Clinical Trial Protocol: THR-1442-C-419

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Bexagliflozin in Subjects with Type 2 Diabetes Mellitus Who Are not Adequately Controlled by Metformin Alone
Study Number:	THR-1442-C-419
Study Phase:	3
Product Name:	Bexagliflozin Tablet
Indication:	Type 2 Diabetes Mellitus
Investigators:	Multicenter Study
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	Date
Protocol V1.0:	26 July 2017

Confidentiality Statement

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SYNOPSIS

Sponsor: Theracos Sub, LLC

Name of Finished Product: Bexagliflozin Tablet

Name of Active Ingredient: Bexagliflozin

Study Title:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Bexagliflozin in Subjects with Type 2 Diabetes Mellitus Who Are not Adequately Controlled by Metformin Alone

Study Number: THR-1442-C-419

Study Phase: 3

Primary Objective:
The primary objective of this study is to determine the effect of bexagliflozin on the placebo-corrected change in HbA1c from baseline to week 24 in adults with T2DM whose disease is inadequately controlled by metformin alone.

Secondary Objectives:

- To assess the effect of bexagliflozin on the change in FPG as a function of time
- To assess the effect of bexagliflozin on the change in SBP as a function of time
- To assess the effect of bexagliflozin on the proportion of subjects achieving HbA1c of ≤ 7% as a function of time
- To assess the change in total body weight as a function of time in subjects with baseline BMI ≥ 25 kg/m^2
- To assess the change in HbA1c as a function of time
- To assess the change in HbA1c as a function of time among subjects who have baseline HbA1c of > 10.5% and ≤ 12.0%

Study Design:
Study THR-1442-C-419 is designed to evaluate the safety and effectiveness of bexagliflozin tablets, 20 mg, for the treatment of T2DM in adult diabetics whose disease is inadequately controlled by metformin alone. The study will recruit 300 subjects with HbA1c between 7.5% and 10.5%, inclusive, to be randomized 1:1 to receive bexagliflozin tablets, 20 mg, or bexagliflozin tablets, placebo, in a double-blind treatment assignment. The primary endpoint of the study will be the placebo-corrected change from baseline to week 24 of the HbA1c percentage. This is the main study and the subjects are in the double-blind treatment group.

The study will also recruit 50 subjects with HbA1c > 10.5% and ≤ 12.0 % into an open-label arm, to receive bexagliflozin tablets, 20 mg, for 24 weeks. The endpoint for the open-label arm will be the change from baseline to week 24 of the HbA1c percentage. The subjects are in the high glycemic group.

All subjects are to have taken metformin at an optimal or near optimal stable dose for ≥ 8 weeks prior to screening and are to have received diet and exercise counseling.

Subjects who meet all the inclusion criteria, none of the exclusion criteria, and who have consented to participate in the study, are eligible for study enrollment. Subjects who successfully complete a 1-week run-in and who remain eligible will be randomized. Approximately 300 subjects with HbA1c values ≥ 7.5 and ≤ 10.5% at screening will be randomized 1:1 to receive bexagliflozin tablets, 20 mg or placebo, in addition to their customary metformin dosage for 24 weeks in an outpatient setting. Study subjects will not change their metformin dosage unless adjustment is medically necessary to manage hypoglycemia. The treatment period will last 24 weeks. Subjects will visit their study sites at weeks 6, 12, 18, and 24 for safety and efficacy evaluation, and at week 26 for a follow-up evaluation.

Up to 50 subjects who have HbA1c > 10.5% and ≤ 12.0% at screening will be assigned to open label treatment group to receive bexagliflozin tablets, 20 mg, in addition to their existing metformin regimen. There will be no placebo arm for the high glycemic group. Subjects enrolled in the open label treatment group will be asked to follow the same procedures as subjects enrolled in the blinded arms of the study.

Subjects with persistent hyperglycemia based on blood glucose levels may receive approved antidiabetic rescue medications.

A sparse sampling assessment of bexagliflozin pharmacokinetics (PK) in the study population will also be performed. A net enrollment of approximately 200 subjects is planned for this aspect of the study. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

Study Population:

Approximately 350 subjects with T2DM will be enrolled in the study. The subjects must:

1. have an age of ≥ 20 years at screening. Women of childbearing potential must test negative for pregnancy and agree to abstinence or contraception for the duration of the study to avoid any possible pregnancy. Females who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months) are eligible if they test negative for pregnancy at screening.
2. a) have a history of T2DM with an HbA1c level of ≥ 7.5% and ≤ 10.5% at screening, or b) have a history of T2DM with an HbA1c level of >10.5% and ≤ 12.0% at screening
3. have been prescribed a stable dose of metformin (≥ 1500 mg per day in the US or ≥ 1000 mg per day in Japan) as their sole anti-diabetic medication
4. have a body mass index (BMI) ≤ 45 kg/m^2
5. be able to comprehend and willing to provide written informed consent in accordance with institutional and regulatory guidelines
6. not have recently changed their medications for hypertension or hyperlipidemia (if applicable)
7. be able to regularly self-administer medication, as evidenced by consumption of all, or at worst one less than all, doses of run-in medication prior to randomization (at visit 3)

Test Product, Dose, and Mode of Administration:

Bexagliflozin tablets, 20 mg or placebo, once daily oral administration in 300 subjects

Bexagliflozin tablets, 20 mg once daily oral administration in 50 subjects

Duration of Treatment:

One week of run-in placebo treatment and 24 weeks of investigational product treatment

Efficacy Assessments:

The primary efficacy assessment is:

- The effect of bexagliflozin on the placebo-corrected change in HbA1c from baseline to week 24 in adults with T2DM whose disease is inadequately controlled by metformin alone.

The key secondary efficacy assessments are:

- To assess the effect of bexagliflozin on the change in FPG as a function of time
- To assess the effect of bexagliflozin on the change in SBP as a function of time
- To assess the effect of bexagliflozin on the change in HbA1c as a function of time
- To assess the effect of bexagliflozin on the change in total body weight as a function of time in subjects with baseline BMI ≥ 25 kg/m^2
- To assess the effect of bexagliflozin on the proportion of subjects achieving an HbA1c $\leq 7.0\%$ over time
- To assess the change in HbA1c as a function of time among subjects who have baseline HbA1c level of $\geq 7.5\%$ and $\leq 10.5\%$
- To measure the change from baseline to week 24 in subjects with baseline HbA1c level of $> 10.5\%$ and $\leq 12.0\%$

Other assessment:

Evaluation of bexagliflozin pharmacokinetics

Safety Assessments:

Adverse events record, laboratory data including hematology, serum chemistry, urinalysis, ECG, vital signs, physical examinations, and concomitant medication use.

Statistical Methods:

Summaries will be presented for double-blinded portion of the study, separately from the 50 subject open-label sub-study. No formal hypothesis testing will be performed for the sub-study.

