Clinical Trial Protocol: THR-1442-C-449

Study Title:	A Phase 2b, Multi-center, Double-blind, Placebo-controlled, Dose Range Finding Study to Evaluate the Effect of Bexagliflozin Tablets on HbA1c in Subjects with Type 2 Diabetes Mellitus
Study Number:	THR-1442-C-449
Study Phase:	2b
Product Name:	Bexagliflozin tablets
Indication:	Type 2 Diabetes Mellitus
Investigators:	Multi-center study
Sponsor:	Theracos, Inc.
Sponsor Contact:	Albert Collinson, Ph.D. Theracos, Inc. 225 Cedar Hill Street, Suite 200, Marlborough, MA 01752 Phone: 508-688-4221
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	Date
Original Protocol:	29 September 2014
Protocol Revision	16 February 2015

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SYNOPSIS

Sponsor:

Theracos, Inc.

Name of Finished Product:
Bexagliflozin tablets

Name of Active Ingredient:

(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)-benzyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol

Code name: EGT0001442

Study Title:
A Phase 2b, Multi-center, Double-blind, Placebo-controlled, Dose Range Finding Study to Evaluate the Effect of Bexagliflozin Tablets on HbA1c in Subjects with Type 2 Diabetes Mellitus

Study Number:
THR-1442-C-449

Study Phase: 2b

Primary Objective:
The primary objective of this study is to identify dose(s) for further clinical study through the comparison of HbA1c change from baseline in each active group that will receive bexagliflozin tablets, 5 mg, 10 mg, or 20 mg, to the placebo group over 12 weeks of treatment.

Secondary Objectives:

- To assess the change in HbA1c over time
- To assess the efficacy of bexagliflozin tablets in lowering FPG as a function of time
- To assess the efficacy of bexagliflozin based on the proportion of subjects who reach the American Diabetes Association (ADA) and the Japan Diabetes Society target HbA1c of <7%
- To assess the effect of bexagliflozin on systolic and diastolic blood pressure over time
- To assess the effect of bexagliflozin on body weight over time
- To assess the safety of bexagliflozin in subjects with T2DM

Other endpoint:
Population pharmacokinetic evaluation of bexagliflozin plasma concentration

Study Design:
THR-1442-C-449 is a phase 2b multicenter, double-blind, placebo-controlled parallel group study to assess the effect of once daily bexagliflozin tablets on HbA1c in either treatment-naïve type 2 diabetic subjects or in subjects who have been treated with one oral anti-diabetic

agent. To be eligible, a prospective subject of either gender must have T2DM and an HbA1c value between 7% and 8.5% at the screening visit if treatment naïve or an HbA1c value between 6.5% and 8.5% if currently treated with one oral hypoglycemic agent and willing to undergo a 6 or 10 week washout.

All eligible subjects who are treatment naïve or who have completed the washout will start a 2 week placebo run-in period. Subjects who are deemed compliant in taking the run-in medication (*i.e.*, miss no more than one dose during the run-in period) and have HbA1c between 7 and 8.5% at the end of the run-in period will be eligible for randomization and will receive investigational product.

Approximately 320 subjects divided equally into 4 groups will be randomly assigned to take oral bexagliflozin tablets, 5 mg, 10 mg, 20 mg, or placebo, once daily for 12 weeks in an out-patient setting. Subjects with hyperglycemia based on fasting blood glucose levels may receive approved anti-diabetic medication.

Subjects will visit their study sites at weeks 2, 6, and 12 for safety and efficacy evaluation, with a follow-up visit at week 14.

Measurement of bexagliflozin plasma concentration over time (sparsely sampled) will also be conducted at 20 centers and will include approximately 240 study subjects as part of a bexagliflozin population PK study.

Study Population:
Approximately 320 diabetic subjects will be randomized.

Prospective subjects must be:

1. Men or women ≥ 20 years of age at screening. Women of childbearing potential must test negative by urine pregnancy test and agree to abstain from coitus or use contraception during the entire study period to avoid any possible pregnancy. Females who are surgically sterile (by reason of hysterectomy or oophorectomy) or postmenopausal (most recent menses more than 12 months prior to screening) are eligible if they test negative by urine pregnancy test.
2. Treatment naïve (*i.e.*, have never received prescription anti-diabetic medications or have received no more than 14 days of prescription medications for diabetes in the 12 weeks prior to enrollment) or currently taking one OHA in combination with diet and exercise
3. Diagnosed with T2DM with HbA1c levels at screening between 7.0% and 8.5% (inclusive) if treatment naïve or with HbA1c levels between 6.5 and 8.5% (inclusive) if on one oral anti-diabetic medication
4. Currently having a body mass index (BMI) ≤ 40 kg/m^2
5. Taking stable doses of medication for hypertension or hyperlipidemia as determined by adherence to a regimen that has not changed for at least 30 days prior to screening (if

applicable)

6. Able to comprehend the study participation requirements and willing to provide written informed consent in accordance with institutional and regulatory guidelines
7. Able to maintain adequate glycemic control at the run-in visit (for subjects who complete the washout)
8. Having an HbA1c between 7.0 and 8.5% (inclusive) prior to randomization (day -3 to -5):
9. Capable of adhering to the investigational product administration requirements as evidenced by omission of no more than one dose of run-in medication

Test Product, Dose, and Mode of Administration:
Bexagliflozin tablets, 5, 10, 20 mg or placebo, once daily by mouth before breakfast

Duration of Treatment:
12 weeks

Efficacy Assessments:
Primary efficacy assessment:

- Change in HbA1c over 12 weeks of treatment

Secondary efficacy assessments:

- Change in HbA1c over time
- Proportion of subjects with HbA1c <7%
- Change in body weight over time
- Change in FPG over time
- Change in systolic and diastolic blood pressure over time

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

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

Statistical Methods:
Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by-subject data listings.

For the primary endpoint of HbA1c change from baseline over 12 weeks of treatment, a

mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA) with baseline HbA1c as a covariate will be fitted on the available data, incorporating all visits at which HbA1c was measured from each subject including the scheduled visits at weeks 2, 6, and 12 as well as the unscheduled visits for measurement of HbA1c. Treatment, study center, and stratification factor for randomization (treatment naïve versus taking one OHA at baseline) will be applied as fixed effects, as will study week and study week-by-treatment interaction. From this model, an estimate of the treatment difference at week 12 will be generated, as will an assessment of whether this estimate is significantly different when comparing placebo with each dose of bexagliflozin at a two-sided 0.05 level of significance. An unstructured within-patient covariance structure will be assumed. HbA1c values obtained after the start of rescue medication will be excluded from this primary analysis.

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

1. Missing HbA1c data (for weeks 2, 6, or 12) will be imputed via multiple imputation, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will be considered missing.
2. Missing HbA1c data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
3. HbA1c values collected after the start of rescue medication will NOT be considered missing, and the MMRM analyses will be re-performed.

The effect of bexagliflozin on fasting blood glucose, blood pressure, body weight, change in HbA1c over time, and proportion of subjects who reach HbA1c < 7% will be evaluated as secondary endpoints. These endpoints are considered exploratory and will not be adjusted for multiplicity.

Safety and tolerability of bexagliflozin in subjects with T2DM will also be assessed descriptively. Data summaries will be produced for AEs, physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology, serum lipids, glycemic control parameters and urinalysis.

Date of Original Approved Protocol: 29 September 2014

Date of Revised Protocol: 16 February 2015

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	American Diabetic Association
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CK	Creatinine kinase
CRF	Case report form
CRO	Contract research organization
CV	Cardiovascular
DPP4	Dipeptidyl peptidase 4
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FPG	Fasting plasma glucose
γ-GTP	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
h	Hour
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDPE	High density polyethylene
HF	Heart failure
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
ICCR	In country caretaker representative
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug

IRAE	Immediately reportable adverse event
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LDH	Lactic dehydrogenase
MACE	Major adverse cardiovascular event
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
NYHA	New York Heart Association
OHA	Oral hypoglycemic agent
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium glucose cotransporter 2
SMBG	Self-monitored blood glucose
SOP	Standard operating procedure
T2DM	Type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
UACR	Urine albumin-to-creatinine ratio
UGE	Urinary glucose excretion
ULN	Upper limit of normal
UPT	Urine pregnancy test
UTI	Urinary tract infection
WOCBP	Woman of child bearing potential
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality worldwide, affecting an estimated 387 million people in 2014 and reaching epidemic proportions in nearly all countries in the world. Approximately 179 million of those affected are estimated to be unaware of their condition and over 80% reside in low- and middle-income countries (International Diabetes Foundation, 2014). T2DM accounts for at least 90% of all diabetes cases. Despite the availability of several classes of therapeutics, the number of people with T2DM is projected to increase by 55% to over 590 million adults by 2035. 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 of insulin resistance and is strongly linked to increased body fat mass in the majority of cases (Schwartz 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 et al., 2013; Scheen and Van Gaal, 2014).

