Clinical Trial Protocol: THR-1442-C-603

Title:	An Integrated Assessment of the Safety and Effectiveness of Bexagliflozin Tablets, 20 mg, for the Management of Essential Hypertension
Protocol Number:	THR-1442-C-603
Study Phase:	2/3
Product Name:	Bexagliflozin Tablets
IND Number:	134049
Indication:	Hypertension
Investigators:	Multicenter
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	Date
Protocol V1.0:	21 May 2017
Protocol V2.0:	28 August 2017

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SYNOPSIS

Sponsor: Theracos Sub, LLC

Name of Finished Product: Bexagliflozin Tablets, 20 mg

Name of Active Ingredient: Bexagliflozin

Study Title: An Integrated Assessment of the Safety and Effectiveness of Bexagliflozin Tablets, 20 mg, for the Management of Essential Hypertension

Protocol Number: THR-1442-C-603

Study Phase: 2/3

Overall Design:

This integrated assessment consists of two studies, 603A and 603B, to be carried out sequentially in a common study population. Participating subjects will be informed of the trial design and their consent to participate in both studies will be obtained in a single consent form.

Primary Objective of Study 603A
In study 603A, the effectiveness of bexagliflozin tablets, 20 mg, will be assessed in a study population randomized 1:1 to receive either active agent or placebo. The primary endpoint will be the change from baseline (Day 1) to week 12 of the average ambulatory systolic blood pressure (SBP) of the bexagliflozin group compared to the placebo group.

Secondary Objectives of Study 603A
Additional effectiveness outcomes will be assessed from ambulatory as well as seated office blood pressure measurements.

Secondary endpoints based on mean ambulatory SBP will include the proportion of subjects who achieve a reduction of mean ambulatory SBP of 10 mm Hg or greater and the proportion of subjects who achieve a mean ambulatory SBP of 135 mm Hg or less at week 12.

Secondary endpoints based on seated office SBP will include the placebo-adjusted change from baseline to week 12 in seated office SBP and the proportion of subjects who achieve a mean seated office SBP of 140 mm Hg or less at week 12.

Secondary endpoints based on mean ambulatory DBP will include: the placebo-adjusted change in mean ambulatory DBP from baseline to week 12; the proportion of subjects who achieve a mean ambulatory DBP of 87 mm Hg or less at week 12; and the proportion of subjects who achieve a reduction of mean ambulatory DBP of 4 mm Hg or greater at week 12.

Secondary endpoints based on seated office DBP will include the placebo-adjusted change from baseline to week 12 in seated office DBP and the proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12.

An additional objective of study 603A will be an assessment of the maximum and minimum treatment effect (peak-trough ratio) by ABPM SBP at week 12.

Primary Objective of Study 603B
In study 603B, the effectiveness of bexagliflozin tablets, 20 mg, will be assessed by measurement of the loss of the treatment effect following randomized withdrawal. All study entrants will first be dosed with bexagliflozin tablets, 20 mg, for 12 weeks. At week 12 the participants will undergo a 1:1 randomization to bexagliflozin tablets, 20 mg, or placebo. The primary endpoint will be the change from week 12 to week 24 of the mean ambulatory SBP of the bexagliflozin group compared to the placebo group.

Secondary Objectives of Study 603B
The secondary objectives of study 603B are based on separate assessments of effects on mean ambulatory and seated office systolic and diastolic blood pressures.

Study 603B will also include a population pharmacokinetic assessment between weeks 6 and 12, when all participants will be receiving bexagliflozin tablets, 20 mg.

Integrative Objectives of Study 603A and 603B
Integration of measures collected in studies 603A and 603B will be used to assess consistent effects on mean ambulatory SBP/DBP after 12 weeks of bexagliflozin treatment, as well as longer treatment periods, i.e., 24 weeks or 36 weeks of bexagliflozin treatment.

In addition, the seated office systolic and diastolic blood pressure will be collected at more frequent intervals than for ambulatory monitoring, and the changes over time will be evaluated to provide a composite profile of treatment effect as a function of time.

Integrated Safety Objectives:
The integrated safety objectives will assess the hazard ratio for adverse events associated with bexagliflozin exposure compared to placebo in all segments of both studies in which a placebo-exposed cohort is present. The assessments will include:

- the frequency and severity of all adverse events
- the frequency and severity of adverse events of special interest
- changes in concomitant medication use
- changes in laboratory test values
- changes in cardiac rhythm determined by 12-lead ECG
- changes in vital signs
- effects on general health detected by physical examination

Design:
THR-1442-C-603 is an integrated assessment of the potential utility of bexagliflozin tablets, 20 mg for the treatment of essential hypertension. It is composed of two studies, 603A and 603B, measuring effects in a common population.

<u>Study 603A</u>
Approximately 680 male or female adult subjects who exhibit an office seated blood pressure ≥140 mm Hg and <180 mm Hg, and who are taking no more than 4 anti-hypertension medications will be enrolled in study 603A. In the desired population, > 10% of the subjects will have a baseline ABPM >160 mm Hg and < 30% of the subjects will have type 2 diabetes

mellitus.

Subjects who meet the eligibility criteria at the screening visit (visit 1) will start a 2 week run-in period. At the end of the run-in period, subjects who have not been disqualified by laboratory testing results based on samples drawn at the screening visit, who have been compliant in taking the run-in medication, and who exhibit a seated SBP ≥ 140 mm Hg and < 180 mm Hg will be eligible for participation. At the investigative site the subjects will take the last dose of run-in drug, will be fitted with an ABPM device and will start a 24-h ambulatory blood pressure monitoring (ABPM) to establish the baseline ABPM SBP and DBP. On the following day, qualified subjects who have completed the 24-h ABPM with a mean 24-h SBP ≥ 135 mm Hg will be randomly assigned to receive bexagliflozin tablets, 20 mg or placebo, using an interactive web response system (IWRS). If < 64 SBP readings are recorded, the ABPM must be repeated within 2 days. Prior to randomization, subjects who cannot successfully complete the ABPM within two attempts will be considered screen failures.

Randomization will be stratified according to diabetes status (history of T2DM or not), renal function (eGFR ≥ 60 or not), presently medicated for hypertension or not, and ABPM SBP (< 160 mm Hg or not).
A bottle of double blind study drug will be dispensed to each randomized subject with an instruction to take one tablet daily in the morning with a glass of water before or after breakfast. It will be recommended that subjects take the study drug at about the same time every day except on the days of scheduled site visit when the study drug will be administered at the investigational site.

A six week visit to the investigational site will allow seated office measures of systolic and diastolic blood pressure to be recorded.
At week 12 (end of study), the subject will visit the investigational site, consume the final tablet, and be fitted for ABPM.

An interim non-binding futility analysis will be conducted when approximate 50% of the randomized subjects have completed study 603A. The data will be analyzed by an independent group that is not part of the study management team. Results from the analysis will be reviewed by an independent Data Monitoring Committee (DMC).

Study 603B
Upon returning to the investigational site to surrender the ambulatory monitor at the conclusion of study 603A, subjects will begin participation in study 603B. They will receive a 12-week supply of bexagliflozin tablets, 20 mg.
At week 6 (cumulative week 18) subjects will return to the investigational site for measurement of seated systolic and diastolic blood pressures.

At week 12 (cumulative week 24) subjects will visit the investigational site to consume the bexagliflozin tablet and to be fitted with an ambulatory monitor to record their baseline mean blood pressure.

The following day, subjects will be randomized 1:1 to receive a 12-week supply of

bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo. Assignment to the active or placebo arm will be balanced to approximately equalize the representation in each arm of the following groups:

- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 20 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 5 mm Hg and ≤ 20 mm Hg reduction in mean SBP between Day 1and cumulative 24
- Subjects not requiring rescue medication prior to week 24 and exhibiting a ≤ 5 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects requiring rescue medication prior to week 24

An assessment of bexagliflozin population pharmacokinetics (PK) will also be conducted, to include approximately 200 subjects. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a separate designated study protocol and the analysis will be reported separately.
Integrated management of hypertension, including use of rescue medications

Subjects will be counseled to be compliant with all their medications, to exercise regularly, lose weight if overweight or obese, adopt a diet rich in fruits, vegetables and low-fat dairy products (the DASH diet, with appropriate modifications for participants with CKD), reduce sodium intake and alcohol consumption to recommended levels. Patients who smoke will be encouraged to stop. Every effort will be made to secure the continued participation of the subjects.

Rescue medications are recommended following the guidance below if the SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements over 3 consecutive days.

Guidance for Hypertensive Rescue Medication Use

Study 603A, cumulative weeks 1-6

- Follow procedures for visits 10 and 11 as early termination visits to obtain 24-h ABPM and collect safety data
- Rescue medication should not be administered unless hypertensive emergency appears imminent. In those situations, refer the subject to seek urgent care in a clinic or hospital. Subject should withdraw from participation in the study and see primary care provider to start or intensify anti-hypertensive therapies

Study 603A, cumulative weeks 7-12

- Follow procedures for visits 5 and 6 to obtain 24-h ABPM and collect safety data
- Start visit 6 (start of 603B) without rescue medication. If a hypertensive emergency appears imminent, refer the subject to seek urgent care in a clinic or hospital. Prescribe rescue medication at Visit 7 if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Study 603B, cumulative weeks 13-18

- Obtain 24-h ABPM and collect safety data
- Rescue medication should not be administered unless hypertensive emergency appears imminent. In those situations, refer the subject to seek urgent care in a clinic or hospital. Prescribe rescue medication at Visit 7 if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Study 603B-Cumulative weeks 19-24

- Obtain 24-h ABPM and collect safety data
- Prescribe rescue medication if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Study 603B-Cumulative weeks 25-36

- Obtain 24-h ABPM and collect safety data
- Prescribe rescue medication if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Additional study procedures for safety and efficacy endpoint assessment will be performed as outlined in the study schedule.

The effectiveness and safety analyses will be conducted after all subjects have completed or withdrawn from study 603B.

To allow safety data to be collected for up to 36 weeks of exposure, the study will not be stopped for overwhelming efficacy. The DMC will review the unblinded safety data at approximately 2 month intervals and may recommend protocol modifications or early termination due to safety concerns.

