Clinical Trial Protocol: THR-1442-C-443

Study Title:	A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of Bexagliflozin on the Pharmacokinetics of Digoxin in Healthy Subjects
Study Number:	THR-1442-C-443
Study Phase:	1
Product Name:	Bexagliflozin Tablets, 20 mg
Indication:	Type 2 Diabetes Mellitus
Investigators:	Single Center
Sponsor:	Theracos Sub, LLC
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	Date
Version 2.0:	13 June 2017

Confidentiality Statement

The information contained in this protocol is confidential and provided only to the investigators, clinical study collaborators, investigational drug managers, study sites and institutional review boards participating in the study. The information may, therefore, not be, disclosed to any third party except for subjects when receiving their consent, or used for purposes other than this study without the written consent of Theracos Sub, LLC

SYNOPSIS

Sponsor: Theracos Sub, LLC

Name of Finished Product: Bexagliflozin Tablets, 20 mg

Name of Active Ingredient: Bexagliflozin

Name of Inactive Ingredient:

Polyethylene oxide, glyceryl behenate, lactose monohydrate, micronized poloxamer 188, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate (vegetable grade). The tablets are film-coated with Opadry II Blue with no markings on the tablets.

Study Title:

A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of Bexagliflozin on the Pharmacokinetics of Digoxin in Healthy Subjects

Study Number: THR-1442-C-443

Study Phase: 1

Primary Objective:

To evaluate the effect of bexagliflozin on the pharmacokinetics (PK) of digoxin

Secondary Objective:

To assess the safety and tolerability of digoxin when it is co-administered with bexagliflozin

Study Design:

This is a phase 1, single center, open-label, two-period, two-treatment, crossover study to evaluate the effect of bexagliflozin tablets, 20 mg, on the pharmacokinetics of digoxin, 0.5 mg, when co-administered in healthy subjects. Approximately 18 eligible healthy subjects will be randomized to one of the two groups (Group 1 and 2) with up to 9 subjects per group. Subjects will reside in the clinic for a total of 16 days, divided into two treatment periods, Periods 1 and 2. Subjects will be discharged and out of the clinic between the 2 treatment periods for 9 days for Group 1 and 7 days for Group 2. During the treatment periods, subjects will receive 2 treatments in differing order: Treatment A, bexagliflozin administered once daily for 8 days with digoxin co-administered on Day 3 and Treatment B, digoxin administered alone on Day 1. Safety monitoring will be conducted throughout the study.

Group 1:

Period 1, Treatment A: Subjects randomized to Group 1 will be admitted to the clinic on Day 0. Starting on Day 1, subjects will receive once daily oral dose of 20 mg bexagliflozin for 8 days; a single dose of 0.5 mg digoxin will be co-administered with bexagliflozin on Day 3. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 3, 24 h (Day 4), 48 h (Day 5), 72 h (Day 6), 96 h (Day 7), and 120 h (Day 8) after administration of digoxin. Subjects will be discharged on Day 8.

Period 2, Treatment B: Subjects will be admitted on Day 18 and receive a single oral dose of 0.5 mg digoxin on Day 19. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 19, 24 h (Day 20), 48 h (Day 21), 72 h (Day 22), 96 h (Day 23), and 120 h (Day 24) after administration of digoxin. Subjects will be discharged

from the clinic on Day 24.

Group 2:

Period 1, Treatment B: Subjects randomized to Group 2 will be admitted to the clinic on Day 0. On Day 1, subjects will receive a single oral dose of 0.5 mg digoxin. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 1, 24 h (Day 2), 48 h (Day 3), 72 h (Day 4), 96 h (Day 5), and 120 h (Day 6) after administration of digoxin. Subjects will be discharged on Day 6.

Period 2, Treatment A: Subjects will be admitted on Day 14. On Day 15, subjects will start to receive once daily oral dose of 20 mg bexagliflozin for 8 days; a single dose of 0.5 mg digoxin will be co-administered with bexagliflozin on Day 17. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 17, 24 h (Day 18), 48 h (Day 19), 72 h (Day 20), 96 h (Day 21), and 120 h (Day 22) after administration of digoxin. Subjects will be discharged from the clinic on Day 22.

Study Population: Approximately 18 healthy subjects are planned.