Asian populations may be particularly at risk for the adverse consequences of increased body mass. Metabolic syndrome, a presentation of diabetes with comorbid hypertension and dyslipidemia, increases more rapidly with increasing weight among Asians than among non-Asians and it has been proposed that the BMI ranges that define the overweight and obese categories should be lower in Asian populations than in non-Asian populations (Palaniappan et al., 2011).

Several classes of agents are available for treating T2DM, including insulin and its secretagogues, PPARγ agonists, biguanides, alpha glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP4) inhibitors. However, 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 will ideally reduce hyperglycemia and avoid common side effects of currently available agents, such as weight gain, gastrointestinal disturbances, 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 (Santer et al., 2003; van den Heuvel et al., 2002). The excretion of glucose in the urine of diabetic subjects in amounts comparable to or greater than that seen in individuals harboring loss of functions mutations in SLC5A2 has the potential to improve both fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia.

1.1 Bexagliflozin for the Treatment of Type 2 Diabetes Mellitus

Bexagliflozin (previously identified as EGT0001442), is a potent and highly specific inhibitor of the SGLT2 with an *in vitro* IC_{50} of 2 nM or 0.9 ng/mL and a 2435-fold selectivity for human SGLT2 compared with SGLT1. Bexagliflozin elicits a prominent and predictable glucosuria in laboratory animals and human subjects.

1.1.1 Summary of Non-clinical Data with Bexagliflozin

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

1.1.2 Summary of Clinical Data with Bexagliflozin

Theracos has completed eight phase 1 studies to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and drug metabolism in healthy subjects, subjects with T2DM, and diabetic subjects with renal impairment. Details of the pharmacology, efficacy, and safety assessments are described in the Investigator's Brochure and summarized in the following sections.

Bexagliflozin exhibits high permeability and is a weak Pgp substrate and inhibitor. It produces dose-proportional exposures in humans and animals. Metabolism in humans is most similar to that in monkeys, and the principal pathway for biotransformation in humans is glucuronide formation. The majority of bexagliflozin and related metabolites are excreted within 48 to 72 h in humans, rats and monkeys, and there is no evidence of accumulation. Bexagliflozin is neither a significant inducer nor inhibitor of cytochrome P450 isozymes relevant for drug-drug interactions.

In the course of bexagliflozin therapeutic development, several formulations have been evaluated. Immediate release capsule formulations have been used in the initial clinical pharmacology and phase 2 studies. A program to develop an extended release tablet formulation that would reduce daily variation in the concentration of the compound was carried out and resulted in the identification of a mucoadhesive formulation with the desired properties. The drug products exhibit a greater than 75% release of drug substance by 8 h in simulated gastric fluid *in vitro*.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to identify the optimal dose(s) through the comparison of mean HbA1c change in subjects who receive bexagliflozin tablets, 5 mg, 10 mg, 20 mg, or placebo, after 12 weeks of treatment.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the change in HbA1c over time
- To assess the efficacy of bexagliflozin tablets in lowering fasting plasma glucose (FPG) over time
- To assess the efficacy of bexagliflozin based on the proportion of subjects who reach the American Diabetes Association (ADA) and the Japan Diabetes Society target HbA1c of <7%
- To assess the effect of bexagliflozin on systolic and diastolic blood pressure over time
- To assess the effect of bexagliflozin on body weight over time
- To assess the safety of bexagliflozin in subjects with T2DM

Other exploratory objective includes:

- Population pharmacokinetic evaluation of bexagliflozin plasma concentration

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

THR-1442-C-449 is a phase 2b multicenter, double-blind, placebo-controlled, dose range finding study to assess the efficacy and safety of once daily bexagliflozin in either treatment-naïve type 2 diabetic subjects or subjects previously treated with one oral hypoglycemic agent (OHA). The primary efficacy endpoint will be placebo-adjusted reduction in HbA1c, measured after 12 weeks of treatment. Treatment naïve subjects are those who have never received prescription anti-diabetic medications or who have received no more than 14 days of prescription medications for diabetes in the 12 weeks prior to enrollment. The study will enroll men and women with T2DM and with HbA1c between 7% and 8.5% (inclusive) at the screening visit (for subjects who are treatment naïve) or with T2DM and with HbA1c between 6.5% and 8.5% (inclusive) at screening visit (for subjects who have received one OHA and who are willing and able to undergo a washout period.)

Approximately 400 subjects who meet all the inclusion criteria, none of the exclusion criteria, and who consent to participate in the study are eligible to be enrolled to complete a 6 to 10 week washout if needed and a 2 week placebo run-in period prior to being randomized. Subjects who can adhere to the run-in medication dosing schedule (i.e., miss no more than one dosage in 2 weeks) and who have HbA1c between 7 and 8.5% at baseline (visit S5) will be eligible for randomization and receive investigational product. A 20% screen fail rate is expected by the end of run-in, leading to approximately 320 subjects eligible for randomization to receive oral bexagliflozin tablets, 5, 10, 20 mg or placebo once daily for 12 weeks in an outpatient setting. Subjects who experience hyperglycemia during the study may receive approved anti-diabetic medication. Subjects will visit their study site at weeks 2, 6, and 12 for safety and efficacy evaluation, with a follow up visit at week 14.

Measurement of bexagliflozin plasma concentration over time (sparsely sampled) will be conducted at 20 centers and will include approximately 240 subjects who consent to participate the PK study. Three samples from each subject will be drawn at weeks 2, 6, or 12.

3.2 Research Methods and Procedures

3.2.1 Washout and Run-in Period

Eligible subjects who are not treatment naïve will discontinue their current OHA and enter a 6- or 10-week washout. Those who are taking any OHA except a thiazolidinedione will discontinue the medication for 6 weeks. Subjects who are taking a thiazolidinedione will discontinue the medication for 10 weeks. At the start of the washout, each subject will be provided with diet and exercise counseling, a glucometer, a glycemic control diary in which to record daily fasting self-monitored blood glucose (SMBG) measurements and instructions regarding the appropriate circumstances under which a call to the clinic to register an observation of hyperglycemia should be made (see *Glycemic Control* below). Two weeks after the start of the washout period each subject will participate in a phone interview with study staff for SMBG data review and general safety evaluation. Subjects who remain

eligible at the end of the 6 or 10 week washout period will proceed to a 2-week placebo run-in period. Subjects will be ineligible if they exhibit fasting blood glucose values ≥ 250 mg/dL on two consecutive days during the wash-out period.

Eligible subjects who are treatment naïve will not require a washout period and will proceed to the run-in period. These subjects will be provided with diet and exercise counseling, a glucometer, and a glycemic control diary in which to record daily fasting SMBG measurements at the start of the 2-week placebo run-in period.

Treatment naïve subjects and subjects on background OHA who complete the washout will enter a 2-week single-blind placebo run-in period. Each subject will be provided with placebo run-in drug, dosing instructions, and instructions regarding the appropriate circumstances under which a call to the clinic to register an observation of hyperglycemia should be made (see *Glycemic Control* below). During the run-in, a placebo tablet should be taken daily in the morning prior to eating or drinking; the medication should be taken with water.

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, 2) omit more than one of the daily doses of placebo, 3) are deemed inappropriate for the study by the investigator, or 4) on day -3 to day -5 prior to randomization, have HbA1c value < 7.0% or > 8.5%. The glycemic control requirement based on HbA1c values is outlined in Figure 1.

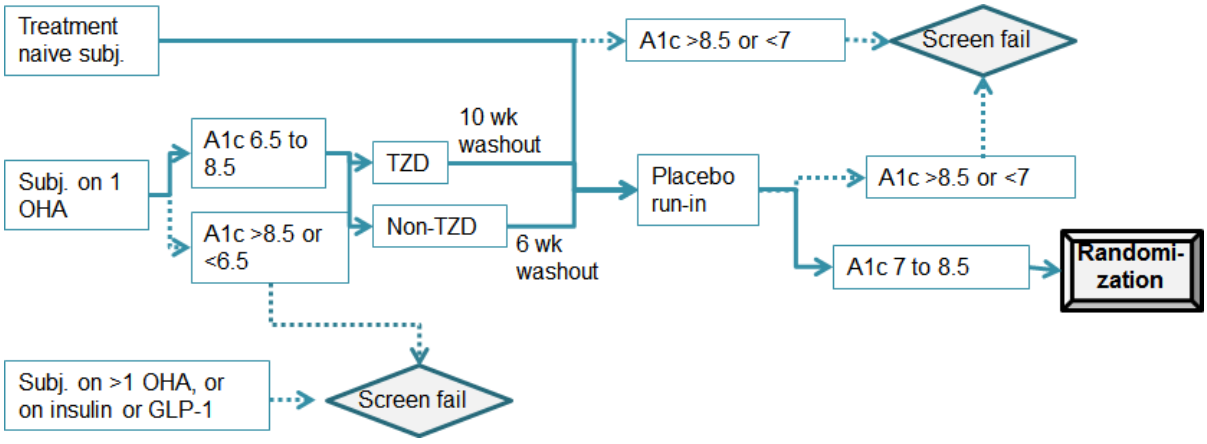

Figure 1. Glycemic Control Requirements Prior to Randomization

Approximately 320 eligible subjects will be randomized in equal ratio. Randomization will be stratified by the background anti-diabetes treatment status (treatment naïve or taking one OHA).