Study Population:
A total of 680 patients with essential hypertension will be initially randomized. The subjects must be:

1. Male or female with age ≥ 20 years
2. Diagnosed with essential hypertension and exhibiting an office seated SBP ≥ 140 and < 180 mm Hg
   Unmedicated or currently treated by a stable regimen for hypertension. Unmedicated subjects are subjects who have never taken pharmacotherapy for hypertension or have not taken any anti-hypertensive medication for at least 12 weeks. To be considered stable, a regimen must exhibit no change in dose or frequency for the 4 weeks prior to the screening visit
3. If female and of childbearing potential, willing to use an adequate method of contraception and to not become pregnant for the duration of the study. Adequate contraceptive measures include, but are not limited to, oral contraceptives, intrauterine devices, Depo-Provera, Norplant, hormonal contraceptive implants, bilateral tubal

ligation, partner with vasectomy, condom or diaphragm plus contraceptive sponge, foam, or jelly, and abstinence
4. Willing and able to return for all clinic visits and to complete all study-required procedures
5. Able to self-medicate during the run-in period, omitting no more than one day of dosing (confirm at visit 2)
6. Shown to have a seated SBP ≥ 140 and < 180 mm Hg (confirm at visit 2)
7. Shown to have a mean 24 h SBP ≥ 135 mm Hg (at visit 3)

Test Product, Dose, and Mode of Administration:
Bexagliflozin tablets, 20 mg or placebo, to be taken by mouth once daily in the morning

Duration of Treatment: up to 36 weeks

Study 603A

Primary effectiveness assessment

- Change from baseline (Day 1) to week 12 of the 24-hour mean SBP

Secondary effectiveness assessments include:

- the proportion of subjects who achieve a reduction of mean ambulatory SBP of 10 mm Hg or greater;
- the proportion of subjects who achieve a mean ambulatory SBP of 135 mm Hg or less;
- the placebo-adjusted change from baseline to week 12 in seated office SBP;
- the proportion of subjects who achieve a seated office SBP of 140 mm Hg or less at week 12;
- the placebo-adjusted change in mean ambulatory DBP from baseline to week 12;
- the proportion of subjects who achieve a mean ambulatory DBP of 87 mm Hg or less at week 12;
- the proportion of subjects who achieve a reduction of mean ambulatory DBP of 4 mm Hg or greater;
- the placebo-adjusted change from baseline to week 12 in seated office DBP;
- the proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12.

Study 603B

Primary effectiveness assessment

- Change from baseline week 12 (cumulative week 24) to week 24 (cumulative week 36) of the 24-hour mean SBP

Secondary effectiveness assessments include:

- the placebo-adjusted change from week 12 to week 24 in seated office SBP
- the placebo-adjusted change in mean ambulatory DBP from week 12 to week 24.
- the placebo-adjusted change from week 12 to week 24 in seated office DBP

Integrated Assessments

Assessments for studies 603A and 603B will be combined to further assess the effectiveness of bexagliflozin after treatment of 12, 24, and 36 weeks.
There are four (4) separate treatment sequences after combining studies 603A and 603B, namely:

Sequence	Period 1	Period 2	Period 3
Seq 1 PBB	(603A) placebo	(603B) bexagliflozin	(603B) bexagliflozin
Seq 2 PBP	(603A) placebo	(603B) bexagliflozin	(603B) placebo
Seq 3 BBB	(603A) bexagliflozin	(603B) bexagliflozin	(603B) bexagliflozin
Seq 4 BBP	(603A) bexagliflozin	(603B) bexagliflozin	(603B) placebo

The following assessments will be assessed:

- Change in mean ambulatory SBP or DBP after 12 weeks treatment of bexagliflozin using week 12 assessments for Seq 3 or 4's Period 1 and Seq 1 or 2's Period 2;
- Change in mean ambulatory SBP or DBP after 24 weeks treatment of bexagliflozin using cumulative week 24 assessments for Seq 3 or 4's Period 2 and Seq 1's Period 3;
- Change in mean ambulatory SBP or DBP after 36 weeks treatment of bexagliflozin using cumulative week 36 assessments for Seq 3's Period 3;
- Change in seated office SBP or DBP after 12 weeks treatment of bexagliflozin using week 12 assessments for Seq 3 or 4's Period 1 and Seq 1 or 2's Period 2;
- Change in seated office SBP or DBP after 24 weeks treatment of bexagliflozin using cumulative week 24 assessments for Seq 3 or 4's Period 2 and Seq 1's Period 3;
- Change in seated office SBP or DBP after 36 weeks treatment of bexagliflozin using cumulative week 36 assessments for Seq 3's Period 3.

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

Safety Assessments:
Safety will be assessed based on an analysis of the adverse events identified by patient histories, laboratory data, including hematology, serum chemistry, urinalysis, urinary electrolytes and creatinine measurements; by ECGs, measurements of vital signs and physical examinations; and by changes in concomitant medication use.

Statistical Methods:
The primary endpoint of study 603A is the change from baseline (Day 1) to week 12 in the 24-hour average SBP of the bexagliflozin group compared to the placebo group using a superiority testing at an overall two-sided 0.05 level of significance.
The primary endpoint of study 603B is the change from week 12 (cumulative week 24) to week 24 (cumulative week 36) in the 24-hour average SBP in the bexagliflozin group compared to the placebo group using a superiority testing at an overall two-sided 0.05 level

of significance.
The assumptions to estimate the sample size for the primary endpoint of study 603A are:

1. The magnitude of the decrease from baseline to week 12 of the 24 h mean SBP in the bexagliflozin treatment arm will exceed that found in the placebo arm by 5 mm Hg;
2. The standard deviation of the change from baseline to Week 12 will be 15 mm Hg for both the active and placebo groups;
3. The two-sided significance level is 0.05.

The assumptions to estimate the sample size required for the primary endpoint of study 603B are:

1. Bexagliflozin will remain effective for at least 24 weeks. The 24-hour average ABPM SBP will not change between week 12 and week 24 in those taking bexagliflozin.
2. Subjects who are randomized to receive placebo will show an increase in the ABPM SBP of 4 mm Hg between week 12 and week 24.
3. The standard deviation of the change will be 15 mm Hg for both the active and placebo groups.
4. The two-sided significance level is 0.05.

A sample size of 254 per arm is required for the measurement to have 85% power to attain significance for the primary endpoint of study 603B. It is estimated that 75% of subjects will complete the 36 weeks of study treatment following the first randomization. Thus a total sample size of 680 subjects is planned for study 603A. It is estimated that approximately 8% of subjects will have ceased to participate by the end of study 603A. A sample size of 626 subjects at the conclusion of study 603A will provide >95% power for the primary endpoint.

An interim non-binding futility analysis when 300 subjects have completed study 603A will be conducted. Using an interpolated spending function of Type II error, i.e., with 0.5 proportion of Type II error being spent at the interim look, the study may stop for futility when the test statistics (Z score) is less than 0.656 (or p-value > 0.512). The overall power for the first primary endpoint remains >95% with this interim look. The interim analysis will be conducted by an independent data monitoring group.
An analysis of covariance (ANCOVA) method will be used in 603A for analyzing the mean change from baseline 24-hour average SBP at week 12, adjusted by diabetes status, renal function, medicated/unmedicated status and baseline mean 24 h SBP. Least squares means with 95% confidence intervals (CI) will be generated for the difference between the treatment groups at Week 12.

A similar method of ANCOVA will be used for the primary efficacy endpoint of study 603B. Changes from week 12 to week 24 in 24 h mean SBP will be analyzed. 24-hour average SBP at week 12 will be used as a covariate. Least squares means with 95% CIs will be generated for the difference between the treatment groups at week 24.

The primary analysis for 603A will be based on all randomized subjects and evaluations prior to the initiation of the rescue hypertensive medication. Last post baseline evaluation will be

used for the primary analysis time point at Week 12.

The primary analysis for 603B will be based on all randomized subjects at week 12, and evaluations prior to the initiation of the rescue hypertensive medication (i.e., rescue medication between week 12 and week 24). Last post week 12 observation but prior to initiation of the rescue medication will be used for the primary analysis time point of week 24.
Sensitivity analyses will be conducted for the primary endpoints.

- Cumulative week 12 and week 36 evaluations after rescue medication will be used in the analyses in place of evaluations prior to the rescue medication
- Analyses will be based on subjects without rescue medication
- Tipping Point analysis will be conducted as follows:
  - Subjects in the bexagliflozin treatment arm who discontinue participation or initiate rescue medication, will be analyzed assuming that their treatment effect has worsened by δ (where $\delta = 0.5$ to 5, in steps of 0.5) compared to the reduction in SBP for subjects who are in the study without rescue medication.
  - Subjects in the placebo treatment arm who discontinue study participation or initiate rescue medication, will be considered to have experienced a treatment effect the same as the change of SBP for subjects who are in the study without rescue medication.

Date of Protocol V.1.0: 21 May 2017

Date of Protocol V2.0: 28 August 2017

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin converting enzyme
AE	adverse event
AEOI	adverse event of interest
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
bid	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
DASH	dietary approaches to stop hypertension
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
DMC	data monitoring committee
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GMI	genital mycotic infections
Hct	hematocrit
HF	heart failure
Hgb	hemoglobin
HUA	hospitalization for unstable angina
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	international normalized ratio
IRAE	immediately reportable adverse event
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system

KDOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NYHA	New York Heart Association
PD	pharmacodynamics
PK	pharmacokinetics
RBC	red blood cell (count)
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT1	sodium glucose linked transporter 1
SGLT2	sodium glucose linked transporter 2
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
UADR	unexpected adverse drug reaction
UGE	urinary glucose excretion
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell (count)
WOCBP	woman of childbearing potential

1 INTRODUCTION

Hypertension affects one billion people worldwide, including 30% of U.S adults. The incidence of hypertension is expected to continue to rise, especially given current trends in the prevalence of obesity and diabetes (Egan et al., 2010). Unfortunately, only half of those afflicted achieve goal blood pressure targets (James et al., 2014). Hypertension is a major preventable risk factor for cardiovascular disease. There is a direct correlation between adverse outcomes and increasing blood pressure over 115/75 mm Hg (Lewington et al., 2002). Thus, novel anti-hypertensive therapies are needed, especially those that may have additional beneficial effects on associated conditions like diabetes mellitus, obesity and chronic kidney disease.

Bexagliflozin is a specific and potent inhibitor of sodium-glucose linked transporter 2 (SGLT2). SGLT2 is responsible for the reabsorption of most of the glucose passing through the S1 and S2 segments of the renal proximal tubule by a 1:1 cotransport of sodium ions and glucose (Hummel et al., 2012; Kanai et al., 1994). Inhibiting SGLT2 action leads to glucosuria and natriuresis. The mechanism of the natriuresis is thought to be at least partially dependent on osmotic diuresis. Individuals affected by familial renal glucosuria (FRG), a syndrome resulting from mutations in the gene encoding SGLT2, *SLC5A2* (Calado et al., 2006; Calado et al., 2004; Calado et al., 2008; Francis et al., 2004; Kleta et al., 2004; Santer et al., 2003; van den Heuvel et al., 2002) present with a prominent glucosuria, mild to moderate polyuria, and, in severe cases, evidence of volume depletion attributable to natriuresis. Affected individuals are euglycemic and exhibit no signs of renal tubular dysfunction apart from their glucosuria. In extreme cases of FRG, evidence of sodium depletion with mild hypotension and a compensatory activation of the renin-angiotensin-aldosterone system (RAAS) have been noted (Calado et al., 2006; Calado et al., 2008).

Several SGLT2 inhibitors have been approved as a single agent or in combination with other hypoglycemic agents for the treatment of patients with T2DM (Vivian, 2015; Whalen et al., 2015). In clinical studies of diabetic adults, SGLT2 inhibitors have been shown to produce an antihypertensive effect (Baker et al., 2014; Lovshin and Gilbert, 2015; Mancia et al., 2016; Oliva and Bakris, 2014; Reed, 2016; Tikkanen et al., 2015; Weber et al., 2016; Weir et al., 2014) A meta-analysis of 27 randomized controlled trials with 12,960 subjects showed SGLT2 inhibitors reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 4.0 and 1.6 mm Hg respectively (Baker et al., 2014). Orthostatic hypotension was rarely observed (Baker et al., 2014). Baseline readings were typically low, around 130 mm Hg for SBP.

