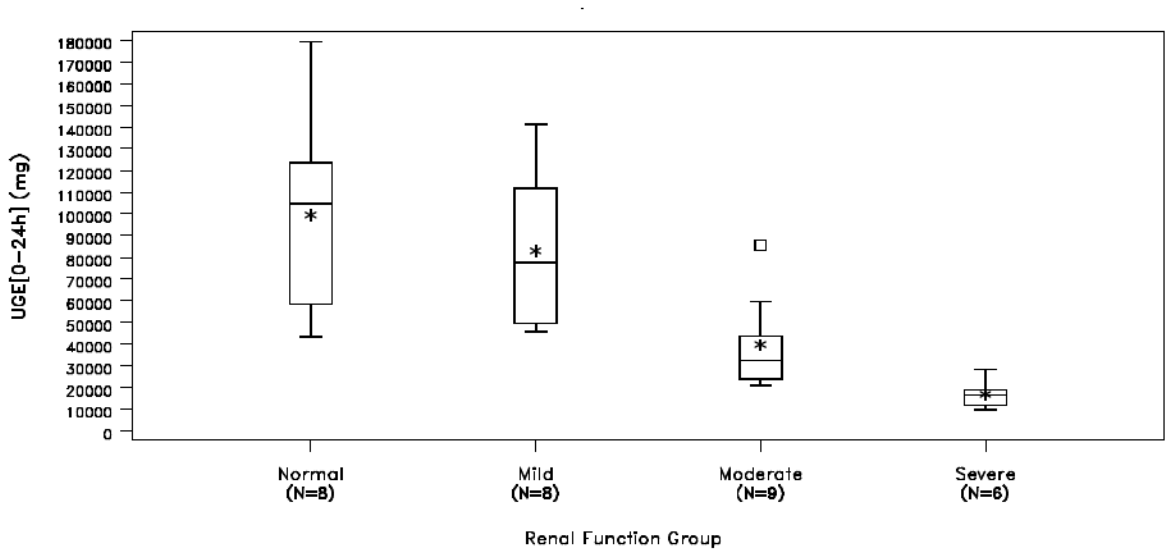
3.3.2 Rationale for the Study Population

EFFICACY CONSIDERATION

Results from published data in individuals with mutations in the gene encoding SGLT2, in healthy volunteers and patients that have been treated with other SGLT2 inhibitors, and in healthy volunteers and patients that have been treated with bexagliflozin at doses up to 100 mg indicate that the risk of induced hypoglycemia as a consequence of the loss of SGLT2 activity should be minimal. Clinical data in the previous studies indicate that bexagliflozin has been well tolerated for 96 weeks (study THR-1442-C-418).

The effect of a single dose of bexagliflozin has been tested in patients with T2DM and normal or impaired renal function (study THR-1442-C-424). Bexagliflozin was well tolerated by patients with normal and impaired renal function and produced clinically significant UGE in patients with normal renal function and in patients with mild and moderate renal impairment (Figure 2). Administration of bexagliflozin produced a mean glucosuria of 40 g/d in patients with moderate renal impairment (GFR 30 to 60) 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. The drug was also well tolerated by patients with severe renal impairment but produced a UGE level that is unlikely to provide therapeutic benefit. These findings provide rationale for examining the clinical efficacy in patients with T2DM and moderate renal impairment.



NOTE: Outer edges of the box denote the 25th and 75th percentiles. The horizontal line across the box denotes the median and the * denotes the mean. Outer limits of the box plot indicate the minimum and maximum values.

Figure 2. Glucosuria in patients with normal and impaired renal function

SAFETY CONSIDERATION

Bexagliflozin is primarily metabolized to inactive glucuronides by phase II metabolism and is cleared through renal or fecal excretion. Pharmacokinetic (PK) parameters of bexagliflozin and its principal metabolites were determined in patients with T2DM and renal impairment. Reduced clearance due to renal impairment was associated with a 34% or 54% higher systemic exposure in subjects with GFR between 30 and 60 mL/min/1.73 m^2 or below 30 mL/min/1.73 m^2, respectively. The half-life was extended from 6.5 h (GRF > 90) to 7.7 h (GFR < 30) with no accumulation of bexagliflozin or its major metabolites. Non-clinical and clinical studies have demonstrated high multiples of safety margins for bexagliflozin tablet, 20 mg. Given the modest increase in drug exposure, dose adjustment in patients with moderate renal impairment is not 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 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 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 moderate renal impairment, bexagliflozin tablets, 20 mg, will be administered in this trial.

3.4 Study Duration and Dates

In the planned study, diabetic subjects will be screened within 3 weeks prior to start of the run-in period. Eligible subjects who sign the written consent will start a 1-week run-in period prior to randomization to receive study drug. Subjects will receive 24 weeks of treatment. The overall study duration from screening until follow-up will be 30 weeks for study subjects. For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 300 subjects diagnosed with sub-optimally controlled T2DM who have moderate renal impairment. Eligible subjects who must be informed of the nature of the study and the potential risk and consent to participate in the study will be enrolled in clinical investigational sites in multiple countries.