An assessment of bexagliflozin pharmacokinetics will also be conducted at 20 centers to include approximately 240 subjects. Samples will be taken during weeks 2, 6, or 12.

3.2.2 Treatment Period

The 12- week treatment period will start at randomization. At the start of the treatment period each subject will be provided with the investigational products, dosing instructions, and a glycemic control diary in which to record SMBG measurements. Information related to the occurrence of hyperglycemic or hypoglycemic events will be recorded. The investigational products will be orally administered in the morning prior to eating or drinking; the medication should be taken with water. Rescue medication for hyperglycemia will be allowed when deemed medically necessary by the investigator.

Each subject will be instructed to return to the clinic at weeks 2, 6, and 12 for safety and efficacy evaluations including review of adverse events and concomitant medications, vital signs, ECG, physical examination, and blood and urine specimen collections. On the day of the clinic visit a minimum fasting period of 10 hours (h) must be confirmed prior to blood draw.

Subjects will return to the clinic for a follow-up exit visit at week 14 or 2 weeks after the last dose of investigational product. Following the exit visit, subjects will be advised to see their primary physician to undergo treatment to control their diabetes. The duration of participation for each subject is up to 29 weeks based on the treatment status of each potential subject.

3.2.3 Glycemic Control Monitoring

WASHOUT AND PLACEBO RUN-IN PERIODS

During the washout and placebo run-in period subjects will be instructed to determine SMBG daily after fasting overnight for a minimum of 10 h. If the fasting blood glucose is ≥ 250 mg/dL (13.9 mmol/L) the subject should contact the clinic within 24 h 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. The participant will be excluded from further participation if fasting blood glucose values are ≥250 mg/dL prior to randomization on 2 or more consecutive days. Subjects with SMBG clinical signs or symptoms of hyperglycemia during the washout or run-in periods, including weight loss, blurred vision, increased thirst, increased urination, or fatigue should be excluded.

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 1 to week 6 or ≥ 240 mg/dL (13.3 mmol/L) from week 6 to week 12. Fasting blood glucose values collected via SMBG will be evaluated at study visits by the investigator. In addition, hyperglycemia will be monitored by FPG measurement at each study visit.

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

During the 12 weeks of the treatment period, hyperglycemia should be managed first with diet and exercise counseling and should be managed with changes in the medical therapy only if the investigator feels it is necessary for the well-being of the subject (see below, Prescription of Rescue Medication).

If a concomitant medication for hyperglycemia is to be prescribed, a sample must be drawn prior to the administration of the rescue medication so that a final HbA1c value can be ascribed to the latest date upon which the subject was taking investigational product as the sole therapy.

PRESCRIPTION OF RESCUE MEDICATION

Rescue medication for hyperglycemia should be prescribed by the investigator at any time it is deemed necessary for the well-being of the subject. During the 12 week treatment period, a review of diet and exercise counseling is suggested prior to prescription of rescue medication in the absence of specific medical indications for rescue medication. Rescue medication is suggested if, after a review of diet and exercise counselling:

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

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, or increased urination, or fatigue), and the signs or symptoms are severe

The investigator may provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated, with the exception of an SGLT2 inhibitor, as study subjects may already be taking a drug in that class as a consequence of being randomized to receive bexagliflozin.

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

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

OTHER SAFETY MONITORING ACTIVITIES

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

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

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

DATA AND SAFETY MONITORING BOARD

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

MAJOR ADVERSE CARDIOVASCULAR EVENT 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.

3.3 Rationale for Study Design and Control Group

THR-1442-C-449 is designed to evaluate the efficacy and safety of bexagliflozin tablets at 5 mg, 10 mg, and 20 mg strengths in the treatment of subjects with T2DM. A randomized, double-blind study reduces bias and confounding by unmeasured factors and is the most suitable design to evaluate a new agent as a monotherapy in diabetic subjects. Under the close monitoring detailed in this study, placebo is the appropriate control treatment in the subject population studied during the 12-week treatment period. In order to exclude the possibility that a subject's HbA1c level at 12 weeks is determined by medications taken prior to the study, up to an 8 or 12 week combined washout and run-in period will be implemented prior to randomization. All subjects will receive a placebo in the last 2 weeks prior to randomization to allow compliance with the dosing regimen to be monitored. Subjects with FPG levels ≥ 250 mg/dL at randomization will be excluded as a safety measure. Diet and exercise counseling will be provided to all participating subjects to reduce risks of worsening diabetic conditions or prolonged hyperglycemia.

Results from published data in individuals with genetic mutations in *SLC5A2*, the gene encoding SGLT2, and in subjects that have been treated with other SGLT2 inhibitors, and from previous clinical studies in healthy or diabetic subjects treated with bexagliflozin, indicate that the risk of induced hypoglycemia as a consequence of the loss of SGLT2 activity should be minimal.

Reduction in HbA1c directly reflects improvement in glycemic control and is a well validated surrogate for the risk of long-term microvascular complications of T2DM. HbA1c reflects mean glycemic control over 2 to 3 months, and therefore the primary endpoint of HbA1c measurement at 12 weeks will reflect the impact of bexagliflozin compared to the placebo. Previous non-clinical and clinical study data have suggested that the glucosuria and changes in HbA1c are likely to be less correlated when the baseline HbA1c is high but more correlated when the HbA1c is modestly elevated. To better demonstrate the dose relatedness of the treatment effect, a baseline HbA1c value of 7% to 8.5% is included in this protocol to allow clinical dose selection. Near maximal glucosuria should be safe for the treatment of minimal diabetes since hypoglycemia has never occurred in trials with healthy subjects.

A previously completed clinical study in Japanese subjects demonstrated that a single dose of bexagliflozin of 3, 10, 30, or 90 mg strength resulted in a dose-dependent glucosuria from 3 mg to 30 mg with no incremental effect from 30 mg to 90 mg (Figure 2). This protocol is designed to assess the effect of bexagliflozin on HbA1c at 12 weeks. Strengths of 5, 10, and 20 mg will be tested.

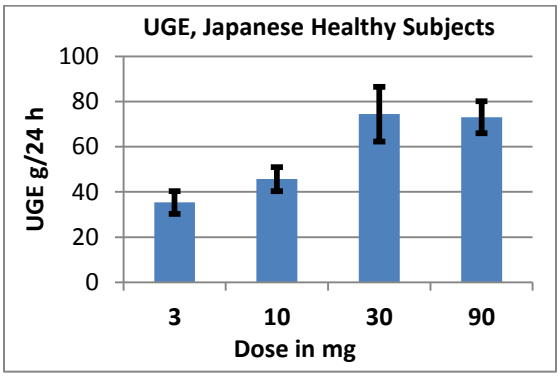

Figure 2. Dose related glucosuria in healthy Japanese subjects

3.4 Study Duration and Dates

Diabetic subjects will be screened within 3 weeks of enrollment. Eligible subjects who provide written consent will start a 2 to 12 week washout and run-in period prior to randomization to receive investigational product. Subjects will receive 12 weeks of treatment and be followed for 2 weeks after the last dose. The study duration from screening to follow-up will be 16 weeks and up to 29 weeks overall (Figure 3). For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1.