In a trial assessing the cardiovascular hazards of administration of empagliflozin (EMPAREG), diabetic patients with increased cardiovascular risk were treated with empagliflozin or placebo in combination with standard of care for approximately 3 years. The primary composite outcome of death, MI, and stroke (MACE) occurred in 10.5% of patients in the empagliflozin groups and in 12.1% of the patients in the placebo group. Empagliflozin has shown decreased rates of eGFR decline in those with mild and moderate chronic kidney disease (Zinman et al., 2015). SBP decreased over the course of the treatment period in empagliflozin arms compared to placebo (Scheen, 2016).

1.1 Bexagliflozin for the Treatment of Hypertension

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

1.1.1 Summary of Bexagliflozin Non-clinical Data

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

1.1.2 Summary of Bexagliflozin Clinical Data

Theracos has completed multiple phase 1 studies to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and drug metabolism in healthy subjects, subjects with T2DM, and diabetic subjects with renal impairment. Bexagliflozin was well tolerated by patients with normal and impaired renal function and produced significant urinary glucose excretion (UGE) and decreases in blood pressure.

In a 96-week double blind, placebo controlled study THR-1442-C-418 in 286 patients with T2DM, study subjects had a baseline SBP of about 128 mm Hg. Subjects in the bexagliflozin treatment group showed a placebo corrected decrease of 6 mm Hg in SBP. The treatment effect was durable and produced reductions from baseline SBP of 4.6 mm Hg at week 96 and4.7 mm Hg at week 97, one week after the last dose. Among the patients with SBP $\geq$140 mm Hg at baseline (mean SBP of 147$\pm$7.8 mm Hg), bexagliflozin treatment resulted in a placebo corrected SBP reduction of 7 mm Hg at week 24. The treatment effect correlated with the baseline BP but was independent of the baseline HbA1c. Details of the pharmacology, efficacy, and safety assessments are described in the Investigator's Brochure and summarized in the following sections.

2 OBJECTIVES

2.1 Objectives of Study 603A

Primary Objective of 603A Study
In study 603A, the effectiveness of bexagliflozin tablets, 20 mg, will be assessed in a study population randomized 1:1 to receive either active agent or placebo. The primary endpoint will be the change from baseline (Day 1) to week 12 of the average ambulatory systolic blood pressure (SBP) of the bexagliflozin group compared to the placebo group.

Secondary Objectives of Study 603A
Additional effectiveness outcomes will be assessed from ambulatory as well as seated office blood pressure measurements.

Secondary endpoints based on mean ambulatory SBP will include the proportion of subjects who achieve a reduction of mean ambulatory SBP of 10 mm Hg or greater and the proportion of subjects who achieve a mean ambulatory SBP of 135 mm Hg or less at week 12.

Secondary endpoints based on seated office SBP will include the placebo-adjusted change from baseline to week 12 in seated office SBP and the proportion of subjects who achieve a mean seated office SBP of 140 mm Hg or less at week 12.

Secondary endpoints based on mean ambulatory DBP will include: the placebo-adjusted change in mean ambulatory DBP from baseline to week 12; the proportion of subjects who achieve a mean ambulatory DBP of 87 mm Hg or less at week 12; and the proportion of subjects who achieve a reduction of mean ambulatory DBP of 4 mm Hg or greater at week 12.

Secondary endpoints based on seated office DBP will include the placebo-adjusted change from baseline to week 12 in seated office DBP and the proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12.

An additional objective of study 603A will be an assessment of the maximum and minimum treatment effect (peak-trough ratio) by ABPM SBP at week 12.

2.2 Objectives of Study 603B

Primary Objective of Study 603B
In study 603B, the effectiveness of bexagliflozin tablets, 20 mg, will be assessed by measurement of the loss of the treatment effect following randomized withdrawal. All study entrants will first be dosed with bexagliflozin tablets, 20 mg, for 12 weeks. At week 12 the participants will undergo a 1:1 randomization to bexagliflozin tablets, 20 mg, or placebo. The primary endpoint will be the change from week 12 to week 24 of the mean ambulatory SBP of the bexagliflozin group compared to the placebo group.

Secondary Objectives of Study 603B
The secondary objectives of study 603B are based on separate assessments of effects on mean ambulatory and seated office systolic and diastolic blood pressures.

Study 603B will also include a population pharmacokinetic assessment between weeks 6 and 12, when all participants will be receiving bexagliflozin tablets, 20 mg.

2.3 Integrative Objectives of Studies 603A and 603B

Integration of measures collected in studies 603A and 603B will be used to assess consistent effects on mean ambulatory SBP/DBP after 12 weeks of bexagliflozin treatment, as well as longer treatment periods, i.e., 24 weeks or 36 weeks of bexagliflozin treatment.

In addition, the seated office systolic and diastolic blood pressure will be collected at more frequent intervals than for ambulatory monitoring, and the changes over time will be evaluated to provide a composite profile of treatment effect as a function of time.

2.4 Safety Objectives

The integrated safety objectives will assess the hazard ratio for adverse events associated with bexagliflozin exposure compared to placebo in all segments of both studies in which a placebo-exposed cohort is present. The assessments will include:

- the frequency and severity of treatment emergent adverse events
- the frequency and severity of treatment emergent adverse events of special interest
- changes in concomitant medication use
- changes in laboratory test values
- changes in cardiac rhythm determined by 12-lead ECG
- changes in vital signs
- effects on general health detected by physical examination

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan

3.1.1 Study 603A

Approximately 680 male or female adult subjects who exhibit an office seated blood pressure ≥ 140 mm Hg and < 180 mm Hg, and who are taking no more than 4 anti-hypertension medications will be enrolled in study 603A. In the desired population, > 10% of the subjects will have a baseline ABPM > 160 mm Hg and < 30% of the subjects will have type 2 diabetes mellitus.

Subjects who meet the eligibility criteria at the screening visit (visit 1) will start a 2 week run-in period. At the end of the run-in period, subjects who have not been disqualified by laboratory testing results based on samples drawn at the screening visit, who have been compliant in taking the run-in medication, and who exhibit a seated SBP ≥ 140 mm Hg and < 180 mm Hg will be eligible for participation. At the investigative site the subjects will take the last dose of run-in drug, will be fitted with an ABPM device and will start a 24-h ambulatory blood pressure monitoring (ABPM) to establish the baseline ABPM SBP and DBP. On the following day, qualified subjects who have completed the 24-h ABPM with a mean 24-h SBP ≥ 135 mm Hg will be randomly assigned to receive bexagliflozin tablets, 20 mg or placebo, using an interactive web response system (IWRS). If < 64 SBP readings are recorded, the ABPM must be repeated within 2 days. Prior to randomization, subjects who cannot successfully complete the ABPM within two attempts will be considered screen failures.

Randomization will be stratified according to diabetes status (history of T2DM or not), renal function (eGFR ≥ 60 or not), presently medicated for hypertension or not, and ABPM SBP (< 160 mm Hg or not).

A bottle of double blind study drug will be dispensed to each randomized subject with an instruction to take one tablet daily in the morning with a glass of water before or after breakfast. It will be recommended that subjects take the study drug at about the same time every day except on the days of scheduled site visit when the study drug will be administered at the investigational site.

A six week visit to the investigational site will allow seated office measures of systolic and diastolic BP to be recorded.

At week 12 (end of study), the subject will visit the investigational site, consume the final tablet, and be fitted for ABMP.

An interim non-binding futility analysis is planned when approximately 50% of the randomized subjects (i.e., 300) have completed study 603A. The data will be analyzed by an independent group who is not part of the study management team. Results from the analysis will be reviewed by an independent Data Monitoring Committee (DMC).

3.1.2 Study 603B

Upon returning to the investigational site to surrender the ambulatory monitor at the conclusion of study 603A, subjects will begin participation in study 603B. They will receive a 12-week supply of bexagliflozin tablets, 20 mg.

At week 6 subjects will return to the investigational site for measurement of seated systolic and diastolic blood pressures.

At week 12, subjects will visit the investigational site to consume the final tablet and to be fitted with an ambulatory monitor to record their baseline mean blood pressure.

The following day, subjects will be randomized 1:1 to receive a 12-week supply of bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo. Assignment to the active or placebo arm will be balanced to approximately equalize the representation in each arm of the following groups:

- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 20 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 5 mm Hg and ≤ 20 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects not requiring rescue medication prior to week 24 and exhibiting a ≤ 5 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects requiring rescue medication prior to week 24

An assessment of bexagliflozin population pharmacokinetics (PK) will also be conducted to include approximately 200 subjects. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

3.1.3 Integrated Management of Hypertension, Including Use of Rescue Medications

Subjects will be counseled to be compliant with all their medications, to exercise regularly, lose weight if overweight or obese, adopt a diet rich in fruits, vegetables and low-fat dairy products (the DASH diet, with appropriate modifications for participants with CKD), reduce sodium intake and alcohol consumption to recommended levels. Patients who smoke will be encouraged to stop (CDC guidance).

Rescue medications are recommended following the guidance below if the SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements over 3 consecutive days.

Guidance for Hypertensive Rescue Medication Use

Study 603A, cumulative weeks 1-6

- Follow procedures for visits 10 and 11 as early termination visits to obtain 24-h ABPM and collect safety data
- Rescue medication should not be administered unless hypertensive emergency appears imminent. In those situations, refer the subject to seek urgent care in a clinic or hospital. Subject should withdraw from participation in the study and see primary care provider to start or intensify anti-hypertensive therapies

Study 603A, cumulative weeks 7-12

- Follow procedures for visits 5 and 6 to obtain 24-h ABPM and collect safety data
- Start visit 6 (start of 603B) without rescue medication. If a hypertensive emergency appears imminent, refer the subject to seek urgent care in a clinic or hospital. Prescribe rescue medication at Visit 7 if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Study 603B, cumulative weeks 13-18

- Obtain 24-h ABPM at an unscheduled visit
- Rescue medication should not be administered unless hypertensive emergency appears imminent. In those situations, refer the subject to seek urgent care in a clinic or hospital. Prescribe rescue medication at Visit 7 if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Study 603B, cumulative weeks 19-24

- Obtain 24-h ABPM and collect safety data
- Prescribe rescue medication if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Study 603B, cumulative weeks 25-36

- Obtain 24-h ABPM and collect safety data
- Prescribe rescue medication if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Additional study procedures for safety and efficacy endpoint assessment will be performed as outlined in the study schedule.

The effectiveness and safety analyses will be conducted after all subjects have completed or withdrawn from study 603B.

To allow safety data to be collected for up to 36 weeks of exposure the study will not be stopped for overwhelming efficacy. The DMC will review the unblinded safety data at approximately 2 month intervals and may recommend protocol modification or early stopping due to safety concerns.

The integrated program is illustrated in Figure 1.