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. Men or non-pregnant women ≥ 20 years of age. Women of childbearing potential must agree to use contraception during the entire study to avoid any possible pregnancy. Females who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible if they test negative on the urine pregnancy test.
2. Subjects with a diagnosis of T2DM with an HbA1c between 7.0 and 10.5% (inclusive) at the time of screening.
3. Subjects who are treatment naïve or are treated with a stable regimen of anti-diabetic medications that do not provide adequate glycemic control when combined with diet and exercise. At the time of screening, the doses and frequency of all anti-diabetic medications must have been stable for 8 weeks.
4. Subjects who have an estimated glomerular filtration rate (eGFR) ≥ 30 and < 60 mL/min/1.73 m^2 at 2 time points: screening (V1), and 1 additional time point between 1 and 12 months of screening (most recent historical value may be obtained from available medical records). The eGFR will be calculated by the MDRD equation (see Appendix 4)
5. Subjects who have a body mass index (BMI) ≤ 45 kg/m^2 (inclusive)
6. Subjects who take stable doses of medications for hypertension or hyperlipidemia for at least 30 days prior to randomization (if applicable)
7. Subjects who have stable eGFR between the most recent historic value and day of screening (no more than 20% change in eGFR between the most recent historical value and the value determined at the screening visit V1).

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, or hospitalization for unstable angina in the prior 3 months
9. Evidence of NYHA class IV heart failure at screening or randomization
10. Currently or within 3 months of taking an SGLT2 inhibitor from screening (Appendix 5)
11. 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
12. Women who are pregnant or breastfeeding
13. Patients who are receiving renal replacement therapy (peritoneal or hemodialysis) or who have undergone renal transplantation
14. Corrected serum calcium < 8 mg/dL (Appendix 4) at screening (V1) or randomization (V3)
15. Uncontrolled hypertension (systolic blood pressure > 170 or diastolic blood pressure > 110)
16. Currently participating in another interventional trial or receiving treatment with an investigational drug within 30 days or 7 half-lives of screening, whichever is longer
17. Previous treatment with bexagliflozin or EGT0001474
18. Missing more than 1 dose of the study drug during the run-in period
19. Fasting blood glucose value during the run-in period ≥ 250 mg/dL (13.9 mmol/L) associated with severe clinical signs or symptoms of hyperglycemia
20. Any episode of symptomatic hypoglycemia during the run-in period in which symptoms are severe
21. Subjects who are unable to read and write in their native language
22. Subjects who are unable to comprehend and willing to provide written informed consent in accordance with institutional and regulatory guidelines

5 STUDY TREATMENTS

5.1 Description of Treatments

Bexagliflozin tablets, 20 mg, and 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 drug products exhibit a greater than 75% release of drug substance by 8 h in simulated gastric fluid *in vitro*. The following investigational drugs 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 Rescue Medications for Hyperglycemia

If hyperglycemia is identified through SMBG or FPG measurements, the investigator will determine whether the subject has fasted for a minimum of 8 hours 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.

The investigator may prescribe rescue medication for hyperglycemia at any time it is deemed necessary for the well-being of the subject. A review of diet and exercise counseling is suggested prior to prescription of rescue medication in the absence of specific medical indications for rescue medication. Rescue medication is suggested if:

1. more than 3 consecutive, daily, fasting SMBG measures are ≥ 270 mg/dL (15 mmol/L) from week 1 to week 6, ≥ 240 mg/dL (13.3 mmol/L) from week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) from week 12 to week 24, or

2. fasting SMBG values are ≥ 250 mg/dL (13.9 mmol/L,), associated with clinical signs or symptoms of hyperglycemia (e.g. weight loss, blurred vision, increased thirst, or increased urination, or fatigue), and the signs or symptoms are severe.

A medication given to treat hyperglycemia will be considered a rescue therapy for hyperglycemia only if it is continued for 2 weeks or longer. 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.

The investigator may provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated, with the exception of an SGLT2 inhibitor, as study subjects may already be taking a drug in that class as a consequence of being randomized to receive bexagliflozin. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended. The investigator should assess the benefits and risks of continuing metformin treatment for patients who have been taking metformin and whose eGFR falls below 45 mL/minute/1.73 m^2. Metformin treatment should be discontinued if the patient's eGFR falls below 30 mL/minute/1.73 m^2.

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

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 at the discretion of the investigator.

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.

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 8 hours prior to the collection of blood samples. During the fasting period, only water will be permitted.

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 30 randomized 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 to receive investigational product. The treatment period for each study subject will start at randomization. Approximately 300 eligible patients will be randomized at the end of the run-in period in a 1:1 ratio to receive once daily bexagliflozin tablets for 24 weeks. Randomization will be stratified by HbA1c level (7.0 to 8.5% or 8.6 to 10.5%), screening anti-diabetic treatment regimen (insulin treated or not) and screening eGFR (30-44 or 45-59 mL/min/1.73 m^2).

Subject randomization will be deactivated for all sites when the planned number of subjects is met. However, if a potential subject is in run-in period already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized.

5.5 Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the cardiovascular adjudication committee members will be blinded to the study medication. 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 assignment, the results of urinary glucose testing will not be made available to any study personnel or subjects.

If knowledge of the treatment 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 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 treatment assignment will continue to be withheld from the cardiovascular adjudication committee members until all global investigational studies are completed and a meta-analysis to assess cardiovascular risk is conducted.