Diagnosis and Main Criteria for Inclusion:

1. Subjects who are between the ages of 18 and 55 years, inclusive, in good health based on medical history, physical examination, ECG, and routine laboratory tests (blood chemistry, electrolytes, hematology, lipids, urinalysis, and drug screen)
2. Subjects with body-mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2, inclusive
3. Subjects who are not surgically sterile must agree to use appropriate birth control when engaging in sexual intercourse for a period of 30 days after discharge from the clinic
4. Subjects who are non-smokers for at least 6 months prior to screening

Test Product; Dose; and Mode of Administration:

Bexagliflozin Tablets, 20 mg, oral administration

Reference Therapy; Dose; and Mode of Administration:

Digoxin Tablets, 0.5 mg, oral administration

Duration of Treatment:

Each study subject will receive a total of 8 doses of bexagliflozin (20 mg) and 2 doses of digoxin (0.5 mg) during 2 treatment periods with a study duration of up to 46 days, including screening and washout periods.

Pharmacokinetic Variables:

The following PK parameters of digoxin, if possible, will be determined after each subject is dosed with either digoxin alone, or the combination of digoxin and bexagliflozin.

C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
λ_z	Terminal elimination phase rate constant
$t_{½}$	Apparent terminal elimination half-life
CL/F	Apparent oral clearance
V_z/F	Apparent volume of distribution

AUC_{0-t} Area under the plasma concentration-time curve from Time 0 to Time t (time of last quantifiable plasma concentration)

$AUC_{0-\infty}$ Area under the plasma concentration-time curve from Time 0 to infinity

Safety Assessments:

Physical examinations

Vital signs

12-lead electrocardiograms

Clinical laboratory tests including blood chemistry and hematology parameters

Urinalysis

Adverse events

Concomitant medication use

Statistical Methods:

Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS, USA). PK parameters of digoxin will be calculated by non-compartmental analyses (NCA) of plasma concentration-time data using Phoenix® WinNonlin® 6.4 (Certara, USA). To assess the effect of bexagliflozin on the PK of digoxin, an analyses of variance (ANOVA) using a linear mixed-effects model will be fitted to the natural logarithmic transformation of PK parameters of digoxin (C_{max}, AUC $_{0-t}$ and AUC $_{0-\infty}$). The linear mixed-effects model will include subject as a random effect, and treatment, period, and sequence as fixed effects. The 90% confidence intervals will be constructed for the (digoxin with bexagliflozin) to (digoxin alone) ratio of the least squares (LS) geometric means of PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), with 80-125% defined as the lack of interaction boundaries.

Descriptive statistics for the PK parameters C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, CL/F, V_z/F, λ_z and $T_{1/2}$ will be tabulated by treatment. Means, standard deviations, medians, ranges (min, max) and geometric means and coefficients of variation will be presented for all PK parameters with exception of T_{max}. Medians and ranges will be presented for T_{max}.

Date of Original Protocol: 09 June 2017

Date of Most Recent Protocol V.2.0: 13 June 2017

Prepared in: Microsoft Word 2007

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransferase
ATPase	adenosine triphosphatase
AUC	area under the time-concentration curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from Time 0 to infinity
AUC_{0-t}	area under the plasma concentration-time curve from Time 0 to Time t (time of last quantifiable plasma concentration)
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C_{max}	maximum plasma drug concentration
CI	confidence interval
CL/F	Apparent oral clearance
CRF	case report form
CRO	contract research organization
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GMI	genital mycotic infection
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference for Harmonisation
IND	Investigational New Drug
IRAE	Immediately Reportable Adverse Event
IRB	Institutional Review Board
K2EDTA	potassium ethylenediaminetetraacetic acid
λ_z	terminal elimination phase rate constant
LC-MS/MS	liquid chromatography – tandem mass spectrometry
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
OHAs	oral hypoglycemic agents
OTC	over-the-counter
PE	physical examination
PR	time from onset of P wave to the start of QRS complex
P-gp	P-glycoprotein

