Clinical Trial Protocol:

Study Title:	A multi-center, randomized, double-blind, placebo-controlled, parallel group study to compare the efficacy and safety of bexagliflozin to placebo in subjects with type 2 diabetes mellitus and inadequate glycemic control
Study Number:	
Study Phase:	3
Product Name:	Bexagliflozin Tablets
Indication:	Type 2 Diabetes Mellitus
Investigators:	Multiple center
Sponsor:	Theracos Sub, LLC
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	Date
Version 4.0	04 April 2017

Confidentiality Statement

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SYNOPSIS

Sponsor:

Theracos Sub, LLC

Name of Finished Product:
Bexagliflozin Tablets

Name of Active Ingredient:
Bexagliflozin

Study Title:
A multi-center, randomized, double-blind, placebo-controlled, parallel group study to compare the efficacy and safety of bexagliflozin to placebo in subjects with type 2 diabetes mellitus and inadequate glycemic control

Study Number:

Study Phase: 3

Primary Objective:
To determine the placebo-adjusted treatment effect of bexagliflozin tablets, 20 mg on the change in HbA1c from baseline to week 24 in subjects with type 2 diabetes mellitus and inadequate glycemic control.

Key Secondary Objectives:

- To assess the effect of bexagliflozin on systolic blood pressure compared to placebo
- To assess the effect of bexagliflozin on body weight in subjects with a baseline BMI ≥ 25 kg/m^2 compared to placebo

Exploratory Secondary Objectives

- To compare the effect of bexagliflozin to the effect of placebo on the proportion of subjects with HbA1c of < 7%
- To compare the effect of bexagliflozin to the effect of placebo on change in HbA1c over time
  To compare the effect of bexagliflozin to the effect of placebo on FPG over time

Safety Objectives:

- To assess the safety of bexagliflozin in subjects with T2DM
- To assess the effect of bexagliflozin on the incidence of AE of special interest
- To contribute MACE+ events to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo or comparator treatment

Study Design:
THR-1442-C-450 is a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once daily oral administration of bexagliflozin tablets, 20 mg versus placebo, in subjects with T2DM who are treatment-naïve or previously treated with one oral hypoglycemic agent (OHA).

The study will enroll male or female subjects with T2DM. If treatment naïve, they must have an HbA1c at the screening visit of between 7% and 10.5%. Alternatively, prospective subjects may be eligible if at the time of the screening visit they are being treated with one OHA, have an HbA1c of between 6.5% and 10.0% and are willing to complete a 6-week washout. Individuals taking thiazolidinediones are not eligible for the study. A candidate will be considered treatment-naïve if he or she has received no more than 14 days of prescription medication for diabetes in the 12 weeks prior to screening.

All eligible subjects will start a 2 week placebo run-in period. Subjects who miss no more than one dose of the run-in medication, have fasting blood glucose values ≥ 250 mg/dL on no more than two consecutive days, and who, at the baseline visit (Visit V5), have an HbA1c level between 7 and 10.5% and a fasting glucose level < 250 mg/dL will be eligible for randomization.

Approximately 210 subjects will be randomly assigned to receive oral bexagliflozin tablets, 20 mg or placebo, in a 2:1 ratio once daily for 24 weeks in an out-patient setting. Subjects with uncontrolled hyperglycemia based on blood glucose levels may receive additional approved anti-diabetic medications. Treatment group assignment at the start of the treatment period will be stratified by baseline (Visit V5) HbA1c level (7.0 to 8.5% or 8.6 to 10.5%) and background anti-diabetes treatment status (treatment naïve or not).

Each subject will be contacted by telephone at week 2 (Visit V7) for safety monitoring and will be instructed to return to the clinic at weeks 6, 12, 18, and 24 (Visits V8, V9, V10, V11, respectively) for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up visit at week 26 or two weeks after the last dose of investigational product if the subject terminates prior to week 24 (Visit V12).

Study Population and main eligibility criteria:

Approximately 210 subjects are planned for this study. The study will enroll:

1. Male or female adult subjects ≥ 18 years of age at screening.
2. Subjects with T2DM who are treatment naïve or receiving one OHA in combination with diet and exercise. Subjects taking thiazolidinediones are not eligible.
3. Subjects with HbA1c levels at screening (Visit V1) between 7.0% and 10.5% (inclusive) if treatment-naïve or with HbA1c levels between 6.5 and 10.0% (inclusive) if on one OHA
4. Subjects with a body mass index (BMI) ≤ 45 kg/m^2
5. Subjects with a fasting plasma glucose < 250 mg/dL (13.9 mmol/L) at baseline (Visit V5)

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

Duration of Treatment:
24 weeks

Efficacy Assessments:
The primary efficacy measure will be the change in HbA1c from baseline to week 24.

The key secondary measures will be the changes from baseline to week 24 of systolic blood pressure and body weight. The exploratory secondary measures will be the change from baseline of the fasting plasma glucose concentration over time, the change from baseline of HbA1c over time, and the proportion of subjects who achieve an HbA1c < 7% over time.

Safety Assessments:
The safety of bexagliflozin will be assessed over the 24-week treatment phase. Adverse events (AEs) of special interest include genital and urinary tract infections, diuretic effects, hepatotoxicity, MACE, hypoglycemia, fractures, malignancy, hypersensitivity reactions, hypotensive episodes, acid-base disorders, renal failure events, and amputations.

Statistical Methods:
Data summaries will report 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.

The primary efficacy hypothesis is that bexagliflozin reduces HbA1c after 24 weeks of treatment when compared to placebo. The analysis of the change in HbA1c at week 24 will be based on ITT Analysis Set using all observed data and a mixed model repeated measures (MMRM) approach that will include terms for treatment, visit, treatment-by-visit interaction and randomization stratification factors as fixed effects and the baseline HbA1c value as a fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the placebo group at week 24 will be estimated from the model with the corresponding p-values and their two-sided 95% CI presented. An unstructured covariance will be used to model the within-subject correlation. If the model with the unstructured covariance structure does not converge, an autoregressive(1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from the 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 on the ITT analysis set:

1. Missing HbA1c data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will not be excluded from the analysis.
2. HbA1c values collected after the start of rescue medication will be excluded (considered missing), and the MMRM analyses will be re-performed.
3. A last observation carried forward (LOCF) method will then be used to impute the missing observations prior to carrying out the MMRM model.

The effect of bexagliflozin on body weight and systolic blood pressure will be tested as key

secondary efficacy endpoints and will be analyzed in a hierarchical testing strategy only if the primary objective is met. ANCOVA models will also be used for the continuous secondary endpoints analyses. Longitudinal data will be evaluated through repeated measures tests. A hierarchical testing in the following order will be applied to preserve experiment-wide alpha at 0.05 in the case each successive determination meets significance:

1. To test the hypothesis that bexagliflozin reduces systolic blood pressure from baseline to week 24 compared with placebo
2. To test the hypothesis that bexagliflozin reduces body weight from baseline to week 24 compared with placebo in subjects with a BMI $\geq$ 25 kg/m2

The effect of bexagliflozin on fasting plasma glucose, on the proportion of subjects reaching < 7.0% HbA1c, and on the change in HbA1c over time will be analyzed as exploratory efficacy endpoints and will not be adjusted for multiplicity.

Safety data will include AEs, physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology, serum lipids, glycemic control parameters and urinalysis. The general safety of bexagliflozin in subjects with type 2 diabetes mellitus will be analyzed as well as the contribution of bexagliflozin to AEs of special interest.