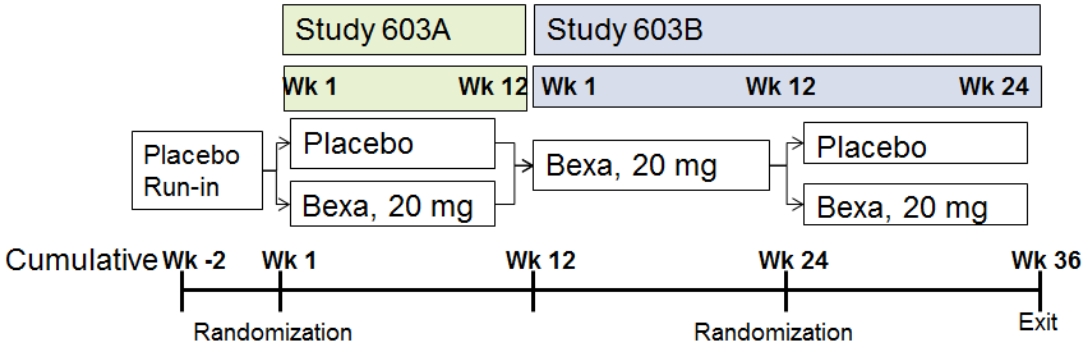

Figure 1. THR-1442-C-603 Study Design

3.2 Rationale for Design and Control Group

3.2.1 Rationale for the Selected Study Design

Bexagliflozin exhibits diuretic and hypotensive effects in hypertensive diabetics. The diuretic effect is immediate and improvement in blood pressure is observed over the first 6 to 12 weeks of treatment. The antihypertensive effect persists for 96 weeks. The magnitude of the effect correlates with the baseline blood pressure but appears to be independent of the baseline hemoglobin A1c, a measure of glycemic control. The two studies of protocol THR-1442-C-603 are designed to explore whether bexagliflozin will reduce blood pressure in adults with essential hypertension regardless of diabetes status. In addition, the use of a single treatment population allows extended safety and effectiveness data to be collected.

Study 603A is planned to evaluate the bexagliflozin treatment effect on SBP after the full effect of bexagliflozin has been achieved. Subjects will be randomized 1:1 to receive bexagliflozin tablets, 20 mg, or bexagliflozin tablets, placebo, for 12 weeks. The primary endpoint is the placebo-corrected change from baseline in ABPM SBP.

Study 603B, a randomized withdrawal study, is intended to measure the persistence of the antihypertensive effect of bexagliflozin. Subjects will receive bexagliflozin tablets, 20 mg for 12 weeks followed by 1:1 randomization to bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo. The primary endpoint is the placebo-corrected change from week 12 to week 24 in the ABPM SBP.

Under the close monitoring detailed in this protocol, placebo is the appropriate control treatment in the subject populations studied during the two 12-week evaluation periods. In order to establish baseline blood pressure and to allow compliance with the dosing regimen to be monitored, participating subjects will have participated in a 2 week run-in period prior to randomization.

3.2.2 Rationale for the Selected Dose and Once daily Dosing Regimen

The pharmacodynamics of bexagliflozin can be directly measured by quantitation of urinary glucose excretion (UGE). The UGE data from healthy volunteers are fit by a logistic equation with maximum effect size of 76.3 g/24 h and an ED_{50} of 3.63 mg. The proposed doses of 20 mg are predicted to produce 85% of the maximum effect. Doses of 20 mg have been administered for 96 weeks to an international study cohort with few adverse consequences. In a shorter-term study a modest dose dependence of adverse event accrual was observed.

The risk of induced hypoglycemia as a consequence of the inhibition of SGLT2 activity is low based on published data reporting the euglycemic status of individuals with genetic mutations in *SLC5A2* (the gene encoding SGLT2), in subjects that have been treated with other SGLT2 inhibitors, and from previous clinical studies in healthy or diabetic subjects treated with bexagliflozin. The potential risk of diuretic effects such as hypotension or electrolyte imbalance has been monitored. There has been one event each of hyponatremia (on day 99), hypokalemia (on day 86), and hypotension (on day 284) among study subjects who have received daily doses of 20 mg bexagliflozin in completed studies. The incidence rate for all electrolyte events is approximately 0.2%.

Bexagliflozin is formulated as a prolonged release tablet. The average plasma concentration is above 10 ng/mL at 24 h after dosing which is about 10 times the *in vitro* IC_{50} for SGLT2 inhibition. These data support a once daily dosing regimen.

3.2.3 Rationale for the Selection of Population

Bexagliflozin is being developed for the management of essential hypertension in the U.S. adult population, and the study sites and entry criteria are consistent with this objective. Subjects who exhibit uncontrolled hypertension despite administration of five or more medications are considered to be likely non-compliant or to have unusual syndromes not representative of the hypertension exhibited by the general population. Otherwise, the entry criteria conform to medically accepted definitions of hypertension. Ambulatory monitoring typically produces mean measurements that are lower than those seen in office visits, because many adult hypertensives experience a decrease in blood pressure while sleeping. The entry criteria reflect this consideration. The target population will contain adequate representation of poorly controlled hypertensives (greater than 10% of the total randomized population must have mean 24 h SBP $\geq$ 160 mm Hg.). Although diabetes and hypertension are common comorbidities, the target population will consist of no more than 30% of subjects with both conditions, to avoid possible confounding influences attributable to potential effects specific to this population.

3.3 Study Duration and Dates

Subjects who complete both studies will spend 38 weeks including the initial 2 weeks of run-in. For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1.

4 POPULATION SELECTION

4.1 Population

The study population for the integrated program will include approximately 680 subjects with essential hypertension. Eligible subjects who consent to participate in the program will be enrolled in clinical investigational sites in the United States. Study subjects will be informed of the purpose of the program, the potential risks of participation in both studies, and will be requested to consent to the procedures and blood collection on a single consent form.

Plasma samples will be collected for population PK analysis in study 603B. Study subjects will be informed of the purpose of the PK study and requested to consent to the additional procedures and blood collection.

4.2 Inclusion Criteria

Approximately 680 patients with essential hypertension will be initially randomized. The subjects must be:

1. Male or female with age ≥ 20 years
2. Diagnosed with essential hypertension and exhibiting an office seated SBP ≥ 140 and < 180 mm Hg
3. Unmedicated or medicated by no more than 4 agents for hypertension. Unmedicated subjects are subjects who have never taken pharmacotherapy for hypertension or have not taken any anti-hypertension medication for at least 3 months. A stable dose means no change in dose or frequency for the 4 weeks prior to the screening visit
4. If female and of childbearing potential, willing to use an adequate method of contraception and to not become pregnant for the duration of the study. Adequate contraceptive measures include, but are not limited to, oral contraceptives, intrauterine devices, Depo-Provera, Norplant, hormonal contraceptive implants, bilateral tubal ligation, partner with vasectomy, condom or diaphragm plus contraceptive sponge, foam, or jelly, and abstinence
5. Willing and able to return for all clinic visits and to complete all study-required procedures
6. Able to self-medicate during the run-in period, omitting no more than one day of dosing (confirm at visit 2)
7. Shown to have a seated SBP ≥ 140 and < 180 mm Hg (confirm at visit 2)
8. Shown to exhibit a mean 24 h SBP ≥ 135 mm Hg (at visit 3)

4.3 Exclusion Criteria

Patients who have any of the following attributes will be excluded from the study.

1. Diagnosis of type 1 diabetes mellitus or maturity–onset/diabetes of the young (MODY)

2. Known history of secondary or malignant hypertension
3. Seated DBP >110 mm Hg at screening
4. Requiring insulin to control blood glucose
5. Taking more than 4 anti-hypertension medications
6. Genitourinary tract infection within 6 weeks of screening or history of ≥ 3 genitourinary infections requiring treatment within the last 6 months
7. Cancer, active or in remission for < 3 years (Non-melanoma skin cancer or basal cell carcinoma or carcinoma *in situ* of the cervix will not be grounds for exclusion)
8. History of alcohol or illicit drug abuse in the past 2 years
9. History of MI, stroke or hospitalization for heart failure in the prior 6 months
10. Previous treatment with bexagliflozin or EGT0001474
11. History of hypertensive emergency (Appendix 3)
12. History of SGLT2 inhibitor treatment in the last 3 months (Appendix 4)
13. Known intolerance or allergy to SGTL2 inhibitors
14. Any condition, disease, disorder, or clinically relevant laboratory abnormality that, in the opinion of the PI, would jeopardize the subject's appropriate participation in this study or obscure the effects of treatment
15. Pregnancy or nursing
16. Current participation in another interventional trial or having been exposed to an investigational drug within 30 days or 7 half-lives of screening, whichever is longer
17. Arm circumference too large or small to allow for accurate blood pressure readings
18. History of kidney transplant
19. Occupational or other lifestyle factors that could hamper the collection of valid ABPM data

The exclusion criteria must be verified at visit 2 after the laboratory report of the samples drawn at screening visit (visit 1) is available from the central laboratory. A subject will be excluded if any of the following laboratory observations are made:

20. Evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase > 1.5 x upper limit of normal (ULN) with the exception of isolated Gilbert's syndrome); or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x ULN
21. eGFR, as calculated by the modification of diet in renal disease study equation (MDRD), < 45 mL/min/1.73 m^2 or requiring dialysis
22. HbA1c > 9.5%
23. Positive urine pregnancy test (performed at the site) in female subjects of child bearing potential only

5 STUDY TREATMENTS

5.1 Description of Treatments

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

The following investigational drugs will be used for oral administration:

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

5.2 Treatments Administered

The study subject will take one tablet per day of the following investigational products in addition to background medications such as drugs to control diabetes, hyperlipidemia, or hypertension:

- Run-in period: placebo run-in medication
- Study 603A: bexagliflozin tablets, 20 mg or placebo
- Study 603B week 1 to week 12: bexagliflozin tablets, 20 mg
- Study 603B week 13 to week 24: bexagliflozin tablets, 20 mg or placebo

5.2.1 Investigational Product

The study drug in bottles will be dispensed by the investigator or designated staff based on kit numbers assigned by the Interactive Web Response System (IWRS) at the specified study visits (Appendix 1). Bexagliflozin tablets, 20 mg or placebo, should be self-administered orally once daily before or after breakfast with a cup of liquid.

5.2.2 Background Anti-hypertensive Medications

Adjustment of treatment for hypertension will not be permitted during the run-in period. If a change in treatment is required to improve management of hypertension, the subject may re-enter screening after the clinical condition and treatment regimen have not changed for at least 4 weeks. The screening activities should be performed and subject will be assigned a new subject number.

Subjects who take anti-hypertensive medications will continue taking background therapies for managing hypertension during the entire study at an unchanged dose, time, and frequency as prescribed to subjects prior to screening unless the investigator deems adjustment (decrease or increase) necessary for the medical well-being of the subject.

Unmedicated subjects who experience persistent hypertension may receive anti-hypertensive medications following the guidance in Section 5.7.

Anti-hypertensive medications can be reduced to mitigate symptomatic hypotension at the discretion of the investigator at any time. Guidance for rescue medications for hypertension is described in Section 5.7. Changes to the dose, frequency, or time of administration should be recorded in the concomitant medication log.

5.2.3 Background Hypoglycemic Agents

Subjects with type 2 diabetes mellitus will continue taking background oral hypoglycemic agents for managing glycemic control at an unchanged dose, time, and frequency as prescribed to subjects prior to screening unless the investigator deems adjustment (decrease or increase) necessary for the medical well-being of the subject.