PK	pharmacokinetics
q.d	once daily
QRS	duration of the QRS complex
QTc	corrected time from start of Q wave to end of T wave
RR	time interval between heart beats
SAE	serious adverse event
SD	standard deviation
SE	standard error
SGLT2	sodium glucose cotransporter 2
SFU	sulfonylureas
SOP	Standard operating procedure
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse events
UGE	urinary glucose excretion
UGT1A9	uridine diphosphate glucuronosyltransferase isoform 1A9
ULN	upper limit of normal
UTI	urinary tract infection
t_{max}	time to maximum plasma concentration
$t_{½}$	apparent terminal elimination half-life
US	United States
V_z/F	apparent volume of distribution
WBC	white blood cell (count)
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

Bexagliflozin is a candidate OHA that is a potent and highly specific inhibitor of SGLT2. (Zhang et al., 2011). Bexagliflozin has been shown to cause dose-dependent increases in urinary glucose excretion (UGE) in humans, rats, dogs and monkeys and to reduce HbA1c in animal models of T2DM and in diabetic subjects. Bexagliflozin is cleared predominantly by metabolism to an inactive metabolite, bexagliflozin 3-O-glucuronide by the uridine diphosphate glucuronosyltransferase isoform 1A9 (UGT1A9) pathway. Detailed information regarding bexagliflozin metabolism, clinical studies and potential risks for study subjects are provided in the Investigator's Brochure.

In vitro studies showed bexagliflozin is a substrate for P-glycoprotein (P-gp) and inhibits P-glycoprotein (P-gp) mediated transport with an IC_{50} of 3.7 μM. P-gp is one of the drug transporters that determine the uptake and efflux of a range of drugs. Drugs that inhibit P-gp can interact with other drugs transported by the pump and therefore affect the exposure of other co-administered drugs that are P-gp substrates.

Digoxin is a P-gp substrate (Tanigawara et al., 1992) that may be co-administered with bexagliflozin. Since individuals with T2DM have an increased risk of heart failure (Nichols et al., 2001) and atrial fibrillation (Nichols et al., 2009), patients with diabetes and hypertension often require treatment with cardiac glycosides such as digoxin. Digoxin has been used for over 2 centuries to treat heart failure and atrial fibrillation. Digoxin acts as a positive inotropic agent by inhibiting the sodium-potassium adenosine triphosphatase (ATPase), causing an increase in myocardial contractility (US FDA, 2002). Digoxin is excreted largely unchanged in urine and bile.

Due to the narrow therapeutic index of digoxin (Smith et al., 1969), small changes in absorption, bioavailability, or clearance of the drug could lead to decreased therapeutic effect or toxicity. Therefore, this study aims to evaluate the effects of co-administered bexagliflozin on the pharmacokinetics of digoxin.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of bexagliflozin on the pharmacokinetics (PK) of digoxin after co-administration.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of digoxin when co-administered with bexagliflozin.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase 1, single center, open-label, two-treatment period, crossover study to evaluate the effect of bexagliflozin tablets, 20 mg, on the PK of digoxin, 0.5 mg after co-administration in healthy subjects. Approximately 18 eligible healthy subjects who consent to the study will be enrolled into the study and randomized to one of the two groups with up to 9 subjects per group. Each subject will participate in 2 periods during which subjects will receive 2 treatments (Treatment A: bexagliflozin co-administered with digoxin, Treatment B: digoxin alone). During the duration of the study, each subject will receive 8 single doses of bexagliflozin and 2 single doses of digoxin.

3.1.1 Group 1

Approximately 9 subjects will be admitted to the clinic on Day 0 and will receive the following study drugs in two treatment periods:

Period 1, Treatment A

Subjects will receive a single oral dose of 20 mg bexagliflozin tablet daily starting on Day 1 for 8 days, and a single oral dose of 0.5 mg digoxin will be co-administered with bexagliflozin on Day 3. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 3, 24 h (Day 4), 48 h (Day 5), 72 h (Day 6), 96 h (Day 7), and 120 h (Day 8) after administration of digoxin. Subjects will be discharged on Day 8 after all study activities are completed.

Period 2, Treatment B

Subjects will be admitted on Day 18. On Day 19, subjects will receive a single oral dose of 0.5 mg digoxin. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 19, 24 h (Day 20), 48 h (Day 21), 72 h (Day 22), 96 h (Day 23), and 120 h (Day 24) after administration of digoxin. Subjects will be discharged on Day 24 after all study activities are completed.

Clinical laboratory tests and safety monitoring will be conducted during Periods 1 and 2.