For the primary efficacy endpoint, a power calculation was performed for significance calculated by a two group t-test with a two-sided α of 0.05. Taking the standard deviation for the change in HbA1c to be 1%, a sample size of 128 in the bexagliflozin group and 64 in the placebo group is predicted to have 90% power to detect a difference between groups of 0.5% in mean HbA1c change. To account for an estimated drop-out rate of approximately 10%, a study design was adopted in which 140 subjects are planned to be randomized to the bexagliflozin group and 70 subjects to the placebo group. Statistical analyses and summaries will be performed using SAS® software (SAS Institute, Cary, NC).

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALB	albumin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic therapeutic chemical
BMI	body mass index
BUN	blood urea nitrogen
Ca	calcium
CEC	Cardiovascular Endpoint Committee
ConMed	concomitant medicines
CFR	Code of Federal Regulations
CI	confidence interval
Cl	chloride
CRF	case report form
CRO	contract research organization
CV	cardiovascular
DKA	diabetic ketoacidosis
dL	deciliter
DPP4	dipeptidyl peptidase-4
DSMB	data and safety monitoring board
ECG	electrocardiogram
eGFR	estimating glomerular filtration rate
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GMI	genital mycotic infection
GLP-1	glucagon-like peptide-1
GGT	gamma glutamyl transferase
GMI	genital mycotic infection
HbA_{1c}	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
Hct	hematocrit
HDL-C	high density lipoprotein cholesterol
Hgb	hemoglobin

HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	independent ethics committee
IRAE	immediately reportable adverse event
IRB	Institutional Review Board
ITT	intention to treat
IWRS	Interactive Web Response System (IWRS)
K	potassium
LDL-C	low density lipoprotein cholesterol
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MCH	mean cell hemoglobin
MCHC	mean cell hematocrit
MCV	mean cell volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurement
mg	milligram
MI	myocardial infarction
mL	milliliter
Na	sodium
NYHA	New York Heart Association
OHA	oral hypoglycemic agent
PR	time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
QRS	graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram
QTC	time between the start of the Q wave and the end of the T wave in the ECG, corrected for heart rate
RBC	red blood cell
RR	time between the start of one R wave and the start of the next R wave in the ECG
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium glucose linked transporter 2
SMBG	self-monitored blood glucose
SUSAR	serious and unexpected suspected adverse reaction
T2DM	type 2 diabetes mellitus

TC	total cholesterol
TEAEs	treatment emergent adverse events
TG	triglycerides
UACR	urine albumin to creatinine ratio
UADR	unexpected adverse drug reaction
UGE	urine glucose excretion
UPT	urine pregnancy test
UTI	urinary tract infection
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

1 INTRODUCTION

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

T2DM is a disease strongly linked to increased body fat mass in the majority of cases (Schwartz, Fabricatore et al. 2012). Weight loss has been shown to improve glycemic control and to reduce the severity of diabetes-associated comorbidities, supporting the view that anti-diabetic agents that promote weight loss may be particularly beneficial for the treatment of the disease (Look, Wing et al. 2013; Scheen and Van Gaal 2014).Several classes of agents are available for treating T2DM, including insulin and its secretagogues, PPARγ agonists, biguanides, alpha glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sulfonylureas, meglitinides and dipeptidyl peptidase 4 (DPP4) inhibitors. However, the increasing 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 would ideally treat hyperglycemia and avoid common side effects of currently available agents, such as weight gain, gastrointestinal disturbance, and hypoglycemia.

The renal Na+/glucose transport protein SGLT2 actively transports extracellular glucose into cells using the driving energy of the transmembrane electrochemical potential for sodium ions. Individuals with disruptions in *SLC5A2*, the gene encoding SGLT2, exhibit prominent glucosuria in the absence of significant co-morbidities (van den Heuvel, Assink et al. 2002; Santer, Kinner et al. 2003). The excretion of glucose in the urine of diabetic subjects in amounts comparable to or greater than that seen in individuals harboring loss of functions mutations in *SLC5A2* has the potential to improve fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia. Several SGLT2 inhibitors have demonstrated these clinical benefits as well as sustained weight loss when used as a mono-therapy or in combination with other oral anti-diabetic medications including insulin (Nauck 2014; Seufert 2015).

1.1 Bexagliflozin for the treatment of type 2 diabetes mellitus

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

the pharmacology, efficacy, and safety assessments are described in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Efficacy Objective

The primary efficacy objective of this trial is to determine the placebo-adjusted treatment effect of bexagliflozin tablets, 20 mg on the change in HbA1c from baseline to week 24 in subjects with T2DM and inadequate glycemic control.

2.2 Secondary Efficacy Objectives

The key secondary efficacy objectives of this study are:

- To compare the effect of bexagliflozin to effect of placebo on the change in systolic blood pressure (SBP) from baseline to week 24
- To compare the effect of bexagliflozin to the effect of placebo on the change in body weight from baseline to week 24 in subjects with a BMI $\geq$ 25 kg/m^2

The other exploratory secondary efficacy objectives are:

- To compare the effect of bexagliflozin to the effect of placebo on the proportion of subjects with HbA1c of < 7%
- To compare the effect of bexagliflozin to the effect of placebo on change in HbA1c over time
- To compare the effect of bexagliflozin to the effect of placebo on FPG over time

2.3 Safety Objectives

- To compare the safety of bexagliflozin to the safety of placebo in subjects with T2DM
- To compare the effect of bexagliflozin to the effect of placebo on the incidence of adverse events (AE) of special interest. AEs of special interest include either upper or lower UTIs, GMI, hepatic toxicity, hypoglycemia, falls and fractures, cardiovascular events, malignancies, hypersensitivity reactions, hypotensive episodes, acid-base disorders, renal failure events and amputations.
- To contribute major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo. MACE+ is defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

THR-1442-C-450 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. It is designed to compare the efficacy and safety of once daily oral administration of bexagliflozin tablets, 20 mg to bexagliflozin tablets, placebo in treatment-naïve type 2 diabetic subjects or subjects previously treated with no more than one oral hypoglycemic agent (OHA).

The study will enroll both male and female subjects with T2DM. If treatment naïve, they must have an HbA1c at the screening visit of between 7% and 10.5%. Alternatively, prospective subjects may be eligible if at the time of the screening visit they are being treated with one OHA, have an HbA1c of between 6.5% and 10.0% and are willing to complete a 6-week washout. Individuals taking thiazolidinediones are not eligible for the study. A candidate will be considered treatment-naïve if he or she has received no more than 14 days of prescription medication for diabetes in the 12 weeks prior to screening.

All eligible subjects will start a 2 week placebo run-in period. Subjects who miss no more than one dose of the run-in medication, have fasting blood glucose values ≥ 250 mg/dL on no more than two consecutive days, and who, at the baseline visit (Visit V5), have an HbA1c level between 7 and 10.5% and a fasting glucose level < 250 mg/dL will be eligible for randomization.

Approximately 210 subjects will be randomly assigned to receive oral bexagliflozin tablets, 20 mg or placebo, in a 2:1 ratio once daily for 24 weeks in an out-patient setting. Subjects with uncontrolled hyperglycemia based on blood glucose levels may receive additional approved anti-diabetic medications. Treatment group assignment at the start of the treatment period will be stratified by HbA1c level at the start of the run-in period (7.0 to 8.5% or 8.6 to 10.5%) and background anti-diabetes treatment status (treatment naïve or not).

