Clinical Trial Protocol: THR-1442-C-423

Study Title:	A Phase 3, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Effects of Bexagliflozin versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin
Study Number:	THR-1442-C-423
Study Phase:	3
Product Name:	Bexagliflozin Tablets
Indication:	Type 2 Diabetes Mellitus
Investigators:	Multicenter study
EudraCT Number:	2017-000420-95
IND Number:	103822
Sponsor:	Theracos Sub, LLC
Sponsor Contact:	Lynelle Cortellini, MSc Translational Medicine Group Massachusetts General Hospital 185 Cambridge Street, Boston, MA 02114 Phone: 617-724-8420 Fax: 617-643-8203 E-mail: lcortellini@ccib.mgh.harvard.edu
Medical Monitor:	Robert Klugman M.D. Theracos Sub, LLC 225 Cedar Hill Road, Suite 200, Marlborough, MA 01752 Phone: 508-735-9491 Fax: 617-643-8203 Email: rklugman@theracos.com

	Date
Protocol Version 2.0	06 April 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Sponsor: Theracos Sub, LLC

Name of Finished Product: Bexagliflozin Tablets

Name of Active Ingredient: Bexagliflozin

Study Title:
A Phase 3, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Effects of Bexagliflozin versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin

Study Number: THR-1442-C-423

Study Phase: 3

Primary Objective:

The primary efficacy objective is to demonstrate that bexagliflozin is non-inferior to sitagliptin by evaluating the treatment effect on hemoglobin A1c (HbA1c) reduction at week 24 in subjects whose type 2 diabetes mellitus (T2DM) is inadequately controlled by metformin.

Secondary Objectives:

The key secondary objectives are:

- To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in fasting plasma glucose (FPG) at week 24
- To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2 at week 24
- To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in systolic blood pressure (SBP) in subjects at week 24

Exploratory Objectives:

- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in the proportion of subjects achieving HbA1c < 7.0% over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in HbA1c over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in fasting plasma glucose (FPG) over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in body weight over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in SBP over time

Safety Objectives:

- To compare the effects of bexagliflozin with sitagliptin on the incidence of adverse events (AE) of interest. AE of interest are urinary tract infections, urosepsis and pyelonephritis, genital mycotic infections (GMI), diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, major adverse cardiovascular events (MACE), falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis(DKA), pancreatitis, amputations, and renal failure events
- To compare the effects of bexagliflozin with sitagliptin on general safety assessments

including treatment emergent AEs, clinical laboratory findings, 12-lead electrocardiograms (ECG) parameters, physical examinations, vital signs including orthostatic blood pressure (BP), and use of concomitant medications.

Study Design:
THR-1442-C-423 is a phase 3, multi-center, randomized, double-blind, active controlled study to evaluate the efficacy and safety of bexagliflozin versus sitagliptin in subjects whose T2DM is not well controlled by metformin alone. A total of 374 subjects are planned to be randomized in a ratio of 1:1 to receive once daily treatment of bexagliflozin tablets, 20 mg, with sitagliptin tablets, placebo (Group 1) or bexagliflozin tablets, placebo, with sitagliptin tablets, 100 mg (Group 2) for 24 weeks in an outpatient setting.
The main eligibility criteria include 1) male or female subjects with T2DM and 2) screening HbA1c between 7.0% and 11% (inclusive).

Qualified subjects must have taken metformin at a stable dose of ≥ 1500 mg/day in addition to diet and exercise counseling for at least 8 weeks prior to screening. Study subjects will continue taking open-labeled metformin during the entire study.

All eligible subjects will start a single-blind run-in period by taking placebo bexagliflozin and placebo sitagliptin once daily for one week. Subjects who meet all inclusion criteria and no exclusion criteria after completion of the run-in period will be eligible for randomization and receive investigational products.

During the treatment period, subjects will receive once daily sitagliptin tablets, 100 mg, and bexagliflozin tablets, placebo, or bexagliflozin tablets, 20 mg, and sitagliptin tablets, placebo, for 24 weeks. Each subject will be instructed to return to the clinic at weeks 6, 12, 18, and 24 for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up exit visit at week 26 or 2 weeks after last dose of study drug if subjects early terminate prior to week 24.

During the study, a Data and Safety Monitoring Board (DSMB) will review the unblinded data periodically and may recommend an early termination of the trial for safety reasons. In the event of administrative changes or other related reasons, the sponsor reserves the right to terminate the study early. There will be no interim analysis; final statistical analysis will be performed after all subjects complete the study.

Study Population and Main Eligibility Criteria:
A total of 374 eligible subjects are planned for this study. The study population will comprise:

1. Male or female adult subjects ≥ 18 years of age
2. If subjects are female of childbearing potential, subjects must be negative on the urine pregnancy test and agree to abstain from coitus or use contraception during the entire study to avoid any possible pregnancy
3. Subjects with a diagnosis of T2DM with HbA1c levels between 7.0% and 11% (inclusive) at screening
4. Subjects whose T2DM is treated with a stable dose of ≥ 1500 mg/day metformin only along with diet and exercise counseling for at least 8 weeks prior to screening

5. Subjects with a BMI ≤ 45 kg/m^2 at screening
6. If applicable, taking stable doses of treatment for dyslipidemia and/or hypertension for 30 days prior to screening. Subjects do not need to be treated for dyslipidemia or hypertension to be eligible for the study
7. Subjects who are willing and able to return for all clinic visits and to complete all study-required procedures, including self-monitoring blood glucose (SMBG) measurements

Prior to randomization, all subjects must:

8. Adhere to the investigational product administration requirements as evidenced by missing no more than 1 day of placebo run-in medication

Test Products, Dose, and Mode of Administration:

Once daily oral administration of bexagliflozin and sitagliptin with or without food taken together in the morning

- Group 1: bexagliflozin tablets, 20 mg, and sitagliptin tablets, placebo
- Group 2: bexagliflozin tablets, placebo, and sitagliptin tablets, 100 mg

Duration of Treatment:

Eligible subjects will receive a total treatment duration of 25 weeks including 1 week of run-in medications and 24 weeks of investigational products.

Efficacy Assessments:

Primary efficacy assessment:

- Change in HbA1c from baseline at week 24

Secondary efficacy assessments:

- Change in FPG from baseline at week 24
- Change in body weight in subjects with baseline BMI ≥ 25 kg/m^2 at week 24
- Change in SBP in subjects from baseline at week 24

Other efficacy endpoints:

- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in the proportion of subjects achieving HbA1c < 7.0% over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in HbA1c over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in (FPG over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in body weight over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in SBP over time

Safety Endpoints:

- Treatment emergent AEs, including AEs of special interest (genital and urinary tract infections, diuretic effects, hepatotoxicity, MACE, hypoglycemia, fractures, malignancy, hypersensitivity reactions, hypotensive episodes, acid-base disorders, pancreatitis,

amputations and renal failure events)
- Laboratory testing, including hematology, serum chemistry, and urinalysis
- Physical examination
- 12-lead ECG
- Vital signs
- Concomitant medication use

Statistical Methods:
The primary hypothesis is that bexagliflozin is non-inferior to sitagliptin by evaluating the treatment effect on HbA1c reduction at week 24 in combination with metformin. The non-inferiority margin for mean change from baseline at week 24 in HbA1c comparing bexagliflozin group with sitagliptin group will be 0.35%. Superiority will be declared without additional statistical testing when the upper bound of the 95% CI for difference in change from baseline at week 24 in HbA1c comparing bexagliflozin group with sitagliptin group is less than 0. The treatment difference will be examined by using a mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA). The model will include treatment, visit, treatment-by-visit interaction, region and the baseline HbA1c value as a fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the comparator group at week 24 in change from baseline will be estimated from the model. An unstructured covariance will be used to model the within-subject correlation. 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. Primary endpoints will be analyzed on both intention-to-treat (ITT) and per protocol (PP) analysis sets.

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 on both ITT and PP analysis sets:

1. Missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputation techniques; HbA1c values collected after the start of rescue medication will be excluded.
2. Missing 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.

The effects of bexagliflozin on the changes from baseline at week 24 in FPG, body weight and SBP will be tested as key secondary endpoints and will be analyzed in a hierarchical testing strategy and only if the primary objective is met. Similar to the primary endpoint, MMRM ANCOVA models will be used. A hierarchical testing strategy will be followed to preserve experiment-wide alpha at 0.05:

1. Superiority test of the change in FPG in the bexagliflozin group vs. the sitagliptin group at week 24

2. Superiority test of the change in body weight in subjects with baseline BMI ≥ 25 kg/m^2 in the bexagliflozin group vs. the sitagliptin group at week 24
3. Superiority test of the change in SBP in the bexagliflozin group vs. the sitagliptin group at week 24

Additional effects of bexagliflozin versus sitagliptin on the changes in HbA1c, FPG, SBP, body weight, and the proportion of subjects who reach an HbA1c < 7%, as well as the general safety in subjects with T2DM, will be analyzed as exploratory efficacy endpoints. These endpoints are considered exploratory and will not be adjusted for multiplicity.