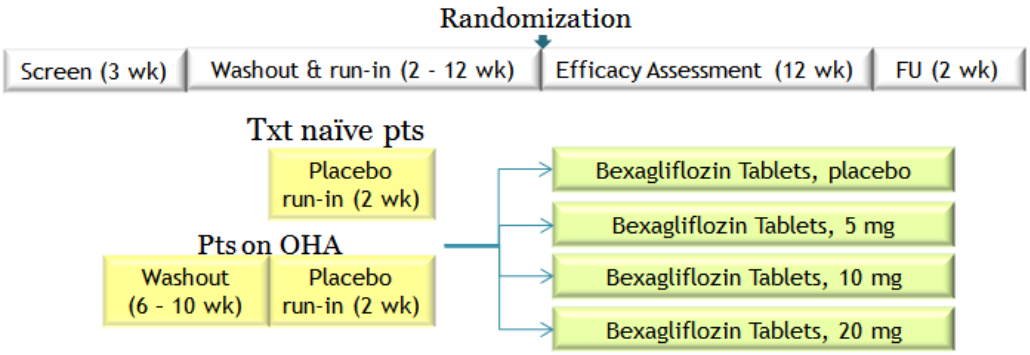

Figure 3. THR-1442-C-449 Study Design

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 320 subjects diagnosed with T2DM who are inadequately controlled by diet and exercise or by treatment with a single oral anti-diabetic agent and who have an HbA1c level between 7% and 8.5% at the time of randomization. Clinical sites in the US and in Japan are anticipated to recruit subjects. Clinical sites in other countries may also participate in the trial.

4.2 Inclusion Criteria

Prospective subjects must be:

1. Men or women ≥ 20 years of age at screening. Women of childbearing potential must test negative by urine pregnancy test and agree to abstain from coitus or use contraception during the entire study period to avoid any possible pregnancy. Females who are surgically sterile (by reason of hysterectomy or oophorectomy) or postmenopausal (most recent menses more than 12 months prior to screening) are eligible if they test negative by urine pregnancy test.
2. Treatment naïve (*i.e.*, have never received prescription anti-diabetic medications or have received no more than 14 days of prescription medications for diabetes in the 12 weeks prior to enrollment) or currently taking one OHA in combination with diet and exercise
3. Diagnosed with T2DM with HbA1c levels at screening between 7.0% and 8.5% (inclusive) if treatment naïve or with HbA1c levels between 6.5 and 8.5% (inclusive) if on one oral anti-diabetic medication
4. Currently having a body mass index (BMI) ≤ 40 kg/m^2
5. Taking stable doses of medication for hypertension or hyperlipidemia as determined by adherence to a regimen that has not changed for at least 30 days prior to screening (if applicable)
6. Able to comprehend the study participation requirements and willing to provide written informed consent in accordance with institutional and regulatory guidelines
7. Able to maintain adequate glycemic control at the run-in visit (for subjects who complete the washout)
8. Having an HbA1c between 7.0 and 8.5% (inclusive) prior to randomization (day -3 to -5)
9. Capable of adhering to the investigational product administration requirements as evidenced by omission of no more than one dose of run-in medication

4.3 Exclusion Criteria

Subjects who exhibit any of the following characteristics will be excluded from the study:

1. A diagnosis of type 1 diabetes mellitus or maturity–onset diabetes of the young (MODY)
2. Current use of parenteral therapy for treatment of diabetes (insulin or glucagon-like peptide-1 (GLP-1) receptor agonist therapy)
3. Pregnancy or current breastfeeding status
4. Hemoglobinopathy or carrier status for hemoglobin alleles that affect HbA1c measurement
5. Genitourinary tract infection (e.g. urinary tract infection, vaginitis, balanitis) within 6 weeks of screening or history of ≥3 genitourinary infections requiring treatment within 6 months of screening
6. Estimated glomerular filtration rate (eGFR), as calculated by the modification of diet in renal disease study equation (MDRD), < 60 mL/min/1.73 m^2 at screening (Appendix 2)
7. Uncontrolled hypertension (average of two sitting measurements of systolic blood pressure >160 mmHg or diastolic blood pressure > 95 mmHg) at screening
8. A positive result on hepatitis B surface antigen (HBsAg), hepatitis C (HCV), or positive result from screen for drugs of abuse
9. History of human immunodeficiency virus (HIV) infection
10. Life expectancy < 2 years
11. History of New York Heart Association (NYHA) Class 4 heart failure within 3 months of screening
12. History of MI, unstable angina, stroke, or hospitalization for heart failure within 3 months of screening
13. History of treatment with an investigational drug within 30 days or within 7 half lives of the investigational drug, whichever is longer
14. Previous treatment with bexagliflozin or EGT0001474
15. Currently or within 6 months of taking any SGLT2 inhibitors from screening
16. Currently participating in another interventional trial
17. Not able to comply with the study scheduled visits
18. Affected by any condition, disease, disorder, or clinically relevant abnormality that, in the opinion of the investigator, would jeopardize the subject's appropriate participation in this study or obscure the effects of treatment
19. ALT or AST ≥ 2.5 x upper limit of normal (ULN) or total bilirubin ≥ 1.5 x ULN with the exception of isolated Gilbert's syndrome at screening
20. Exhibiting fasting plasma glucose ≥ 250 mg/dL (13.9 mmol/L) on two or more consecutive days prior to randomization or exhibiting severe clinical signs or symptoms of hyperglycemia during the washout or run-in periods, including weight loss, blurred vision, increased thirst, or increased urination, or fatigue
21. FPG ≥ 250 mg/dL at randomization
22. Prior renal transplantation or evidence of nephrotic syndrome, defined as a urine albumin-to-creatinine ratio (UACR) > 2000 mg/g at screening

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Investigational Product

Bexagliflozin tablets, 5 mg, 10 mg, 20 mg, and placebo, are blue caplet-shaped, film-coated tablets that are intended for use in investigational studies in humans. The tablets contain excipients designed to promote extended release through a gastroretentive mechanism. The drug products exhibit a greater than 75% release of drug substance by 8 h in simulated gastric fluid *in vitro*.

The following investigational drugs will be used for oral administration:

- Bexagliflozin tablets, 5 mg: tablets containing 5 mg of bexagliflozin
- Bexagliflozin tablets, 10 mg: tablets containing 10 mg of bexagliflozin
- Bexagliflozin tablets, 20 mg: tablets containing 20 mg of bexagliflozin
- Bexagliflozin tablets, placebo: tablets containing no bexagliflozin

5.2 Treatments Administered

Bexagliflozin tablets should be taken in the morning prior to eating or drinking. The medication should be taken with water.

5.3 Selection and Timing of Dose for Each Patient

Prior clinical experience has shown bexagliflozin tablets in strengths up to 90 mg per tablet are safe and well tolerated. The highest planned dosage of 20 mg per day is not expected to produce serious drug-related adverse events. Doses of 10 mg and 30 mg bexagliflozin in the tablet formulation have produced near saturation of UGE and statistically significant FPG lowering activity in prior studies. The dose strengths of 5, 10, and 20 mg have been selected to evaluate safety and efficacy of bexagliflozin.

Dosing with bexagliflozin tablets, 5, 10, 20 mg or placebo, will be based on randomized assignment. All study subjects will be instructed to self-administer one tablet with water every morning prior to eating or drinking. There will be no change of dose during the 12-week treatment period.

5.4 Method of Assigning Patients to Treatment Groups

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized in a 1:1:1:1 ratio to receive investigational product according to a computer-generated randomization schedule. Subjects will be assigned to treatment groups in sequential order as they qualify for the study, using a centrally located and managed IWRS. Randomization will be stratified according to background anti-diabetic treatment status (treatment naïve or taking one OHA).

The study will be conducted at multiple investigative sites and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but each site will be capped at 32 subjects. Activation of investigational sites will be centrally controlled by IWRS. Subject randomization will be deactivated for all sites when the planned number of subjects is met. However, if a potential subject is in the washout period and wishes to participate in the study, the subject will be allowed to continue and, if eligible, to be randomized.

5.5 Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the cardiovascular adjudication committee members will be blinded to the study medication. Upon randomization, each subject will receive a subject randomization number and a drug kit assigned to the subject. To maintain blinding of the individual treatment assignment, the results of urinary glucose testing will not be made available to any study personnel or subjects.

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

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

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

5.6 Concomitant Therapy

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.

During the run-in period, blood pressure medications can be altered to optimize blood pressure control at the discretion of the investigator. Blood pressure medications should not be altered during the treatment period unless it is medically necessary to do so. If it is medically necessary to alter blood pressure medications during the treatment period, new diuretic medications should not be initiated and the dose and frequency of existing diuretic medications should not be altered.

Subjects with hyperglycemia during the treatment period will review diet and exercise counseling and/or receive rescue medication at the discretion of the investigator during the study. Anti-diabetic therapies prescribed to subjects for the purpose of treating hyperglycemia will be considered rescue medications (see Prescribing Rescue Medication, above). A blood sample will be collected to measure the last HbA1c value prior to administration of any rescue medications. The rescue medications must be recorded as concomitant medications in the CRF.

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

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

5.7 Restrictions

5.7.1 Prior Therapy

All subjects will continue regimens for medical conditions other than diabetes during the study as indicated above. No subject shall have been treated with an 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 6 months of screening. Subjects taking insulin or GLP-1 receptor agonists 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. The diet should be low in saturated fat, high in fiber, and low in simple carbohydrates and should contain appropriate caloric content to maintain weight. Subjects will fast for a minimum of 10 h prior to the scheduled blood sample draws. During fasting, only water will be permitted.