Each subject will be contacted by telephone at week 2 (Visit V7) for safety monitoring and will be instructed to return to the clinic at weeks 6, 12, 18, and 24 (Visits V8, V9, V10, V11) for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up visit at week 26 or two weeks after the last dose of investigational product if the subject terminates prior to week 24 (Visit V12).

3.2 Research Methods and Procedures

3.2.1 Wash-out and Run-in Period

Eligible subjects who are not treatment naïve will discontinue their current OHA and enter a 6 week wash-out period. At the start of the wash-out (Visit V2), each subject will be provided with diet and exercise counseling, a glucometer, a glycemic control diary in which to record symptoms related to any hyper- or hypoglycemic events, and instructions as to when to call the clinic for hyperglycemia (see *Glycemic Control Monitoring*, below). Two weeks after the start of the wash-out period (Visit V3), each subject will participate in a

phone interview visit with study staff for self-monitored blood glucose (SMBG) data review and general safety evaluation. Subjects who remain eligible at the end of the wash-out period will proceed to a 2-week placebo run-in period. Subjects who have fasting blood glucose values ≥ 250 mg/dl on two consecutive days during the washout will not be eligible for the run-in period.

Eligible subjects who are treatment naïve will not require a wash-out 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 symptoms related to any hyper- or hypoglycemic events at the start of the placebo run-in period (Visit V4).

Treatment naïve subjects and subjects on background anti-diabetic therapy who complete the 6-week wash-out will enter the 2-week single-blind placebo run-in period. At the start of the run-in period, each subject will be provided with placebo drug, dosing instructions, and instructions as to when to call the clinic should hyperglycemia develop (see *Glycemic Control Monitoring*, below). During the run-in, placebo will be taken daily in the morning with 250 mL of water prior to eating or drinking.

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 consecutive days, 2) miss more than 1 dose of placebo, 3) are deemed inappropriate for the study by the investigator or 4) at the base line visit (Visit V5), have HbA1c value < 7.0% or >10.5%. At the baseline visit, subjects must have a fasting glucose level < 250 mg/dL (13.9 mmol/L) to be eligible for randomization.

Approximately 210 subjects will be randomly assigned in 2:1 ratio to receive bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo once daily for 24 weeks. Randomization at the start of the treatment period will be stratified by HbA1c level at the final assessment prior to randomization (Visit V5) (7.0 to 8.5% or 8.6 to 10.5%) and by background anti-diabetes treatment status (treatment naïve or not).

3.2.2 Treatment Period

The treatment period will start at randomization (Visit V6) and end after 24 weeks. At the start of the treatment period, each subject will be provided investigational product, dosing instructions, and glycemic control diary in which to record symptoms related to any hyper- or hypoglycemic events as well as information related to the occurrence of such events. Subjects with uncontrolled hyperglycemia based on blood glucose levels may receive additional approved anti-diabetic rescue medications (see Prescription of Rescue Medication below). Bexagliflozin tablets will be orally administered in the morning with 250 mL of water prior to eating or drinking.

Each subject will participate in a telephone consultation at week 2 (Visit V7) for safety monitoring. Each subject will be instructed to return to the clinic at weeks 6, 12, 18, and 24 (Visits V8, V9, V10, V11, respectively) for efficacy assessment and safety monitoring, including review of adverse events and concomitant medication, evaluation of vital signs, electrocardiogram (ECG), and a physical examination, and for a blood draw and urine

collection for clinical laboratory. On the day of the clinic visit, a fasting time of approximately 10 hours must be confirmed prior to blood draw.

To minimize the effect of missing values on data analysis and study outcome interpretation, considerable effort will be made to prevent missing data, to train site staff to encourage study subject participation and to remain vigilant to signs of non-compliance, to remain in contact with study subjects who have withdrawn from the study to collect as nearly complete a data set as is feasible, and to determine all reasons for missing data.

Subjects will return to the clinic for a follow-up exit visit at week 26 (Visit V12) or two weeks after the last dose of investigational product if the subject terminates prior to week 24. Following the exit visit, subjects will be advised to see their primary physician and resume treatment to control their diabetes. The duration of participation for each subject can be up to 37 weeks depending on prior treatment status.

3.2.3 Glycemic Control Monitoring

3.2.3.1 Washout Period

During the wash-out period, subjects will be instructed to determine SMBG daily after an overnight fast of approximately 10 hour duration. If the fasting blood glucose is ≥ 250 mg/dL (13.9 mmol/L) during the wash-out period, the subject should contact the clinic within 24 hours, 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. If fasting blood glucose is ≥ 250 mg/dL (13.9 mmol/dL) on two consecutive days during the washout, the subject should contact the clinic staff and will be excluded from participation in the study Subjects with SMBG readings ≥ 250 mg/dL (13.9 mmol/L) and severe clinical signs or symptoms of hyperglycemia during the wash-out period, including weight loss, blurred vision, increased thirst, increased urination, or fatigue will be excluded from participation in the study.

3.2.3.2 Placebo Run-in Period

During the placebo run-in period, subjects will be instructed to determine SMBG daily after an overnight fast of approximately 10 hour duration. If the fasting blood glucose is ≥ 250 mg/dL (13.9 mmol/L) during the run-in period, the subject should contact the clinic within 24 hours, 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. If fasting blood glucose is ≥ 250 mg/dL (13.9 mmol/dL) on two consecutive days during the run-in, the subject should contact the clinic staff and will be excluded from participation in the study.

The investigator or designee will review the glucometer data and glycemic control diary at the end of the run-in period. Subjects with fasting blood glucose ≥ 250 mg/dL (13.9 mmol/dL) on two consecutive days during the run-in period will excluded from participation. In addition, subjects with SMBG readings ≥ 250 mg/dl (13.9 mmol/L) and clinical signs or

symptoms of severe hyperglycemia, including weight loss, blurred vision, increased thirst, increased urination, or fatigue will be excluded from participation in the study.

3.2.3.3 Main Treatment

During the 24-week 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, ≥ 240 mg/dL (13.3 mmol/L) after week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) after week 12 to week 24. Blood glucose values collected via SMBG will be evaluated at study visits by the investigator. In addition, hyperglycemia will be monitored by fasting plasma glucose (FPG) measurement at each study visit.

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

During the treatment period, hyperglycemia should be managed first with diet and exercise counseling 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*). After the treatment period, changes to the medical therapy for hyperglycemia should occur at the discretion of the investigator based on SMBG, FPG, and HbA1c information using local standards of care for subjects with T2DM.

If a concomitant medication for hyperglycemia is to be prescribed, a blood sample must be drawn prior to the administration of the rescue medication so that a final HbA1c value can be determined.

3.2.3.4 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 24 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 during the treatment period if, after a review of diet and exercise counseling:

1. more than 3 consecutive, daily, fasting SMBG measures are ≥ 270 mg/dL (15 mmol/L) from week 1 to week 6, ≥ 240 mg/dL (13.3 mmol/L) from week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) from week 12 to week 24
2. persistent clinical signs or symptoms of hyperglycemia are present (*e.g.* weight loss, blurred vision, increased thirst, or increased urination, or fatigue)

The investigator may provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated, with the exception of an SGLT2 inhibitor.

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, during the treatment period. Following the exit visit, subjects will be advised to see their primary care physician and resume standard 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.