For the primary efficacy endpoint, a minimum of 172 subjects are needed in each treatment arm to detect non-inferiority of bexagliflozin to sitagliptin with respect to the change in HbA1c from baseline at week 24 by a margin of 0.35%, assuming an estimated pooled standard deviation (SD) of 1.0%. This estimation is based on a one-sided t-test with 90% power at a 0.025 level of significance. To allow for an estimated 8.0% dropout rate, 187 patients will be randomized in each treatment arm, and the total sample size will be 374 subjects for this study.

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

Date of Protocol V2.0: 06 April 2017

Date of Protocol V1.0: 01 February 2017

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	American Diabetes Association
AE	adverse event
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CEC	cardiovascular endpoint committee
CI	confidence interval
CRF	case report form
CRO	contract research organization
DKA	diabetic ketoacidosis
DPP4	dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eGFR	estimating glomerular filtration rate
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GMI	genital mycotic infection
h	hour
HbA1c	hemoglobin A1c
Hct	hematocrit
HDL-C	high-density lipoprotein cholesterol
HDPE	high-density polyethylene
Hgb	hemoglobin
HUA	hospitalization for unstable angina
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IRAE	immediately reportable adverse event
IRB	Institutional Review bBoard
ITT	intention-to-treat
IWRS	Interactive Web Response System
LDL-C	low density lipoprotein cholesterol
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
MI	myocardial infarction
MMRM	mixed model repeated measures
MODY	maturity–onset diabetes of the young
N	number of subjects
OHA	oral hypoglycemic agent
PP	per protocol
PR	time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
QRS	QRS complex the combination of three of the graphical deflections seen on a typical electrocardiogram
QT	a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RBC	red blood cell (count)
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
SU	sulfonylurea
SUSAR	serious and unexpected suspected adverse event
TIA	transient ischemic attack
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TEAE	treatment emergent adverse event
TG	triglycerides
TZD	thiazolidinedione
UACR	urine albumin to creatinine ratio
UADR	unexpected adverse drug reaction
UGE	urinary glucose excretion
ULN	upper limit of normal
UPT	urinary pregnancy test
UTI	urinary tract infection
WBC	white blood cell (count)
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality worldwide, affecting an estimated 415 million people in 2015. Approximately 187 million of those affected are thought to be unaware of their condition and over 80% reside in low- and middle-income countries (IDF 2015).

1.1 Type 2 Diabetes Mellitus

T2DM is the predominant form of diabetes and accounts for at least 90% of all diabetes cases, which is characterized by insulin resistance and relative or absolute insulin insufficiency. Despite the availability of several classes of therapeutics, the number of people with diabetes is projected to increase by nearly 55% to over 642 million adults by 2040 (IDF 2015). Among the debilitating consequences of T2DM are peripheral neuropathy, retinopathy, renal failure, peripheral ischemia and exacerbations of cardiovascular disease, which result in blindness, amputation, dialysis, and death.

T2DM is a disease strongly linked to increased body fat mass in the majority of cases (Schwartz, Fabricatore et al. 2012). Weight loss has been shown to improve glycemic control and to reduce the severity of diabetes-associated comorbidities, supporting the view that anti-diabetic agents that promote weight loss may be particularly beneficial for the treatment of the disease (Look, Wing et al. 2013; Scheen and Van Gaal 2014). Several classes of agents are available for treating T2DM, including insulin and its secretagogues, such as sulfonylureas (SU), PPARγ agonists, biguanides, alpha glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, meglitinides, dipeptidyl peptidase 4 (DPP4) inhibitors, and sodium glucose linked transporter 2 inhibitors (SGLT2i). Metformin is the first line medication for treating T2DM; however, as T2DM progresses over time, metformin monotherapy is not able to adequately manage hyperglycemia. T2DM patients often receive more than one antidiabetic medication after an initial treatment period of metformin monotherapy. DPP4 inhibitors are considered second-line therapy for T2DM in clinical practice and are often prescribed with metformin as a combination therapy for treating T2DM. Sitagliptin is a DPP-4 inhibitor, which prevents the degradation of incretin. Incretin increases insulin production and reduces hepatic glucose production, leading to better glucose metabolism. Sitagliptin is primarily excreted unchanged in the urine. DPP4 inhibitors can reduce the risk of long-term microvascular complications via effective glycemic control and do not have weight gain or increased hypoglycemia risk compared with placebo.

The rapid growth rate in the incidence of T2DM has led to an increasing recognition that additional therapeutics are needed to provide safe and effective reductions of elevated plasma glucose levels. New agents to treat T2DM, either as monotherapy or add-on therapy to other anti-diabetic medications, would ideally treat hyperglycemia and avoid common side effects of currently available agents, such as weight gain, gastrointestinal disturbance, and hypoglycemia.

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 (van den Heuvel, Assink et al. 2002; Santer, Kinner et al. 2003). The excretion of glucose in the urine of diabetic subjects in amounts comparable to or greater than that seen in individuals harboring loss of function mutations in *SLC5A2* has the potential to improve fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia. Several SGLT2 inhibitors have demonstrated these clinical benefits, as well as sustained weight loss, when used as a monotherapy or in combination with other oral anti-diabetic medications including insulin (Nauck 2014; Seufert 2015).

1.2 Bexagliflozin for the Treatment of Type 2 Diabetes Mellitus

Bexagliflozin is a candidate oral hypoglycemic agent (OHA) that is a potent and highly specific inhibitor of SGLT2. It was identified following a synthetic program aimed at creating molecules with high selectivity and potency for SGLT2 (Zhang, Welihinda et al. 2011). Bexagliflozin has been shown to cause dose-dependent increases in urinary glucose excretion (UGE) in humans, rats, dogs, and monkeys and to reduce HbA1c in animal models of T2DM as well as in diabetic subjects. In a 12 week monotherapy study, bexagliflozin tablets, 20 mg, showed greater placebo adjusted HbA1c reduction (-0.80%) than bexagliflozin, 10 mg (-0.68%), and bexagliflozin, 5 mg (-0.55%). Bexagliflozin administration has been well tolerated. The safety and efficacy of bexagliflozin tablets, 20 mg, were evaluated in a 96-week study that measured reduction in hemoglobin A1c (HbA1c) as the primary endpoint. This 96 week study showed bexagliflozin tablets, 20 mg, to be superior to placebo in reducing HbA1c. Details of the pharmacology, efficacy, and safety assessments are described in the Investigator's Brochure. The safety profile supports continued evaluation of the treatment effect when used in combination with metformin.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary efficacy objective of this trial is to demonstrate that bexagliflozin is non-inferior to sitagliptin by evaluating the treatment effect on HbA1c reduction at week 24 in subjects whose T2DM is inadequately controlled by metformin.

2.2 Key Secondary Objectives

- To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in fasting plasma glucose (FPG) at week 24
- To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2 at week 24
- To evaluate the treatment effect of bexagliflozin vs. sitagliptin on the change in systolic blood pressure (SBP) in subjects at week 24

2.3 Exploratory Objectives

- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in the proportion of subjects achieving HbA1c < 7.0% over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in HbA1c over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in FPG over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in body weight over time
- To assess the treatment effect of bexagliflozin vs. sitagliptin on the change in SBP over time

Safety Objectives:

- To compare the effects of bexagliflozin vs. sitagliptin on the incidence of adverse events (AE) of interest. AE of interest are urinary tract infections including urosepsis and pyelonephritis, genital mycotic infections (GMI), diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, major adverse cardiovascular events (MACE), falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis (DKA), amputations, pancreatitis, and renal failure events
- To compare the effects of bexagliflozin vs. sitagliptin on general safety assessments including treatment emergent AE, clinical laboratory events, 12-lead electrocardiograms (ECG) parameters, physical examinations, vital signs including orthostatic blood pressure(BP), and use of concomitant medications

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

THR-1442-C-423 is a phase 3, multi-center, randomized, double-blind, parallel-group study and aims to demonstrate that bexagliflozin is non-inferior to sitagliptin as add-on therapy in subjects whose T2DM is not adequately controlled by metformin treatment. The primary efficacy endpoint is the change in HbA1c from baseline at week 24. The study will enroll T2DM patients who are treated with only metformin.