5.7.3 Patient Activity Restrictions

Throughout the study period, subjects are to be counseled and encouraged to engage in a level of physical activity that is appropriate for their physical condition. For those without specific restrictions or limitations, at least 150 min/week of moderate activity is advised by the American Diabetes Association (American Diabetes, 2014) and an amount of exercise to balance energy intake in food by the Japanese Diabetes Association (JapanDiabetesSociety, 2012).

5.8 Treatment Compliance

Subjects will be provided with dosing instructions when the investigational product is dispensed. Subjects will also be instructed to bring their medication with them at every visit. During the run-in period, subjects will be excluded from randomization if more than one dose has been omitted.

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

5.9 Packaging and Labeling

The finished products are packaged in HDPE bottles with a child resistant cap. There are two types of investigational products.

5.9.1 Run-in Kit

One run-in kit contains a bottle of 15 bexagliflozin tablets, placebo.

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

5.9.2 Investigational Product Kit

One investigational product kit contains a bottle of 90 bexagliflozin tablets, 5 mg, 10 mg, 20 mg, or placebo.

The label attached to each investigational product kit will contain the following information: the kit number, protocol number, product identification, blinded batch number, subject number, storage conditions, sponsor's name and address, CRO or ICCR name and address, investigator's name, and the investigational drug caution statement.

5.10 Storage and Accountability

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

5.11 Investigational Product Retention at Study Site

The investigational products should be stored in a secure area with limited access at controlled room temperature until ready for dispensing to study subjects. The drug storage facility must comply with the medication storage instructions. The trial staff must record the amount of investigational product 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. At the completion of the trial, all unused drug must be returned to a sponsor-designated depot after drug accounting is verified by the sponsor or its designee.

6 STUDY PROCEDURES

6.1 Informed Consent

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

6.2 Medical History

The following information will be collected at the screening visit:

6.2.1 General Demographics and Characteristics

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

6.2.2 Diabetes History

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

6.2.3 Cardiovascular Disease History

History of cardiovascular disease including presence of angina, congestive heart failure (classification, if present), known atherosclerotic cardiovascular disease, prior MI, cerebrovascular ischemia (TIA or stroke/cerebrovascular accident) and prior cardiac or peripheral re-vascularization procedures.

History should include date of diagnosis and current status of diagnosis (resolved or ongoing).

6.2.4 Medication History

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

include the medication used, indication for usage, start and stop dates, dose, and frequency.

6.3 Physical Examination

A complete physical examination will be performed by the investigator at screening and at the last study visit. A complete physical examination will include measurement of body weight and height (height will be measured only at screening), general assessment of all body systems including the skin, head, eyes (including fundoscopic exam), ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, and extremities (including Achilles tendon reflex and foot exam). The fundoscopic examination should be characterized as normal or abnormal with description of any detected abnormality. The Achilles tendon reflex should be graded as normal or abnormal. The foot exam should assess skin and toenail lesions and be documented as normal or abnormal with description of any detected abnormality.

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

The body weight must be determined at clinical visits specified in the Schedule of Events (Appendix 1) using a scale that is calibrated regularly.

6.4 Vital Signs

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

6.4.1 Blood Pressure and Pulse Measurements

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

At each visit, BP measurements will be obtained using a calibrated sphygmomanometer while the subject is in sitting, supine, and standing positions. A single pulse 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 pulse 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 evaluated orthostatic vital signs. Supine and standing blood pressure measures will not be

used to determine eligibility for the study. First, the subject will lie flat for 5 minutes and have pulse and supine blood pressure measured using the same equipment and arm as described for sitting BP. Once the supine BP measurement is complete, the subject will stand. Standing BP and pulse 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.

6.4.2 Temperature and Respiratory Rate

Oral, axillary, or ear temperatures are acceptable but they must be taken from the same measurement site during the study. The subject should be advised to rest after strenuous physical activity prior to a temperature measurement. When taking the temperature orally, the subject must not have eaten, drunk, or smoked anything in at least the previous 15 to 20 minutes, as the temperature of the food, drink, or smoke can dramatically affect the reading.

Respiratory rate should be measured after at least 5 minutes of rest.

6.5 Electrocardiography

A 12-lead electrocardiogram (ECG) will be conducted as listed 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 measured will be the RR interval, PR interval, QRS duration, and QT, P-wave axis, and QRS-axis. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities.

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

6.6 Diet and Exercise Counseling

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

6.7 Clinical Laboratory Tests

6.7.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Each laboratory test is outlined in Table 1 and the schedule is provided in Appendix 1.

Table 1. List of Laboratory Tests

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

1. *Blood for clinical chemistry and hematology will be drawn after at least 10 h of fasting prior to breakfast (i.e. only water is allowed, no caloric intake).*
2. *Lactate dehydrogenase (LDH), gamma-glutamyl transferase (γ-GTP), creatinine kinase (CK),*

Test Name	Blood or urine Vol. (mL)	Shipment

and alkaline phosphatase (ALP) are not required routinely but will be included when clinically indicated.

3. *LDL-C will be calculated by the Friedewald equation. If triglycerides are > 400 mg/dL, the calculated LDL-C value is invalid by this equation and will be set as missing. Direct LDL-C will be determined in subjects whose baseline triglycerides are > 300 mg/dL. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only.*
4. *Urinalysis will be collected routinely at all clinic visits except S3 and V1 from a clean catch sample. Glucose results in the urinalysis reports must be suppressed so the dosing blind can be maintained. Testing strips with only the leucocytes and nitrate will be provided for immediate assessment at the clinical sites.*
5. *Urine drug screen will be performed on screening visit only. Drug abuse screening includes amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.*
6. *Infectious disease testing will be conducted at screening only.*
7. *Urine pregnancy test (UPT) will be performed for WOCBP at all clinic visits, except Visits S3 and V1. For surgically sterile or post- menopausal women, it will only be done at Visit S1.*
8. *Blood samples for the population PK analysis will be drawn at or during the weeks of V2, V3 or V4 from 240 randomly selected subjects in participating trial centers.*

6.7.2 Sample Collection, Storage, and Shipping

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

Blood samples for hematology, chemistry, serum lipids and glycemic control assessments will be collected. Timing of collection is described in Section 7 and the Schedule of Events (see 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 the proper fasting procedure. A subject must be queried to assess compliance with a minimum 10 h fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for at least 10 h, the subject must return as soon as can be arranged (within 7 days) to provide a specimen after proper fasting. If the 10 h fasting sample is not collected within 7 days of the initially scheduled visit, the FPG will be considered missing.

6.7.3 Urinalysis

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

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

Urinalysis strips that assess leukocyte esterase and nitrite and that do not report the presence or absence of glucose will be provided for immediate assessment at the clinical sites. Urine samples will also be transported to the central laboratory.

Urine culture and microscopy will be conducted at the central lab if the subject has a positive result on the leukocyte esterase or nitrite dipstick tests at the clinical site. Dipstick urinalysis will also be conducted at the central laboratory for assessment of parameters not measured at the clinical site. Positive leukocyte esterase or nitrite results recorded from the central laboratory dipstick measurement will not trigger urine culture and microscopy.

6.7.4 Population PK Sampling

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

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

Plasma concentrations of bexagliflozin will be determined by a validated LC-MS/MS method. Approximately 540 measurements of bexagliflozin plasma concentrations will be collected from an estimated 180 subjects who will have received active drug in this study.

6.8 Dispensing Investigational product

Each study subject will receive 1 run-in kit at visit S4 and 1 investigational product kit at visits V1 (week 1).

6.9 Efficacy Assessments

6.9.1 HbA1c Determination

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

6.9.2 Body Weight

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

6.9.3 Blood Pressure

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

6.10 Adverse Events Assessments

Adverse event (AE*):* Any untoward medical occurrence experienced by a subject administered an investigational product. An AE does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended accident, sign (including an abnormal laboratory finding), symptom, or disease occurring during the period of use of an investigational product or the period of follow-up, whether or not related to the investigational product.

Serious adverse event (SAE*):* Any event that results in any of the following outcomes:

1. Death
2. A life-threatening event, *i.e*., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (this does not include an event that, had it occurred in a more severe form, might have caused death)
3. A persistent or significant disability/incapacity
4. An event that requires hospitalization or prolongs hospitalization
5. A congenital anomaly/birth defect
6. Any other medically significant events that, based upon appropriate medical judgment, may harm the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, *e.g*. allergic bronchospasm requiring intensive treatment in an emergency room or home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

Non-serious adverse events are all events that do not meet the criteria for a serious adverse event.