3.2.4 OTHER SAFETY MONITORING ACTIVITIES

The safety monitoring activities will include assessment of vital signs, physical examinations, urinalysis, blood chemistry, hematology, AEs, and concomitant medication (ConMed) 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 either upper or lower UTI, GMI, hepatic toxicity, hypoglycemia, falls and fractures, MACE+, malignancies, hypersensitivity reactions, hypotension episodes, acid-base disorders, and renal failure events. All such events must be appropriately documented within source documentation.

DATA AND SAFETY MONITORING BOARD (DSMB)

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

MAJOR ADVERSE CARDIOVASCULAR EVENT ADJUDICATION

An independent cardiovascular endpoint committee (CEC) has been established to review, under blind, all potential cardiovascular events occurring during the study. The events of interest include cardiovascular mortality, myocardial infarction, stroke, hospitalization for acute coronary syndromes, 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. Events occurring in this study will be classified as belonging to MACE+ or not. MACE+ is defined as cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. 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 Dose Selection

3.3.1 Rational for Study Design and Control Group

This study is designed to evaluate the efficacy and safety of bexagliflozin for the treatment of subjects with T2DM. A randomized, double-blind study design 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 protocol, placebo is the appropriate control for the subject population studied during the treatment period (24 weeks). In order to reduce the possibility that the change in HbA1c level from baseline to 24 weeks is determined by medications taken prior to the study, an up to 8 week washout and run-in period will be implemented prior to randomization of subjects on prior OHAs. All subjects will receive a placebo in the 2 weeks immediately prior to randomization to allow compliance with the dosing regimen to be monitored. Subjects with FPG levels ≥ 250 mg/dL at the visit prior to randomization (Visit V5) 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. A monitoring plan based on the measurements of SMBG, FPG, and HbA1c, as well as criteria to initiate rescue medications, is included in the protocol to prevent prolonged hyperglycemia.

Results from studies of individuals with genetic mutations in the gene encoding SGLT2, of subjects that have been treated with other SGLT2 inhibitors, and of previous clinical studies in healthy or diabetic subjects treated with bexagliflozin, indicate that the risk of hypoglycemia caused by inhibition of SGLT2 activity is likely to be minimal.

Reduction in HbA1c is considered a well validated surrogate for the long-term microvascular complications of diabetes mellitus. HbA1c levels reflect mean glycemic control over 2 to 3 months, and therefore the primary endpoint of HbA1c measurement at 24 weeks will assess the effect of bexagliflozin compared to placebo over a sustained period.

3.3.2 Rational for Dose Selection

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

3.4 Study Duration and Dates

Potential subjects will be screened within 3 weeks of the start of wash-out or run-in period. Eligible subjects who are taking a background OHA and sign the informed consent will start a 6-week wash-out period, followed by a 2-week single-blind placebo run-in period. Eligible subjects who are treatment naïve and sign the informed consent form will immediately start the 2-week single blind placebo run-in period. Subjects who remain eligible at the end of the run-in period will receive 24 weeks of treatment. All subjects who are randomized will be followed for 2 weeks after the last dose of investigational product.

The overall study duration from screening to follow-up could be a maximum of 37 weeks. The duration of the overall study depends on the rate of subject accrual. For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 210 subjects diagnosed with T2DM who are inadequately controlled by diet and exercise or by treatment with a single OHA and who have an HbA1c level between 7% and 10.5% at the time of randomization. Clinical sites in the US and in Canada are anticipated to recruit subjects. Clinical sites in other countries may also participate in the trial.

4.2 Inclusion Criteria

The study population will include:

At the Screening Visit (V1)

1. Male or female adults subject ≥ 18 years of age at screening.
2. Subjects who are treatment naïve or receiving one OHA in combination with diet and exercise.
3. Subjects with a diagnosis of T2DM
4. Subjects with HbA1c levels at screening between 7.0% and 10.5% (inclusive) if treatment-naïve or with HbA1c levels between 6.5 and 10.0% (inclusive) if on one oral anti-diabetic agent
5. Subjects with a body mass index (BMI) ≤ 45 kg/m^2
6. Subjects whose doses of medications for hypertension or hyperlipidemia (if applicable) have not changed for at least 30 days prior to screening
7. Subjects who are willing and able to return for all clinic visits and to complete all study required procedures, including SMBG measurement
8. Female subjects of childbearing potential who are willing to use an adequate method of contraception and to not become pregnant for the duration of the study. Adequate contraceptive measures include, but are not limited to, oral contraceptives, intrauterine devices, Depo-Provera®, Norplant®, hormonal contraceptive implants, bilateral tubal ligation, partner with vasectomy, condom or diaphragm plus contraceptive sponge, foam, or jelly, and abstinence

At the Run-in Visit (V4)

9. Subjects who have maintained glycemic control throughout washout, if applicable.

Prior to Randomization (V5)

10. Subjects who have HbA1c levels between 7.0 and 10.5% (inclusive)
11. Subjects who have been compliant in investigational product administration by missing no more than one dose of run-in medication

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. A diagnosis of type 1 diabetes mellitus or maturity–onset diabetes of the young
2. Current use of injected therapy for treatment of diabetes (insulin or GLP-1 receptor agonist therapy) or thiazolidinedione class drugs
3. Female subjects who are pregnant or breastfeeding
4. Hemoglobinopathy or carrier status for hemoglobin alleles that affect HbA1c measurement
5. Genitourinary tract infection (e.g. UTI, GMI, vaginitis, balanitis) within 6 weeks of screening or history of ≥ 3 genitourinary infections requiring treatment within 6 months from 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
7. Uncontrolled hypertension defined as a sitting systolic blood pressure >160 mmHg or diastolic blood pressure > 95 mmHg at screening
8. A positive result for hepatitis B surface antigen (HBsAg) or hepatitis C (HCV)
9. History of alcohol or illicit drug abuse in the past 2 years
10. Known human immunodeficiency virus (HIV) positive based on medical history
11. Life expectancy < 2 years
12. New York Heart Association (NYHA) Class IV heart failure within 3 months of screening
13. MI, unstable angina, stroke, or hospitalization for heart failure within 3 months of screening
14. Treatment with an investigational drug within 30 days or within 7 half-lives of the investigational drug, whichever is longer
15. Previous treatment with bexagliflozin or EGT0001474
16. Use of any SGLT2 inhibitors, either at the time of screening or in the prior 3 months
17. Currently participating in another interventional trial
18. Not able to comply with the study scheduled visits
19. Any condition, disease, disorder, or clinically relevant abnormality that, in the opinion of the primary investigator, would jeopardize the subject's appropriate participation in this study or obscure the effects of treatment
20. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 2.5 x ULN or total bilirubin $\geq$ 1.5 x ULN with the exception of isolated Gilbert's syndrome at screening
21. Two or more consecutive FPG measures $\geq$ 250 mg/dL (13.9 mmol/L) prior to randomization or 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
22. At last visit prior to randomization (Visit V5), FPG level $\geq$ 250 mg/dL
23. Prior renal transplantation or evidence of nephrotic syndrome (defined as a urine albumin-to-creatinine ratio (UACR) > 2000 mg/g at screening).

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Investigational Product

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

The following investigational products will be used for oral administration:

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

5.2 Treatments Administered

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

5.3 Selection and Timing of Dose for Each Subject

Dosing with bexagliflozin tablets, 20 mg or placebo, will be based on randomized assignment. All study subjects will be instructed to self-administer tablets once daily with 250 mL of water in the morning prior to eating or drinking. There will be no change of dose during the 24-week treatment period.