All subjects must have taken metformin at a stable dose of ≥ 1500 mg/day for ≥ 8 weeks prior to screening and have received diet and exercise counseling.

A total of 374 subjects who meet all the inclusion criteria, none of the exclusion criteria, and who consent to participate in the study, are eligible for study enrollment. Subjects who successfully complete a 1-week run-in and who meet all eligibility criteria will be randomized in a 1:1 ratio to receive once daily double-blind treatment of either active bexagliflozin tablets with placebo sitagliptin tablets (Group 1) or placebo bexagliflozin tablets and active sitagliptin tablets (Group 2). Active treatment in Group 1 will be bexagliflozin tablets, 20 mg. Active treatment in Group 2 will be sitagliptin tablets, 100 mg. Study subjects will continue receiving open-labeled metformin background medication during the entire study at a stable dose and frequency. The treatment period will last 24 weeks and be conducted in an outpatient setting.

3.2 Research Methods and Procedures

3.2.1 Run-in Period

All subjects who are eligible at the screening visit will begin a 1 week run-in period. At the start of the run-in period, subjects will receive diet and exercise counseling as well as instructions on contacting the clinic in the event of hyperglycemia, hypoglycemia, or symptoms that may suggest ketoacidosis. At the start of run-in, subjects will be provided with a glucometer and instructions for its daily use. During the run-in, subjects will receive placebo bexagliflozin and placebo sitagliptin. Bexagliflozin tablets and sitagliptin tablets will be taken with water at the same time everyday. Metformin dose and frequency will remain unchanged from time of screening throughout the course of the study.

Subjects will not be eligible for randomization if during the run-in period they:

1. have fasting blood glucose values ≥ 250 mg/dL on two or more consecutive days, accompanied by symptoms of hyperglycemia
2. omit more than 1 day of run-in medication, or
3. are deemed inappropriate for the study by the investigator,

Inclusion and exclusion criteria are described in more detail in sections 4.2 and 4.3.

Changes in the dose of treatment for dyslipidemia or hypertension will not be permitted during the screening and run-in periods. Management of concomitant medications is described in Section 5.6 Concomitant Therapy.

If a change in treatment for hypertension or dyslipidemia is deemed necessary by the investigator for the well-being of the study subject during the run-in period, the subject will be considered as screen failed and discontinue study activities; there will be no opportunity to re-screen for subjects who have started run-in and screen failed.

3.2.2 Treatment Period

The double-blind treatment period will start at randomization and last 24 weeks. A total of 374 subjects of 187 subjects per group will be randomized in a 1:1 ratio to the two groups as shown in Table 1.

Table 1. Treatment Groups and Assigned Treatment

Treatment Group	Treatment
1	Bexagliflozin tablets, 20 mg, (once daily P.O.) Sitagliptin tablets, placebo, (once daily P.O.)
2	Bexagliflozin tablets, placebo, (once daily P.O.) Sitagliptin tablets, 100 mg, (once daily P.O.)

Randomization will be stratified by HbA1c at Visit V1 (≤ 8.5% vs. > 8.5%) at screening. At the start of the treatment period, each subject will be provided with bexagliflozin tablets, sitagliptin tablets, and dosing instructions. Symptoms and blood sugars related to the occurrence of hyperglycemia, hypoglycemic events, or symptoms that may suggest ketoacidosis will be recorded. Bexagliflozin tablets, 20 mg or placebo, and sitagliptin tablets, 100 mg or placebo, will be taken once daily at approximately the same time each day either before or after breakfast with approximately one cup (250 mL) of water. Background metformin shall be taken at the same dose and frequency from screening throughout the entire study.

Each subject will be instructed to return to the clinic at weeks 6, 12, 18 and 24 for efficacy assessment and safety monitoring, including review of AEs and concomitant medication, vital signs, ECG, physical examination, and blood and urine specimen collections. On the day of a clinic visit at which blood samples are scheduled to be collected, approximately 10 hours (h) fasting must be confirmed prior to blood draw. On the day of the scheduled clinic visits at which there is fasting and blood is to be drawn, administration of bexagliflozin and sitagliptin shall be withheld until after blood is drawn and taken with water at the clinic or home.

Subjects will return to the clinic for a follow-up exit visit at week 26 or 2 weeks after the last dose of study drugs if subjects early terminate prior to week 24. Following the exit visit, subjects will be advised to see their primary physician to undergo treatment to control their diabetes.

3.2.3 Glycemic Control Monitoring

3.2.3.1 Placebo Run-in Period

During placebo run-in period, subjects will be instructed to determine self-monitored blood glucose (SMBG) daily after fasting overnight for approximately 10 h. Subjects should contact the clinic if any fasting glucose value is ≥ 250 mg/dL (13.9 mmol/L), and the investigator will determine whether the participant should attempt to improve diet and exercise to maintain glycemic control or if the participant must withdraw from the study and initiate a more intense pharmacological regimen for glucose control.

A subject will be excluded from further participation if the SMBG is ≥ 250 mg/dL on 2 consecutive days, and is accompanied by symptoms of hyperglycemia. Subjects with clinical signs or symptoms of severe hyperglycemia during the run-in period, including weight loss, blurred vision, increased thirst, increased urination, or fatigue, should also be excluded.

3.2.3.2 Treatment Period

During the treatment period, subjects will be advised to continue daily, fasting SMBG measurements. Subjects should contact the clinic if any fasting SMBG is ≥ 270 mg/dL (15 mmol/L) from week 0 to week 6, ≥ 240 mg/dL (13.3 mmol/L) after week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) after week 12. Blood glucose values collected via SMBG will be evaluated at study visits by the investigator. In addition, hyperglycemia will be monitored by FPG at scheduled visits.

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

During the treatment period, hyperglycemia should be managed first with diet and exercise counseling. If hyperglycemia continues after diet and exercise counseling, the investigator may prescribe rescue medication if it is necessary for the well-being of the subject.

3.2.3.3 Rescue Medication

Rescue medication is suggested during the treatment period if, after diet and exercise counseling, subjects meet the following glycemic criteria:

1. More than 3 consecutive, daily, fasting SMBG measures are ≥ 270 mg/dL (15 mmol/L) from baseline to week 6, ≥ 240 mg/dL (13.3 mmol/L) from week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) or HbA1c > 8.0% from week 12 to week 24
2. Fasting SMBG values are ≥ 250 mg/dL (13.9 mmol/L) and associated with clinical signs or symptoms of hyperglycemia (e.g., weight loss, blurred vision, increased thirst, increased urination, or fatigue), and the signs or symptoms are severe.

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 ascribed to the latest date upon which the subject's glycemic control will be impacted by the rescue medication.

The investigator may provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated. Other SGLT2 inhibitors (Appendix 3), DPP-4 inhibitors, or GLP-1 agonists may not be prescribed. Metformin dose can be increased at the discretion of the investigator. SUs and insulins are known to increase the risk of hypoglycemia in combination with sitagliptin. As subjects may be taking active sitagliptin, investigators should use caution in prescribing these medications.

If hypoglycemia occurs in any subject who has been 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. If recurrent symptomatic hypoglycemia occurs after discontinuation of the rescue medication, the study drug can be discontinued at the discretion of the investigator.

If recurrent symptomatic hypoglycemia occurs in subjects who are not prescribed rescue medication, the total daily dose of metformin should be decreased at the discretion of the investigator. If recurrent symptomatic hypoglycemia continues after decreasing the dose of metformin, subjects should be discontinued from the study and treated in accordance with local standards of care.

Subjects who receive rescue medication due to poor glycemic control will continue to receive investigational products 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.

3.2.4 Other Safety Monitoring Activities

The safety monitoring activities will include assessments of vital signs, 12-lead ECG, physical examinations, urinalysis, blood chemistry, hematology, AEs, and concomitant medication use. The occurrence of blood, liver, or skin disorders will be monitored through laboratory testing and evaluation of AE documentation.

Sitagliptin treatment may increase the risk of developing acute pancreatitis, acute renal failure, hypersensitivity reactions, and arthralgia. Subjects experiencing these conditions should be immediately discontinued from taking bexagliflozin tablets and sitagliptin tablets and treated in accordance with local standards of care until the AE is resolved. The subject will be permanently discontinued from participation in the clinical trial if the subject's condition worsens or if the subject starts dialysis or other renal replacement therapies. If discontinued, subjects should be advised to consult with their primary physician for managing T2DM.