5.3 Selection and Timing of Dose for Each Subject

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

On the day of scheduled clinic visits for which a fasting blood sample is to be drawn or an ABPM is to be initiated, administration of investigational product should be delayed until after blood is drawn. The product should be taken in the clinic with one cup (250 mL) of fluid.

5.4 Method of Assigning Subjects to Treatment Groups

The study will be conducted in multiple investigative sites and will involve variable numbers of subjects at each site. Enrollment will be on a competitive basis, but each site will be capped at 68 randomized subjects. Activation of investigational sites will be centrally controlled by IWRS.

Subjects who meet the eligibility criteria required at the screening visit (visit 1) must be registered in the IWRS in order to be assigned a subject number and a bottle of run-in drug. A new bottle will be assigned to the subject every 12 weeks by the IWRS at visits 3, 6, and 9. There are two randomization procedures planned in this program, at visit 3 and visit 9 (Appendix 1).

Subjects who complete the run-in period and meet the ABPM SBP ≥ 135 mm Hg criterion at visit 3 will be randomized to receive a bottle of bexagliflozin, 20 mg or placebo. Subjects will be assigned to each group in a 1:1 ratio. Randomization will be stratified according to diabetes status (history of diabetes or not), baseline ABPM SBP (≥ 160 mm Hg or not), unmedicated or not, and renal function (eGFR ≥ 60 or not). The investigator or designated staff will log into the IWRS to receive the randomization code and assigned kit number for bexagliflozin tablets, active or placebo.

At visit 6 after a subject has completed the ABPM successfully, a second bottle of study drug will be assigned to the subject by IWRS. All subjects will receive active treatment for the following 12 weeks. Subjects who experience persistent hypertension during the first 12 weeks of treatment may complete visits 5 and 6 prior to week 12 as described in Section 5.7.

At visit 9 after a subject has completed the 24 h-ABPM successfully, the subject will be randomly assigned to receive either active or placebo in a 1:1 ratio. A new randomization number and a new bottle of double blind study drug will be assigned and dispensed to the subject. Assignment to the active or placebo arm will be balanced to approximately equalize the representation in each arm of the following groups:

- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 20 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 5 mm Hg and ≤ 20 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects not requiring rescue medication prior to week 24 and exhibiting a ≤ 5 mm Hg reduction in mean SBP between Day 1 and cumulative 24
- Subjects requiring rescue medication prior to week 24

If the mean SBP is missing at cumulative week 24, the subject will be withdrawn.

Subject randomization will be deactivated for all sites when the planned number of subjects is met and a minimum of 10% of the subjects have an average 24 h ABPM SBP ≥ 160 and < 180 mm Hg at visit 3. However, if a potential subject has started the run-in period at that time and wishes to continue to participate, the subject will be allowed to continue and, if eligible, to be randomized.

5.5 Blinding

Both studies will have double-blind treatment phases. The sponsor study management team, investigators, study coordinators, pharmacists, study subjects and cardiovascular endpoint committee (CEC) will be blinded to the study medications.

To maintain blinding of the individual treatment assignment, the results of urinary glucose testing will not be made available to any study personnel or subjects. If knowledge of the test results is needed to manage a subject's condition, the investigator will contact the IWRS to obtain the treatment assignment. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded on the case report form (CRF) and the sponsor must be notified within 24 h.

A designated independent personnel who is not involved with the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DMC 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 adjudication committee members until all global investigational studies are completed and final analyses to assess cardiovascular risks are conducted.

There is a planned interim futility analysis after approximately 50% of the randomized subjects (i.e., 300) have received at least 12 weeks of treatment to evaluate the effectiveness of bexagliflozin. All study subjects will continue to receive the investigational products during the data cleaning and analysis time. Results of the futility analysis will be reviewed by an independent DMC.

5.6 Concomitant Therapy

During the course of the study, investigators will manage glucose and lipid levels according to local or regional standard of care guidance documents. Subjects will be allowed to take any medications or medicinal supplements prescribed except another SGLT2 inhibitor (Appendix 4) to manage medical conditions during the study. Any concurrent medication or supplemental treatment of other 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 is signed 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 periods.

Medications that are prescribed for non-blood pressure modifying purpose but are known to cause blood pressure change should be used judiciously. For example, using a beta-blocker to manage unstable angina may lower blood pressure. Other examples of medications that are frequently prescribed in this population are provided in Appendix 5.

5.7 Hypertension Rescue Therapies

A rescue medication is defined as a dose increase of an existing blood pressure medication or initiation of a new blood pressure medication for the purpose of lowering blood pressure. Medications prescribed for other treatment indications are not considered rescue medications. Investigators can use any approved agent to treat blood pressure above the rescue threshold. Titrating up existing medications to the maximally tolerated/recommended doses prior to adding additional agents is recommended.

Subjects will be counseled to be compliant with all their medications, to exercise regularly, lose weight if overweight or obese, adopt a diet rich in fruits, vegetables and low-fat dairy products (the DASH diet, with appropriate modifications for participants with CKD), reduce sodium intake and alcohol consumption to recommended levels. Patients who smoke will be encouraged to stop (CDC guidance). Every effort will be made to secure the continued participation of the subjects.

Rescue medications are recommended following the guidance below if the SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements over 3 consecutive days. The confirmatory measurements should be performed in the clinic if possible. If the subjects cannot complete the recommended office visits to confirm blood pressure elevation, an appropriate cuff may be provided by the clinic so the subject can report the blood pressure from home measurements.

Any subject with elevated blood pressure with symptoms suggestive of a hypertensive emergency should be immediately evaluated by the investigator, and/or referred for emergency evaluation, at the investigator's discretion. The following guidance should be followed when a subject meets the rescue criteria:

Table 1. Guidance for Hypertension Rescue Medication Use

Study/ Cumulative weeks	Procedure
603A weeks 1 to 6	• Follow procedures for visits 10 and 11 as early termination visits to obtain 24-h ABPM and collect safety data • Rescue medication should not be administered unless hypertensive emergency appears imminent. In those situations, refer the subject to seek urgent care in a clinic or hospital. Subject should withdraw from participation in the study and see primary care provider to start or intensify anti-hypertensive therapies
603A weeks 7 to 12	• Follow procedures for visits 5 and 6 to obtain 24-h ABPM and collect safety data • Start visit 6 (start of 603B) without rescue medication. If a hypertensive emergency appears imminent, refer the subject to seek urgent care in a clinic or hospital. Prescribe rescue medication at Visit 7 if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities
603B weeks 13 to 18	• Obtain 24-h ABPM and collect safety data • Rescue medication should not be administered unless hypertensive emergency appears imminent. In those situations, refer the subject to seek urgent care in a clinic or hospital. Prescribe rescue medication at Visit 7 if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities
603B weeks 19 to 24	• Obtain 24-h ABPM and collect safety data • Prescribe rescue medication if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities
603B weeks 25 to 36	• Obtain 24-h ABPM and collect safety data • Prescribe rescue medication if SBP shows an increase of 30 mm Hg from baseline or exceeds 189 mm Hg in office measurements and continue study activities

Choice of rescue therapy should take into consideration current antihypertensive treatment, as well as co-morbidities, such as cardiovascular or renal disease, and severity of BP elevation. Site investigators should use their best clinical judgement when determining rescue medications.

The following strategies are recommended, but not required:

- Amlodipine should be considered first line among calcium channel blockers.
- For patients with diabetes or chronic kidney disease with proteinuria, consider addition of an ACE inhibitor or ARB, but not both in combination.
- For patients with cardiovascular disease, consider use of a beta blocker.
- For patients with volume overload, consider use of diuretics, though caution should be used if the patient is on an additional diuretic such as a thiazide.

Step down therapy: For SBP < 110 with symptoms attributable to hypotension, investigators should decrease the dose or remove the most recently added agent, at the investigator's discretion. Investigational product should be continued unless the investigator feels it is necessary to stop for the safety of the patient.

5.8 Restrictions

5.8.1 Prior Therapy

All subjects will continue regimens for medical conditions during the study as indicated above. No subject shall have been treated with an investigational drug within 30 days of screening or within a period equal to less than 7 half-lives of the investigational drug, whichever is longer. No subject shall have been treated with insulin or an SGLT2 inhibitor within 3 months of screening.

5.8.2 Fluid and Food Intake

During the study, subjects will be counseled to remain adequately hydrated at all times. In addition, subjects should be counseled by site staff to eat a diet low in saturated fat, high in fiber, low in simple carbohydrates, and contain appropriate caloric intake to maintain weight.

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

5.8.3 Patient Activity Restrictions

Lifestyle modification should be counseled at the screening visit. Specific recommendations will include: a) weight loss in those who are overweight or obese; b) adoption of a diet rich in fruits, vegetables and low-fat dairy products (the DASH diet) with appropriate modifications for participants with CKD; c) reduction in sodium intake to recommended levels; d) reduction of alcohol consumption to recommended levels; and e) participation in regular aerobic exercise. Patients who smoke will be encouraged to stop (CDC guidance).

5.9 Treatment Compliance

Subjects will be provided with dosing instructions when the study drugs are dispensed. Subjects will also be instructed to bring their study drug 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.

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

5.10 Packaging and Labeling

Investigational products will be provided to the pharmacist or designated site personnel in high-density polyethylene (HDPE) bottles of 90 tablets sealed with a child-resistant cap. A bottle of 15 bexagliflozin tablets, placebo will be provided for the 2-week run-in portion of the study. All investigational product supplies will be prepared and labeled according to the requirements of local laws and regulations. The pharmacist or designated site personnel will dispense the investigational products for each subject according to the randomization assignment.

5.11 Storage and Reconciliation

Bexagliflozin tablets should be stored below 30^{o}C (86°F). The sponsor will notify the sites of the process for returning unused drug.

5.12 Investigational Product Retention at Study Site

The investigational products shall 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 in a room temperature < 30^{o}C 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. The clinical investigator must personally conduct the informed consent process while other study tasks may be delegated to qualified staff after training is completed. Procedures that require clinical /medical knowledge must be performed by the investigator or qualified sub-investigators.

6.1 Informed Consent

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

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

6.2 Medical History

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

6.3 Medical History

The following information will be collected at the screening visit:

6.3.1 General Demographics and Characteristics

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

6.3.2 Diabetes History

- Date of diabetes diagnosis
- 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 diabetic ketoacidosis, glaucoma, retinopathy, neuropathy, gastroparesis, nephropathy, foot ulcerations, or non-traumatic amputations, including date of diagnosis
- Frequency of hypoglycemic events (per week) that are symptomatic or require assistance

6.3.3 Renal and Cardiovascular Disease History

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

6.3.4 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 should include the agent used, indication for usage, start and stop dates, dose, and frequency
- History of medication allergies and intolerance

6.4 Physical Examination

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

6.5 Abbreviated Physical Examination

An abbreviated physical examination will include measurement of height at screening V1 only and a general assessment of the skin, heart, lungs and abdomen. The investigator will

perform abbreviated physical examinations at the time points indicated in the Schedule of Events (Appendix 1), unless clinically indicated.

6.6 Body Weight

Body weight will be determined in the visits indicated in the Schedule of Events (Appendix 1). The weight must be determined using a scale that is calibrated. Every effort should be made to use the same scale throughout the study duration.