On the day of each scheduled clinic visit, subjects must fast for approximately 10 hours prior to the collection of blood samples. On the day of each scheduled clinic visit, bexagliflozin tablets should be taken with water in the morning prior to eating or drinking (as above) and prior to the collection of blood samples. During the fasting period, only water will be permitted.

5.4 Method of Assigning Subjects to Treatment Groups

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized in a 2:1 ratio to receive once daily bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo during the 24-week treatment period. Subjects will be assigned to treatment groups in sequential order as they qualify for the study, using a centrally located and managed Interactive Web Response System (IWRS). Randomization will be stratified according to HbA1c measured at the last assessment prior to randomization (Visit V5) (HbA1c at 7.0 to 8.5% or 8.6 to 10.5%) and background anti-diabetic treatment status (treatment-naïve or on treatment).

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

be capped at 21 randomized subjects. However, when a site reaches 21 randomized subjects, if a potential subject at that site is in washout or run in already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized. Subject randomization will be deactivated for all sites when the planned number of subjects has been enrolled. However, if a potential subject is in washout or run in already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized.

5.5 Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the CEC 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 assignments, central laboratory glucose urinalysis data will not be made available to any study personnel or subjects.

If knowledge of the test substance 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 in the case report form (CRF) and the sponsor must be notified within 24 hours.

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

The treatment assignment will continue to be withheld from the CEC members at the conclusion of the study 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 supplement treatment of non-diabetic medical conditions should be continued at a stable dose and frequency for the entire study duration unless there is clinical reason to change the dose or frequency.

During the run-in period, blood pressure medications can be altered to optimize blood pressure control at the discretion of the investigator, although adjustment of blood pressure medications during the first 12 weeks of the treatment period should be avoided unless it is medically necessary to do so. If it is medically necessary to alter blood pressure medications during the first 12 weeks of the treatment period, new diuretic medications should not be initiated and the dose and frequency of existing diuretic medications should not be altered.

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

To minimize the effect of missing values on data analysis and study outcome interpretation, considerable effort will be made to prevent missing data, to train site staff to encourage study subject participation and to remain vigilant to signs of non-compliance, to remain in contact with study subjects who have withdrawn from the study to collect as nearly complete a data set as is feasible, and to determine all reasons for missing data.

Subjects may receive any medications for AEs that are necessary in the investigators' judgment. Concomitant medications prescribed at the time of the run-in period and during the study are to be recorded in the CRF. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. This documentation should continue through the treatment 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 3 months of screening. Subjects taking insulin or GLP-1 receptor agonists or members of the thiazolidinedione class of drugs are not eligible for this study.

5.7.2 Fluid and Food Intake

During the study, subjects will be counseled to remain well 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 approximately 10 hours prior to the scheduled blood sample draws. During fasting, only water will be permitted.

5.7.3 Subject Activity Restrictions

Throughout the study period, subjects are counseled and encouraged to engage in a level of physical activity that is appropriate for their physical condition. For those without specific

restrictions or limitations, at least 150 min/week of moderate activity is advised by the American Diabetes Association (ADA, 2013). Alternatively, local guidelines may be followed.

5.8 Treatment Compliance

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

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

5.9 Packaging and Labeling

Investigational product will be provided to the pharmacist or designated site personnel in bottles of 90 tablets enclosed with a child-resistant cap. Bottles of 15 placebo tablets will be provided for the 2-week run-in portion of the study. All investigational product supplies will be prepared and labeled according to the requirements of local laws and regulations and will be kept in a secure storage facility at controlled room temperature, 15 to 30 °C (59 to 86°F).

The pharmacist or designated site personnel will dispense the investigational products for each subject according to randomization assignment made in the Interactive Web Response System (IWRS). During the treatment period, subjects will be provided with an investigational product kit at randomization (Visit V6) and a new investigational product kit at 12 weeks (Visit V9). There will be no intra-subject dose escalation or back-titration.

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

There are two types of investigational product kits:

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.

INVESTIGATIONAL PRODUCT KIT

One investigational product kit contains a bottle of 90 bexagliflozin tablets, 20 mg or bexagliflozin tablets, 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, 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' prescription information. The sponsor will notify the sites of the process for returning unused drug.

5.11 Investigational Product Retention at Study Site

The investigational products should be stored in a secure area with limited access. The drug storage facility must comply with the medication storage instructions. Bexagliflozin tablets should be stored at controlled room temperature until ready for dispensing to study subjects. The trial staff must record the amount of investigational product dispensed to each subject 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 Theracos or its designee.

6 STUDY PROCEDURES

6.1 Informed Consent

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

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

6.2 Screening or Confirmation for I/E Criteria

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

6.3 Medical History

The following information will be collected at the screening visit:

6.3.1 General Demographics and Characteristics

1. Date of birth, age, sex, and race, and whether a female subject is of childbearing potential or not.
2. Significant medical (including alcohol/illicit drug abuse within the last 2 years) and surgical history, including dates of diagnoses and procedures and whether the condition is ongoing, if applicable.

6.3.2 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.

6.3.3 Cardiovascular Disease History

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

6.3.4 Medication History

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

6.4 Diet and Exercise Counseling

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

6.5 Physical Examination

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

The body weight must be determined using a scale that is calibrated. Every effort should be made to use the same scale throughout the study duration.

6.6 Abbreviated Physical Examination

An abbreviated physical examination will include body weight and height (height will be measured only at screening), and general assessment of the skin, heart, lungs and abdomen. Abbreviated physical examinations will be performed by the investigator at the time points indicated in the Schedule of Events (Appendix 1), unless clinically indicated.

The body weight must be determined using a scale that is calibrated. Every effort should be made to use the same scale throughout the study duration.

6.7 Vital Signs

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

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

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

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

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

6.8 Electrocardiography

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

It is the investigator's responsibility to review the results of the ECG as they become available. For each abnormal ECG result, the investigator shall ascertain if the observation represents a clinically significant change from the screening ECG for that individual subject (this determination, however, does not necessarily need to be made the first time an abnormal

result is observed. The investigator may repeat the ECG to verify the results of the original result). If the ECG result is determined to be a clinically significant and abnormal change from baseline for that subject, it is considered to reflect an AE.

6.9 Clinical Laboratory Tests

6.9.1 Laboratory Parameters

Clinical laboratory tests are listed in Table 1.

6.9.2 Sample Collection, Storage, and Shipping

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

Blood samples for hematology, chemistry, serum lipids and glycemic control assessments will be collected. Subjects will be in a seated or supine position during blood collection. Samples will be collected at the time points indicated in the schedule of events in Appendix 1 and Appendix 2.

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

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

6.9.2.2 Urinalysis

Urine samples will be collected routinely at designated clinic visits from a clean catch sample. Urinalysis will be performed at the time points indicated in the schedule of events (Appendix 1 and Appendix 2). Investigator or staff should document if pre-menopausal female subjects are menstruating and note it in the source documents since hematuria is likely to be identified on dipstick urinalysis.

Urine samples will be transported to the central laboratory for urinalysis. Samples should be stored and shipped as detailed in the Laboratory Manual. Microscopy will be conducted if the subject has a positive result on the leukocyte esterase or nitrite dipstick tests to clarify the significance of the finding. Results of glucose measurement in the urinalysis must be suppressed from the laboratory reports so the sponsor, investigators, study coordinators,

pharmacists, study subjects, and the CEC members will remain blinded to the dosing assignment.