Sitagliptin administration should be suspended if estimated glomerular filtration rate (eGFR) decreases to < 60 mL/min/1.73 m^2 and laboratory values should be retested within 48 h.

Sitagliptin dosing may resume if the eGFR returns to ≥ 60 mL/min/1.73 m^2. If eGFR remains below 60 mL/min/1.73 m^2, the subject should discontinue from participation in the clinical trial and be advised to see their primary physician to undergo treatment to control their diabetes and other medical conditions.

AEs 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.

- Acid-base disorders including DKA
- Amputations
- Diuretic effects including hypovolemia
- Falls and fractures
- GMI
- Hepatotoxicity
- Hypersensitivity reactions
- Hypoglycemia
- Hypotension episodes
- MACE
- Malignancies
- Pancreatitis
- Renal failure events
- Urinary tract infections including urosepsis and pyelonephritis

3.2.5 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 will be defined in its charter.

3.2.6 Major Adverse Cardiovascular Event (MACE) Adjudication

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 (MI), stroke, hospitalization for acute coronary syndromes, 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. No separate cardiovascular risk assessment will be performed based on events in the study population of the current protocol.

3.2.7 Diabetic Ketoacidosis (DKA) Event Adjudication

An independent adjudication committee will be established to review all potential DKA under blind. The adjudicated events will be documented and archived. All adjudicated DKA

events in the bexagliflozin phase 3 program will be pooled at the end of the program and a final analysis will be conducted.

3.3 Rational for Study Design and Procedures

3.3.1 Rationale for the Study Design

THR-1442-C-423 is designed to assess the non-inferiority of bexagliflozin to sitagliptin as add-on therapy to metformin for glycemic control in T2DM subjects. To assess the effect of bexagliflozin or sitagliptin in addition to an effective dose of metformin background therapy, all subjects must be taking a stable dose of ≥ 1500 mg metformin daily for at least 8 weeks prior to screening. If a potential subject has taken < 1500 mg/day metformin, the subject can enter screening once the dose of metformin has been be increased to at least 1500 mg/day for at least 8 weeks. Changes in the dose of metformin will not be permitted at any time during the study unless persistent hypoglycemia occurs during the treatment period.

Diet and exercise counseling will be provided to all participating subjects to reduce risks of worsening diabetic conditions. A monitoring plan and criteria to initiate rescue medications are included in the protocol to prevent prolonged hyperglycemia.

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.

3.3.2 Rationale for Background Medication and Active Comparator

Metformin is the most commonly prescribed OHA and is recommended as first-line therapy for the treatment of T2DM. It is a biguanide that decreases hepatic glucose production and may improve peripheral glucose uptake and utilization.

Subjects who have T2DM often require multiple anti-diabetic medications for glycemic control. DPP-4 inhibitors are often prescribed with metformin as a combination therapy for treating T2DM. DPP-4 inhibitors can reduce the risk of long-term microvascular complications via effective glycemic control. Sitagliptin in addition to metformin does not have additional risk of hypoglycemia. Sitagliptin is one of the most commonly prescribed DPP-4 inhibitors. Thus, it is an appropriate active comparator in the subject population studied during the treatment period (24 weeks).

Bexagliflozin is an SGLT2 inhibitor developed for the treatment of T2DM that reduces hyperglycemia via an insulin-independent pathway of inhibiting glucose re-uptake and promoting urinary glucose excretion. Individuals treated with metformin and with inadequate glycemic control have reduced HbA1c, reduced body weight, and less incidence of hypoglycemia when treated with approved SGLT2 inhibitors canagliflozin, dapagliflozin or empagliflozin. Thus T2DM subjects on metformin therapy with inadequate glycemic control may benefit from combination treatment with bexagliflozin.

3.3.3 Rationale for the Dose Selection

Bexagliflozin produces a dose-dependent and saturable increase in UGE in healthy volunteers and subjects with T2DM. Population pharmacodynamic modeling has indicated that bexagliflozin doses of 20 mg result in approximately 90% of the maximal UGE. In a 12-week dose range finding study, daily administration of 20 mg bexagliflozin was found to reduce HbA1c by 0.80% compared to placebo at week 12, a greater reduction than found in 10 mg and 5 mg cohorts. A higher proportion of patients that have been treated with bexagliflozin tablets at 20 mg per day has achieved the target of HbA1c below 7%. FPG reduction, weight loss, and decreased systolic and diastolic BPs compared to baseline were also observed following 12 weeks of treatment. In addition, AEs, particularly those involving urinary tract infections (UTI) and GMIs, were found to be similar between placebo and active agent cohorts. To evaluate the safety and efficacy of bexagliflozin compared to sitagliptin for the treatment of subjects with T2DM, bexagliflozin tablets, 20 mg, will be administered in this trial.

3.4 Study Duration and Dates

Subjects will be enrolled within 2 weeks of screening. Eligible subjects who provide written consent will start a run-in period of 1 week prior to randomization to receive study drugs to demonstrate compliance. Subjects who successfully complete the run-in will begin 24 weeks of treatment and will be followed for 2 weeks after the last dosing. The study duration from screening to follow-up will be no more than 29 weeks overall. For details of the schedule and nature of the investigations, see the Schedule of Events in Appendices 1 and 2.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 374 subjects whose T2DM is inadequately controlled by metformin and who meet all of the inclusion criteria and none of the exclusion criteria. Clinical sites in the North America and Europe are anticipated to recruit subjects.

4.2 Inclusion Criteria

Prospective subjects must be:

1. Male or female adult subjects ≥ 18 years of age
2. If subjects are female of childbearing potential, subjects must be negative on the urine pregnancy test and agree to abstain from coitus or use contraception during the entire study
3. Subjects with a diagnosis of T2DM with HbA1c levels between 7.0% and 11% (inclusive) at screening
4. Subjects whose T2DM is treated with a stable dose of ≥ 1500 mg/day metformin only along with diet and exercise counseling for at least 8 weeks prior to screening
5. Subjects have a BMI ≤ 45 kg/m^2 at screening
6. If applicable, taking stable doses of treatment for dyslipidemia and/or hypertension for 30 days prior to screening
7. Subjects who are willing and able to return for all clinic visits and to complete all study-required procedures, including SMBG measurements

Prior to randomization, all subjects must:

8. Adhere to the investigational product administration requirements as evidenced by missing no more than 1 day of run-in medications. If run-in medication doses are missed for reasons that, in the judgement of the investigator, are appropriate, this requirement may be waived

4.3 Exclusion Criteria

Subjects 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. Any contraindication to the safe use of DPP4 therapy or sitagliptin, including known hypersensitivity reaction
4. History of pancreatitis

5. Genitourinary tract infection within 6 weeks of screening or history of ≥ 3 genitourinary infections requiring treatment within 6 months from screening
6. 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)
7. History of alcohol or illicit drug abuse in the past 2 years
8. Triglycerides > 500 mg/dl at Visit V1
9. 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
10. eGFR, as calculated by the modification of diet in renal disease study equation (MDRD), < 60 mL/min/1.73 m^2 at screening.
11. Uncontrolled hypertension (SBP > 160 mmHg or diastolic BP > 95 mmHg) at Visit V1
12. Life expectancy < 2 years
13. History of MI, unstable angina, stroke, or hospitalization for heart failure within 3 months of screening
14. History of treatment with an investigational drug within 30 days or within 7 half-lives of the investigational drug, whichever is longer
15. Previous treatment with bexagliflozin or EGT0001474 study drug (run-in or double-blind investigational product)
16. Currently or within 3 months of taking any SGLT2 inhibitor (Appendix 3)
17. Currently participating in another interventional trial
18. Prior renal transplantation or evidence of nephrotic syndrome (defined as a urine albumin-to-creatinine ratio (UACR) > 1500 mg/g at screening).
19. Any condition, disease, disorder, or clinically relevant abnormality that, in the opinion of the primary investigator, would jeopardize the subject's appropriate participation in this study or obscure the effects of treatment
20. Female subjects who are pregnant or nursing
21. Two or more consecutive SMBG measures ≥ 250 mg/dL (13.9 mmol/L) prior to randomization accompanied by clinical signs or symptoms of hyperglycemia prior to randomization, including weight loss, blurred vision, increased thirst, increased urination, or fatigue

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Investigational Product

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

The following investigational products will be used for oral administration:

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

5.1.2 Active Comparator

Sitagliptin tablets, 100 mg or placebo, are beige, round, film-coated tablets with “277” on one side.