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.

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 the intention-to-treat (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 the baseline HbA1c value, country (US or Japan) as fixed effect covariates. 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% CIs 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 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 analysis steps will be performed on the ITT analysis set:

- 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.
- HbA1c values collected after the start of rescue medication will be excluded (considered missing), and the MMRM analyses will be re-performed.
- A last observation carried forward (LOCF) method will be used to impute the missing observations prior to carrying out the MMRM model.

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

Safety data will include AE descriptions, physical exam results, vital sign measurements, ECG results, and clinical lab results from analysis of 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.

The sample size calculation for this study is based on two group t-test with a two-sided significance of 0.05 level. The assumptions that led to the estimated required sample size of 150 per group with 1:1 ratio for a power of 90% are as follows:

- A treatment effect of 0.4%.
- A population HbA1c standard deviation of 1%.
- A two-sided significance level of 0.05.
- A drop-out rate of 12%.

Date of Protocol V1.0: 26 July 2017

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
MI	myocardial infarction
MMRM	mixed model repeated measures
MODY	maturity–onset diabetes of the young
N	number of subjects
OHA	oral hypoglycemic agent
PP	per protocol
PR	time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
QRS	QRS complex the combination of three of the graphical deflections seen on a typical electrocardiogram
QT	a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RBC	red blood cell (count)
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium glucose cotransporter 2
SMBG	self-monitored blood glucose
SOP	standard operating procedure
SU	sulfonylurea
SUSAR	serious and unexpected suspected adverse event
TIA	transient ischemic attack
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TEAE	treatment emergent adverse event
TG	triglycerides
TZD	thiazolidinedione
UACR	urine albumin to creatinine ratio
UADR	unexpected adverse drug reaction
UGE	urinary glucose excretion
ULN	upper limit of normal
UPT	urinary pregnancy test
UTI	urinary tract infection
WBC	white blood cell (count)
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

1 INTRODUCTION

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

1.1 Type 2 Diabetes Mellitus

T2DM is the predominant form of diabetes and accounts for at least 90% of all diabetes cases. T2DM 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 acceleration of cardiovascular disease. Diabetes is the leading cause in the developed world of blindness, amputation and dialysis. .

T2DM is a disease strongly linked to increased body fat mass(Schwartz et al., 2012). Weight loss has been shown to improve glycemic control and to reduce the severity of diabetes-associated comorbidities, supporting the view that anti-diabetic agents that promote weight loss may be particularly beneficial for the treatment of the disease (Look et al., 2013; Scheen and Van Gaal, 2014)Scheen2014. Several classes of agents are available for treating T2DM, including insulin, insulin secretagogues, (such as sulfonylureas (SU) and meglitinides), PPARγ agonists, biguanides, alpha glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP4) inhibitors, and sodium glucose linked transporter 2 inhibitors (SGLT2i).

Metformin is often prescribed for the initial management of T2DM. However the disease typically progresses and additional agents must be prescribed to maintain adequate glycemic control.

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

The renal Na+/glucose transport protein SGLT2 actively transports extracellular glucose into cells using the driving energy of the transmembrane electrochemical potential for sodium ions. Individuals with disruptions in *SLC5A2*, the gene encoding SGLT2, exhibit prominent glucosuria in the absence of significant co-morbidities(Santer et al., 2003; van den Heuvel et al., 2002). The excretion of glucose in the urine of diabetic subjects in amounts comparable to or greater than that seen in individuals harboring loss of function mutations in *SLC5A2* has the potential to improve fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia. Several SGLT2 inhibitors have

demonstrated these clinical benefits, as well as sustained weight loss, when used as a monotherapy or in combination with other oral anti-diabetic medications including insulin (Nauck, 2014; Seufert, 2015).

1.2 Bexagliflozin for the Treatment of Type 2 Diabetes Mellitus

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

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the placebo-corrected change in HbA1c from baseline to week 24 in adults with T2DM whose disease is inadequately controlled by metformin alone.

2.2 Secondary Objectives

- To assess the effect of bexagliflozin on the change in FPG as a function of time
- To assess the effect of bexagliflozin on the change in SBP as a function of time
- To assess the effect of bexagliflozin on the proportion of subjects achieving HbA1c of ≤ 7% as a function of time
- To assess the change in total body weight as a function of time in subjects with baseline BMI ≥25 kg/m^2
- To assess the change in HbA1c as a function of time
- To assess the change in HbA1c as a function of time among subjects who have baseline HbA1c of > 10.5% and ≤ 12.0%

2.3 Safety Objectives

The safety objectives of the study are:

- To determine the frequency and severity of treatment emergent adverse events
- To determine the frequency and severity of treatment emergent adverse events of interest
- To record and evaluate changes in concomitant medication use that may affect subject safety
- To evaluate any potentially adverse changes in laboratory test values
- To assess changes in cardiac rhythm through 12-lead ECG
- To evaluate vital signs
- To assess general health by physical examination

2.4 Other Objectives:

The other objective is:

- To measure bexagliflozin plasma concentrations as a function of time from dosing (sparsely sampled)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

THR-1442-C-419 is a phase 3, multi-center study in which 300 subjects will participate in a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of orally administered bexagliflozin tablets, 20 mg or placebo, in subjects whose T2DM is not adequately controlled by metformin along with diet and exercise. The primary endpoint is the placebo corrected change in HbA1c from baseline at week 24 in subjects whose HbA1c values are ≥ 7.5% and ≤ 10.5% at screening. This is the main study and the subjects are in the double-blind treatment group. In addition, 50 subjects who have baseline HbA1c values > 10.5% and ≤ 12.0% will participate in an open labelled, uncontrolled sub-study to assess bexagliflozin effects on glycemic control. The subjects are in the high glycemic group.

All subjects must have taken metformin at an optimal or near-optimal stable dose for ≥ 8 weeks prior to screening and have received diet and exercise counseling.

Approximately 350 subjects who meet all the inclusion criteria, none of the exclusion criteria, and who consent to participate in the study, are eligible for study enrollment. Approximately 300 subjects with HbA1c values ≥ 7.5% and ≤ 10.5% at screening (the double-blind treatment group) who successfully complete a 1-week run-in and who remain eligible will be randomized in a 1:1 ratio to receive once daily double-blind treatment of bexagliflozin tablets, 20 mg or placebo. Study subjects will continue receiving open-labeled metformin background medication during the entire study at a stable dose and frequency. The treatment period will last 24 weeks. The study will be conducted in an outpatient setting. Study subjects will have clinic visits at weeks 6, 12, 18, and 24 for safety and efficacy evaluation. A final follow up visit will be conducted at week 26.