5.6 Concomitant Therapy

During the course of the study investigators will manage glucose, blood pressure, lipid levels, and anemia according to local or regional standard of care guidance documents for the management of T2DM and other comorbidity or disease as issued by the relevant professional bodies (e.g. ADA, the National Kidney Foundation, etc.). Subjects should be provided access to all additional therapies and interventions during the course of the study 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 anemia, or dyslipidemia during the screening period, the subject may re-enter the screening after the clinical condition and treatment regimen have not changed for at least 30 days. If it is medically necessary to alter blood pressure medications during the first 12 weeks of the treatment period to mitigate symptomatic hypotension, new diuretic medications should not be initiated and the dose and frequency of existing diuretic medications should not be increased. Changes to the dose or frequency of anti-hypertensive and diuretic medications must be recorded in the concomitant medications log.

Subjects who do not meet protocol-specified glycemic targets at specified time points during the study may 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 (Section 5.2.4 Rescue Medications for Hyperglycemia).

Subjects may receive any medications for AEs that are necessary in the investigators' judgments. Any medication prescribed to a subject after enrollment and prior to randomization, including contraceptives, must be recorded in 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.

5.7 Restrictions

5.7.1 Prior Therapy

All subjects will continue regimens for medical conditions during the study as indicated above. No subject shall have been treated with an investigational drug within 30 days of screening or within a period equal to less than 7 half-lives of the investigational drug,

whichever is longer. 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 8 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, glucometer record, 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 1-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. 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. There will be no intra-subject dose escalation or back-titration.

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 label 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, the investigational drug caution statement, and any other required study drug information.

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, a designated space for subject number, storage conditions, sponsor's name, manufacturer's name and address, investigator's name, expiration date, the investigational drug caution statement, and any other required study drug information.

5.10 Storage and Accountability

Bexagliflozin tablets will be stored in a secure area with limited access at controlled room temperatures of 15°C to 30°C (59°F to 86°F) until ready for dispensing to study subjects. The sponsor will notify the sites of the process for returning unused drug.

5.11 Investigational Product Retention at Study Site

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 clinic 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. At the last day of dosing (V8 visit), the study drug bottle and any remaining tablets will be collected from the patient and stored at the site until the close-out visit. All unused drug must be returned to a sponsor-designated depot after the sponsor or its designee verifies drug accounting.

6 STUDY PROCEDURES

6.1 Phone Interview

Some scheduled visits will be conducted by phone. During a phone interview, the investigator or designee will review the daily SMBG and glycemic control record with the subject. Potential AEs and change in medication use should be queried. An additional clinic visit may be scheduled if clinically necessary.

6.2 Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The investigator should educate potential subjects about the scientific importance of their data and the vital role that their participation has for the outcome of the entire study. The subject must be informed that he/she is free to withdraw from the study at any time. He or she will receive all information that is required by national regulations and Good Clinical Practice (GCP) guidelines.

The informed consent document must be signed and dated; one copy will be given to the patient, and the investigator will retain a copy as part of the clinical study records. The investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

6.3 Screening for I/E Criteria

At the initial screening, the investigator should review the inclusion and exclusion criteria based on the information collected at the screening visit. He or she should evaluate any change to status affecting conformance to inclusion and exclusion criteria at subsequent visits prior to randomization. At randomization, the investigator should confirm the run-in drug compliance.

6.4 Medical History

The following information will be collected at the screening visit:

6.4.1 General Demographics and Characteristics

1. Date of birth, age, sex, and race, and whether a female subject is of childbearing potential or not.
2. Significant medical and surgical history, including dates of diagnoses and procedures and whether the condition is ongoing, if applicable.

6.4.2 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.

6.4.3 Renal and Cardiovascular Disease History

1. Chronic kidney disease stage, based on KOQI CKD classification and duration (Appendix 3)
2. Currently receiving erythropoiesis-stimulating agent (ESA) for anemia and time of starting ESA
3. History of bone disease
4. History of disorders of calcium and phosphorus metabolism or hyperparathyroidism
5. History of neuropathy
6. History of cardiovascular disease including presence of angina, congestive heart failure (including NYHA classification), known atherosclerotic cardiovascular disease, prior MI, transient ischemic attack or stroke, and prior cardiac or peripheral re-vascularization procedures. The history should include the date of diagnosis and the current status of diagnosis (resolved or ongoing).

6.4.4 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, iron supplement, 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.

6.5 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.

6.6 Physical Examination

A complete physical examination will be performed by the investigator at the time points indicated in the Schedule of Events (Appendix 1). The examination will include a general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, and extremities.

6.7 Abbreviated Physical Examination

An abbreviated physical examination will include measurement of height at screening V1 only and a general assessment of the skin, heart, lungs and abdomen. The investigator will perform abbreviated physical examinations at the time points indicated in the Schedule of Events (Appendix 1), unless clinically indicated.

6.8 Body Weight

Total body weight will be determined in every clinical visit except visit V2. The weight must be determined using a scale that is calibrated. Every effort should be made to use the same scale throughout the study duration.

6.9 Vital Signs

Vital signs will be measured at the time points indicated in the Schedule of Events (Appendix 1) and will include supine, sitting and standing BP measurements, and heart rate. Only the BP measured in the sitting position will be used to determine eligibility.