Immediately Reportable Adverse Event (IRAE): Any serious adverse event or any adverse event that necessitates discontinuation of investigational product, including pregnancy.

Clinical Laboratory Changes: 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 an AE.

Hypoglycemia is defined as any FPG or SMBG value ≤ 70 mg/dL and documented as described in Section 6.10.9.

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

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

1 = Mild: discomfort noticed, but no disruption to daily activity;

2 = Moderate: discomfort sufficient to reduce or affect normal daily activity;

3 = Severe: 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 adverse event 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 unclear.

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

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

6.10.1 Eliciting and Reporting Adverse Events

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

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

6.10.2 Immediately Reportable Adverse Events

The investigator must report any serious adverse event (SAE), by telephone, email, or fax, to Theracos or its representative immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by email or fax or overnight courier to the sponsor within 24 h of knowledge of the event.

Non-serious events that require discontinuation of investigational product (including laboratory abnormalities) should be reported to Theracos within 3 working days. The IRAE form should be completed and sent by email or fax or overnight courier 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.

6.10.3 Pregnancy

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

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

1. General information
2. Informed consent form
3. Pregnancy prevention information
4. Drug interactions with hormonal contraceptives.
5. Contraceptives in current use.
6. Guidelines for the follow-up of a reported pregnancy.

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

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

If a subject or investigator suspects that the subject may be pregnant prior to investigational product administration, the investigational product administration must be withheld until the

results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the investigational product and must not remain or be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the investigational product must be withheld immediately until the result of the pregnancy is known. If pregnancy is confirmed, the investigational product will be permanently discontinued and the subject will be withdrawn from the trial. [Exceptions to study discontinuation may be considered for life-threatening conditions only after consultations with a Theracos Medical Monitor or designated personnel.]

The investigator must immediately notify the Medical Monitor of any female subject who becomes pregnant within 30 days after investigational product exposure. The investigator must record the event on the Pregnancy Surveillance form and forward it to Theracos clinical or designated personnel.

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

6.10.4 Procedure for Breaking the Blind

As indicated in Section 5.5 above, the sponsor, study coordinators, pharmacists, study subjects, and the cardiovascular adjudication committee 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 cardiovascular adjudication committee members until all phase 3 studies are completed.

6.10.5 Follow-up of Adverse Events

6.10.5.1 Follow-up of Non-serious Adverse Events

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

6.10.5.2 Follow-up of Post-Study Serious Adverse Events

SAEs that are identified on the last scheduled contact must be recorded on the AE CRF page and reported to Theracos according to the reporting procedures outlined in Section 6.10.2. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these 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 Theracos 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 Theracos 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 at least 14 days after the last treatment.

6.10.6 Urinary Tract Infections (UTIs)

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

The investigator should query the subject at every 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 $\geq 10^5$ CFU of any species. The investigator may also perform a urine culture using local resources if necessary for clinical care.

6.10.7 Genital Mycotic Infections (GMIs)

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

6.10.8 Hepatotoxicity

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

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

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

- ALT or AST > 8 x ULN;
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

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

6.10.9 Hypoglycemia

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

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

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

1. Signs and symptoms attributed to hypoglycemia and the time and date on which they occurred
2. SMBG reading at the time of the signs and symptoms attributed to hypoglycemia
3. Time elapsed from the most recent meal to the onset of signs and symptoms
4. Duration, intensity, and type of any exercise within the 24 h prior to the signs and symptoms
5. 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
6. SMBG reading 15 minutes after treatment with carbohydrate and the time at which this was measured
7. 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 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 serious adverse events 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 alert 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.

6.11 Concomitant Medication Assessments

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

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

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

All prescription and over-the-counter medications, including vitamins and herbal supplements, that subjects receive during the trial must be documented 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.

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

The investigator must emphasize to potential subjects the importance of continued participation for the full duration of the trial during the informed consent process. Potential subjects should be informed that the trial procedures will allow additional medications to control hyperglycemia or other adverse conditions. It is also important to emphasize that missing data and missed visits could affect the entire trial. If subjects are dissatisfied with the conduct of the trial but have not withdrawn, the investigator should make an effort to address their concerns and retain them in the trial if possible. In doing so, investigators must be careful that the efforts do not cross over into coercion**.** Investigator should encourage a subject to remain in the study even if the investigational product administration is stopped so that safety information can be collected.

Participation in a clinical trial is voluntary. A subject can withdraw from the study at any time. The sponsor or investigator may terminate the study for medical or administrative reasons. If a decision is made to withdraw a subject from the study, no further investigational product should be administered. Even if the subject discontinues study medication, every attempt should be made to complete all required study evaluations and procedures. Reasons for all withdrawals should be recorded on the CRF. Examples of reasons for withdrawal include:

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

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

Subjects who withdraw from the study will not be replaced.

6.13 Appropriateness of Measurements

The percentage of HbA1c is a widely used measure of chronic glycemia, reflecting average blood glucose levels over a 2- to 3-month period of time. It is an accepted surrogate marker for risk of microvascular complications and is widely used as a measurement for the adequacy of glycemic management. Other study procedures and measurements in this protocol are widely used and generally recognized as reliable, accurate, and relevant for subjects with T2DM.

7 STUDY ACTIVITIES

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

A visit window of ± 3 days is allowed for all visits except visit V1. Visit V1 is to be scheduled 3 days after visit S5 is complete and can be extended to 5 days depending on HbA1c value availability.

7.1 Screening (Up to 15 weeks prior to randomization, visit S1)

The screening can be performed from 3 weeks to 3 days before the start of the washout period for subjects who are taking background OHA or 3 weeks to 3 days before the start of the run-in period for subjects who are treatment naïve. At the screening visit the study investigator will:

- Explain the content of informed consent to the subject and collect signed informed consent
- Obtain medical history and demographic information
- Perform a complete physical examination including height and weight
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Perform a 12-lead ECG measurement
- Draw blood if a minimum 10-h fast has been completed by the subject as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample for drug abuse screening, urinalysis, and for UPT for all females
- Evaluate the subject's suitability for enrollment according to the inclusion and exclusion criteria based on the information collected.

7.2 Washout and Run-in Periods (Up to 12 weeks prior to randomization)

The washout and run-in period is required for all enrolled subjects who are taking an OHA. Enrolled treatment naïve subjects will not require any washout and will enter the run-in period.

7.2.1 Washout of OHA (Visits S2 and S3)

Two visits will be conducted during the washout period. Visit S2 is a clinic visit. At Visit S3 each subject will be evaluated by the investigator or study staff via a phone interview 2 weeks after washout starts; there will be no on-site evaluation at Visit S3.

7.2.1.1 Visit S2 (subjects taking one OHA)

At the S2 visit the study investigator will:

- Evaluate inclusion/exclusion criteria for eligibility
- Counsel subject on appropriate diet and exercise
- Dispense glucometer and train subject in SMBG determination and recording
- Discontinue the OHA for 10 weeks if a subject is taking a TZD; discontinue the OHA for 6 weeks if a subject is taking a non-TZD OHA
- Collect clean-catch, mid-stream urine for urinalysis and UPT for women of child bearing potential.
- Assess pre-treatment signs and symptoms and record pre-treatment concomitant medications.

7.2.1.2 Visit S3 – Phone interview (subjects in washout)

At the S3 visit the study investigator will:

- Review daily SMBG and glycemic control record for each day during the prior 2 weeks
- Assess any signs and symptoms of severe hyperglycemia, including increased urination, increased thirst, weight loss, and changes in vision
- Assess pre-treatment signs and symptoms and record pre-treatment concomitant medications.

7.2.2 Run-in Period:

7.2.2.1 Visit S4 (Week -2)

At the S4 visit the study investigator will:

- Counsel subject on appropriate diet and exercise (for subjects who are treatment naïve and do not require washout)
- Dispense glucometer and instruct subject in SMBG determination and recording (for subjects who are treatment naïve and do not require washout)
- Review glycemic control diary and SMBG (for subjects who complete 6 or 10 weeks of washout)
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Collect clean-catch, mid-stream urine sample for urinalysis and UPT for women of child bearing potential.
- Dispense run-in kit for run-in period
- Assess pre-treatment signs and symptoms and record pre-treatment concomitant medications.

7.2.2.2 Visit S5 (Days -3 to -5)

At the S5 visit the study investigator will:

- Confirm inclusion/exclusion criteria for eligibility and review run-in drug compliance
- Perform an abbreviated physical examination including weight
- Review glycemic control diary and SMBG results
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Perform a 12-lead ECG measurement
- Draw blood from subject if a fast of 10 h or greater has been completed as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect clean-catch, mid-stream urine sample for urinalysis and UPT for women of child bearing potential.
- Assess pre-treatment signs and symptoms and record pre-treatment concomitant medications.