Up to 50 subjects who have HbA1c > 10.5% and ≤ 12.0% at screening will be assigned to the high glycemic group to receive open labeled bexagliflozin tablets, 20 mg, in addition to metformin. There will be no placebo control cohort for the high glycemic group. Subjects assigned to the high glycemic group will be asked to follow the same study procedures as subjects assigned to the two study arms.

Subjects with persistent hyperglycemia based on blood glucose levels may receive approved antidiabetic rescue medications.

A sparse sampling assessment of bexagliflozin pharmacokinetics (PK) in the study population will also be performed. A net enrollment of approximately 200 subjects is planned for this aspect of the study. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

3.2 Research Methods and Procedures

3.2.1 Run-in Period

All subjects who are eligible at the screening visit will begin a one-week run-in period. At the start of the run-in period, subjects will receive diet and exercise counseling as well as instructions to contact the clinic in the event of hyperglycemia, hypoglycemia, or symptoms that may suggest ketoacidosis. At the start of the run-in period, subjects will be provided with a glucometer and instructions for its daily use. During the run-in period, subjects will be asked to self-administer placebo tablets. The tablets are to be taken with water at the same time every day. The metformin dose and frequency are expected to remain unchanged from the time of screening through the end of the study.

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

1. omit more than 1 day of run-in medication, or
2. are deemed inappropriate for the study by the investigator,

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

Changes in the doses of medications used to treat dyslipidemia or hypertension will not be permitted during the screening and run-in periods. Management of concomitant medications is described in Section 5.6.

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

3.2.2 Treatment Period

The double-blind treatment period will start at randomization and end after 24 weeks of treatment. Approximately 300 subjects with $7.5\% \leq \text{HbA1c} \leq 10.5\%$ will be randomized in a 1:1 ratio to the active or placebo arms.

Randomization will be stratified by HbA1c ($\leq 8.5\%$ or $> 8.5\%$) and country (US or Japan) at screening (Visit 1). At the start of the treatment period, each subject will be provided with bexagliflozin or placebo tablets and dosing instructions. Symptoms and blood glucose measurements related to the occurrence of hyperglycemia, hypoglycemic events, or symptoms that may suggest ketoacidosis will be recorded. Bexagliflozin tablets, 20 mg or placebo, will be taken once daily at approximately the same time each day either before or after breakfast with approximately one cup (250 mL) of water. Metformin shall be taken at the same dose and frequency throughout the study.

Each subject will be instructed to return to the clinic at weeks 6, 12, 18 and 24 for efficacy assessment and safety monitoring, including review of AEs and concomitant medications,

measurements of vital signs and ECG, physical examination, and blood and urine specimen collections. On the day of a clinic visit at which blood samples are scheduled to be collected, a fast of approximately 8 hours (h) duration must be confirmed prior to blood draw. On the day of the scheduled clinic visits, administration of study drug shall be withheld until after blood is drawn and taken with water at the clinic.

Up to 50 subjects in the high glycemic group will follow the same study procedures as the randomized subjects.

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

3.2.3 Glycemic Control Monitoring

3.2.3.1 Placebo Run-in Period

During the placebo run-in period, subjects will be instructed to determine self-monitored blood glucose (SMBG) daily after fasting overnight for approximately 8 h. Subjects in the double-blind treatment group should contact the clinic if any fasting glucose value is ≥ 250 mg/dL (13.9 mmol/L). Subjects in the high glycemic group should contact the clinic if any fasting glucose value is ≥ 300 mg/dL (16.7 mmol/L). 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.

Subjects with clinical signs or symptoms of severe hyperglycemia during the run-in period, including weight loss, blurred vision, increased thirst, increased urination, or fatigue, should also be excluded.

3.2.3.2 Treatment Period

During the treatment period, subjects will be advised to continue daily, fasting SMBG measurements. Subjects should contact the clinic if fasting SMBG is ≥ 270 mg/dL (15 mmol/L) from week 0 to week 6 if in the double-blind treatment group or ≥ 300 mg/dL (16.7 mmol/L) if in the high glycemic group, ≥ 240 mg/dL (13.3 mmol/L) after week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) after week 12. Blood glucose values collected via SMBG will be evaluated at study visits by the investigator. In addition, hyperglycemia will be monitored by measurement of FPG at scheduled visits.

If hyperglycemia is identified through SMBG or FPG measurements, the investigator will determine whether the subject has fasted for approximately 8 h prior to the morning blood draw to ensure that the SMBG or FPG value is based on a fasting sample. If proper fasting has not occurred, the subject will be asked to return for a repeat blood test within a week.

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

3.2.3.3 Rescue Medication

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

1. More than 3 consecutive, daily, fasting SMBG measures are ≥ 270 mg/dL (15 mmol/L) from baseline to week 6 if in the double-blind treatment group or ≥ 300 mg/dL (16.7 mmol/L) if in the high glycemic group, ≥ 240 mg/dL (13.3 mmol/L) from week 6 to week 12, or ≥ 200 mg/dL (11.1 mmol/L) or HbA1c > 8.0% from week 12 to week 24
2. Fasting SMBG values are ≥ 250 mg/dL (13.9 mmol/L) and associated with clinical signs or symptoms of hyperglycemia (e.g., weight loss, blurred vision, increased thirst, increased urination, or fatigue), and the signs or symptoms are severe.

If a rescue medication for hyperglycemia is to be prescribed, a blood sample must be drawn prior to the administration of the rescue medication so that a final HbA1c value can be ascribed to the latest date upon which the subject's glycemic control will not be impacted by the rescue medication.

The investigator may provide rescue treatment with any approved medication for diabetes that is not otherwise contraindicated. Other SGLT2 inhibitors (Appendix 3) may not be prescribed.

If hypoglycemia occurs in any subject who has been prescribed rescue medication for hyperglycemia during the study, the total daily dose of the rescue medication should be reduced 50% or more at the discretion of the investigator. If recurrent symptomatic hypoglycemia occurs after discontinuation of administration of the rescue medication, the study drug administration can be discontinued at the discretion of the investigator.

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

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

3.2.4 Other Safety Monitoring Activities

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

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

- Acid-base disorders including diabetic ketoacidosis (DKA)
- Amputations
- Diuretic effects including hypovolemia
- Falls and fractures
- Genital mycotic infections (GMI)
- Hepatotoxicity
- Hypersensitivity reactions
- Hypoglycemia
- Hypotension episodes
- Major adverse cardiovascular events (MACE)
- Malignancies
- Renal failure events
- Urinary tract infections including urosepsis and pyelonephritis

3.2.5 Data and Safety Monitoring Board (DSMB)

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

3.2.6 Major Adverse Cardiovascular Event (MACE) Adjudication

An independent cardiovascular 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 (MI), stroke, hospitalization for acute coronary syndromes, urgent revascularization procedures, and other possible serious cardiovascular events. The adjudicated events will be documented and archived to allow a meta-analysis to be performed at a later time. No separate cardiovascular risk assessment will be performed based on events in the study population of the current protocol.