3.1.2 Group 2

Approximately 9 subjects will be admitted to the clinic on Day 0 and will receive the following study drugs in two treatment periods:

Period 1, Treatment B

Subjects will receive a single oral dose of 0.5 mg digoxin on Day 1. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 1, 24 h

(Day 2), 48 h (Day 3), 72 h (Day 4), 96 h (Day 5), and 120 h (Day 6) after administration of digoxin.

Period 2, Treatment A

Subjects will be admitted on Day 14. Subjects will receive a single oral dose of 20 mg bexagliflozin daily for 8 days starting on Day 15, and a single oral dose of 0.5 mg digoxin will be co-administered with bexagliflozin on Day 17. Blood samples for PK will be drawn at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (h) on Day 17, 24 h (Day 18), 48 h (Day 19), 72 h (Day 20), 96 h (Day 21), and 120 h (Day 22) after administration of digoxin. Subjects will be discharged on Day 22 after all study activities are completed.

Clinical laboratory tests and safety monitoring will be conducted during Periods 1 and 2.

For overall study design and dosing schedule, see the Study Design in Figure 1 and the Dosing Schedule in Appendix 2.

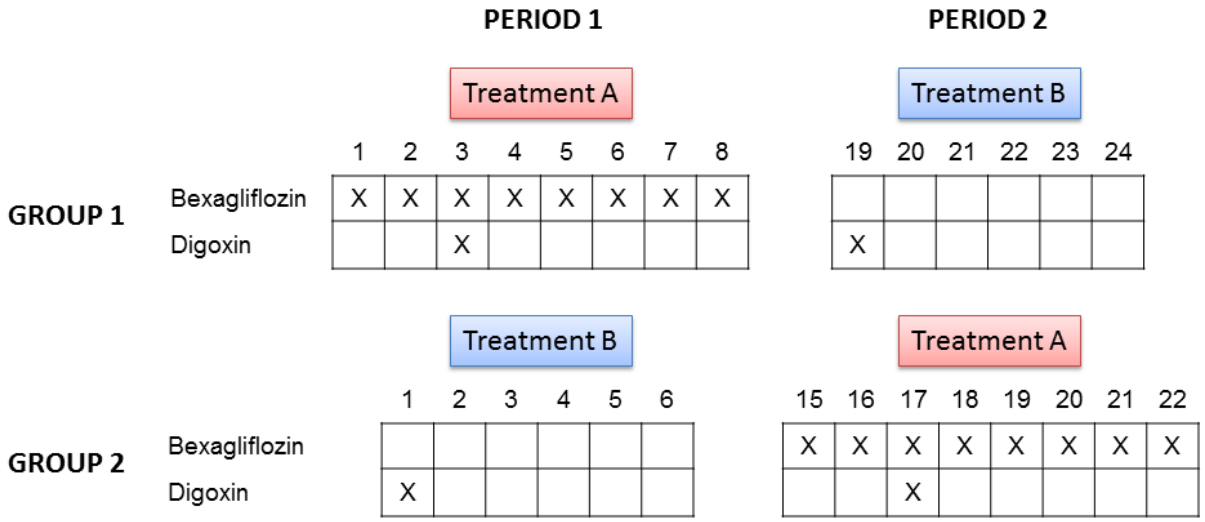

Figure 1 Study Design

3.2 Rationale for Study Design and Control Group

3.2.1 Rationale for Study Design

The primary goal of the study is to test the effect of bexagliflozin on the PK of digoxin. The two treatment period, crossover design will allow the PK of digoxin to be studied with and without the co-administration of bexagliflozin. This design was chosen to properly separate treatment effects from period effects.

Bexagliflozin is cleared predominantly by metabolism to an inactive metabolite, bexagliflozin 3-O-glucuronide by uridine diphosphate glucuronosyltransferase isoform 1A9 (UGT1A9) pathway. *In vitro* metabolism studies demonstrated that bexagliflozin is not a

potent inhibitor or inducer of CYP450 enzymes. In the urine, unchanged parent drug accounted for less than 2% of the dose. *In vitro* studies showed bexagliflozin is a substrate for P-glycoprotein (P-gp) and inhibits P-gp mediated transport with an IC_{50} of 3.7 μM. P-gp is one of the drug transporters that determine the uptake and efflux of a range of drugs. Drugs that inhibit P-gp can interact with other drugs transported by the pump and therefore affect the exposure of other co-administered drugs that are P-gp substrates.