The following active comparator products will be used for oral administration:

- Sitagliptin tablets, 100 mg: tablets containing 100 mg of sitagliptin
- Sitagliptin tablets, placebo: tablets containing no sitagliptin

5.2 Treatments Administered

5.2.1 Investigational Product

Bexagliflozin tablets, 20 mg or placebo, should be taken at approximately the same time each day, before or after breakfast, with one cup (250 mL) of water.

On the day of scheduled clinic visits when there is fasting and blood is to be drawn, administration of bexagliflozin should be delayed until after blood is drawn and taken in the clinic or at home with one cup (250 mL) of water.

5.2.2 Active Comparator

Sitagliptin tablets, 100 mg or placebo, should be taken once daily at the same time as bexagliflozin, before or after breakfast, with one cup (250 mL) of water.

On the day of scheduled clinic visits when there is fasting and blood is to be drawn, administration of sitagliptin should be delayed until after blood is drawn and taken in the clinic or at home with one cup (250 mL) of water.

5.2.3 Background Metformin Therapy

Subjects will continue receiving metformin as background therapy during the entire study period at an unchanged dose (≥ 1500 mg/day), time, and frequency as prescribed to subjects prior to screening.

The dose, frequency, and time of administration should remain stable unless the investigator deems adjustment (decrease or increase) necessary for the medical well-being of the subject. Guidance for adjustment to metformin dose is provided in Section 3.2.3. Changes to the dose, frequency, or time of administration of metformin should be recorded in the concomitant medication log.

5.3 Selection and Timing of Dose for Each Patient

5.3.1 Bexagliflozin

Dosing with bexagliflozin tablets, 20 mg or placebo, will be based on randomized assignment at the beginning of the treatment period. All study subjects will be instructed to take bexagliflozin tablets once daily in the morning, before or after breakfast, with one cup (250 mL) of water. The dose and frequency of bexagliflozin will be unchanged during the 24-week treatment period.

On the day of each scheduled clinic visit, subjects must fast for approximately 10 h prior to the collection of blood samples. During the fasting period, only water will be permitted.

5.3.2 Sitagliptin

Dosing with sitagliptin tablets, 100 mg or placebo, will be based on randomized assignment at the beginning of the treatment period. All study subjects will be instructed to take sitagliptin tablets once daily in the morning, before or after breakfast, with one cup (250 mL) of water. The dose of sitagliptin will be unchanged during the 24-week treatment period.

5.4 Method of Assigning Treatment Groups and Study Drugs

The study will be conducted at multiple investigative sites and will 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. Activation of investigational sites in each country will be centrally controlled by an Interactive Web Response System (IWRS).

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized in a 1:1 ratio to receive active bexagliflozin with placebo sitagliptin or active sitagliptin with placebo bexagliflozin. Subjects will be assigned to treatment groups in sequential order as they qualify for the study. Randomization will be stratified according to screening (Visit V1) HbA1c (< 8.5% or ≥ 8.5%). The investigator or designated staff will log into the IWRS to receive the randomization code and assigned kit numbers.

Subject randomization will be deactivated for all sites when the planned number of subjects (N) is met. However, if a potential subject has been screened 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, double dummy study. The sponsor, investigators, study coordinators, pharmacists, study subjects, the cardiovascular endpoint committee (CEC), and the DKA committee will be blinded to the study medications.

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 test results is needed to manage a 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 CEC and DKA adjudication committee members until all global investigational studies are completed and final analyses to assess cardiovascular and ketoacidosis risks are conducted.

5.6 Concomitant Therapy

During the course of the study, investigators will manage glucose, BP, and lipid levels according to local or regional standard of care guidance documents for the management of T2DM. Instructions for rescue medication for hyperglycemia are provided in Section 3.2.3.3. 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 a clinical reason to change the dose or frequency.

Subjects may receive any medications for AEs that are necessary in the investigators' judgment. Medications prescribed after the informed consent are to be recorded on the CRF. The medication name, dose, frequency, route of administration, date(s) of administration, and reason for administration must be recorded. This documentation should continue through the treatment period and the follow-up period.

5.6.1 Diuretics and Medications for Treatment of Dyslipidemia and Hypertension

Subjects who are prescribed diuretics, anti-hypertensive agents, or medications to treat dyslipidemia will continue the current dose, frequency, and time of administration of these medications throughout the study. Subjects do not need to be treated with dyslipidemia or hypertension to be eligible for the study. Adjustment of these medications will not be permitted during the screening and run-in periods.

If a change in diuretics, anti-hypertensive agents, or medications to treat dyslipidemia is required during the screening period, the subject will discontinue study activities and may be re-screened after the clinical condition and treatment regimen have been stable for at least 30 days.

If a subject re-enters screening after treatment adjustment, a new subject number will be assigned. During the treatment period, adjustments in the treatment for hypertension or dyslipidemia are permitted if required for the well-being of the subject. New diuretic medications should not be initiated during the first 2 weeks of the treatment period. The dose and frequency of existing diuretic medications should not be changed during the first 2 weeks of therapy. Changes to the dose or frequency of anti-hypertensive and diuretic medications will be recorded in the concomitant medications log.

5.7 Restrictions

5.7.1 Prior Therapy

All subjects will continue regimens for medical conditions other than diabetes during the study as indicated above. No subject shall have been treated with an 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. Subjects taking any hypoglycemic agents other than metformin during the 8 weeks prior to screening are not eligible for this study.

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. For example, the recommended diet might be low in saturated fat, high in fiber, low in simple carbohydrates, and contain appropriate caloric intake to maintain weight. Subjects will also be counseled consume alcohol in moderation. Subjects with a known history of alcohol abuse should be excluded from the study as indicated in Section 4.3.

Subjects will fast for approximately 10 h prior to the scheduled blood sample draws. During fasting, only water will be permitted.

5.7.3 Subject Activity Restrictions

Throughout the study period, subjects are 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 (ADA) (American Diabetes, 2014). Alternatively, local regulatory guidelines may be used.

5.8 Treatment Compliance

Subjects will be provided with dosing instructions when the investigational products are dispensed. Subjects will also be instructed to bring their medications with them at every visit. During the run-in period, subjects will be excluded from randomization if more than 1 day of placebo run-in medication doses has been omitted. If, in the judgement of the investigator, it was appropriate for the subject to omit these doses, this requirement may be waived (e.g., if the subject was hospitalized overnight during run-in).

At each visit after the start of the run-in period, the study staff will review SMBG diary and medications 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 products will be provided to the pharmacist or designated site personnel in high-density polyethylene (HDPE) bottles of 90 tablets enclosed with a child-resistant cap. A bottle of 15 bexagliflozin tablets, placebo, and a bottle of 15 sitagliptin tablets, placebo, 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.

5.9.1 Run-in Kits

Two types of run-in kits are provided:

- Bexagliflozin tablets, placebo, 15 tablets per bottle
- Sitagliptin tablets, placebo, 15 tablets per bottle

The label attached to each run-in kit will contain the protocol number, product identification, kit number, batch number, expiration date, subject number, investigator name, storage condition, directions for use, sponsor’s name and address, and the investigational drug caution statement.

5.9.2 Bexagliflozin Kit

One bexagliflozin kit contains a 90 count bottle of bexagliflozin tablets, 20 mg or placebo.

The label attached to each bexagliflozin kit will contain the protocol number, product identification, kit number, batch number, expiration date, subject number, investigator name, storage condition, directions for use, sponsor's name and address, and the investigational drug caution statement.

5.9.3 Sitagliptin Kit

One sitagliptin kit contains a 90 count bottle of sitagliptin tablets, 100 mg or placebo.

The label attached to each sitagliptin kit will contain the protocol number, product identification, kit number, batch number, expiration date, subject number, investigator name, storage condition, directions for use, sponsor's name and address, and the investigational drug caution statement.

5.10 Storage and Accountability

Bexagliflozin tablets and sitagliptin tablets will be stored at controlled room temperatures of below 30°C (86°F). The sponsor will notify the sites of the process for returning unused drug.

5.11 Investigational Product Retention at Study Site

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

6 STUDY PROCEDURES

The following sections describe procedures that are conducted in the protocol. The clinical investigator must personally conduct or supervise the procedures that are required in the protocol. Study tasks may be delegated to qualified staff after training is completed. Procedures that require clinical /medical knowledge must be performed by the investigator or qualified sub-investigators.

6.1 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, 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 federal regulations and the Good Clinical Practice (GCP) guidelines of the International Conference for Harmonisation (E6).

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.

6.2 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.