3.2.7 Diabetic Ketoacidosis (DKA) Event Adjudication

An independent adjudicator will review all potential DKA events without unblinding the subject treatment. The adjudicated events will be documented and archived. All adjudicated DKA events in the bexagliflozin phase 3 program will be pooled at the end of the program and a final analysis will be conducted.

3.3 Rationale for Study Design and Control Group

3.3.1 Rationale for Study Design

THR-1442-C-419 is designed to assess the effect of the addition of bexagliflozin or placebo to an existing dose of metformin in subjects inadequately controlled by metformin alone. The metformin dosage should not have changed within the 8 weeks prior to screening. The dose of metformin should remain unchanged throughout the treatment period.

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

The HbA1c percentage reflects average plasma glucose concentration and is considered a well-validated surrogate for the degree of diabetes control.

3.3.2 Rationale for Background Medication

Metformin is the most commonly prescribed OHA and is often recommended as a first-line therapy for the treatment of T2DM. It is a biguanide that decreases hepatic glucose production and may improve peripheral glucose uptake and utilization. The mechanism of action of metformin is not believed to overlap with that of bexagliflozin, and hence the addition of bexagliflozin to metformin monotherapy is likely to produce improvement in glycemic control. Metformin prescribing practices vary by country. In the US a maximum dose of 1500 mg per day is typical, whereas in Japan a maximum dose of 1000 mg per day is typical.

3.3.3 Rationale for Dose Selection

In a 12 week monotherapy study, bexagliflozin tablets, 20 mg, elicited a greater placebo-adjusted HbA1c reduction (-0.80%) than bexagliflozin tablets, 10 mg (-0.68%), or bexagliflozin tablets, 5 mg (-0.55%). Bexagliflozin administration has been well tolerated in multiple studies. The safety and efficacy of bexagliflozin capsules, 20 mg, for the treatment of T2DM have been demonstrated in a 96-week study that measured reduction in HbA1c at week 24 as the primary endpoint.

3.4 Study Duration and Dates

Subjects will be enrolled within 2 weeks of screening. Eligible subjects who provide written consent will start a run-in period of 1 week prior to randomization to demonstrate

compliance. Subjects who successfully complete the run-in will begin 24 weeks of treatment and will be followed for 2 weeks after the last dosing. The study duration from screening to follow-up will be no more than 29 weeks overall. For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1 and Appendix 2.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 350 subjects whose T2DM is inadequately controlled by metformin and who meet all of the inclusion criteria and none of the exclusion criteria. Eligible subjects who consent to participate in the study will be enrolled in clinical investigational sites. Study subjects will be informed of the purpose of the study, the potential risks of participation, and will be requested to consent to the procedures and blood collection.

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

Clinical sites in the US and Japan are anticipated to recruit subjects.

4.2 Inclusion Criteria

Approximately 350 subjects with T2DM will be enrolled in the study. The subjects must:

1. have age ≥ 20 years at screening. Women of childbearing potential must test negative for pregnancy and agree to abstinence or contraception for the duration of the study to avoid any possible pregnancy. Females who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months) are eligible if they test negative for pregnancy at screening.
2. a) have a history of T2DM with an HbA1c level of ≥ 7.5% and ≤ 10.5% at screening, or b) have a history of T2DM with an HbA1c level of >10.5% and ≤ 12.0% at screening
3. have been prescribed a stable dose of metformin (≥1500 mg per day in the US or ≥ 1000 mg per day in Japan) as their sole anti-diabetic medication
4. have a body mass index (BMI) ≤ 45 kg/m^2
5. be able to comprehend and willing to provide written informed consent in accordance with institutional and regulatory guidelines
6. not have recently changed their medications for hypertension or hyperlipidemia (if applicable)
7. be able to regularly self-administer medication, as evidenced by consumption of all, or at worst one less than all, doses of run-in medication prior to randomization (at visit 3)

4.3 Exclusion Criteria

Subjects who meet any of the following criteria are to be excluded from the study:

1. Having a diagnosis of type 1 diabetes mellitus or maturity–onset diabetes of the young
2. Pregnant or breastfeeding

3. Having one or more hemoglobin alleles that affect HbA1c measurement
4. Having a history of genitourinary tract infection (e.g., UTI, GMI, vaginitis, balanitis) within 6 weeks of screening or a history of ≥3 genitourinary infections requiring treatment within 6 months of screening
5. Having an 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
6. Having a sitting systolic blood pressure >180 mmHg or a sitting diastolic blood pressure > 110 mmHg at screening
7. Subject is taking any hypoglycemic agent(s) other than metformin during the 8 weeks prior to screening
8. Having a history of illicit drug use or alcohol abuse in the past 2 years
9. Having a life expectancy < 2 years
10. Having received a diagnosis of New York Heart Association (NYHA) Class IV heart failure within 3 months of screening
11. Having experienced an MI, unstable angina, stroke, or hospitalization for heart failure within 3 months of screening
12. Having been exposed to an investigational drug within 30 days
13. Having previously received bexagliflozin or EGT0001474
14. Having a history of SGLT2 inhibitor treatment
15. Currently participating in another interventional trial
16. Not able to comply with the study scheduled visits
17. Having 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
18. Having an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 × ULN or total bilirubin ≥ 1.5 × ULN 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

5.2.1 Investigational Product

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

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

5.2.2 Background Metformin Therapy

The metformin dose should reflect the prevailing standard of care. In the United States, metformin ≥ 1500 mg/day is recommended (Garber et al., 1997). In Japan, metformin ≥ 1000 mg/day is recommended (Suzuki et al., 2014).

The dose, frequency, and time of administration should remain stable unless the investigator deems a decrease in the daily dose necessary for the medical well-being of the subject.

5.3 Selection and Timing of Dose for Each Subject

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

On the day of each scheduled clinic visit, subjects must fast for 8 h 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, meet all study inclusion/exclusion requirements, and have HbA1c ≥ 7.5% and ≤ 10.5% at screening will be randomized in a 1:1 ratio to receive bexagliflozin tablets, 20 mg or 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 by high (8.5% ≤ HbA1c ≤ 10.5%) and low (7.5% ≤ HbA1c < 8.5%) baseline measurement at screening (Visit V1) and by country (US or Japan). Eligible subjects who have HbA1c > 10.5% and ≤ 12.0% at screening will be assigned to the open label treatment group.

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 30 randomized subjects. However, after a site has recruited 30 randomized subjects, if a potential subject at that site is in the run-in phase and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized.