Digoxin is a P-gp substrate that may be co-administered with bexagliflozin. The co-administration of digoxin with P-gp modulators could result in marked changes in the renal elimination of digoxin. Meanwhile, digoxin has a narrow therapeutic index and small changes in absorption, bioavailability, or clearance of the drug could lead to decreased therapeutic effect or toxicity.

This study is designed to evaluate the extent of the effect of bexagliflozin (a potential P-gp inhibitor) on the PK of digoxin (a P-gp substrate). The study results are important for the safe and effective use of digoxin and bexagliflozin.

3.2.2 Rationale for Dose Selection

Bexagliflozin produces a dose-dependent, saturable increase in urinary glucose excretion (UGE) in healthy volunteers and diabetic subjects. Population pharmacodynamic modeling has indicated that bexagliflozin doses of 20 mg result in 90% of the maximal UGE and the bexagliflozin tablet, 20 mg will be the commercial product.

The dosage for digoxin, 0.5 mg, was chosen as it is a safe and effective dose that is in between an acute treatment dose and maintenance treatment dose for a 70 kg adult. The dose is considered a safe dose at which possible drug-drug interactions and plasma concentrations of digoxin can be detected.

3.2.3 Rationale for PK Sampling Time Points

The $T_{½}$ of bexagliflozin is 7.80 to 9.71 h, while the $T_{½}$ of digoxin is significantly longer at approximately 35 h. Due to the long half-life of digoxin, the study is designed so that PK samples are collected up to 7 half-lives of digoxin. A minimum duration of 16 days (~11 half-lives of digoxin) is required between the two digoxin administrations to ensure the wash-out period is sufficiently long.

For Treatment A, digoxin will be administered on Day 3 after 2 days (~5 half-lives of bexagliflozin) of dosing with bexagliflozin. It is predicted that steady state of bexagliflozin will have been achieved at that time.

3.3 Study Duration and Dates

Subjects will be screened within 21 days prior to the start of enrollment. Eligible subjects who consent to the study will be randomized to one of two treatment groups (Group 1 and Group 2). Each treatment group will receive 2 treatments (Treatment A and Treatment B) in a different order during each of the treatment periods (Period 1 and Period 2). The duration

of Treatment A is 9 days and Treatment B is 7 days. Subjects will remain in the clinic for 16 days during the entire study. Subjects will be out of the clinic between the 2 treatment periods for 9 days for Group 1 and 7 days for Group 2. Overall, each study subject will receive 8 single oral doses of 20 mg bexagliflozin tablets and 2 single oral doses of 0.5 mg digoxin in each treatment period. The duration of the overall study from screening until study termination is estimated to be a maximum of 46 days.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 18 healthy subjects who consent to participate in this study will be enrolled.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subjects who are between the ages of 18 to 55 years, inclusive at time of consent, in good health based on medical history, physical examination (PE), electrocardiogram (ECG), and routine laboratory tests, including blood chemistry, hematology, urinalysis, and drug screen.
2. Subjects with body-mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2 at screening, inclusive.
3. Subjects who are non-smokers for at least 6 months prior to screening.
4. Subjects with adequate venous access at multiple sites in both arms.
5. Subjects who are willing to refrain from smoking, alcohol, grapefruit, grapefruit juice or related products, caffeine consumption (including chocolate), and strenuous exercise within 72 h prior to first dose and through the end of the study.
6. Male subjects who are surgically sterile or agree to refrain from donating sperm and use appropriate birth control when engaging in sexual intercourse for a period of 30 days after discharge from the clinic. Appropriate birth control methods include condoms with spermicide, female partner's use of diaphragm with spermicide, female partner's use of stable oral, implanted, or injected contraceptive hormones, or with an intrauterine device.
7. Female subjects of childbearing potential who are willing to use an adequate method of contraception and to not become pregnant for the duration of the study. Adequate methods of contraception for female subjects of childbearing potential include bilateral tubal ligation, intrauterine device, diaphragm with spermicide and male partner's use of male condom with spermicide. Female subjects who are surgically sterile (i.e. have undergone partial or full hysterectomy, or bilateral oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 50 years) are eligible if they test negative on the urine pregnancy test.
8. Subjects who are willing and able to be confined to the clinical research facility and comply with study activities and restrictions as required by the protocol.
9. Subjects who have the ability to comprehend and who are willing to provide written informed consent in accordance with institutional and regulatory guidelines