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 at the screening visit or during the study for BP measurements, the reason should be documented, and the right arm should be used for BP measurements for all subsequent 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 min 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 min 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 min of standing. For standing BP measurements, the arm should be supported and extended such that the cuff is at heart level.

6.10 Electrocardiography

A 12-lead electrocardiogram (ECG) will be conducted at the time points indicated in the Schedule of Events in Appendix 1 and whenever clinically indicated. This procedure should be performed in the supine position after at least 10 min of rest. 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.

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 does not necessarily need to be made the first time an abnormal result is observed. The investigator may repeat the ECG to verify 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.

6.11 Clinical Laboratory Tests

Clinical laboratory test parameters are listed in Table 1.

Table 1. List of Laboratory Tests

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

6.11.1 Sample Collection, Storage, and Shipping

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

Blood samples for hematology, chemistry, serum lipids and glycemic control assessments will be collected. Subjects will be in a seated or supine position during blood collection. Samples will be collected at the time points indicated in 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 minimal of 8 h fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for a minimal of 8 h, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting.

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 triglycerides are >350 mg/dL at screening visit. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only.

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 turnaround time is necessary to determine treatment plan.

6.11.1.2 Urinalysis

Urine samples will be collected routinely at designated clinic visits from a clean catch sample. Urinalysis will be performed at the time points indicated in the schedule of events (Appendix 1 and Appendix 2). 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. 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 CEC members will remain blinded to the dosing assignment.

In addition, strips to assess leukocyte esterase and nitrite but not glucose will be provided for immediate assessment at the clinical sites. If more than traces of positive results are shown in the leukocyte esterase and /or nitrite testing, a urine culture should be performed in a designated laboratory regardless of patient reported signs or symptoms. Results of the urinalysis and possible urine culture will be documented in the CRFs.

6.11.1.3 Renal function testing

Serum creatinine will be measured as part of the serum chemistry at the scheduled clinical visits. UACR will be determined at time points specified in the schedule of laboratory tests (Appendix 2).

At the screening and randomization visits (V1 and V3), serum samples must be submitted to the central laboratory for serum creatinine testing. The serum creatinine value determined at the screening visit by the central laboratory will be the value for assessing eligibility, assigning stratum at randomization, and the central lab serum creatinine value determined at the randomization (V3) will be the baseline value for the data analyses.

During the study period, if a rapid turnaround time is necessary for clinical assessment of a potential kidney injury, testing from local laboratories should be used.

6.11.1.4 Population PK Sampling

Blood samples for the population PK analysis will be drawn when the subjects return to the clinic between weeks 6 and 12 from 144 subjects who consent to participating in the PK study in participating 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 72 subjects will be sampled at 0.25 to 1 h, 7 to 10 h, and 20 to 24 h post dose (routine 1). Another 72 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 dose does not need to be taken at the clinic however the precise dosing time and sample draw time must be recorded in the CRF.

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 at the site. Processed frozen plasma samples will be transferred on dry ice to the central laboratory at specified shipment intervals and will be stored at or below -20° C until analysis.

Plasma concentrations of bexagliflozin will be determined by a validated LC-MS/MS method. Approximately 216 measurements of bexagliflozin plasma concentrations will be collected from an estimated 72 subjects who will have received active drug in this study.

6.12 Diary and Glucometer Record Review

Review glycemic control diary, glucometer record, and symptoms that may indicate potential DKA with the subject and record the findings in the CRF.

6.13 Dispensing Run-in Drug

Each eligible study subject will receive one bottle of run-in drug based on the scheduled visit outlined in Appendix 1.

Patients should self-administer first dose of run-in drug with 250 mL of water under observation during the scheduled visit.

6.14 Randomization

Subjects who have met all the inclusion criteria and none of the exclusion criteria at the end of the run-in period will be randomized to receive investigational product using the IWRS. A randomization number and a drug kit number will be assigned to the subject. The subject should be instructed to refrain from taking the run-in medication on the day of randomization. The date and time of the last dose of run-in drug should be recorded. Subject will take the first dose of the double-blind study drug at the clinic.

6.15 Dispensing Investigational Product

At randomization and at week 12, each study subject will receive one bottle of the investigational product based on the kit number assigned to the subject by the IWRS. One bottle of the investigational product will provide daily dosing for 12 weeks.

Patients should self-administer first dose of investigational product with 250 mL of water under observation during the scheduled visits, if they have not already taken investigational product that day.

6.16 Adverse Events Assessments

6.16.1 Definition of Adverse Events

Adverse event (AE*)*: Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment.

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

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 this context refers to an event in which the subject 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,
- is a congenital anomaly/birth defect, or
- is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject 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 events in which 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 in 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.

6.16.2 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 investigators responsibility to review the results of all laboratory tests as they become available. For each abnormal laboratory test result the investigator needs to 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 6.16.11.

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 sponsors 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.

6.16.3 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 hours 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. The CRF AE form should be completed and sent to the sponsor.

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.

6.16.4 Pregnancy

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. Acceptable birth control methods 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.