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

Renal functional testing by UACR will be determined at time points specified in the schedule of events (Appendix 1 and Appendix 2).

6.9.2.3 Urine Pregnancy Test (UPT)

UPT will be performed for all women, including surgically sterile or post-menopausal women, at the screening visit. Additionally, women of child bearing potential (WOCBP) will receive a UPT at the clinical visits indicated in Appendix 2.

Table 1 List of Laboratory Tests

Test Name (sample volume)

Hematology (2 mL blood)

- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Platelet count

Serum Chemistry and Electrolytes (3 mL serum)

- Albumin (ALB)
- ALT
- AST
- Blood urea nitrogen (BUN)
- Creatinine
- Uric acid
- Calcium (Ca)
- Magnesium
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total Protein
- Glucose
- Bicarbonate (HCO_3)
- Chloride (Cl)
- Total bilirubin
- Direct bilirubin

Glycemic Control (2 mL plasma, 2 mL blood)

- FPG
- HbA1c

Serum Lipids

- Total cholesterol (TC)
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C), calculated, or
- LDL-C, direct
- Triglycerides (TG)

Infectious Disease Testing (3 mL serum)

- Hepatitis B surface antigen (HBsAg)
- Hepatitis C virus (HCV)

Urinalysis

- Appearance
- Bilirubin
- Color
- Glucose (blinded)
- Ketones
- Microscopic examination of sediment
- Nitrite
- Leukocyte esterase
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Renal Functional Test

- UACR

Urine Pregnancy Test

6.10 Diary and Glucometer Dispensation and Review

A glucometer, testing strips, and a glycemic control diary will be provided to each subject at the start of OHA washout or when a potential subject starts taking run-in medications for SMBG. Subjects will be trained to use the glucometer and record any events in the glycemic control diary. The SMBG record from the glucometer and diary entries must be reviewed by the investigator at all subsequent visits including both phone interview and clinic visits. The SMBG record for all subjects should be sent to the site monitor once per month or as directed by the sponsor.

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

6.11 Dispensing Run-in Drug

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

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

6.12 Dispensing Investigational Product

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

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

6.13 Adverse Events Assessments

6.13.1 Definition of Adverse Events

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

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

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

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

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

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

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

- Suspected adverse reaction
- Serious
- Unexpected

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

1 = Mild: event is medically significant but produces no disruption to daily activity;
2 = Moderate: event is medically significant and reduces or affects normal daily activity;

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

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

- **Definite:** The event responds to withdrawal of the investigational product (dechallenge), and recurs with rechallenge by administration of the investigational product.
- **Probable:** There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- **Possible:** There is a reasonable causal relationship between the investigational product and the AE. Dechallenge is lacking or dechallenge response is unclear.
- **Not Likely**: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the event.
- **Unrelated:** There is not a temporal or causal relationship to investigational product administration.

6.13.2 Eliciting and Reporting AEs

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

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

Hypoglycemia is defined as any FPG or SMBG value ≤ 70 mg/dL and should be documented based on the ADA hypoglycemia categories.

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

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

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

6.13.3 Immediately Reportable AEs

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

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

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

6.13.4 Pregnancy

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

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 be enrolled or remain in the study. If pregnancy is suspected while the subject is receiving study treatment, the investigational product must be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the investigational product will be permanently discontinued and the

subject will be withdrawn from the trial. (Exceptions to study discontinuation may be considered for life-threatening conditions only after consultations with a sponsor Medical Monitor or designated personnel.) The investigator must notify the Medical Monitor within 3 working days of any female subject who becomes pregnant. This reporting requirement will continue until 4 weeks after the last investigational product exposure.

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

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

6.13.5 Procedure for Breaking the Blind

As indicated in Section 5.5 above, the sponsor, medical monitor, study coordinators, pharmacists, study subjects, and the CEC members will be blinded to the treatment assignment during the study period. The investigator should also remain blinded to the subject treatment during the entire study unless knowledge of the subject's treatment is required for clinical care and safety. The Emergency Code Break module in the IWRS is used for such situations. The investigator must confirm the intention to unblind the subject's treatment to obtain the dose information in IWRS. Upon completion of the unblinding, the system will send an alert to designated study team members that an unblinding event has occurred. Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken, and the names of the personnel requesting and authorizing unblinding. The treatment assignment will continue to be withheld from the CEC members until all phase 3 studies are completed.

6.13.6 Follow-up of Non-Serious AEs

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

6.13.7 Follow-up of Post-Study SAEs

SAEs that are identified on the last scheduled contact must be recorded on the AE CRF page and reported to the sponsor according to the reporting procedures outlined in Section 6.13.3. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved.

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

6.13.8 Urinary Tract Infections (UTIs)

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

The investigator should query the subject at every 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 (1+ or greater). If the subject reports symptoms consistent with a UTI or the urinalysis at the clinical site is positive, a urine culture will be performed in a designated 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.

6.13.9 Genital Mycotic Infections (GMIs)

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

6.13.10 Hepatotoxicity

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

Any clinically significant increase in hepatic enzymes and specifically any ALT or AST > 3 x ULN requires immediate repeat test within 48 to 72 hour to confirm the hepatic enzyme

elevation and should be repeated based on the clinical situation at least every 96 hour (4 days) until ALT and AST return to < 2.5 x ULN. Study medication should be stopped and the event should be reported as a laboratory AE within the CRF if the enzyme elevation is confirmed or worsening.

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

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

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

6.13.11 Hypoglycemia

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

All subjects will be provided with a glucometer and glycemic control diary in which to record symptoms related to any hyper- or hypoglycemic events. During the study the subject is expected to record 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 hour 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 to hypoglycemia. In addition, the investigator should query the subject with regard to the occurrence of signs and symptoms potentially related to hypoglycemia even if none are recorded in the diary.

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

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

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

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

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

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

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

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

6.13.12 Diabetic Ketoacidosis (DKA)

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

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

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

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

6.13.13 Major Adverse Cardiovascular Event (MACE)

Evaluation of MACE will be undertaken across the development program for bexagliflozin. All MACE reports should also be captured as SAEs and every effort will be made to ensure that events recorded as MACE are coded in a similar manner within the safety database. The SAE listing will also be reviewed periodically by the CEC members to identify potential

MACE that may not have been reported by the site investigators. All subjects will be followed by investigators for MACE for the duration of the study even if study medication has been permanently withdrawn.

The independent CEC will receive and adjudicate the following events.

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

6.13.14 Amputation

Amputation and related adverse events will be recorded in a dedicated case report form. During each study visit, the investigator should query the subject for any amputation and related adverse events and procedures. Investigators are reminded to counsel appropriate foot care to avoid cuts or sores and to treat even minor cuts or sores to prevent infection and ulceration. Patients who have had a previous amputation should be closely monitored. Special attention may be appropriate for patients who are also receiving thiazide diuretics as these have been shown to increase the risk of amputation in diabetics.

6.14 Concomitant Medication Assessments

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

The medications or treatment for controlling hypoglycemia must be recorded as concomitant medications in the CRF. Any medication given to treat hyperglycemia and continued for more than 2 weeks is considered a rescue therapy and should be recorded in the concomitant medication log.

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

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

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

7 STUDY ACTIVITIES

The activities that must be performed 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 6. V6 is the day of randomization and the basis for the visit window.