6.3 Medical History

The following information will be collected at the screening visit:

6.3.1 General Demographics and Characteristics

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

6.3.2 Diabetes History

- 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
- History of complications due to diabetes, including nephropathy, retinopathy, neuropathy, non-traumatic amputations, and DKA, including date of diagnosis
- Frequency of hypoglycemic events (per week) that are symptomatic or require assistance

6.3.3 Cardiovascular Disease History

History of cardiovascular disease, including presence of angina, congestive heart failure (including NYHA classification), known atherosclerotic cardiovascular disease, prior MI, transient ischemic attack (TIA) 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).

6.3.4 Medication History

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

6.4 Diet and Exercise Counseling

Subjects will receive counseling regarding 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.

6.5 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 measurement of body weight and a general assessment of all body systems, including the skin, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, vascular system and extremities. The body weight must be determined using a scale that is calibrated. The same scale should be used for the duration of the study if possible.

6.6 Abbreviated Physical Examination

An abbreviated physical examination will be performed by the investigator at the time points indicated in the Schedule of Events (Appendix 1). An abbreviated physical examination will include height (only at the screening visit) and general assessment of the skin, heart, lungs and abdomen, and extremities. The body weight must be determined using a scale that is calibrated. The same scale should be used for the duration of the study if possible.

6.7 Body Weight

The body weight will be measured at every visit except visit V2. The weight must be determined using a scale that is calibrated. The same scale should be used for the duration of the study, if possible.

6.8 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 minutes with feet on the floor and arm supported at heart level.

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

6.9 Electrocardiography

A 12-lead 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 minutes of rest. ECG parameters to be recorded on the CRF are 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.

6.10 Clinical Laboratory Tests

6.10.1 Laboratory Parameters

Clinical laboratory tests are listed in Table 2.

6.10.2 Sample Collection, Storage, and Shipping

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 an approximately 10 h fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for approximately 10 h, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting.

Low density lipoprotein cholesterol (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 AE progression or resolution. Clinical samples should be analyzed in a local laboratory if a fast turn-around time is necessary to determine treatment plan.

6.10.3 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 & Appendix 2). The investigator or study 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.

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.

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.

6.11 Laboratory Tests

Table 2 List of Laboratory Tests

TEST NAME		SHIPMENT
Hematology		Ambient
• Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Platelet count	• Mean corpuscular volume (MCV) • Red cell distribution width (RDW) • Red blood cell (RBC) count • White blood cell (WBC) count with differential	
Serum Chemistry and Electrolytes		Ambient
• Albumin (ALB) • Alanine aminotransferase (ALT) • Alkaline Phosphatase (ALP) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Glucose • Bicarbonate (HCO_3) • Creatinine • Chloride (Cl)	• Total protein • Calcium (Ca) • Magnesium • Phosphorus • Potassium (K) • Sodium (Na) • Total bilirubin • Direct bilirubin • Uric acid	
Glycemic Control		Ambient
• Fasting plasma glucose (FPG) • Hemoglobin A1c (HbA1c)		
Serum Lipids		Ambient
• Total cholesterol (TC) • High-density lipoprotein cholesterol (HDL-C) • Triglycerides (TG)	• Low-density lipoprotein cholesterol (LDL-C), calculated • LDL-C, direct	
Urinalysis		Ambient
• Appearance • Bilirubin • Color • Glucose • Ketones • Microscopic examination of sediment • UACR	• Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen • Leukocyte esterase	
Urine Pregnancy Test (WOCBP)		Local

6.12 Diary and Glucometer Dispensation

A glucometer, testing strips, and a glycemic control diary will be provided to each subject at the start of the run-in period for SMBG. Subjects will be trained to use the glucometer and record any hypoglycemic events in the glycemic control diary. The SMBG record from the glucometer and diary entries must be reviewed by the investigator at all subsequent visits.

During the SMBG training, symptoms that may indicate hypoglycemia, hyperglycemia, or ketoacidosis will be reviewed with study subjects. Instructions to contact the clinic when the subjects experience potential hypoglycemia or DKA must be provided.

6.13 Dispensing Run-in Drug

Each eligible study subject will receive one bottle of sitagliptin run-in drug and one bottle of bexagliflozin run-in drug at the visit indicated in Appendix 1.

Patients should self-administer the first dose of each run-in drug with 1 cup (250 mL) of water under observation during the scheduled visit.

6.14 Diary and Glucometer Record Review

At each visit after the beginning of run in, the investigator will review the glycemic control diary, glucometer record, and symptoms that may indicate potential DKA with the subject and record the findings in the CRF.

6.15 Dispensing Investigational Product

At randomization and at every 12 weeks of treatment thereafter, each study subject will receive two bottles of the investigational product based on the kit number assigned to the subject by the IWRS. One bottle will be bexagliflozin, 20 mg or placebo, and the other bottle will be sitagliptin, 100 mg or placebo. Each bottle of the investigational product will provide daily dosing for 12 weeks.

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

6.15.1 Drug Accountability

To ensure adequate recordkeeping, subjects must bring all investigational products to each visit. The remaining tablets will be accounted for in the CRF and drug consumption forms. All unused drug must be returned to a sponsor-designated depot after drug accountability is verified by the sponsor or its designee.

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 AE (SAE) 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
- is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether a situation should be considered serious. Important medical events which jeopardize the subject or require intervention to prevent one of the outcomes listed above should 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 AE caused by a drug. Adverse reactions are a subset of all suspected AEs 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): A serious UADR. The sponsor must report any suspected SUSAR in an IND safety report (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 AE 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

After a subject consents to participation in the study, the investigator will periodically assess subjects for the occurrence of AEs. 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 in the source documents and CRFs.

It is the investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal laboratory test result, the investigator 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.

In addition, the sponsor’s Medical Monitor or its designated personnel must be notified immediately by telephone, email, or fax of any immediately reportable AEs (IRAE)

according to the procedure outlined below. Special attention should be paid to recording hospitalization and concomitant medications.

6.16.3 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 or its representative 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 as directed by 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

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

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

- 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 confirming that 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 Medical Monitor.

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

6.16.5 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 6.16.2. 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. Documentation of signs, symptoms, culture results for infectious agent, and treatment should be undertaken when appropriate.

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

- 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 hours to confirm the hepatic enzyme elevation. Testing should be repeated based on the clinical situation at least every 96 hours (4 days) until ALT and AST return to < 2.5 x ULN or until the liver function test results are stable and significant changes are not expected anymore. 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.

Should it be determined that the etiology is an unrelated acute or chronic medical condition (e.g.; NASH, Hepatitis A) and the return of LFT abnormalities to normal is unlikely during the course of the illness, further testing and follow up is at the investigator's discretion.

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 for recording blood glucose measurements and a diary to record 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, if appropriate, consume carbohydrates to treat hypoglycemia.

The subject will be expected to record the following information for each hypoglycemic event in the glycemic control diary:

- Signs and symptoms attributed to hypoglycemia and the time and date on which they occurred

- SMBG reading at the time of the signs and symptoms attributed to hypoglycemia
- Time elapsed from the most recent meal to the onset of signs and symptoms
- Duration, intensity, and type of any exercise within the 24 h prior to the signs and symptoms
- 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
- SMBG reading 15 minutes after treatment with carbohydrate and the time at which this was measured
- 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 which will include data from the glycemic control diary and action items to reduce future hypoglycemia episodes.

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

1. Severe hypoglycemia: an event requiring assistance by another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. All such events should be recorded as SAEs in the CRF
2. Documented symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration < 70 mg/dL (3.9 mmol/L)
3. Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured blood glucose concentration < 70 mg/dL (3.9 mmol/L)
4. Probable symptomatic hypoglycemia: an event during which symptoms of hypoglycemia are not accompanied by a blood glucose determination but that is presumably caused by a blood glucose concentration < 70 mg/dL (3.9 mmol/L)
5. Relative hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of

hypoglycemia, but with a measured plasma glucose concentration ≥ 70 mg/dL (3.9 mmol/L).

While each event meeting the criteria above will be entered into the hypoglycemia log, only 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. All subjects will be followed by investigators for MACE for the duration of the study even if study medication has been permanently withdrawn.

The independent CEC will receive and adjudicate the following events.

- All deaths
- Suspected non-fatal MI
- Suspected hospitalization for unstable angina (HUA)
- Suspected 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, 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. Laboratory values should be 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. The 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 Amputation

Amputation and related AEs will be recorded in a dedicated CRF. During each study visit, the investigator should query the subject for any amputation and related AEs 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. Subjects with history of amputation, or risk factors for amputation should be counseled to seek preventive care to prevent further complications. Such risk factors include peripheral vascular disease and diabetic neuropathy. 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.