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

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives.
- Contraceptives in current use.
- 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 be enrolled or remain 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 test 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 a sponsor Medical Monitor or designated personnel.) The investigator must notify the Medical Monitor within 3 working days of any female subject who becomes 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 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, any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of six months.

6.16.5 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 in 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.

6.16.6 Follow-up of Non-Serious AEs

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

6.16.7 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 the sponsor according to the reporting procedures outlined in Section 6.16.3. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these SAEs 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 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.

6.16.8 Urinary Tract Infections (UTIs)

Events potentially representing UTIs, including 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 visit for symptoms that may be related to a UTI and, if appropriate, document these events as symptomatic UTI in the CRF unless an alternative diagnosis is present. In addition, a clean catch urine sample will be obtained and a urinalysis will be performed on that sample at every clinical visit except the visit V2. 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 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.

6.16.9 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.

6.16.10 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 hour to confirm the hepatic enzyme elevation and should be repeated based on the clinical situation at least every 96 hour (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
- 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.

6.16.11 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 of hypoglycemia. During the study the subject is expected to record daily SMBG readings and all signs and symptoms that may potentially reflect hypoglycemia. In the event of such signs or symptoms, 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 for each hypoglycemic event:

1. Signs and symptoms attributed to hypoglycemia and the time and date on which they occurred
2. SMBG reading at the time of the signs and symptoms attributed to hypoglycemia
3. Time elapsed from the most recent meal to the onset of signs and symptoms
4. 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
5. SMBG reading 15 minutes after treatment with carbohydrate and the time at which this was measured
6. Whether or not the signs and symptoms attributed to hypoglycemia resolved after blood glucose returned to normal.

Subjects are encouraged to call the study clinic should signs and symptoms potentially related to hypoglycemia occur.

At each study visit, the investigator is expected to review the glucometer 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 that 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 critical 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 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.

6.16.12 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. Investigators will follow all subjects 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 heart failure (HF)
- Reported coronary revascularization procedure

6.16.13 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 clinic and seek treatment should such signs and symptoms occur.

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

6.16.14 Renal failure events

Renal function and potential AKI will be monitored closely as described in Section 3.2.5.1. Events potentially representing renal failure events, including reversible and irreversible AKI, oliguria, and use of renal replacement therapy, etc. should be evaluated with documentation of signs, symptoms, laboratory results, and treatment.

6.16.15 Amputation

Amputation and related adverse events will be recorded in a dedicated case report form. During each study visit, the investigator should query the subject for any amputation and related adverse events and procedures. 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.

6.17 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 and continued for more than 2 weeks 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 on the CRF. This documentation should continue until the subjects complete the study.

Insulin and its route of administration will be recorded as total daily dose.

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 (ATC) classification code 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.

6.18 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 investigator 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**.** Investigator should encourage a subject to remain in the study even if the investigational product administration is stopped so that safety information can be collected.

Participation in a clinical trial is voluntary. A subject can withdraw from the study at any time. The sponsor or investigator may terminate the study for medical or administrative reasons. 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 adverse event has occurred,
3. A clinically significant change in a laboratory parameter has occurred,
4. The sponsor or investigator 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.

6.19 Appropriateness of Measurements

HbA1c is a widely used measure of chronic glycemia, reflecting average blood glucose levels over an approximately 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 (3 days to 3 weeks before run-in period, Visit V1)

- Explain the content of the informed consent materials to the subject and collect signed informed consent
- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Obtain medical history and demographic information
- Perform an abbreviated physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Perform a 12-lead ECG measurement
- Draw blood if a minimum 8-h fast has been completed by the subject as described in Section 6.11.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample

7.2 Visit V2 (Start of Run-in)

- Counsel subject on appropriate diet and exercise
- Dispense run-in kit for run-in period
- Assess adverse events and DKA assessment
- Record medications used

7.3 Visit V3 (Randomization)

- Perform a complete physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Draw blood if a minimum 8 hour fast has been completed by the subject as described in Section 6.11.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample
- Review SMBG and glycemic control record
- Confirm the eligibility and perform the randomization procedures
- Record drug accountability, collect run-in bottle and dispense investigational product based on randomization
- Adverse events & DKA Assessments
- Record medications used

7.4 Visit V4 (week 2)

- Review SMBG and glycemic control record
- Record drug accountability
- Adverse events & DKA Assessments
- Record medications used
- This is a phone visit. A site visit may be scheduled if clinically needed.

7.5 Visit V5 (week 6)

- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Draw blood if a minimum 8-h fast has been completed by the subject as described in Section 6.11.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers. Alternatively, blood samples can be on any of the days during the week of the clinical visit
- Review SMBG and glycemic control record
- Record drug accountability
- Adverse events & DKA Assessments
- Record medications used

7.6 Visit V6 (week 12)

- Perform an abbreviated physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Draw blood if a minimum 8-h fast has been completed by the subject as described in Section 6.11.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers. Alternatively, blood samples can be on any of the days during the week of the clinical visit.
- Review SMBG and glycemic control record
- Record drug accountability, collect previous investigational product bottle and dispense new bottle of investigational product based on randomization
- Adverse events & DKA Assessments
- Record medications used

7.7 Visit V7 (week 18)

- Review SMBG and glycemic control record

- Record drug accountability
- Adverse events & DKA Assessments
- Record medications used
- This is a phone visit. A site visit may be scheduled if clinically needed.