5.5 Blinding

Approximately 300 subjects will participate in the double-blind placebo-controlled portion of the trial. The sponsor, investigators, study coordinators, pharmacists, study subjects, the CEC members or DKA adjudicator will be blinded to the study medication of these participants. Upon randomization, each subject will receive a subject randomization number and a drug kit. 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 a subject's condition, the investigator will contact the IWRS to obtain the treatment assignment. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded 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 or the DKA event adjudicator at the conclusion of the study until all global investigational studies are completed and a meta-analysis to assess cardiovascular risk is conducted.

Subjects in the high glycemic group (*i.e.,* > 10.5% and ≤ 12.0% at screening) will receive open labeled study drug. There will be no placebo cohort for the high glycemic group.

5.6 Concomitant Therapy

During the course of the study, investigators will manage glucose, BP, and lipid levels according to local or regional standard of care guidance documents for the management of T2DM. Instructions for rescue medication for hyperglycemia are provided in Section 3.2.3.3. Subjects will be allowed to take medications or medicinal supplements prescribed to manage non-diabetic medical conditions during the study. Any concurrent medication or supplemental treatment of other non-diabetes medical conditions should be continued at a stable dose and frequency for the entire study duration unless there is a clinical reason to change the dose or frequency.

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

5.6.1 Diuretics and Medications for Treatment of Dyslipidemia and Hypertension

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

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

5.7 Restrictions

5.7.1 Prior Therapy

All subjects will continue regimens for medical conditions other than diabetes during the study as indicated above. No subject shall have been treated with an investigational drug within 30 days of screening. No subject shall have been treated with an SGLT2 inhibitor within 3 months of screening. Subjects taking any hypoglycemic agents other than metformin during the 8 weeks prior to screening are not eligible for this study. During the treatment period, metformin dose may not be up-titrated.

5.7.2 Fluid and Food Intake

During the study, subjects will be counseled to remain adequately hydrated at all times. In addition, subjects will receive counseling regarding an appropriate diet to achieve glycemic

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

Subjects will fast for approximately 8 h prior to the scheduled blood sample draws. During fasting, only water will be permitted.

5.7.3 Subject Activity Restrictions

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

5.8 Treatment Compliance

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

At each visit after the start of the run-in period, the study staff will review the SMBG diary and medications history 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 sealed with a child-resistant cap. Bottles of 15 placebo tablets will be provided for the 1-week run-in portion of the study. All investigational product supplies will be prepared and labeled according to the requirements of local laws and regulations and will be kept in a secure storage facility at below 30°C (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 V3) and a new investigational product kit at 12 weeks (Visit V5). 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 3 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.

BLINDED INVESTIGATIONAL PRODUCT KIT

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

The label attached to each blinded 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.

OPEN LABEL INVESTIGATIONAL PRODUCT KIT

One open label investigational product kit contains a bottle of 90 bexagliflozin tablets, 20 mg.

The label attached to each blinded investigational product kit will contain the following information: the kit number, protocol number, product identification, 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 and placebo tablets will be stored below 30°C (86°F). The sponsor will notify the sites of the process for returning unused drug.

Metformin tablets will be stored as specified in the prescribing information.

5.11 Investigational Product Retention at Study Site

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

6 STUDY PROCEDURES

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

For the purposes of this protocol, except as specifically noted, "Investigator" refers to the Principal Investigator or his/her staff who have been appropriately delegated to perform a study task.

6.1 Informed Consent

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

The informed consent document must be signed and dated by the study subject. One copy will be given to the subject, 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 study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

6.2 Screening for I/E Criteria

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

6.3 Medical History

The following information will be collected at the screening visit:

6.3.1 General Demographics and Characteristics

- Date of birth, age, sex, and race, and whether a female subject is of childbearing potential or not

- Significant medical and surgical history, including dates of diagnoses, procedures and whether the condition is ongoing, if applicable

6.3.2 Diabetes History

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

6.3.3 Cardiovascular Disease History

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

6.3.4 Medication History

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

6.4 Diet and Exercise Counseling

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

6.5 Physical Examination

A complete physical examination will be performed by the investigator at the time points indicated in the Schedule of Events (Appendix 1). The examination will include measurement of body weight and a general assessment of all body systems, including the skin, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, vascular system and extremities. The body weight must be determined using a scale that is calibrated. The same scale should be used for the duration of the study if possible.

6.6 Abbreviated Physical Examination

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

6.7 Vital Signs

Vital signs will be measured at the visits indicated in the Schedule of Events (Appendix 1) and will include sitting, supine, and standing BP measurements, and heart rate. Only the BP measured in the sitting position will be used to determine eligibility. The vital signs shall be obtained before the scheduled blood draw.

BP shall be measured using an appropriately sized cuff (cuff bladder encircling at least 80% of the arm) that is applied on the upper arm at heart level. The left arm and same cuff size 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 shall be obtained using a calibrated sphygmomanometer while the subject is in sitting, supine, and standing (if subject is physically able to stand) positions. Prior to measuring sitting BP, the subject should be seated quietly in a chair, not an examination table, for at least 5 minutes with feet on the floor and arm supported at heart level.

A single heart rate measurement shall be taken just prior to the BP evaluation in the sitting, supine, and standing positions. Blood pressure must be taken twice with at least 2 minutes apart with the cuff fully deflated between each reading. If any of the two SBP measurements differ by more than 8 mm Hg or if any of the two DBP measurements differ by more than 5 mm Hg, a second set of 2 BP measurements should be obtained. The second set of readings should be entered into the CRF. Original and repeat readings must all be recorded in the source documents with an explanation. The average of the 2 serial blood pressure measurements will be used for the efficacy analyses.

BP will be assessed first in the sitting position. 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. The subject will lie flat for 5 min and have heart rate and supine blood pressure measured using the same equipment and arm as described for sitting BP. Once the supine BP measurement is complete, the subject will stand. Standing BP and heart rate will be measured after 2 min of standing. For standing BP measurements, the arm should be supported and extended such that the cuff is at heart level. The procedure for vital sign measurement is shown in Figure 1.