6.16.15 Pancreatitis

Subjects should be informed that persistent severe abdominal pain, sometimes radiating to the back or accompanied by vomiting, is the symptom of acute pancreatitis. Subjects must contact the clinic immediately if they experience these symptoms. The investigator should observe carefully for signs and symptoms of pancreatitis. Laboratory testing, including

amylase and lipase, should be performed using local resources if necessary for diagnosis and clinical care. If pancreatitis is suspected, administration of study products should be discontinued promptly and appropriate management should be initiated. Diagnosis of pancreatitis must be documented in the CRF.

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. Changes in dose and/or frequency from therapies taken prior to randomization and their rationale must be recorded in the CRF.

The medications or treatment for controlling hyperglycemia 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.

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.

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

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 V1/ Screening

- 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 vital signs, including BPs and heart rate
- Measure weight
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10-h fast has been completed by the subject as described in section _Sample_Collection,_Storage,6.10.2. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample

7.2 V2/ Run In

- Counsel subject on appropriate diet and exercise
- Dispense glucometer and instruct subject in SMBG determination and recording
- Dispense two run-in kits for run-in period
- Assess AEs
- Record concomitant medications

7.3 V3/ Randomization

- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Perform a complete physical examination
- Measure vital signs, including BPs and heart rate
- Measure weight
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10 h fast has been completed by the subject as described in section 6.10.2. 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
- Record drug accountability, collect run-in product bottles
- Dispense investigational product based on randomization

- Assess AEs
- Record concomitant medications

7.4 V4/ 6 weeks

- Measure vital signs, including BPs and heart rate
- Measure weight
- Draw blood if an approximately 10-h fast has been completed by the subject as described in section 6.10.2. 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
- Record drug accountability
- Assess AEs
- Record concomitant medications

7.5 V5/ 12 weeks

- Measure vital signs, including BPs and heart rate
- Measure weight
- Draw blood if an approximately 10-h fast has been completed by the subject as described in section 6.10.2. 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
- Record drug accountability and collect previous investigational product bottles
- Dispense investigational product based on randomization
- Assess AEs
- Record concomitant medications

7.6 V6/ 18 weeks

- Measure vital signs, including BPs and heart rate
- Measure weight
- Draw blood if an approximately 10-h fast has been completed by the subject as described in section 6.10.2. 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
- Record drug accountability
- Assess AEs
- Record concomitant medications

7.7 V7/ End of Treatment

- Perform an abbreviated physical examination

- Measure vital signs, including BPs and heart rate
- Measure weight
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10-h fast has been completed by the subject as described in section 6.10.2. 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
- Record drug accountability and collect previous investigational product bottles
- Assess AEs
- Record concomitant medications

7.8 V8/ Follow up

- Perform a complete physical examination
- Measure vital signs, including BPs and heart rate
- Measure weight
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10-h fast has been completed by the subject as described in section 6.10.2. 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
- Assess AEs
- Record concomitant medications

7.9 Early Termination Procedures

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

8 QUALITY CONTROL AND ASSURANCE

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

Quality control principles will be applied throughout the performance of this study by following the Standard Operating Procedures (SOPs) of the contract research organization (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 SAS Version 9.2 or higher.

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.

The primary efficacy non-inferiority test will be one-sided at 0.025 significance level. The upper bound of the 95% confidence interval (CI) on the difference of HbA1c reduction between bexagliflozin and sitagliptin will be used to determine the study's conclusion. That is, if the upper bound of the CI is within 0.35%, then the primary objective of the study is met. Superiority will be declared without additional statistical testing when the upper bound of the 95% CI for the difference in change from baseline at week 24 in HbA1c comparing bexagliflozin group with sitagliptin group is less than 0.

The secondary efficacy objectives will be tested at two-sided 0.05 significance level following a sequential testing procedure to control the overall type I error of 0.05. The secondary efficacy endpoints will be tested only if the primary efficacy assessment achieves significance, and following the hierarchy as below:

1. Superiority test of the change in FPG in the bexagliflozin group vs. the sitagliptin group at week 24
2. Superiority test of the change in body weight in subjects with baseline BMI $\geq$ 25 kg/m^2 in the bexagliflozin group vs. the sitagliptin group at week 24
3. Superiority test of the change in SBP in the bexagliflozin group vs. the sitagliptin group at week 24

The exploratory efficacy objectives and safety objectives will be analyzed descriptively.

9.2 Determination of Sample Size

Approximate total 374 subjects will be randomized and equally allocated to receive bexagliflozin tablets (20 mg) + sitagliptin tablets (placebo), or bexagliflozin tablets (placebo) + sitagliptin tablets (100 mg)

The sample size calculation for this study is based on a two group t-test with a one-sided significance at the 0.025 level and the following assumptions:

1. The non-inferiority limit (margin) for mean change from baseline to week 24 in HbA1c comparing bexagliflozin group to sitagliptin group will be 0.35%
2. The pooled SD for the change from baseline to week 24 in HbA1c for bexagliflozin group and sitagliptin group will be 1.0%

Under the above assumptions, an estimated sample size of 172 patients is needed in each treatment arm to detect non-inferiority of bexagliflozin to sitagliptin with respect to change in HbA1c at week 24 from baseline. This estimation is based on a one-sided t-test with 90% power at a 0.025 level of significance. A sample size of 187 per arm has been selected to account for approximate 8% drop-out rate and to allow adequate safety evaluation. The total sample size for this study will be 374 subjects.

This study will be conducted at multiple investigative sites and will likely involve various 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 regardless of treatment adherence or availability of follow-up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized assigned treatment. 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 was actually taken by each subject. 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 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. The subject assignment to the PP analysis set will be determined prior to database lock. The PP analysis set will serve as the secondary set for efficacy assessments.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively based on the ITT and PP analysis set for each treatment group as well as for all subjects combined. Key variables include age, gender, race, ethnicity, baseline HbA1c values, BP, body weight, BMI, FPG level, eGFR, duration of diabetes and prior anti-diabetic treatment status at screening (including type of therapy used [metformin, SU, DPP-4 inhibitor, alpha-glucosidase inhibitor etc.). In general, baseline measurement is defined as the last measurement prior to the first dose of double-blind medication.

9.4.1 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), and include medications that are either started prior to the study treatment and continue to be taken during the study treatment period, or medications started after the start of study treatment. Concomitant medications will be summarized by ATC term and by treatment groups.

9.5 Primary Efficacy Analyses

9.5.1 Hypotheses for the Primary Endpoint

The null and alternative hypotheses for the primary endpoint are:

$$H_0: \mu_{\text{bexagliflozin}} - \mu_{\text{comparator}} > \delta$$

$$H_a: \mu_{\text{bexagliflozin}} - \mu_{\text{comparator}} \leq \delta$$

Where $\mu_{\text{bexagliflozin}}$ and $\mu_{\text{comparator}}$ represent the mean change in HbA1c at week 24 from baseline for bexagliflozin and comparator groups, respectively. Non-inferiority margin δ is chosen to be 0.35% using clinical judgment, with reference to relevant regulatory guidance.

9.5.2 Statistical Methods for Primary Analyses

For the primary endpoint, the treatment difference will be examined by using a mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA). The model will include treatment, visit, treatment-by-visit interaction, region and the baseline HbA1c value as a fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the comparator group at week 24 will be estimated from the model. An unstructured covariance will be used to model the within-subject correlation. 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 in the analysis. These analyses will be conducted on both ITT (primary) and PP analysis sets, and conclusions can be considered more robust when both approaches support the non-inferiority of the treatment.

In non-inferiority analysis, a CI is calculated to estimate the range of values in which the treatment difference is likely to lie. This CI is used to provide the basis for drawing the study's conclusions. In this specific test, if the 95% CI lies below the specified non-inferiority margin 0.35%, the results would lead to a conclusion of non-inferiority of bexagliflozin treatment to sitagliptin treatment. Superiority of bexagliflozin group over sitagliptin group at week 24 in HbA1c change from baseline will be declared if the upper bound of 95% CI is less than 0.

Sensitivity analyses will also be performed as the following, and these analyses will be conducted for ITT and PP analysis sets.

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

9.5.3 Analysis of Dropouts Pattern

The early termination rate is estimated to be 8%. 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 in FPG in the bexagliflozin group vs. the sitagliptin group at week 24, similar to the primary endpoint analysis method, MMRM ANCOVA will be implemented (values obtained after the start of rescue medication will not be excluded in the analysis). The model will include treatment, visit, treatment-by-visit interaction, region and the baseline FPG value as fixed effects/covariates. Least squares mean treatment differences between the bexagliflozin group and the comparator group will be estimated from the model. The corresponding 95% CI and p-value will be provided.