7.1 V1 (Screening Visit (up to Week -11)

- Explain the content of the informed consent materials to the subject and collect signed informed consent
- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Obtain medical history and demographic information
- Perform an abbreviated physical exam
- Measure vital signs, including blood pressures and heart rate
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample

7.2 V2 (Beginning of washout for OHA subjects) (Week -8)

- Evaluate any change to status affecting conformance to inclusion and exclusion criteria. Verify compliant fasting status
- Counsel subject on appropriate diet and exercise
- Dispense glucometer and instruct subject in SMBG determination and recording
- Assess adverse events and DKA
- Record concomitant medications

7.3 V3 (Phone interview for washout OHA subjects) (Week -6)

- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.4 V4 (Beginning of run in) (Week -2)

- Counsel subject on appropriate diet and exercise if treatment naive subject
- Dispense glucometer and instruct subject in SMBG determination and recording if treatment naive subject
- Dispense run-in kit for run-in period

- Review SMBG and glycemic control record if subject was on prior OHA treatment
- Assess adverse events and DKA
- Record concomitant medications

7.5 V5 (Baseline Visit) (Day -3 to -5)

- Evaluate any change to status affecting conformance to inclusion and exclusion criteria. Verify compliant fasting status
- Perform a complete physical examination
- Measure vital signs, including blood pressures and heart rate
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample.
- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.6 V6 (Randomization Visit) (Week 0)

- Review SMBG and glycemic control record
- Dispense investigational product based on randomization
- Assess adverse events and DKA
- Record concomitant medications

7.7 V7 (Phone Interview) (Week 2)

- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.8 V8 (Treatment Visit) (Week 6)

- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample.
- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.9 V9 (Treatment Visit) (Week 12)

- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample.
- Review SMBG and glycemic control record
- Dispense investigational product based on randomization
- Assess adverse events and DKA
- Record concomitant medications

7.10 V10 (Treatment Visit) (Week 18)

- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample.
- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.11 V11 (Treatment Visit) (Week 24)

- Perform an abbreviated physical examination
- Measure vital signs, including blood pressures and heart rate
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample.
- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.12 V12 (Follow Up Visit) (Week 26)

- Perform a complete physical examination
- Measure vital signs, including blood pressures and heart rate
- Perform a 12-lead ECG measurement
- Draw blood if an approximately 10 hour fast has been completed by the subject. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect a clean-catch, mid-stream urine sample.

- Review SMBG and glycemic control record
- Assess adverse events and DKA
- Record concomitant medications

7.13 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 is withdrawn from the study.

To minimize the effect of missing values on data analysis and study outcome interpretation, every effort should be made to prevent missing data. Site staff should explain that withdrawing consent is the study subjects' decision and emphasize to the subjects the importance of continued participation to complete the full study. If study subjects express dissatisfaction with the trial conduct and have not withdrawn yet, the investigator shall make efforts to address the subjects' concerns, explain the impact of withdrawal on the study outcomes, and retain subjects in the study to the best of her or his ability. In doing so, the investigator must be careful to avoid coercion.

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). Study investigators shall understand the value of data collection after early termination and make effort to collecting data after a subject discontinues the study treatment.

8 QUALITY CONTROL AND ASSURANCE

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

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

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

Unless otherwise specified, all statistical 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 Multiple Comparisons / Multiplicity

A sequential testing procedure will be used to control familywise error rate for the primary efficacy endpoint and key secondary efficacy endpoints at a two-sided 5% significant level. The key secondary efficacy endpoints will be tested only if the primary efficacy measure achieves significance.

9.2 Determination of Sample Size

Approximately 210 subjects will be randomized 2:1 to bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo.

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

1. The difference in mean change from baseline to week 24 in HbA1c in the bexagliflozin group compared to that of the placebo group will be -0.5%.
2. The standard deviation for the difference in mean change from baseline to week 24 in HbA1c between the bexagliflozin group and the placebo group will be 1.0%.

Under the above assumptions, an estimated sample size of 128 and 64 evaluable subjects in the bexagliflozin and placebo arms, respectively, yielded a 90% power that bexagliflozin treatment will be found to be significantly different from placebo. To account for an estimated drop-out rate of approximately 10%, the study design anticipates randomizing 140 and 70 subjects in the bexagliflozin or placebo arm, respectively.

This study will be conducted at multiple investigative sites and will likely randomize different numbers of subjects at each site. Enrollment will be on a competitive basis but will be capped at 21 subjects from any one site.

9.3 Analysis Populations

9.3.1 Intention to Treat Analysis Set

All subjects who are randomized will be included in the Intention to Treat (ITT) Analysis Set. All analyses of the ITT Analysis Set will be based on the randomization schedule. The ITT analysis set will serve as the primary set for the efficacy analyses.

9.3.2 Safety Analysis Set

All subjects who are randomized and take at least one dose of double-blind study medication will be included in the Safety Analysis Set (SAS). Safety analyses will be based on the medication that each subject has taken. The SAS is the primary analysis set for safety evaluation.

9.3.3 Per Protocol Analysis Set

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

9.4 Demographics and Baseline Characteristics

Subjects must meet all of the inclusion criteria and none of the exclusion criteria in order to participate in the study. Demographic characteristics include age, gender, race, ethnicity and country of investigational site. Baseline characteristics will be determined at Visit 5 and include HbA1c, blood pressure, body weight, BMI, FPG, duration of diabetes from diagnosis to V1, and stratification factors including HbA1c values at V5 and background anti-diabetic treatment status (treatment naïve or not). Summary descriptive statistics by treatment will include counts and percentages for discrete variables and estimation of means, standard deviations, medians, inter-quartile range, minimum, and maximum for continuous variables. Baseline is defined as the last non-missing value before randomization date.

9.5 Primary Efficacy Analysis

Efficacy data include HbA1c, FPG, body weight, and blood pressure. All changes from baseline will be calculated as the post-treatment value minus the last non-missing assessment before randomization (Visit V5).

9.5.1 Primary Efficacy Endpoint

The primary efficacy hypothesis is that bexagliflozin reduces HbA1c after 24 weeks of treatment when compared to placebo. The analysis of the change in HbA1c at week 24 will be based on ITT Analysis Set using all observed data and a mixed model repeated measures (MMRM) approach that will include terms for treatment, visit, treatment-by-visit interaction and randomization stratification factors as fixed effects and the baseline HbA1c value as a

fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the placebo group at week 24 will be estimated from the model with the corresponding p-values and their two-sided 95 % CI presented. An unstructured covariance will be used to model the within-subject correlation. If the model with the unstructured covariance structure does not converge, an autoregressive(1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from the analysis.

Sensitivity analyses will be performed as:

1. A multiple imputation method will be used to impute missing observations (including observations obtained after rescue medication) in the ITT Analysis Set prior to carrying out the MMRM analysis.
2. A multiple imputation method will be used to impute missing observations (not including observations obtained after rescue medication) in the ITT Analysis Set prior to carrying out the MMRM analysis.
3. A last observation carried forward (LOCF) method will be used to impute the missing observations in the ITT Analysis Set prior to carrying out the MMRM model.

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

9.5.2 Handling Dropouts and Missing Data

Randomized subjects who withdraw consent to participate in the study will not be replaced.

The early termination rate is estimated to be 10%. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. But if data are missing for the primary endpoints, they will be handled as follows:

1. Only available data will be analyzed and data obtained after rescue will not be excluded. This will be considered the primary analysis.
2. Missing endpoint information will be imputed by a multiple imputation linear regression approach for continuous variables. Adequate imputed datasets will be generated, and the corresponding primary analyses will be carried out on each imputed dataset; the results will be combined across the datasets using the standard techniques for multiple imputed data sets in order to yield overall treatment comparison results using the imputed data.