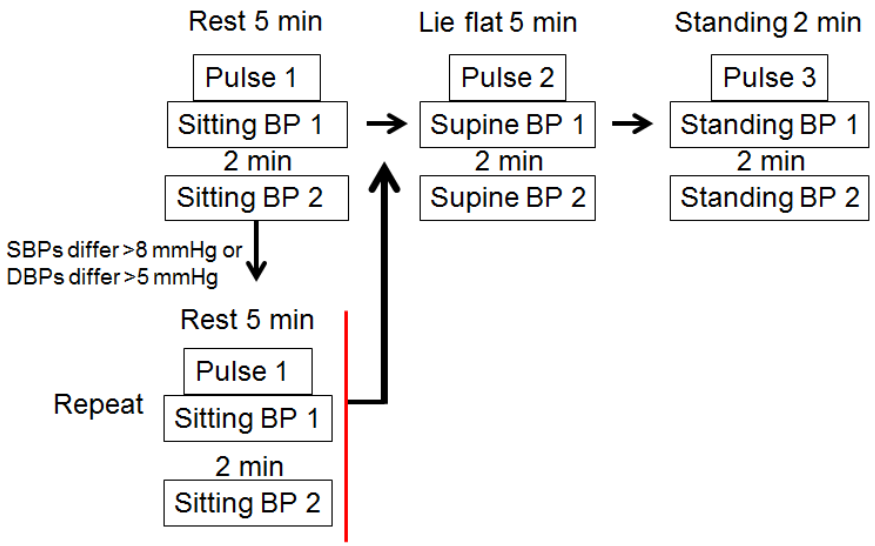

Figure 1. BP Measurement Procedure

The date, time, and all readings are to be entered into the source document and CRF for all subjects.

6.8 Electrocardiography

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

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

6.9 Clinical Laboratory Tests

6.9.1 Laboratory Parameters

Clinical laboratory tests are listed in Table 1.

Table 1. List of Laboratory Tests

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

6.9.2 Sample Collection, Storage, and Shipping

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

The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of proper fasting practice. A subject must be queried to assess compliance with an approximately 8 h fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for approximately 8 h, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting.

Low density lipoprotein cholesterol (LDL-C) will be calculated by the Friedewald equation. If triglycerides are > 400 mg/dL (4.5 mmol/L), 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 (4.0 mmol/L) at screening visit. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only.

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

6.9.3 Urinalysis

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

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

Urine samples will be transported to the central laboratory for urinalysis. Microscopy will be conducted if the subject has a positive result on the leukocyte esterase or nitrite dipstick tests to clarify the significance of the finding. Results of glucose measurement in the urinalysis must be suppressed from the laboratory reports so the sponsor, investigators, study coordinators, pharmacists, study subjects, and the CEC members will remain blinded to the dosing assignment.

Urine pregnancy tests (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.

6.9.4 Population PK Sampling

Blood samples for the population PK analysis will be drawn when the subjects return to the clinic during week 6 (V4) and/or week 12 (V5) from 200 subjects who consent to participating in the PK study in selected trial centers. One blood sample will be drawn at each of the 3 timepoints from each subject for a total of 3 post-dose samples per subject. Approximately 100 subjects will be sampled at 0.25 to1 h, 7 to 10 h, and 20 to 24 h post dose (routine 1). Another 100 subjects will be sampled at 1.5 to 3 h, 3.5 to 6.5 h and 7 to 10 h post-dose (routine 2). The sampling time should take into consideration the study subject availability and can be on any of the days during the week of the specified clinical visits. The precise dosing time and sample draw time must be recorded in the CRF. Subjects in double blind or open labelled study may participate in the PK study.

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

Plasma concentrations of bexagliflozin will be determined by a validated LC-MS/MS method.

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 the run-in period for SMBG. Subjects will be trained to use the glucometer and record any hypoglycemic events in the glycemic control diary. The SMBG record from the glucometer and diary entries must be reviewed by the investigator (or designee) at all subsequent visits.

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

6.11 Dispensing Run-in Drug

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

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

6.12 Diary and Glucometer Record Review

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

6.13 Dispensing Investigational Product

At randomization and at every 12 weeks of treatment thereafter, each study subject will receive a bottle of investigational product based on the kit number assigned to the subject by the IWRS. The bottle will contain bexagliflozin tablets, 20 mg or placebo. The bottle provides sufficient tablets for daily dosing for 12 weeks with a 6 tablet overage.

Subjects should self-administer the investigational product with one cup (250 mL) of water under observation during the scheduled visits.

6.14 Adverse Events Assessments

6.14.1 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.

6.14.2 Eliciting and Reporting AEs

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

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

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

6.14.3 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 administration (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.

6.14.4 Pregnancy

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

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

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

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

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

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

The investigator must record the event on the Pregnancy Surveillance Form and forward it to sponsor’s Medical Monitor.

Protocol required procedures for discontinuation of dosing 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.

6.14.5 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 the breaking of 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.

6.14.6 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.

6.14.7 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 6.14.2. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved.

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the sponsor or designated personnel. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined study period. 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.

6.14.8 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 shall be obtained at all clinical visits and a urinalysis shall 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 shall 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.

6.14.9 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.

6.14.10 Hepatotoxicity

If plasma AST and/or ALT concentrations > 3 × ULN are detected, the investigator will record in the source documents:

- the date corresponding to the date of the laboratory abnormality
- the type, frequency, and dose of any concurrent medications or supplements taken by the subject within the 14 days of the detected abnormality
- any symptoms or change in physical exam that have occurred since the prior assessment

The investigator should perform additional laboratory and imaging tests to attempt to establish the cause of the AST and ALT elevations, including ruling out any potential contribution from bone or muscle etiologies.

Any clinically significant increase in hepatic enzymes and specifically any ALT or AST > 3 × ULN requires immediate repeat test within 48 to 72 hours to confirm the hepatic enzyme elevation. Testing should be repeated based on the clinical situation at least every 96 hours (4 days) until ALT and AST return to < 2.5 × ULN or until the liver function test results are stable and significant changes are not expected anymore. Study medication should be stopped and the event should be reported as a laboratory AE within the CRF if the enzyme elevation is confirmed or worsening.

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

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

- ALT or AST > 8 × ULN
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5
- ALT or AST > 3 × 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, administration of 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.

6.14.11 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:

- Signs and symptoms attributed to hypoglycemia and the time and date on which they occurred
- SMBG reading at the time of the signs and symptoms attributed to hypoglycemia
- Time elapsed from the most recent meal to the onset of signs and symptoms
- Duration, intensity, and type of any exercise within the 24 h prior to the signs and symptoms
- Type of treatment used (e.g., juice, crackers) for the signs and symptoms and whether assistance was required from another person to administer the treatment
- SMBG reading 15 minutes after treatment with carbohydrate and the time at which this was measured
- Whether or not the signs and symptoms attributed to hypoglycemia resolved after blood glucose returned to normal

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

At each study visit, the investigator is expected to review the glucometer and glycemic control diary with particular attention to any SMBG value < 70 mg/dL (3.9 mmol/L) 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 (3.9 mmol/L) 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 and documented symptomatic 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.

6.14.12 Major Adverse Cardiovascular Event (MACE)

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

The independent CEC will review 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

6.14.13 Diabetic Ketoacidosis (DKA)

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

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

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

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

6.14.14 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. Subjects who have had a previous amputation should be closely monitored. Special attention may be appropriate for subjects who are also receiving thiazide diuretics as these have been shown to increase the risk of amputation in diabetics.