6.7 Vital Signs

Vital signs will be measured at the time points 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 seated position will be used to determine eligibility. The vital signs shall be obtained before the scheduled blood draw.

Devices designed to measure BP from the finger or wrist may not be used. 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 positions. Prior to measuring seated 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 seated position. After seated 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 seated 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 2.

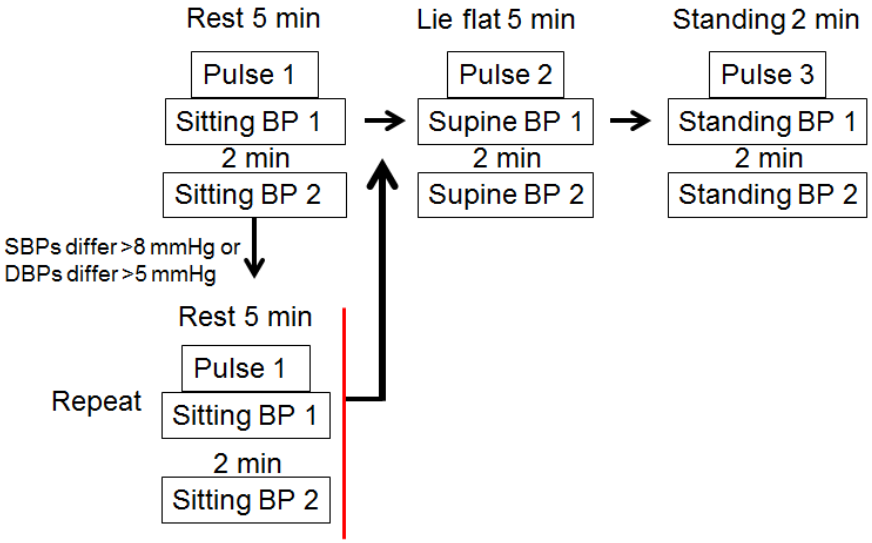

Figure 2. BP Measurement Procedure

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

6.8 12-Lead ECG

A 12-lead electrocardiogram (ECG) shall be conducted at the time points indicated in the Schedule of Events in Appendix 1 and whenever clinically indicated. This procedure should be performed in the supine position after 10 min without exertion. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT interval. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities or arrhythmia.

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

6.9 Clinical Laboratory Tests

6.9.1 Laboratory Parameters

Clinical laboratory test parameters are listed in Table 1.

Table 2. List of Laboratory Tests

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

Urinalysis:
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- pH
- Protein
- Specific gravity
- Urobilinogen

Pregnancy test:
Urine human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

Serum Chemistry:
- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- creatinine kinase (CK)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Bicarbonate (HCO_3)
- Chloride (Cl)
- Creatinine
- Glucose
- Magnesium (Mg)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- Total protein
- Triglycerides
- Uric acid

Glycemic control
- HbA1c

Population PK Sampling
- Bexagliflozin plasma level

6.9.2 Sample Collection, Storage, and Shipping

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

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

The study staff shall 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 approximately 8 h fast prior to blood draw to ensure the lipid values can be accurately determined. If a subject has not fasted, the subject should return as soon as can be arranged to provide a specimen after proper fasting.

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

An investigator can perform additional laboratory testing to diagnose or to follow up an adverse event progression or resolution. Clinical samples should be analyzed in a local laboratory if a fast turnaround is necessary to determine the treatment plan.

6.9.2.2 Urinalysis

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

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

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

6.9.2.3 Population PK Sampling

Blood samples for the population PK analysis will be drawn when the subjects return to the clinic during week 18 (V7) and/or week 24 (V8) 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.

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^{o}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. Approximately 600 measurements of bexagliflozin plasma concentrations will be collected from an estimated 200 subjects who will have received active drug in this study.

6.10 Dispensing Study Drug

6.10.1 Run-in Drug

The investigator or designated personnel will dispense one bottle of 15-count bexagliflozin tablets at visit 1. Prior to registering a subject in the IWRS at visit 1 to receive the designated kit numbers of run-in drug, the signed ICF and eligibility criteria required at screening visit must be confirmed.

Subjects shall be instructed to take the first dose of run-in drug at the clinic with 1 cup (~250 mL) of water. Subjects shall be instructed to withhold the study drug administration on the day of visit 2 until they are in the clinic.

6.10.2 Double-Blind Study Drug

The double blind study drug shall be dispensed to the subject after the 24 h-ABPM values are retrieved and ≥ 51 day time and ≥ 13 night time BP readings are recorded successfully. The 24 h-ABPM may be repeated if necessary.

The IWRS will assign a double blind study drug kit number for each subject at visits 3, 6, and 9. The subject will be provided with a bottle of the double blind study drug and instructed to self-administer the first dose of investigational product at the clinic and to take one tablet at approximately the same time each day, before or after breakfast, with one cup (250 mL) of liquid. The day of first double blind study drug dosing is considered Day 1 of the study day. Each bottle of the investigational products will provide daily dosing for 90 days.

On the days of clinic visit, subject should not take the study drug until the visit procedures are completed.

6.11 Efficacy Assessments

6.11.1 24-h ABPM

ABPM will be performed for 24 hours, with measurements every 15 minutes during the day (16 h) and every 30 minutes during the night (8 h). Subjects will be fitted with the ABPM device, administer one tablet of study drug, and wear the cuff for 24 consecutive hours at the specified visit (Appendix 1). Subjects should take the study drugs while taking all their normal medications and performing normal daily activities. Subjects will be instructed to refrain from strenuous exercise or shower during this period. The ABPM device will be

placed on the arm by study staff and begin recording values immediately following the dosing.

If the ABPM is not completed or if < 64 BP readings (51 day time and 13 night time BP readings) are recorded, the procedure must be repeated. A new bottle of double blind study drug can be dispensed to a subject only after the 24 h ABPM is completed successfully.

Prior to randomization, subject who cannot complete the 24h ABPM within two attempts will be considered a screen fail. After randomization, if a subject cannot complete a 24h ABPM within two attempts, the data will be considered missing.

6.11.2 SBP and DBP from office visits BP

Vital signs will be measured as indicated in the Schedule of Events (Appendix 1) and will include pulse, sitting, supine, and standing BP. Vitals should be measured prior to blood draws following the procedures described in Section 6.7.

6.11.3 Body weight

The body weight must be determined using a scale that is calibrated. The same scale should be used throughout the study duration.

6.11.4 Pulse Pressure

The pulse pressure will be calculated as the difference between mean systolic and diastolic BP of the ABPM.

6.11.5 Trough/Peak Ratio

Trough/Peak ratio will be calculated based on the four valid measurements centered on approximate T_{max} (4 h post-dose) and the four valid measurements immediately preceding the removal of the monitor and prior to administering a tablet.

6.12 Adverse Events Assessments

6.12.1 Definition of Adverse Events

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

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

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

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

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

Expectedness:

- Defines any adverse events that are expected, based on the Investigator Brochure and previous clinical trials.
- Describe the means for determining and reporting unexpected adverse events.

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

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A serious UADR. The sponsor must report any suspected SUSAR in an IND safety report (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

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

1 = Mild: event is medically significant but produces no disruption to daily activity

2 = Moderate: event is medically significant and reduces or affects normal daily activity

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

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

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

6.12.2 Eliciting and Reporting AEs

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

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

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

6.12.3 Immediately Reportable AEs

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

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

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

6.12.4 Pregnancy

Women of childbearing potential (WOCBP) are defined as any female who has experienced menarche and who is not permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. WOCBP who are sexually active must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

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

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

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

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

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

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

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

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

6.12.6 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.

6.12.7 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 6.12.3. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved.

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

follow SAEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor until the event has been resolved. This study requires that subjects be actively monitored for SAEs for at least 4 weeks after the last treatment.

6.12.8 Adverse Events of Special Interest (AEOI)

AEOI include the following categories: genital mycotic infections, urinary tract infections including urosepsis and pyelonephritis, diuretic effects including hypovolemia, hypotension episodes, hepatotoxicity, hypoglycemia, falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders including DKA, renal failure events, and major adverse cardiovascular events. AEOI should be monitored carefully and documented in the CRFs.

6.12.8.1 Genital Mycotic Infections (GMIs)

The investigator shall 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.

6.12.8.2 Urinary Tract Infections (UTIs)

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

The investigator should query the subject at specified clinical visit for symptoms that may be related to a UTI and, if appropriate, document these events as symptomatic UTI in the CRF unless an alternative diagnosis is present. In addition, a clean catch urine sample will be obtained at the time points indicated in the schedule of events and a urinalysis will be performed on that sample at these visits. A positive urinalysis will be defined as one with detectable leukocyte esterase and/or nitrites. If the subject reports symptoms consistent with a UTI or the urinalysis at the clinical site is positive, a urine culture will be performed at the central laboratory. A positive urine culture will be defined as one with 10^5 CFU of any species. The investigator may also perform a urine culture using local resources if necessary for clinical care.

6.12.8.3 Hepatotoxicity

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

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

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

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

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

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

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

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

6.12.8.4 Hypoglycemia

Events of hypoglycemia or potentially representing hypoglycemia should be carefully evaluated. In the event of signs or symptoms, a diabetic subject is expected to check the blood glucose if it is reasonably safe to do so, and, if appropriate, consume carbohydrates to treat hypoglycemia.

Subjects who have type 2 diabetes mellitus will be expected to record the following information for each hypoglycemic event in the glycemic control diary:

- Signs and symptoms attributed to hypoglycemia and the time and date on which they occurred
- SMBG reading at the time of the signs and symptoms attributed to hypoglycemia
- Time elapsed from the most recent meal to the onset of signs and symptoms
- Duration, intensity, and type of any exercise within the 24 h prior to the signs and symptoms
- Type of treatment used (e.g., juice, crackers) for the signs and symptoms and whether assistance was required from another person to administer the treatment

- SMBG reading 15 minutes after treatment with carbohydrate and the time at which this was measured
- Whether or not the signs and symptoms attributed to hypoglycemia resolved after blood glucose returned to normal

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

At each study visit, the investigator should query the subject with regard to the occurrence of signs and symptoms potentially related to hypoglycemia.

In the event of a blood glucose value < 70 mg/dL or signs and symptoms potentially related to hypoglycemia, the investigator should complete the supplemental CRF w.

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

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

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

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

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

If hypoglycemia occurs, the total daily dose of the hypoglycemic medication should be reduced 50% or more at the discretion of the investigator.

6.12.8.5 Diabetic Ketoacidosis (DKA)

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

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

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

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

6.12.8.6 Acute Kidney Injury

Evaluation and management of subjects with and at risk for acute kidney injury (AKI) should be performed during the study period based on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline in 2012 (KDIGO Clinical Practice Guideline for AKI, 2012). The classification/staging System for AKI is described in Appendix 5.

If serum creatinine increases suggesting a possible stage 1 AKI, the investigator should confirm the increase in serum creatinine within one week of learning the result and enter an

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

If serum creatinine increases or other signs suggesting a possible stage 2 or 3 AKI, the subject should be monitored daily and nephrology consultation or hospitalization within 24 h should be considered. Study drug administration should be stopped until the creatinine value returns to < 0.3 mg/dL from baseline. If potentially life-threatening conditions (*i.e.*, uremia, pulmonary edema, arrhythmia, disseminated intravascular coagulation, hyperkalemia, metabolic acidosis) are present occurring in the setting of a possible stage 2 or 3 AKI event, the administration of study drug must be stopped and the medical monitor should be informed. The medical monitor will advise on whether the study drug can be restarted after the resolution of the potentially life-threatening condition. Local laboratory testing will be acceptable when immediate lab results are necessary for clinical assessment.