7.3 Treatment Period (week 1 to week 12)

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

7.3.1 Visit V1 (Day 1 of week 1)

Visit 1, day of randomization, must be conducted after the HbA1c value from the sample of S5 visit is available for eligibility confirmation.

At the V1 visit the study investigator will:

- Confirm HbA1c value of 7.0 to 8.5% based on the S5 sample results
- Review SMBG and glycemic control record
- Dispense investigational product based on randomization
- Assess adverse events and record concomitant medications

7.3.2 Visit V2 (week 2)

At the V2 visit the study investigator will:

- Review SMBG and glycemic control record
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Draw blood from subjects who have fasted a minimum of 10 h as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2

- Collect blood specimens for sparse PK sampling from selected subjects in participating centers
- Collect clean-catch, mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Assess adverse events and record concomitant medications

7.3.3 Visit V3 (week 6)

At the V3 visit the study investigator will:

- Review SMBG and glycemic control record
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Draw blood from subjects who have fasted a minimum of 10 h as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers
- Collect clean-catch, mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Assess adverse events and record concomitant medications.

7.3.4 Visit V4 (week 12)

At the V4 visit the study investigator will:

- Review SMBG and glycemic control record
- Perform an abbreviated physical examination including weight
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Perform a 12-lead ECG measurement
- Draw blood from subjects who have fasted a minimum of 10 h as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers
- Collect clean-catch, mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Retrieve remaining study medication and record the number of remaining tablets
- Assess adverse events and record concomitant medications.

7.4 Exit Visit or Early Termination Visit

7.4.1 Visit V5 (week 14 or two weeks after the last dose of investigational product if a subject early terminates)

At the V5 visit the study investigator will:

- Review SMBG and glycemic control record
- Perform a complete physical examination including weight
- Measure vital signs, including blood pressures, pulse, temperature, and respiratory rate
- Perform a12-lead ECG measurement
- Draw blood from subjects who have fasted a minimum of 10 h as described in Section 6.7.2.1. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect clean-catch, mid-stream urine sample for urinalysis in all subjects and for UPT for women of child bearing potential
- Assess adverse events and record concomitant medications: If subjects have an ongoing serious adverse event, the subject should be followed until the adverse event is resolved or returns to baseline. All possible attempts should be made to document resolution of acute and chronic toxicities.

7.5 Early Termination Procedures

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

Subjects who withdraw consent and have received investigational product will have a follow-up examination, including a complete physical examination, vital signs, ECG, and clinical laboratory tests (hematology, serum chemistry, and glycemic control).

8 QUALITY CONTROL AND ASSURANCE

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

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All statistical analyses will be performed using Version 9.4 or later of Statistical Analysis Software (SAS®).

Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by-subject data listings.

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

9.1.1 Handling Dropouts, and Missing Data

Discontinuation criteria are explained in Section 6.12. Subjects who discontinue will not be replaced. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. But if missing data are present for the primary efficacy endpoint, they will be handled using a multiple imputation approach. The imputation method is as follows:

As the primary analysis, only available data will be analyzed and data obtained after rescue will be excluded and considered as missing. The following sensitivity analyses will be conducted:

- Missing endpoint information (including data obtained after rescue) will be imputed via multiple imputation linear regression approach. A total of 10 imputed datasets will be generated, and the primary efficacy endpoint analysis described below will be carried out on each imputed dataset; the analyses results will be combined across the 10 datasets using the standard techniques for multiple imputed data sets in order to yield overall treatment comparison results on the imputed data.
- Missing endpoint data will also be handled based on the last observation carried forward (LOCF) technique. The last non-missing observation for a subject (i.e., excluding data obtained after rescue) will be carried forward for analysis.
- Data collected after the start of rescue medication will NOT be considered missing, and the primary efficacy endpoint analyses will be performed based on all observed data.

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

The number, timing, pattern, reason for and possible implications of missing values in efficacy and safety assessments will be investigated. The dropout patterns may be assessed by graphical methods.

9.1.2 Multiple Comparisons / Multiplicity

The primary objective of this study is to identify the effect of bexagliflozin tablets in three strengths on the placebo-corrected change in HbA1c from baseline after 12 weeks of treatment. All secondary endpoints are considered exploratory and adjustment for multiple endpoints will not be performed.

9.2 Determination of Sample Size

Approximately 320 subjects will be randomized and equally allocated to receive bexagliflozin tablets, 5 mg, 10 mg, 20 mg, or placebo.

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

1) The placebo-corrected population mean change from baseline to Week 12 in HbA1c in the highest dose group of 20 mg will be -0.5%.
2) The pooled standard deviation for the change from baseline to Week 12 in HbA1c for the active and placebo groups will be 0.9%.

Under the above assumptions, an estimated sample size of 70 evaluable subjects per treatment arm yields approximately 90% power to detect a treatment difference between bexagliflozin and placebo. A sample size of 80 per arm has been selected to account for a potential drop-out and to allow adequate safety evaluation. The total sample size for this study will be 320 subjects.

This study will be conducted at multiple investigative sites and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but will be capped at 32 subjects from each site.

9.3 Analysis Populations

9.3.1 Full Analysis Set

All subjects who are randomized, take at least one dose of double-blind study medication, and have at least one post-randomization HbA1c measurement will be included in the Full Analysis Set (FAS). All analyses of the FAS will be based on each subject's randomized assigned treatment.

9.3.2 Safety Analysis Set

All subjects who are randomized and take at least one dose of double-blind study medication will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually dispensed to each subject.

9.3.3 Per Protocol Analysis Set

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

9.4 Demographics and Baseline Characteristics

Demographic characteristics include age, gender, race, ethnicity, and study center. Baseline characteristics include baseline HbA1c values, blood pressure, body weight, body mass index (BMI in kg/m^2), fasting plasma glucose level, and prior anti-diabetic treatment status (whether treatment naïve or not). Summary statistics by treatment group will include counts and percentages for discrete variables, and means, SD, Q1, medians, Q3, minimum and maximum for continuous variables.

9.5 Analysis of Efficacy

All efficacy analyses will be performed based on the FAS. The primary endpoint analysis will also be conducted using the PP Analysis Set.

For the primary endpoint of HbA1c change from baseline over 12 weeks of treatment, the MMRM analysis of covariance model (ANCOVA) with baseline HbA1c as a covariate will be fitted to the available data, incorporating all visits at which HbA1c was measured for each subject including the scheduled visits at weeks 2, 6, and 12 as well as the unscheduled visits for measurement of HbA1c (NationalResearchCouncil, 2010). Treatment, study center, and stratification factor for randomization (treatment naïve versus taking one OHA at baseline) will be applied as fixed effects, as will study week and study week-by-treatment interaction. From this model, an estimate of the treatment difference at week 12 will be generated, as will an assessment of whether this estimate is significantly different when comparing placebo with each dose of bexagliflozin at a two-sided 0.05 level of significance. An unstructured within-patient covariance structure will be assumed. HbA1c values obtained after the start of rescue medication will be excluded from this primary analysis.

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

3) Missing HbA1c data (for weeks 2, 6, or 12) will be imputed via multiple imputation (MI), following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will be considered missing.
4) Missing HbA1c data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
5) HbA1c values collected after the start of rescue medication will NOT be considered missing, and the MMRM analyses will be re-performed.

For the primary efficacy model, a test for a significant baseline-by-treatment interaction will be performed in a separate model, using a 0.100 alpha level. If the baseline-by-treatment interaction is significant, then the ANCOVA assumptions are violated and an analysis of variance (ANOVA) model will be used instead, omitting the baseline covariate.

A treatment by study center interaction effect will be added to the MMRM ANCOVA (or ANOVA) model used for the analyses of the primary efficacy variable. If a statistically significant treatment by study center interaction effect is noted using a 0.1 level of significance, then separate analyses will be performed for each study center.

In addition to the week 12 comparisons, the change from baseline to week 2 and week 6 will also be analyzed from the same MMRM ANCOVA model using 95% CIs for the between-group mean changes. The secondary efficacy endpoint, changes in HbA1c over time will be assessed descriptively using graphical methods

To examine the dose response, tests for linear and quadratic dose-response relationships between the doses (0 [placebo], 5, 10 and 20 mg bexagliflozin) and the change from baseline in HbA1c at week 12 will be conducted using a general linear model and appropriate orthogonal polynomial contrasts.

Fasting plasma glucose, systolic and diastolic blood pressure, and weight will be analyzed using the same MMRM ANCOVA model used in the primary efficacy analysis.

For each subject, the post-baseline HbA1c values on or before week 12 will be assigned to a category of $< 7\%$ or $\geq 7\%$. Incidences of reduction of HbA1c to $< 7\%$ will be analyzed using a logistic regression model with effects for treatment, study center and baseline HbA1c. Odds ratio and the corresponding 95% CI will also be presented.