6.15 Concomitant Medication Assessments

A concomitant medication is any medication that the subject has been taking prior to enrollment and that the subject is expected to continue to take for some portion of the trial, as well as any medication other than the investigational product that the subject takes during the course of the trial. Changes in dose and/or frequency from therapies taken prior to randomization and their rationale must be recorded in the CRF.

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

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

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A table of concomitant medications based on the anatomic therapeutic chemical classification (ATC) and preferred name will be produced. A listing of

concomitant medications will include all medications taken by any subjects during the course of the study.

6.16 Removal of Subjects from the Trial or Treatment Discontinuation

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

The investigator may withdraw a subject from the study for any of the following reasons:

- A protocol violation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,
- The sponsor or investigator terminates the study, or
- The subject requests to withdraw from the study.

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

6.17 Appropriateness of Measurements

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

7 STUDY ACTIVITIES

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

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

7.1 Visit 1/ Screening (up to 3 weeks prior to randomization)

- Explain the content of the informed consent materials to the subject and collect signed informed consent
- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Obtain Medical History and Demographic Information
- Perform an abbreviated physical examination
- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2.

7.2 Visit 2/ Run In (1 week prior to randomization)

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

7.3 Visit 3/ Randomization

- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Perform a complete physical examination
- Measure vital signs, including blood pressures and heart rate
- Perform urine pregnancy test (WOCBP only)
- Perform a 12-lead ECG measurement
- Review SMBG and glycemic control record
- Dispense investigational product based on randomization
- Assess adverse events
- Record concomitant medications

7.4 Visit 4/ 6 Weeks

- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Perform urine pregnancy test (WOCBP only)
- Review SMBG and glycemic control record
- Assess adverse events
- Record concomitant medications

7.5 Visit 5/ 12 Weeks

- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Perform urine pregnancy test (WOCBP only)
- Review SMBG and glycemic control record
- Dispense investigational product based on randomization
- Assess adverse events
- Record concomitant medications

7.6 Visit 6/ 18 Weeks

- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Perform urine pregnancy test (WOCBP only)
- Review SMBG and glycemic control record
- Assess adverse events
- Record concomitant medications

7.7 Visit 7/ 24 Weeks

- 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 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Perform urine pregnancy test (WOCBP only)
- Review SMBG and glycemic control record
- Assess adverse events
- Record concomitant medications

7.8 Visit 8/ Follow Up

- Perform a complete physical examination
- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Perform urine pregnancy test (WOCBP only)
- Review SMBG and glycemic control record
- Assess adverse events
- Record concomitant medications

7.9 Early Termination Procedures

Subjects who withdraw consent and have received investigational products should have a follow-up visit that captures the V8 procedures, if possible. The sponsor must be notified in the event that a subject withdraws or has been withdrawn from the study.

- Perform a complete physical examination
- Measure vital signs, including blood pressures and heart rate
- Draw blood if an approximately 8 h fast has been completed by the subject as described in Section 6.9. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Perform urine pregnancy test (WOCBP only)
- Review SMBG and glycemic control record
- Assess adverse events
- Record concomitant medications

8 QUALITY CONTROL AND ASSURANCE

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

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The following sections provide a summary of the planned analysis of the trial but a complete statistical analysis plan will be developed as a separate document and will become the final plan. All statistical analyses will be performed using SAS Version 9.2 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.

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.

In general, for safety endpoints, baseline is defined as the last non-missing value before the first dose of double-blind study medication. For baseline demographics and efficacy endpoints, baseline is defined as the last non-missing value before the randomization date.

Note that data for subjects with screening HbA1c > 10.5% and ≤ 12% will be separately summarized and/or listed. Only descriptive summaries will be provided for this group of subjects. No formal hypothesis testing will be performed. The following sections of analysis methods will be applied to this sub-study with exceptions of modeling and hypothesis testing. Henceforth, analyses for this sub-study will not be specifically mentioned unless it differs from the main study.

9.2 Determination of Sample Size

In the blinded segment of the study approximately 300 subjects will be randomized 1:1 to bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo. With this sample size, the study has approximately 90% power to detect a 0.4% difference in HbA1c between the active arm and the placebo arm, assuming a standard deviation of 1% HbA1c for the study population and that 12% of the study participants will have dropped out by week 24.

With similar assumptions, a single group of 50 subjects has approximately 90% power to detect a difference from baseline of 0.5% HbA1c, assuming a 12% dropout rate and a population standard deviation of 1%.

9.3 Analysis Populations

9.3.1 Intention-to-Treat Analysis Set

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

9.3.2 Safety Analysis Set

All subjects who are randomized and take at least one dose of study medication will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually taken by each subject. The Safety Analysis Set is the primary analysis set for safety evaluation. For sub-study, all subjects who take at least one active dose of the study medication will be included in this analysis set, and all analyses will be based on this analysis set.

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 assessments.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the safety, ITT and PP analysis sets for each treatment group and for all subjects combined. Key variables include (but are not limited to): age, gender, race, ethnicity and country of investigational site, baseline HbA1c and FPG assessments, baseline blood pressures, baseline body weight, BMI, and stratification factors including HbA1c value categories at randomization.

9.5 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. For the main study, all efficacy analyses will be based on ITT analysis set, and if it is deemed that the PP analysis set is much different from the ITT analysis set, the analyses applied to the ITT set will be applied to the PP analysis set as well. For the sub-study, all summaries will be based on the Safety analysis set.

9.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change of HbA1c from baseline to week 24 in the 20 mg dose group compared to placebo group.

The MMRM analysis of covariance model (ANCOVA) will be fitted to the available data, incorporating all visits at which HbA1c was measured (i.e., including the scheduled and the unscheduled visits for measurement of HbA1c (NationalResearchCouncil, 2010). Treatment, visit, treatment-by-visit, baseline HbA1c value and country (US or Japan) will be applied as fixed effects. From this model, an estimate of the treatment difference at week 24 will be generated, as will an assessment of whether the effect is significant at a two-sided 0.05 level. An unstructured within-patient covariance structure will be assumed. If the model with the

unstructured covariance structure does not converge, an autoregressive covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from this primary analysis.

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

1. Missing HbA1c data will be imputed via multiple imputation (MI), following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will not be considered missing. Non-monotone (intermediate visits) missing data will be imputed first using the Monte Carlo Markov Chain (MCMC) method under the Missing at Random (MAR) assumption in both treatment groups. One method to impute monotone missing values of the HbA1c will be for all subjects who withdrew from the study (regardless of treatment group) using an imputation model at each time point estimated from subjects with available data in the placebo treatment group only.
2. Missing HbA1c data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
3. HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be re-performed.