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

The renal function monitoring plan is summarized in Figure 3.

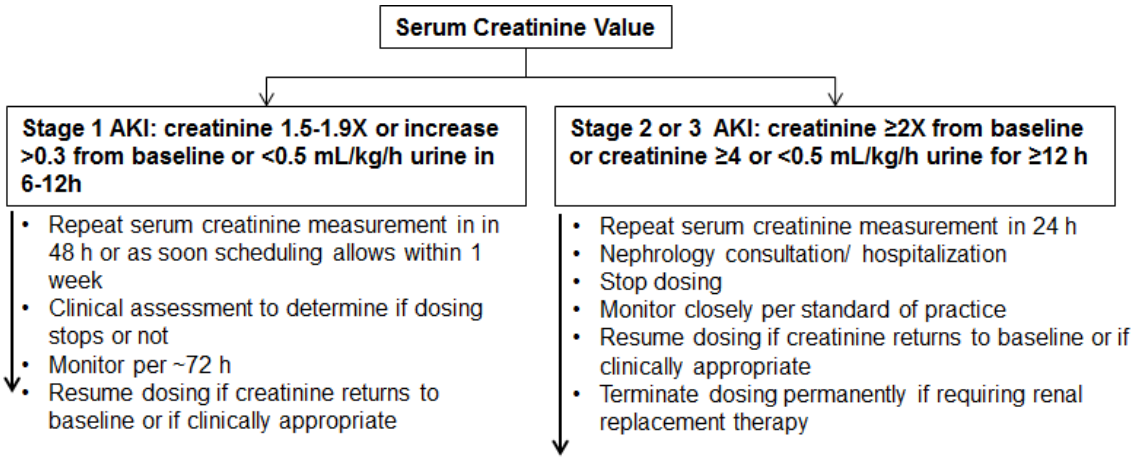

Figure 3. Renal Function Monitoring Plan

6.12.9 Major Adverse Cardiovascular Event (MACE)

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

The independent CEC will receive and adjudicate the following events.

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

6.13 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 hypertension must be recorded as concomitant medications in the CRF. Any medication given to treat hypertension and continued for more than 2 weeks is considered a rescue therapy and should be recorded in the rescue medication form and 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.

6.14 Removal of Patients from the Trial or Study Drug

The investigator must emphasize to potential subjects the importance of continued participation for the full duration of the trial during the informed consent process. Potential subjects should be informed that the trial procedures will allow additional medications to

control hypertension or other adverse conditions. It is also important to emphasize that missing data and missed visits could affect the entire trial. If subjects are dissatisfied with the conduct of the trial but have not withdrawn, the investigators should make an effort to address their concerns and retain them in the trial if possible. In doing so, investigators must be careful that the efforts do not cross over into coercion**.**

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 IRB/EC 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. Reasons for all withdrawals should be recorded on the CRF. Examples of reasons for withdrawal include:

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

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

Subjects who withdraw from the study will not be replaced.

6.15 Appropriateness of Measurements

The study procedures and measurements in this protocol are widely used and generally recognized as reliable, accurate, and relevant for subjects with essential hypertension.

7 STUDY ACTIVITIES

The 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 procedures are described in Section 6.

A visit window of ± 3 days is allowed for post-randomization visits. Visit 3 is the day of randomization and the basis for the visit window. A repeat ABPM shall be performed within 2 days if the 24h-ABPM is incomplete. Only the second set of ABPM data will be entered in the case report form on visits 2-3, 5-6, 8-9, and 10-11. The other specified procedures in the same assessment period do not need to be repeated. If the ABPM fails twice at visit 3 prior to randomization, the subject is considered a screen failed subject. If the ABPM fails twice after randomization, the ABPM BP on that assessment period is considered missing.

Procedures listed for visit 10 will be completed if a subject is withdrawn from the study.

7.1 Visit 1 (Day -13 to day -12)

- Explain the content of the informed consent materials to the subject and collect signed informed consent
- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Obtain Medical History and Demographic Information
- Perform an abbreviated physical examination
- Measure vital signs, including BPs and heart rate
- Perform a 12-lead ECG measurement
- Draw blood and collect a urine sample for clinical laboratory tests. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Dispense kits for the run-in period

7.2 Visit 2 (Day -1)

- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Perform a complete physical examination
- Measure vital signs, including BPs and heart rate
- Perform a 12-lead ECG measurement
- Draw blood and collect a urine sample for clinical laboratory tests. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Begin 24 hour ABPM
- Assess AEs
- Record concomitant medications

7.3 Visit 3 (Day 1)- Study 603A

- Collect needed information and evaluate conformance to inclusion and exclusion criteria
- Measure vital signs, including BPs and heart rate

- End 24-h ABPM and download readings. The 24-h ABPM should be repeated within 2 days if <64 BP readings (51 day time and 13 night time BP readings) are recorded successfully.
- Complete subject randomization using IWRS
- Dispense investigational product based on randomization

7.4 Visit 4 (Cumulative Week 6)

- Measure vital signs, including BPs and heart rate
- Assess AEs
- Record concomitant medications

7.5 Visit 5 (Cumulative Week 12)

- Perform an abbreviated physical examination
- Measure vital signs, including BPs and heart rate
- Perform a 12-lead ECG measurement
- Draw blood and collect a urine sample for clinical laboratory tests. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Begin 24 hour ABPM
- Assess AEs
- Record concomitant medications

7.6 Visit 6 (Cumulative Week 12 + 1 Day) – Study 603B

- Measure vital signs, including BPs and heart rate
- End 24-h ABPM and download readings. The 24-h ABPM should be repeated within 2 days if <64 BP readings (51 day time and 13 night time BP readings) are recorded successfully.
- Dispense investigational product based on randomization

7.7 Visit 7 (Cumulative Week 18)

- Measure vital signs, including BPs and heart rate
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers. Alternatively, blood sample can be on any of the days during the week of the clinical visit
- Assess AEs
- Record concomitant medications

7.8 Visit 8 (Cumulative Week 24)

- Perform an abbreviated physical examination
- Measure vital signs, including BPs and heart rate
- Perform a 12-lead ECG measurement

- Draw blood and collect a urine sample for clinical laboratory tests. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Collect blood specimens for sparse PK sampling from selected subjects in participating centers. Alternatively, blood sample can be on any of the days during the week of the clinical visit
- Begin 24 hour ABPM
- Assess AEs
- Record concomitant medications

7.9 Visit 9 (Cumulative Week 24 + 1 Day)

- Measure vital signs, including BPs and heart rate
- End 24-h ABPM and download readings. The 24-h ABPM should be repeated within 2 days if <64 BP readings (51 day time and 13 night time BP readings) are recorded successfully.
- Complete subject randomization using IWRS
- Dispense investigational product based on randomization

7.10 Visit 10 (Cumulative Week 36)

- Perform an abbreviated physical examination
- Measure vital signs, including BPs and heart rate
- Perform a 12-lead ECG measurement
- Draw blood and collect a urine sample for clinical laboratory tests. The specific laboratory tests scheduled for this visit are listed in Appendix 2
- Begin 24 hour ABPM
- Assess AEs
- Record concomitant medications

7.11 Visit 11 (Cumulative Week 36 + 1 Day)

- Measure vital signs, including BPs and heart rate
- End 24-h ABPM and download readings. The 24-h ABPM should be repeated within 2 days if <64 BP readings (51 day time and 13 night time BP readings) are recorded successfully
- Assess AEs
- 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.

The laboratory testing will be performed by a CLIA certified central laboratory to ensure the laboratory values are determined consistently.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The following sections provide a summary of the planned analysis of the trial data but a complete statistical analysis plan will be developed with further details before any unblinding occurs.

In general, descriptive summary statistics for continuous variables will include the number of subjects [N], mean, median, standard deviation [SD], quartiles, and minimum and maximum. Descriptive statistics in categorical variables will include number and percentage of subjects in each category. Summary statistics will be presented by treatment groups. Statistical analysis will be carried out using SAS version 9.2 or later.

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

9.2 Determination of Sample Size

The primary endpoint of study 603A is the change from baseline (Day 1) to week 12 in the 24-hour average SBP of the bexagliflozin group compared to the placebo group using a superiority testing at an overall two-sided 0.05 level of significance.

The primary endpoint of study 603B is the change from week 12 (cumulative week 24) to week 24 (cumulative week 36) in the 24-hour average SBP in the bexagliflozin group compared to the placebo group using a superiority testing at an overall two-sided 0.05 level of significance.

The assumptions to estimate the sample size for the primary endpoint of study 603A are:

1. The magnitude of the decrease from baseline (Day 1) to week 12 of the 24 h mean SBP in the bexagliflozin treatment arm will exceed that found in the placebo arm by 5 mm Hg;
2. The standard deviation of the change from baseline to week 12 will be 15 mm Hg for both the active and placebo groups;
3. The two-sided significance level is 0.05.

The assumptions to estimate the sample size required for the primary endpoint of study 603B are:

1. Bexagliflozin will remain effective for at least 24 weeks. The 24-hour average ABPM SBP will not change between week 12 and week 24 (cumulative week 24 and week 36).
2. Subjects who are randomized to receive placebo will show an increase in the ABPM SBP of 4 mm Hg between week 12 and week 24 (cumulative week 24 and week 36).
3. The standard deviation of the change is 15 mm Hg for both the active and placebo groups.
4. The two-sided significance level is 0.05.

A sample size of 254 per arm is required for the measurement to have 85% power to attain significance for the second primary endpoint. It is estimated that 75% of subjects will have completed the 36 weeks of study treatment since the first randomization. Thus a total sample size of 680 subjects is planned for the first randomization. It is estimated that approximately 8% will drop out for the first 12 weeks. With a sample size of 626 subjects at the end of study 603A, it will provide >95% power for the first primary endpoint.

An interim non-binding futility analysis when approximately half (i.e., 300) patients completed the first 12 weeks of the treatment will be conducted. Using interpolated spending function of Type II error, i.e., with 0.5 proportion of Type II error being spent at the interim look, the study may stop for futility when the test statistics (Z score) is less than 0.656 (or p-value>0.512). The overall power for the first primary endpoint maintains >95% with this interim look.

9.3 Analysis Populations

The following populations will be used for analyses:

9.3.1 Study 603A

- Intention-to-Treat (ITT) Analysis Set: Include all subjects who are randomized to the study. All subjects will be analyzed according to the treatment to which they were randomized to receive.
- Safety Analysis Set: Include all subjects who are randomized to the study and are treated. This data set will be used for both study 603A alone summaries and combined study 603A and 603B summaries.

9.3.2 Study 603B

- Intention-to-Treat (ITT) Analysis Set: Include all subjects who are randomized at week 12 (cumulative week 24). All subjects will be analyzed according to the treatment to which they were randomized to receive.
- Safety Analysis Set: Include all subjects who are treated.
- Safety Analysis Set for withdrawal period: Include all subjects who are randomized at week 12 and are treated with at least one dose.