7.8 Visit V8 (week 24)

- Perform an abbreviated physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Draw blood if a minimum 8-h fast has been completed by the subject as described in Section 6.11.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample
- Perform a 12-lead ECG measurement
- Review SMBG and glycemic control record
- Record drug accountability and collect previous investigational product bottle
- Adverse events & DKA Assessments
- Record medications used

7.9 Visit V9 (week 26)

- Perform an abbreviated physical examination
- Measure body weight
- Measure vital signs, including blood pressures and heart rate
- Draw blood if a minimum 8-h fast has been completed by the subject as described in Section 6.11.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample
- Review SMBG and glycemic control record
- Adverse events & DKA assessments
- Record medications used

7.10 Early Termination Procedures

Subjects removed from the study due to drug related toxicity will be followed until resolution or stabilization of the adverse event. Sponsor must be notified in the event that a subject withdraws or is withdrawn from the study.

Subjects who withdraw consent and have received study drug will have a follow-up examination, two weeks after the last dose of study drug, following the schedule of events as outlined in visit V8.

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 SOPs 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 complete statistical analysis plan will be developed as a separate document and will be the final plan. All statistical analyses will be performed using Version 9.2 or later of Statistical Analysis Software (SAS®).

In general, descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) will be presented for continuous variables, and frequency and percentage for categorical variables.

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

The primary superiority test on lowering of HbA1c at week 24 from baseline for bexagliflozin when compared to placebo will be conducted at 0.05 level of significance. If it is successful, the following hierarchical testing strategy will be followed in testing secondary efficacy end points in order to preserve experiment-wide type I error at 0.05:

1. Superiority test of the change in body weight in subjects with baseline body mass index (BMI) $\geq$ 25 kg/m^2 in the bexagliflozin group compared to the placebo group
2. Superiority test of the change in systolic blood pressure (SBP) over time in subjects with SBP $\geq$ 130 mmHg in the bexagliflozin group compared to the placebo group
3. Superiority test of the change in HbA1c over time in subjects with eGFR 45 to 59 mL/min/1.73m^2 in the bexagliflozin group compared to the placebo group
4. Superiority test of the change in HbA1c over time in subjects with eGFR 30 to 44 mL/min/1.73m^2 in the bexagliflozin group compared to the placebo group

9.2 Determination of Sample Size

Approximately 300 subjects will be randomized and equally allocated to receive bexagliflozin tablets, 20 mg, or placebo.

The sample size calculation for this study is based on a two group t-test with a two-sided significance at the 5% level and the following assumptions:

1) The placebo-corrected population mean change from baseline to Week 24 in HbA1c in the dose group of 20 mg will be -0.4%.
2) The pooled standard deviation for the change from baseline to Week 24 in HbA1c for the active and placebo groups will be 1.0%.

Under the above assumptions, an estimated sample size of 133 evaluable subjects per treatment arm yields approximately 90% power to detect a treatment difference between bexagliflozin and placebo. A sample size of 150 per arm has been selected to account for a

potential 12% drop-out and to allow adequate safety evaluation. The total sample size for this study will be 300 subjects.

This study will be conducted at multiple investigative sites and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but will be capped at 30 subjects from each site.

9.3 Analysis Populations

9.3.1 Intention-to-treat Analysis Set

All subjects who are randomized will be included in the Intention-to-treat (ITT) Analysis Set. All analyses of the ITT analysis set will be based on each subject's randomized assigned treatment. The ITT analysis set will serve as the primary set for the efficacy analyses.

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 a subject was actually taken. The Safety Analysis Set is the primary analysis set for safety evaluation.

9.3.3 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will include all subjects in the ITT analysis set who meet the study eligibility requirements and have no major protocol deviations that 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.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively based on the ITT and PP (if applicable) analysis sets for each treatment group as well as for all subjects combined. Key variables include age, gender, race, ethnicity, baseline HbA1c values, blood pressure, body weight, body mass index (BMI in kg/m^2), fasting plasma glucose level, eGFR, and anti-diabetic treatment status at screening (including type of therapy used [treatment naïve, metformin, sulfonylurea, DPP-4 inhibitor, alpha-glucosidase inhibitor, GLP-1 agonist, insulin). In general, baseline measurement is defined as the last measurement prior to the first dose of double-blind medication.

9.5 Analysis of Efficacy

All efficacy analyses will be performed based on the ITT analysis set. The primary endpoint analysis will also be conducted using the PP Analysis Set (if deemed different from ITT analysis set).

For the primary endpoint of HbA1c change from baseline over 24 weeks of treatment, the MMRM analysis of covariance model (ANCOVA) with baseline HbA1c as a covariate will be fitted to the available data, incorporating all visits at which HbA1c was measured for each subject including the scheduled and the unscheduled visits for measurement of HbA1c (NationalResearchCouncil, 2010). Treatment, visit, treatment-by-visit, and stratification factors for randomization (HbA1c level [7.0 to 8.5% or 8.6 to 10.5%), screening anti-diabetic treatment regimen [insulin treated, other], eGFR [30-44 or 45-59 mL/min/1.73m^2] will be applied as fixed effects. From this model, an estimate of the treatment difference at week 24 will be generated, as will an assessment of whether this estimate is significantly different when comparing at a two-sided 0.05 level of significance. An unstructured within-patient covariance structure will be assumed. If 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 this primary analysis.