9.5.2 Secondary Efficacy Endpoints

To assess the treatment effect on the change of FPG, similar methods as described for the primary endpoint will be implemented. The model will also include treatment, the baseline value of FPG, and country as fixed effects/covariates. Least squares mean treatment differences between the bexagliflozin and placebo arms will be estimated from the model. The corresponding 95% CI and p-value will be provided as well.

Analysis of the change in systolic blood pressure (SBP) in the bexagliflozin group compared with placebo over time will also be performed using a similar method as for the primary endpoint with baseline SBP measure and country as fixed covariates.

A summary of the proportion of subjects achieving HbA1c $\leq$7% by visit will be provided. Generalized estimation equations (GEE) method will be used for estimation of treatment effect.

The change in total body weight in subjects with baseline BMI $\geq$25 kg/m^2 will be analyzed using the MMRM method with baseline body weight as a fixed covariate.

The change in HbA1c over time will also be presented by treatment groups and differences between bexagliflozin and placebo at each time point will be estimated using same methods as described for the primary end point.

9.6 Safety Analysis

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

9.6.1 Adverse Events

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

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

9.6.2 Adverse Events of Special Interest

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

The number and percentage of subjects who have experienced a TEAE of special interest will be summarized for each treatment group by types of events. Additional analyses will be specified in the statistical analysis plan to evaluate other event associated safety parameters and potential risks in subpopulations based on age, gender, or other baseline characteristics, if there are sufficient samples.

9.6.3 Clinical and Laboratory Events and Analyses

Clinical laboratory parameters (see Section 6.9 for a complete list), vital signs, and 12-lead ECG will be measured at scheduled visits (see Appendix 1). These data will be summarized as actual values and changes from baseline by treatment for each visit for selected parameters.

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

9.6.4 Physical Examination

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

9.7 Other Analyses

A population pharmacokinetic assessment of bexagliflozin will be conducted across multiple phase 3 studies and will include approximately 200 subjects from THR-1442-C-419. Samples will be taken from these subjects at Weeks 6 or 12 of treatment. Analysis methods will be specified in a separate document.

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 independent review board (IRB) or independent ethics committee (IEC) for review and must be approved by the sponsor and the IRB/IEC before the study is initiated. Any amendments or addenda to the protocol must also be approved by the IRB/IEC prior to implementing changes in the study. The investigator is responsible for keeping the IRB/IEC informed of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once a year. The investigator must also keep the IRB/IEC informed of any SAEs occurring to subjects under his or her supervision.

10.3 Ethical Conduct of the Study

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor and investigator follow ICH GCP guidelines (E6) and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. An inspection by the sponsor representatives and/or their designee and/or other authorized regulatory authorities representatives may occur at any time. The investigator must agree to the inspection of study-related records by the regulatory authority/sponsor representatives, and must allow direct access to source documents to the regulatory authority/sponsor representatives.

The investigator is responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform their assigned tasks and that written and contemporaneously signed records documenting the training be retained at the study site.

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

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

10.4 Subject Information and Consent

Prior to the beginning of the study, the investigator must have received from the IEC or IRB the written approval or favorable opinion of a competent authority of the informed-consent form and any other written information to be provided to subjects. The written approval of the IRB/IEC together with the approved subject information/informed consent forms must be filed. The informed consent form must contain all elements required by authorized regulatory authorities 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 the date of informed consent given by the subject should be documented appropriately in the subject's files. A copy of the signed informed consent form must be provided to the subject. If applicable, it will be provided in a certified translation in the language understood by the subject, if not English. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

10.5 Subject Confidentiality

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

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

10.6 Study Monitoring

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

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

10.7 Case Report Forms and Study Records

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

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

All CRFs and source documents should be completed following GCP and the sponsor or its designee's SOPs.

10.8 Data Monitoring Committee

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

10.9 Protocol Violations and Deviations

Protocol violations include departures from the inclusion and exclusion criteria, concomitant medication restrictions, and any other protocol requirement that results in a significant added risk to the subject or has an impact on the quality of the data collected or the outcome of the study.

A protocol deviation is a non-adherence to study procedures or schedules, as specified by the protocol, which does not involve inclusion/exclusion criteria or the primary endpoint and which does not place the subject at any added risk or affect the data quality or study outcome. Examples of deviations may include out-of-window visits, missed procedures, etc.

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

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

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

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

10.10 Access to Source Documentation

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

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

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

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

10.11 Retention of Data

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

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

10.12 Publication and Disclosure Policy

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

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

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Appendix 1 Schedule of Events

Procedure	**Screening**	**Run-in**	**Treatment**					**Follow-up**
Visit Number	V1/ Screening	V2/ Run In	V3/ Random-ization	V4	V5	V6	V7	V8/ Follow Up
Time to Randomization (week)	-3	-1	0	6	12	18	24	26
Informed Consent	X							
Screening for I/E Criteria	X		X					
Medical History	X							
Diet and Exercise Counseling		X						
Physical Examination			X					X
Abbreviated Physical Examination	X						X	
Vital Signs	X		X	X	X	X	X	X
Electrocardiography			X				X	
Clinical Laboratory Tests	X			X	X	X	X	X
Urine Pregnancy Test (local, WOCBP only)	X (all women)		X	X	X	X	X	X
Diary and Glucometer Dispensation and Review		X						
Dispensing Run-in Drug		X						
Diary and Glucometer Record Review			X	X	X	X	X	X
Dispensing Investigational Product			X		X			
Adverse Events Assessments		X	X	X	X	X	X	X
Concomitant Medication Assessments		X	X	X	X	X	X	X

Appendix 2 Schedule of Clinical Laboratory Tests

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

Appendix 3 Examples of SGLT2 Inhibitors

The following medications are prohibited during the study. Other SGLT2 inhibitors that may be approved for the treatment of T2DM during the THR-1442-C-419 study will also be prohibited as a concomitant medication in this protocol.

Generic Name	**Trade Name**
canagliflozin	Invokana™
canagliflozin plus metformin	Invokamet™
dapagliflozin	Farxiga™ or Forxiga™
empagliflozin	Jardiance®
empagliflozin plus linagliptin	Glyxambi®
empagliflozin/metformin HCl	Synjardy
dapagliflozin/metformin HCl extended release tablet	Xigduo XR

Appendix 4 Sponsor Signatures

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Bexagliflozin in Subjects with Type 2 Diabetes Mellitus Who Are not Adequately Controlled by Metformin Alone

Study Number: THR-1442-C-419

Final Date: 26 July 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: 27 July 2017

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

Signed: _____ MD Date: 7.28-17

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

Signed: _____ Date: 01 Aug 2017

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

Appendix 5 Investigator's Signature

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Bexagliflozin in Subjects with Type 2 Diabetes Mellitus Who Are not Adequately Controlled by Metformin Alone

Study Number: THR-1442-C-419

Final Date: 26 July 2017

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

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

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

Signed:_____ Date:_____
Clinical Investigator