The change in body weight for subjects with baseline BMI $\geq$ 25 kg/m^2 in the bexagliflozin group vs. the sitagliptin group at week 24, and the change in SBP in the bexagliflozin group compared with sitagliptin group at week 24 will be analyzed using the same method.

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

9.7 Other Efficacy Analyses

Changes in HbA1c, FPG, SBP, and body weight for all subjects during the treatment period will be summarized descriptively by each time point (i.e., Weeks 6, 12, 18, 24, …, etc.). In addition, these endpoints may be analyzed using a similar MMRM model as used for the primary analysis of HbA1c to compare two treatment groups at different time points.

Cumulative summary on the proportion of subjects achieving HbA1c < 7% will be presented over time. Generalized estimation equation (GEE) logistic regression method may be utilized for assessment of treatment effects.

Analyses will be conducted using ITT analysis set.

9.8 Analysis of Safety

Safety data include AEs, physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology, serum lipids, glycemic control parameters and urinalysis. Observed data will be summarized by treatment using safety analysis set.

9.8.1 Adverse Events

AEs will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs that begin at or after the first administration of double-blind study medication or existing AEs that worsen in severity after the first dose of double-blind study medication are considered treatment emergent AEs (TEAE). 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 AE will be considered those to be at least possibly related to the study treatments based on the investigators 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 Interest

AE of interest include UTI, GMI, diuretic effects, hypotension episodes, hypoglycemia, hepatotoxicity, MACE, falls and fractures, malignancy, hypersensitivity reactions, pancreatitis, amputations and renal failure events. These AEs of interest except DKA, MACE and amputations will be prospectively identified based on the MedDRA preferred terms in the AE log by a medical expert prior to the data base lock and unblinding of the individual subject treatment assignment. The list of AE of interest will be confirmed in a peer review process. DKA and MACE will be identified by the investigator and documented in the CRF, and subsequently adjudicated by seperate independent committees. Adjudicated results will be used for summary. Amputation events will be recorded in the procedures and amputation CRF.

The number and percentage of subjects experienced TEAE of interest will be summarized for each treatment group by types of events. The incidence rate of AE of 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.

9.8.3 Clinical and Laboratory Events and Analyses

Clinical laboratory (see Section 6 for a complete list), vital signs, and 12-lead ECG will be measured at scheduled visits (see Appendix 1). These data 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

Physical examination findings will be presented in a by subject listing.

9.9 Interim Analysis

No interim analysis will be performed during this study.

9.10 Final Analysis

After all subjects have completed the planned 24 weeks of blinded study treatment and the subsequent follow-up visit, the final analysis of the clinical study will be completed. At this time, the database will be cleaned and locked, and the treatment codes will be unblinded.

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.

The clinical investigator must personally conduct or supervise the procedures that are required in the protocol. Procedures that require clinical or medical knowledge must be performed by the investigators or qualified sub-investigators. The investigator may delegate tasks to any individual to whom a task is delegated is qualified by education, training, and experience (and local licensure where relevant). The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks and maintain records of the training that individuals have received that qualifies them to perform delegated tasks (e.g., individual's CV, certifications), and identify the dates of involvement in the study. No study-related procedures should be conducted unless the delegated individual has adequate training on the protocol and assigned task

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

The study protocol, informed consent document, relevant supporting information, and all types of subject recruitment or advertisement information must be submitted to the independent 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 ICH 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 the ICH GCP guidelines (E6), in addition to any other elements required by local regulations or institutional policy.

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

10.5 Subject Confidentiality

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

protocol will be posted on clinicaltrials.gov and any local regulatory registry websites, as required by regulation.

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

10.6 Study Monitoring

An authorized sponsor representative will conduct site visits to inspect study data, subjects' medical records, and CRFs in accordance with ICH guidelines, GCP, 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 CRF, in paper or 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 a subject is withdrawn must be recorded in the CRF.

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 sponsor or its designee's SOPs.

10.8 Data Monitoring Committee

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

10.9 Protocol Violations/Deviations

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

procedure, etc. Protocol violations will reported in the final clinical study report, whereas protocol deviations may be mentioned but are not required to be reported.

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

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

Protocol deviations/violations 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.

11 REFERENCE LIST

IDF (2015). "International Diabetes Federation Diabetes Atlas Seventh Edition."

Look, A. R. G., R. R. Wing, et al. (2013). "Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes." N Engl J Med 369(2): 145-154.

Nauck, M. A. (2014). "Update on developments with SGLT2 inhibitors in the management of type 2 diabetes." Drug Design, Development and Therapy 8: 1335-1380.

Santer, R., M. Kinner, et al. (2003). "Molecular analysis of the SGLT2 gene in patients with renal glucosuria." J Am Soc Nephrol 14(11): 2873-2882.

Scheen, A. J. and L. F. Van Gaal (2014). "Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes." Lancet Diabetes Endocrinol 2(11): 911-922.

Schwartz, S., A. N. Fabricatore, et al. (2012). "Weight reduction in diabetes." Adv Exp Med Biol 771: 438-458.

Seufert, J. (2015). "SGLT2 inhibitors - an insulin-independent therapeutic approach for treatment of type 2 diabetes: focus on canagliflozin." Diabetes Metab Syndr Obes 8: 543-554.

Van den Heuvel, L. P., K. Assink, et al. (2002). "Autosomal recessive renal glucosuria attributable to a mutation in the sodium glucose cotransporter (SGLT2)." Hum Genet 111(6): 544-547.

Zhang, W., A. Welihinda, et al. (2011). "EGT1442, a potent and selective SGLT2 inhibitor, attenuates blood glucose and HbA(1c) levels in db/db mice and prolongs the survival of stroke-prone rats." Pharmacol Res 63(4): 284-293.

Appendix 1 Schedule of Events

Procedure	**Screening**	**Run-in**	**Treatment**					**Follow-up**
Visit Number	V1/ Screening	V2/ Run In	V3/ Randomization	V4/ 6 weeks	V5/ 12 weeks	V6/ 18 weeks	V7/ End of Treatment	V8/ Follow up
Time to Randomization	-3	-1	0	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					X
Abbreviated Physical Examination	X						X	
Vital Signs	X		X	X	X	X	X	X
Measure Weight	X		X	X	X	X	X	X
Electrocardiography	X		X				X	X
Clinical Laboratory Tests	X		X	X	X	X	X	X
Diary and Glucometer Dispensation		X						
Dispensing Run-in Drug		X						
Diary and Glucometer Record Review			X	X	X	X	X	X
Dispensing Investigational Product			X		X			
Adverse Events Assessments		X	X	X	X	X	X	X
Concomitant Medication Assessments		X	X	X	X	X	X	X

Appendix 2 Schedule of Clinical Laboratory Tests

Procedure	**Screening**	**Run-in**	**Treatment**					**Follow-up**
Visit number	V1/ Screening	V2/ Run In	V3/Randomi-zation	V4/ 6 weeks	V5/ 12 weeks	V6/ 18 weeks	V7/ End of Treatment	V8/ Follow up
Time to Randomization Visit (weeks)	-3	-1	0	6	12	18	24	26
Hematology	X		X	X	X	X	X	X
Serum Chemistry and Electrolytes	X		X	X	X	X	X	X
Glycemic Control	X		X	X	X	X	X	X
Serum Lipids	X		X		X		X	X
Urinalysis	X		X	X	X	X	X	X
Infectious Disease Testing	X							
Urine Pregnancy Test (WOCBP)	X		X	X	X	X	X	X

Appendix 3 Examples of SGLT2 Inhibitors

The following medications are prohibited during the study. Other SGLT2 inhibitors that may be approved for the treatment of T2DM during the THR-1442-C-423 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 4 Sponsor Signatures

Study Title: A Phase 3, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Effects of Bexagliflozin versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin

Study Number: THR-1442-C-423

V2.0 Final Date: 06 April 2017

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

Signed: _____ Date: 4/11/17

Adrian Banerji
Protocol Originator
Massachusetts General Hospital
Consultant for Theracos Sub, LLC

Signed: _____ Date: 4-18-17

Robert Klugman M.D.
Medical Monitor
Consultant for Theracos Sub, LLC

Signed: _____ Date: 11 Apr 2017

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

Appendix 5 Investigator's Signature

Study Title: A Phase 3, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Effects of Bexagliflozin versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin

Study Number: THR-1442-C-423

V2.0 Final Date: 06 April 2017

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 me and my sub-investigators at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signed:_____ Date:_____
Clinical Investigator