9.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be descriptively summarized for all ITT subjects by treatment group for study 603A and study 603B. Key variables include, but are not limited to: age, gender, race, ethnicity, baseline vital signs, ECG measures, and renal function. In general, baseline measurement is defined as the last measurement prior to the randomization for each study.

9.5 Primary Efficacy Endpoints

The primary endpoint of study 603A is the change from baseline (Day 1) to week 12 of the 24 h mean SBP in the bexagliflozin group compared to the change in the placebo group, testing for superiority at a two-sided 0.05 level of significance.

The primary endpoint of study 603B is the change from week 12 to week 24 (cumulative week 24 to week 36) of the 24 h mean SBP in the bexagliflozin group compared to the change in the placebo group, testing for superiority at a two-sided 0.05 level of significance.

For the primary efficacy assessment in study 603A, an analysis of covariance (ANCOVA) will be applied to analyze the mean change from baseline to week 12 of the 24-hour average ABPM SBP, adjusted for diabetes status, renal function, medicated or unmedicated status, and baseline ABPM SBP value. Least squares means with 95% confidence intervals (CIs) will be generated for the difference between the treatment groups at week 12. If a subject receives rescue medication or is withdrawn from the study early, the last post baseline observed value will be used for the primary analysis time point of week 12.

For the primary efficacy assessment in study 603B, a similar ANCOVA method will be applied, adjusted by the ABPM SBP evaluations at week 12 (cumulative week 24). Changes from week 12 to week 24 ABPM SBP will be analyzed. Least squares means with 95% CIs will be generated for the difference between the treatment groups at week 24.

Additional sensitivity analyses will be conducted as follows for missing data due to early withdrawal of the study or receiving rescue medications.

- Cumulative week 12 and week 36 evaluations after rescue medication will be used in the analyses in place of evaluations prior to the rescue medication
- Analyses will be based on subjects without rescue medication
- Tipping Point analysis will be conducted as follows:
    - Subjects in the bexagliflozin treatment arm who discontinue study participation or initiate rescue medication, will be analyzed assuming that their treatment effect has worsened by δ (where $\delta = 0.5$ to 5, with steps of 0.5) compared to the reduction of SBP for subjects who are in the study without rescue medication.
    - Subjects in the placebo treatment arm who discontinue study participation or initiate rescue medication, will be considered to have experienced a treatment effect the same as the reduction of SBP for subjects who are in the study without rescue medication.

9.6 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be accessed without multiplicity adjustment. Analyses will be primarily based on ITT analysis sets.

Absolute values and changes from baseline (Day 1 for study 603A or Week 12 value for study 603B) in vital signs measurements, pulse pressure, body weight, peak-trough ratio of ABPM SBP, and HbA1c will be summarized descriptively. Mean treatment effects will be estimated based on ANCOVA using similar method as described for the primary endpoint.

The responder assessments, such as the proportion of subjects who achieve specific goals, will be summarized by frequency table; logistic regression will be used to analyze the treatment effect with 95% CIs for the fraction responding within each treatment group and between treatment groups. Analyses will be based on all observed assessments prior to rescue medication or study end. In addition, a sensitivity analysis by assuming non-responder for subjects who had no post baseline assessments prior to early withdrawal of the study or initiation of the rescue medication, will also be performed.

In addition, changes in mean ambulatory SBP/DBP or office seated SBP/DBP after 12, 24, or 36 weeks of bexagliflozin treatment will also be summarized using combined 603A and 603B evaluations.

Detailed analyses will be defined in the statistical analysis plan.

9.7 Analysis of Safety

Safety data include AEs, physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology parameters and urinalysis. Observed data will be summarized by treatment group within each study (603A, 603B) or pooled studies using the safety analysis sets as defined in sections 9.3.1 and 9.3.2.

9.7.1 Adverse Events

AEs will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs that begin at or after the first administration of double-blind study medication (i.e., first dose of study 603A) or existing AEs that worsen in severity after the first dose of double-blind study medication are considered treatment emergent AEs (TEAE). Treatment emergent periods will be divided into three periods: study 603A, study 603B prior to randomization, and study 603B after randomization. The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA system organ class and preferred term, for each period as well as all periods combined. 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.

Similarly, 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.

In addition, adverse events of special interest include, but not limited to UTI, GMI, hypoglycemia, hepatotoxicity, MACE, and DKA events, will be separately summarized.

9.7.2 Laboratory Evaluations and Other Safety Assessments

Clinical laboratory tests (see Section 6 for a complete list), vital signs, and 12-lead ECG assessments will be descriptively summarized for actual values and changes from baseline (Day 1 for study 603A, and week 12 for study 603B), by treatment group and for each visit.

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 by study with shift tables for selected parameters.

In addition, summaries based on assessments from both studies (603A and 603B) will also be presented. The changes from the last assessment prior to first dose of bexagliflozin to after bexagliflozin treatment of 12 weeks, 24 weeks, and 36 weeks will be provided.

9.7.3 Physical Examination

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

9.8 Interim Analysis

An interim non-binding futility analysis when approximately half patients completed the first 12 weeks of study 603A will be conducted. Using interpolated spending function of Type II error, i.e., with 0.5 proportion of Type II error being spent at the interim look, the study may stop for futility when the test statistics (Z score) is less than 0.656 (or p-value>0.512). The overall power for the first primary endpoint maintains > 95% with this interim look. The interim analysis will be conducted by an independent data monitoring group.

10 ADMINISTRATIVE CONSIDERATIONS

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.

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

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

10.1 Ethical Conduct of the Study

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

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

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

Any deviations from the protocol must be fully explained and documented by the investigator. The circumstances, action taken, and impact of the deviation on the trial must be

communicated by the principal investigator to the designated medical monitor. Any subsequent actions will be assessed by the designated medical monitor and documented.

10.2 Subject Information and Consent

Prior to the beginning of the study, the investigator must have received from the IEC or IRB the written approval or favorable opinion of the informed-consent form and any other written information to be provided to subjects. The written approval of the IRB/IEC together with the approved subject information/informed consent forms must be filed. The informed consent form must contain all elements required by authorized regulatory authorities and the ICH GCP guidelines (E6), in addition to any other elements required by local regulations or institutional policy.

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

10.3 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.

10.4 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.

10.5 Case Report Forms and Study Records

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

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

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

10.6 Data Monitoring Committee

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

10.7 Protocol Violations/Deviations

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

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

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

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

10.8 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.

10.9 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.

10.10 Publication and Disclosure Policy

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

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

11 REFERENCE LIST

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Appendix 1 Schedule of Events

	Screening/ Run-in		Study 603A			Study 603B					
Procedures			**weeks 1 to 12**			**weeks 1 to 12**			**weeks 13 to 24**		
Cumulative study week			**1 -12**			**13-24**			**25-36**		
Visit Number	1	2	3	4	5	6	7	8	9	10	11
Time to randomization	-13 or -12 d	-1d	0w +1d	6w	12w	12w +1d	18w	24w	24w +1d	36 w	36w +1d
Informed Consent	X										
Medical History	X										
Inclusion/Exclusion Criteria	X	X	X								
Run-in drug dispensation	X										
Randomization			X						X		
Begin 24-h ABPM		X			X			X		X	
End 24-h ABPM			X			X			X		X
Double blind drug dispensation			X			X			X		
Clinical Laboratory Tests	X	X			X			X		X	
Population PK Sampling							X	X			
12-Lead ECG	X	X			X			X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Abbreviated PE & weight	X				X			X		X	
Complete PE & weight		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 Laboratory Tests

	Screening/ Run-in		**Study 603A**			**Study 603B**					
Procedures			**weeks 1 to 12**			**weeks 1 to 12**			**weeks 13 to 24**		
Cumulative study week			**1 -12**			**13-24**			**25-36**		
Visit Number	1	2	3	4	5	6	7	8	9	10	11
Time (week) to randomization	-12 to -13 d	-1d	0w +1d	6w	12w	12w +1d	18w	24w	24w +1d	36w	36w +1d
Randomization			X						X		
Whole blood sample	X	X			X			X		X	
Hematology	X	X			X			X		X	
HbA1c	X	X			X			X			
Serum sample										X	
Chemistry	X	X			X			X		X	
Lipids	X	X			X			X		X	
Urine sample											
Urinalysis	X	X			X			X		X	
Pregnancy test (WOCBP)	X	X			X			X		X	
Population PK Sampling							X	X			

Appendix 3 Hypertensive Emergency

A hypertensive emergency is defined as a blood pressure above either 180 mm Hg SBP or 120 mm Hg DBP (or an acute rise deemed significant by the clinician's judgement) with symptoms reflecting the possibility of end organ damage. These can include: generalized neurologic symptoms (agitation, delirium, stupor, seizures, visual disturbances), focal neurologic symptoms consistent with ischemic or hemorrhagic stroke, funduscopic findings consistent with hypertensive retinopathy (flame hemorrhages, exudates, papilledema), nausea/vomiting, chest pain consistent with myocardial infarction/aortic dissection, acute back pain consistent with aortic dissection, dyspnea consistent with pulmonary edema.

Appendix 4 Examples of SGLT2 Inhibitors

The following medications are prohibited during the study. Other medications containing SGLT2 inhibitors that may become approved for the treatment of T2DM during the THR-1442-C-603 study will also be prohibited in this study.

Generic Name	**Trade Name**
canagliflozin	Invokana™
canagliflozin plus metformin	Invokamet™
dapagliflozin	Farxiga™ or Forxiga™
empagliflozin	Jardiance®
empagliflozin plus linagliptin	Glyxambi®

Appendix 5 Examples of Medications with Hypotensive Effects

Class of Medications	Indication	Example
Diuretics	heart failure associated edema	furosemide, hydrochlorothiazide
Alpha blocker	prostrate enlargement	prazosin, terazosin
Beta blocker	angina, tachycardia	atenolol, propranolol
Dopamine agonist	Parkinson's disease	pramipexole, levodopa
Tricyclic antidepressants	Depression	doxepin, imipramine
Phosphodiesterase inhibitor	Erectile dysfunction	sildenafil, tadalafil

Appendix 6 KDOQI Chronic Kidney Disease Classification and Acute Kidney Injury Stage Definition

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

Stages of CKD are outlined in Table 2.

KDOQI CKD Stages

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

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

Table 3. Classification/Staging System for Acute Kidney Injury

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

Appendix 7 Sponsor Signatures

Study Title: An Integrated Assessment of the Safety and Effectiveness of Bexagliflozin Tablets, 20 mg, for the Management of Essential Hypertension

Study Number: THR-1442-C-603

Final Date: 28 August 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: 28 August 2017

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

Signed: _____ Date: August 28, 2017

Andrew S. Allegretti, M.D., M.Sc.
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Signed: _____ Date: 29 Aug 2017

Wenjiong Zhou, Ph.D.
Statistician
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Appendix 8 Investigator's Signature

Study Title: An Integrated Assessment of the Safety and Effectiveness of Bexagliflozin Tablets, 20 mg, for the Management of Essential Hypertension

Study Number: THR-1442-C-603

Final Date: 28 August 2017

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

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

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

Signed:_____ Date:_____
Clinical Investigator