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following will be performed:

1) Missing HbA1c data will be imputed via multiple imputation (MI), following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will not be considered missing.
2) Missing HbA1c data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
3) HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be re-performed.

If it is deemed that the PP analysis set is different from the ITT analysis set, same analyses as described above will be conducted in PP analysis set as well.

9.5.1 Analysis of Dropouts Pattern

The early termination rate is estimated to be 12%. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct.

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.

9.6 Secondary Efficacy Analyses

To assess the treatment effect on the change of body weight in subjects with baseline BMI $\geq$ 25 kg/m^2 at week 24, an analysis of covariance model (ANCOVA) will be implemented using all available data at week 24 (values obtained after the start of rescue medication will not be excluded in the analysis). MMRM modeling approach will be utilized. The model will include treatment, visit, treatment-by-visit, randomization stratification factors, and the

baseline weight value as fixed effects/covariates. Least squares mean treatment differences between the bexagliflozin and placebo will be estimated from the model. The corresponding 95% CI and p-value will be provided.

The change in systolic blood pressure (SBP) in subjects with baseline SBP ≥ 130 mmHg in the bexagliflozin group compared with placebo at week 24 will be analyzed using the similar method with baseline SBP measure as a covariate. The same analysis method applies for the testing of changes in HbA1c at week 24 for subjects with baseline eGFR 45-59 mL/min/1.73m^2, and for subjects with baseline eGFR 30-44 mL/min/1.73m^2.

All analyses will be conducted in ITT analysis set. A hierarchical testing procedure will be applied to above four endpoints in the sequence provided in Section 9.1.

9.7 Other Efficacy Analyses

Changes in HbA1c, FPG, SBP/DBP, body weight, and albumin level in urine for all subjects during the treatment period will be summarized descriptively by each time point (i.e., Weeks 6, 12, 24). In addition, these endpoints may be analyzed using a similar MMRM model as used for the primary analysis of HbA1c to compare bexagliflozin with placebo.

Cumulative summary on the proportion of subjects achieving HbA1c < 7%, and the proportion of subjects achieving body weight reduction of at least 5% will also be presented.

Analyses will be conducted using ITT analysis set.

9.8 Analysis of Safety

All safety analyses will be conducted based on the Safety Analysis Set.

Safety data will include AEs, physical exam results, vital signs, ECG results, and clinical lab measurements of serum chemistry, hematology, serum lipids, glycemic control parameters and urine specimens. Observed data will be summarized using descriptive statistics by treatment group based on the Safety Analysis Set.

9.8.1 Adverse Events

Adverse events will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). AE records that begin at or after the first administration of investigational products are considered treatment emergent AEs (TEAEs). The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred term. Further summaries by severity, and by relationship to study treatment will also be provided. 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 serious AEs, 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.

9.8.2 Adverse Events of Special Interest

Adverse events of special interest include UTI, GMI, diuretic effects, hepatotoxicity, hypoglycemia, MACE, fracture, malignancy, hypersensitivity reactions, hypotensive episodes, acid base disorders, DKA, renal failure and amputation. These will be prospectively identified based on the MedDRA preferred terms in the adverse event log by a medical expert prior to the data base lock and unblinding of the individual subject treatment assignment. The list of adverse events of special interest will be confirmed in a peer review process.

The number and percentage of subjects experienced TEAE of special interest will be summarized for each treatment group by types of events. The incidence rate of adverse events of special interest per 100 patient years will also be summarized. Additional analyses will be specified in the statistical analysis plan to evaluate other event associated safety parameters and potential risks in subpopulations based on age, gender, or other baseline characteristics (if sample size allows).

9.8.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory parameters will be measured at baseline, during the treatment period and at follow-up. These variables include vital signs (blood pressure, pulse, respiration rate, and temperature), clinical laboratory outcomes and ECG data. They will be summarized as actual values and changes from baseline by treatment for each visit for selected parameters.

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.

9.8.4 Physical Examination

Abnormal findings will be presented in a by subject listing.

9.9 Interim Analysis

There will be no interim analysis. The final analysis will be performed after all subjects have completed the follow up assessments and all subject data have been cleaned and locked in the study database.

An independent Data and Safety Monitoring Board (DSMB) will monitor the safety of the subjects in this study. The objectives of the DSMB are to assess drug safety and to allow for protocol modification or early stopping due to safety concerns.

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 or Independent Ethics Committee Approval

The study protocol, informed consent document, relevant supporting information, and all types of subject recruitment or advertisement information must be submitted to the Institutional Review Board (IRB) or Independent Ethics Committee (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 International Conference of Harmonisation GCP Guidelines (E6) 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 ICH GCP guidelines.

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 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 for subject withdrawal must be recorded in the case report form.

Entries made in the CRF must be verifiable against source documents. Source documents are defined as all medical records, medical notes, laboratory results, ECG traces and any additional document other than the CRF that has original subject information contained within it.

All CRFs and source documents should be completed following GCP and the CRO's standard operating procedures.