9.6 Analysis of Safety

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

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

9.6.1 Adverse Events

Adverse events will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). AEs that begin after the first administration of investigational products or existing AEs that worsen after the first dose of study medication are considered treatment emergent AEs (TEAEs). TEAEs will be assigned to the run-in period or the double blind randomization period in the same manner. The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred term, then by severity, and by relationship to study treatment. Drug-related AEs will be considered those to be at least possibly related to

investigational product based on the investigator's assessment. The number and percentage of subjects reporting 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

Adverse event listings will be provided for the following subsets:

1. All TEAEs
2. All TEAEs at least possibly related to bexagliflozin
3. Serious AEs (if any)
4. AEs leading to treatment discontinuation (if any)

9.6.2 Adverse Events of Special Interest

Adverse events of special interest include the following categories:

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

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

Event terms, signs, and symptoms will be documented in the listings. The number and percentage of subjects who have experienced TEAEs of special interest will be summarized for each treatment group by type of AE.

9.6.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory parameters will be measured at baseline, during the treatment period and at follow-up. These variables include vital signs (blood pressure, pulse, respiration rate, and temperature), clinical laboratory outcomes (see Section 6.7 for a complete list) and ECG data. They will be summarized as changes from baseline.

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.

Abnormalities as well as percent changes from baseline in the clinical and laboratory assessment will be listed.

9.6.4 Physical Examination

Physical examination findings including body weight will be collected at baseline and during the treatment period, safety extension phase and at follow-up. Abnormal findings at each visit will be tabulated as incidences by body system.

9.6.5 Concomitant Medications

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

9.7 Interim Analysis

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

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

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

10.2 Institutional Review Board or Independent Ethics Committee Approval

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

10.3 Ethical Conduct of the Study

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

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

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

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

10.4 Subject Information and Consent

Prior to the beginning of the study, the investigator must have received from the Ethics Committee (EC) 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 Good Clinical Practices (GCP) Guidelines (E6), in addition to, any other elements required by Japan regulations or institutional policy.

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

10.5 Subject Confidentiality

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

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

10.6 Study Monitoring

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

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

10.7 Case Report Forms and Study Records

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

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

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

10.8 Data and Safety Monitoring Board

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

10.9 Protocol Violations/Deviations

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

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

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

10.10 Access to Source Documentation

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

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

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

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

10.11 Retention of Data

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

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

10.12 Publication and Disclosure Policy

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

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

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Appendix 1 Schedule of Events

	Screen-ing	Washout		Run-in		Treatment				Follo w Up
Visit number	S1	S2	S3	S4	S5	V1	V2	V3	V4	V5
Time to Randomization (weeks)[1]	up to 15 weeks	-12 or -8	-10 or -6	-2	-0.5	0	2	6	12	14
Informed Consent	X									
Screening for I/E criteria	X	X			X					
Demographics and medical history	X									
Diet & exercise counseling[2]		X		X						
Physical exam[3]	X				X				X	X
Body weight	X	X			X		X	X	X	X
Diary & glucometer record review[4]			X	X	X	X	X	X	X	X
Start washout		X								
Dispense Run-in Medication				X						
Randomization						X				
Vital signs	X			X	X		X	X	X	X
ECG	X				X				X	X
Dispense study medication[5]						X				
Blood draw for clinical lab test[6]	X				X		X	X	X	X
Population PK sampling							X	X	X	
Urine collection[7]	X	X		X	X		X	X	X	X
AE		X	X	X	X	X	X	X	X	X
Con Med		X	X	X	X	X	X	X	X	X

[1] *Screening period may last up to 3 weeks; washout period will be 10 weeks for subjects on a TZD or 6 weeks for subjects on other OHA, which includes a clinic visit (S2) and a phone interview (S3); run-in period is to be 2 weeks (S4 to S5); the treatment period (V1 to V4) will be 12 weeks. A visit window of ± 3 days is allowed for all visits except visit V1. Visit V1 is to be scheduled at 3 days after visit S5 and can be extended to 5 days pending on HbA1c value availability.*

[2] *Counseling will be performed at S2 for washout and at S4 for treatment naïve subjects.*

[3] *A complete physical examination will be performed by the investigator at screening (S1) and at the termination visit (V5). Abbreviated physical examinations will be performed by the investigator at all other time points, unless clinically indicated. General assessment of the skin, heart, lungs and abdomen will be performed.*

[4] *Glucometer and diary will be dispensed to each enrolled subject at visit S2 (for subjects undergoing washout) or S4 (for subjects not undergoing washout), and subjects will be trained in glucometer use and SMBG recording. The SMBG record will be reviewed by the investigator at all subsequent visits.*

[5] *At visit V1, an investigational product kit will be dispensed; subjects should bring in their study medication to be checked on visits V2, V3, and V4.*

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

[7] *UPT is scheduled for all women at screening and for WOCBP thereafter.*

Appendix 2 Schedule of Laboratory Tests

	Screening	Washout		Run-in		Treatment Period				FU
Visit Number	**S1**	**S2**	**S3**	**S4**	**S5**	**V1**	**V2**	**V3**	**V4**	**V5**
Time to Randomization (weeks)	up to 3 wks	-12 or -8	-10 or -6	**-2**	**0.5**	**0**	**2**	**6**	**12**	**14**
Hematology[1]	X				X		X		X	X
Serum chemistry electrolytes[1]	X				X		X		X	X
Fasting Plasma Glucose[1]	X				X		X	X	X	X
HbA1c	X				X		X	X	X	X
Lipids[2]	X				X				X	X
Infectious disease testing[3]	X									
Urine drug screen[4]	X									
Urinalysis[5, 6]	X	X		X	X		X	X	X	X
Urine pregnancy test (UPT)[7]	X	X		X	X		X	X	X	X
PK sampling[8]							X	X	**X**	
Total blood drawn (mL) without PK	**28**	**0**	**0**	**0**	**22**	**0**	**16**	**4**	**22**	**22**
Total blood drawn (mL) with PK	**28**	**0**	**0**	**0**	**22**	**0**	**18**	**6**	**24**	**22**

1. *Blood for clinical chemistry and hematology will be drawn after 10 h of fasting prior to breakfast (i.e. only water is allowed, no caloric intake).*
2. *LDL-C will be calculated by the Friedewald equation. If triglycerides are > 400 mg/dL, the calculated LDL-C value is invalid by this equation and will be set as missing. Direct LDL-C will be determined in subjects whose baseline triglycerides are > 300 mg/dL. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only.*
3. *Infectious disease testing will be conducted at screening only.*
4. *Urine drug screen will be performed on screening visit only. Drug abuse screening includes amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.*
5. *Urinalysis will be collected routinely at all clinic visits except S2 from a clean catch sample. Glucose in the urinalysis results must be suppressed from the laboratory report so the dosing blind can be maintained. Testing strips with only the leucocytes and nitrate will be provided for immediate assessment at the clinical sites.*
6. *UACR will be determined at screening only.*
7. *Urine pregnancy test (UPT) will be performed for WOCBP at all clinic visits, except Visits S2. For surgically sterile or post- menopausal women, it will only be done at Visit S1.*
8. *Blood samples for the population PK analysis will be drawn at or during the week of V2, V3, or V4 from 240 randomly selected subjects in participating trial centers.*

Appendix 3 Estimating Glomerular Filtration Rate

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

The eGFR for non-Japanese subjects should be calculated based on following equation

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

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

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

Appendix 4 Sponsor Signatures

Study Title: A Phase 2b, Multi-center, Double-blind, Placebo-controlled, Dose Range Finding Study to Evaluate the Effect of Bexagliflozin Tablets on HbA1c in Subjects with Type 2 Diabetes Mellitus

Study Number: THR-1442-C-449

Final Date: 16 February 2015

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

Signed: RA for Yuan-Di Halvorsen Date: 18 February 2015

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

Signed: Date: 17 February 2015

Geoffrey A. Walford, M.D.
Medical Monitor
Massachusetts General Hospital
Consultant for Theracos, Inc.

Signed: Heidy Russell Date: 23 Feb 2015

Heidy Russell, Ph.D.
Study Statistician
Prometrika, ~~Inc.~~ LLC
Consultant for Theracos, Inc.

Appendix 5 Investigator's Signature

Study Title: A Phase 2b, Multi-center, Double-blind, Placebo-controlled, Dose Range Finding Study to Evaluate the Effect of Bexagliflozin Tablets on HbA1c in Subjects with Type 2 Diabetes Mellitus

Study Number: THR-1442-C-449

Final Date: 16 February 2015

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____
Principal Investigator