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

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

9.6 Secondary Efficacy Endpoints

9.6.1 Key secondary Efficacy Endpoints

The key secondary efficacy endpoints include:

- Change in SBP from baseline to week 24
- Change in body weight from baseline to week 24 in subjects with a BMI $\geq$ 25 kg/m^2

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

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

Change from baseline in body weight at week 24 will be analyzed using ANCOVA method.

9.6.2 Exploratory Efficacy Endpoints

The exploratory secondary efficacy endpoints include:

- Change from baseline in HbA1c over time
- Proportion of subjects reaching HbA1c < 7% over time
- Change from baseline in FPG over time

For changes from baseline in HbA1c, FPG over time, a similar MMRM ANCOVA model will be used as for the key secondary efficacy endpoint of change in SBP at week 24 in subjects with baseline SBP $\geq$ 130 mmHg (the treatment-by-visit interaction term will be removed if not significant). Of interest in the MMRM ANCOVA model is the difference between treatments on these endpoints across all post-baseline time points. Also, changes from baseline for each endpoint will be estimated and analyzed at each study visit using this MMRM model. Specifically, for each endpoint, treatment difference in least squares means will be estimated by visit from the model with the corresponding p-values and the two-sided 95% CIs of the difference between treatments.

Endpoints measuring proportions over time will be analyzed using generalized estimating equation logistic regression using similar independent variables as the MMRM ANCOVA models above (the treatment-by-visit interaction term will be removed if not significant), and using an unstructured correlation structure (or autoregressive(1) if the model with the

unstructured structure does not converge). Of interest is the difference between treatments across all post-baseline time points. Also, odds ratios will be estimated from the model with the corresponding p-values and their two-sided 95% CIs presented at each visit.

9.7 Analysis of Safety

Safety data include AEs, physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology, serum lipids, glycemic control parameters and urinalysis. Observed data will be summarized by treatment group as counts and percentages for discrete variables and means, standard deviations, medians, inter-quartile range, minimum, and maximum for continuous variables. All subjects who are randomized and receive at least one dose of double-blind study medication will be included in the safety analysis. All safety data will be presented in by-subject listings and included in the clinical trial report.

9.7.1 Adverse Events

AEs will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs that begin after the first administration of double-blind study medication or existing AEs that worsen after the first dose of double-blind study medication are considered treatment emergent AEs (TEAE). The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred term, then by severity, and by relationship to study treatment. Drug-related adverse events will be considered those to be at least possibly related to bexagliflozin administration based on the investigators assessment.

The number and percentage of subjects reporting serious AEs, and the number and percentage of subjects reporting AEs leading to treatment discontinuation will also be summarized for each treatment group by MedDRA system organ class and preferred term.

Adverse event listings will be provided for the following subsets:

1. TEAEs
2. All TEAEs at least possibly related to bexagliflozin
3. Serious AEs
4. AEs leading to treatment discontinuation
5. AEs leading to death

9.7.2 Adverse Events of Special Interest

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

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

9.7.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory metrics will be measured at the time points indicated in the Schedule of Events (Appendix 1). These measurements include vital signs, clinical laboratory (see Section 6 for a complete list) and ECGs. These data will be summarized as actual values and changes from baseline by treatment for each visit for selected parameters.

Laboratory data will be classified as low, normal or high relative to the parameter's reference range. Laboratory abnormalities for each treatment will also be summarized with shift tables for selected parameters.

All clinical laboratory, ECG and vital sign data will be listed.

9.7.4 Physical Examination

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

9.7.5 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 listed and flagged as prior in the listing. Only the concomitant medications will be summarized by ATC term and treatment.

9.8 Interim Analysis

No interim analysis will be performed during this study.

9.9 Final Analysis

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

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

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

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

10.3 Ethical Conduct of the Study

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor and investigator follow Good Clinical Practice 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 IRB/IEC, 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 maintained at the site. The informed consent form must contain all elements required by authorized regulatory authorities and the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (E6), in addition to any other elements required by local regulations or institutional policy.

Written informed consent must be obtained before any study-specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files. A copy of the signed informed consent form must be provided to the subject. If applicable, it will be provided in a certified translation in the language understood by the subject. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

If a protocol amendment is required, then the informed consent document may need to be revised to reflect the changes to the protocol. If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/Independent Ethics Committee (IEC), and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

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 CRF, in paper or electronic format, will be supplied and maintained by the CRO staff and signed by the investigator or authorized designee to indicate that he/she has reviewed and agrees with the entered data. This also applies to those subjects who fail to complete the trial. The reason a subject is withdrawn must be recorded in the 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 Monitoring Committee

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

10.9 Protocol Violations/Deviations

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

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

11 REFERENCE LIST

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Appendix 1 Schedule of Events

Procedure	Screen -ing	Washout		Run In		Treatment Period						Follow-Up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Time to Randomization Visit (weeks)	-11	-8	-6	-2	-0.5	0	2	6	12	18	24	26
Informed Consent	X											
Screening or Confirmation for I/E Criteria	X	X			X							
Medical History	X											
Diet and Exercise Counseling		X		X								
Physical Examination					X							X
Abbreviated Physical Examination	X										X	
Vital Signs	X				X			X	X	X	X	X
Electrocardiography	X				X						X	X
Hematology, Blood Chemistry, Serum Lipids, and Glycemic Control Assessments	X				X			X	X	X	X	X
Urinalysis	X				X			X	X	X	X	X
Diary and Glucometer Dispensation		X		X								
Dispensing Run-in Drug				X								
Diary and Glucometer Record Review			X	X	X	X	X	X	X	X	X	X
Dispensing Investigational Product						X			X			
Adverse Events & DKA Assessments		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessments		X	X	X	X	X	X	X	X	X	X	X

Appendix 2 Schedule of Laboratory Tests

Procedure	**Screening**	**Washout**		**Run-In**		**Treatment Period**						**Follow-up**
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Time to Randomization Visit (weeks)	-11	-8	-6	-2	-0.5	0	2	6	12	18	24	26
Hematology	X				X			X	X	X	X	X
Serum Chemistry and Electrolytes	X				X			X	X	X	X	X
Glycemic Control	X				X			X	X	X	X	X
Serum Lipids	X				X				X		X	X
Urinalysis	X				X			X	X	X	X	X
Infectious Disease Testing	X											
UACR	X				X						X	
Urine Pregnancy Test (all women)	X											
Urine Pregnancy Test (WOCBP)					X			X	X	X	X	X

Appendix 3 Sponsor Signatures

Study Title: A multi-center, randomized, double-blind, placebo-controlled, parallel group study to compare the efficacy and safety of bexagliflozin to placebo in subjects with type 2 diabetes mellitus and inadequate glycemic control

Study Number: THR-1442-C-450

Final Date: 04 April 2017

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

Signed: _____ Date: 4/19/17

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

Signed: _____ Date: 4/4/2017

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

Signed: _____ Date: 4 APRIL 2017

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

Appendix 4 Investigator's Signature

Study Title: A multi-center, randomized, double-blind, placebo-controlled, parallel group study to compare the efficacy and safety of bexagliflozin to placebo in subjects with type 2 diabetes mellitus and inadequate glycemic control

Study Number: THR-1442-C-450

Final Date: 04 April 2017

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

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

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

Signed:_____ Date:_____
Clinical Investigator