10.8 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will monitor overall safety information during the bexagliflozin development program. The safety review activity and potential risk benefit assessments utilized by the DSMB will be defined in its charter.

10.9 Protocol Violations/Deviations

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 if 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.

Protocol violations/deviations must be reported in the final study report.

10.10 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.

10.11 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.

10.12 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 the 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 Theracos Sub, LLC and the investigator. If results of this study are reported in medical journals or at meetings, all subjects' identities will remain confidential.

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Appendix 1 Schedule of Events

Procedure	Screening	Run-in	Treatment						Follow-up
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Time to Randomization	**3 days - 3 weeks to V2**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**26**
Informed Consent	X								
Screening for I/E Criteria	X		X						
Medical History	X								
Diet and Exercise Counseling		X							
Physical Examination			X						
Abbreviated Physical Examination	X					X		X	X
Weight	X		X		X	X		X	X
Vital Signs	X		X		X	X		X	X
Electrocardiography	X							X	
Clinical Laboratory Tests	X		X		X	X		X	X
Urinalysis	X		X		X	X		X	X
Population PK Sampling					X	X			
Diary and Glucometer Record Review			X	X	X	X	X	X	X
Dispensing Run-in Drug		X							
Randomization			X						
Dispensing Investigational Product			X			X			
Adverse Events & DKA Assessments		X	X	X	X	X	X	X	X
Concomitant Medication Assessments		X	X	X	X	X	X	X	X

Appendix 2 Schedule of Laboratory Tests

Procedure	**Screening**	**Run-in**	**Treatment**						**Follow-up**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Time to Randomization Visit (weeks)	3 days - 3 weeks to V2	-1	0	2	6	12	18	24	26
Hematology	X		X		X	X		X	X
Serum Chemistry and Electrolytes	X		X		X	X		X	X
Glycemic Control	X		X		X	X		X	X
Serum Lipids	X		X			X		X	X
Urinalysis	X		X		X	X		X	X
UACR	X		X					X	X
Urine Pregnancy Test (WOCBP)	X		X		X	X		X	X
Population PK sampling					X	X			

Appendix 3 KDOQI Chronic Kidney Disease Classification and Acute Kidney Injury Stage Definition

Chronic kidney disease (CKD) is defined as either kidney damage or GFR < 60 mL/min/1.73 m^3 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (NFK KDOQ guidelines).

Stages of CKD are outlined in Table 2.

Table 2. KDOQI CKD Stages

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑↓GFR	≥ 90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	< 15 (or dialysis)

Acute kidney injury stages based on the Definition by the Acute Kidney Injury Network (AKIN) are outlined in Table 3 (KDIGO Clinical Practice Guideline for AKI, 2012).

Table 3. Classification/Staging System for Acute Kidney Injury

Stage	Serum creatinine criteria	Urine output criteria
1	1.5 to 1.9 times baseline or ≥ 0.3 mg/dL (≥ 26.5 µmol/L) increase from baseline	<0.5 mL/kg/h for 6 to 12 h
2	2.0 to 2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 h
3	3.0 times baseline, or Increase in serum creatinine to ≥4.0 mg/dL (≥ 353.6 µmol/L), or Initiation of renal replacement therapy, or In patients < 18 years, decrease in eGFR to < 35 mL/min per 1.73 m^2	< 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

Appendix 4 Estimating GFR and Correcting Calcium

eGFR

The equation for estimating glomerular filtration rate (GFR) from serum creatinine is the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) study equation. This eGFR calculator applies serum creatinine (Scr) reported in mg/dL.

The eGFR should be calculated based on following equation

eGFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

The eGFR for Japanese subjects should be calculated based on following equation (Matsuo et al., 2009) :

eGFR (mL/min/1.73 m^2) = 194 × $(Scr)^{-1.094}$ × $(Age)^{-0.287}$× (0.739 if female)

Corrected Serum Calcium

Corrected serum calcium = 0.8 * [4 g/dL– measured serum albumin [in g/dL]) + measured calcium [in mg/dL]

Appendix 5 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 THR-1442-C-448 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®
empagliflozin/metformin HCl	Synjardy
dapagliflozin/metformin HCl extended release tablet	Xigduo XR

Appendix 6 Sponsor Signatures

Study Title: A double blind placebo controlled study to evaluate the effect of bexagliflozin tablets on hemoglobin A1c in patients with type 2 diabetes mellitus and moderate renal impairment

Study Number: THR-1442-C-448

Final Date: 25 October 2016

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

Signed: _____ Date: 26 October 2016

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

Signed: _____ Date: 10/27/2016

Andrew Allegretti, M.D.
Lead Medical Monitor
Massachusetts General Hospital
Consultant for Theracos Sub, LLC

Signed: _____ Date: 26 Oct 2016

Wenjiong Zhou, Ph.D.
Statistician
FMD K&L
Consultant for Theracos Sub, LLC

Appendix 7 Investigator's Signature

Study Title: A double blind placebo controlled study to evaluate the effect of bexagliflozin tablets on hemoglobin A1c in patients with type 2 diabetes mellitus and moderate renal impairment

Study Number: THR-1442-C-448

Final Date: 25 October 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:_____
Principal Investigator