4.3 Exclusion Criteria

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

1. Subjects who are determined by the investigator or sub-investigator to be unsuitable for participating in the study based on medical conditions or factors that would influence adherence to study activities.
2. Subjects with a clinically significant history of allergy to drugs or latex.
3. Subjects with a history of alcohol or drug dependence in the 12 months prior to the first dose.
4. Subjects who have donated 400 mL of whole blood within 56 days, 200 mL of whole blood within one month, or donated blood components within 14 days prior to first dose.
5. Subjects who have used prescription or over-the-counter (OTC) drugs within 14 days prior to the first dose.
6. Subjects who have used vitamin preparations within 7 days or supplements (including St. John's Wort and ginseng) within 14 days prior to the first dose.
7. Subjects who have been treated with an investigational drug within 30 days or 7 half-lives of the investigational drug, whichever is longer, prior to the first dose.
8. Subjects who have previously received EGT0001474 or bexagliflozin, or any other SGLT2 inhibitors within three months prior to the first dose, or have participated in previous bexagliflozin clinical trials, regardless of whether they received bexagliflozin or placebo in those trials.
9. Subject who had previously taken digoxin or drugs of the same class within 3 months prior to the first dose.
10. Subjects whose screening ECG demonstrates at least one of the following: heart rate > 100 bpm, QRS > 120 msec, QTc > 430 msec (corrected by Bazett's formula), PR > 220 msec (a subject with PR > 220 msec will generally be excluded but exceptions may be allowed at the discretion of the investigator), or any rhythm other than sinus rhythm, sinus bradycardia, or sinus arrhythmia.
11. Subjects whose sitting blood pressure is above 140/90 mmHg at screening. If the sitting blood pressure at screening is above 140/90 mmHg, one repeat measurement is allowed and the subject may be randomized if the repeat screening blood pressure is 140/90 +/-5 mmHg at the discretion of the Investigator.
12. Subjects with a heart rate <60 beats per minute.
13. Subjects with 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.
14. Subjects who have had a cholecystectomy.
15. Subjects with estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2 or a history of kidney transplant.

16. Subjects who have a positive result of hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, urinary drug or urinary cotinine test.
17. Subjects with known human immunodeficiency virus (HIV) infection.
18. Subjects with a history of recurrent yeast or urinary tract infections or any such infection in the 6 months prior to the first dose.
19. Subjects who have had a febrile illness within 5 days prior to first dose.
20. Subjects vaccinated (within the exception of the flu vaccine) within 30 days prior to first dose.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Investigational Product: Bexagliflozin

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

5.1.2 Cardiovascular Drug: Digoxin

Digoxin is a cardiac glycoside that mediates its effects on Na/K ATPase to increase cardiac output. Majority of digoxin is excreted in urine and bile unchanged, and metabolism of digoxin appears to be minimal (Iisalo, 1977). After oral administration, the absorption of digoxin is mediated by P-glycoprotein (P-gp). 0.25 mg digoxin tablets are white, round tablets with an imprint code JSP-545. 0.25 mg digoxin tablets are the highest available tablet dose, and two 0.25 mg tablets will be taken q.d. for this study.

5.2 Treatment(s) Administered

Each study subject will be administered 8 single oral doses of bexagliflozin tablet, 20 mg and 2 single oral doses of 0.5 mg digoxin in 2 treatment periods. See Appendix 2 for the Dosing Schedule.

5.3 Selection and Timing of Dose for Each Subject

5.3.1 Bexagliflozin

After an overnight fast of at least 10 hours, subjects will take a 20 mg bexagliflozin tablet orally in the morning with approximately 240 mL of water at least 1 hour prior to drinking and 4 hours prior to eating.

5.3.2 Digoxin

After an overnight fast of at least 10 hours, subjects will take 0.5 mg digoxin orally in the morning with approximately 240 mL of water at least 1 hour prior to drinking and 4 hours prior to eating.

5.3.3 Bexagliflozin and digoxin

After an overnight fast of at least 10 hours, 0.5 mg digoxin and 20 mg bexagliflozin tablet will be co-administered orally with approximately 240 mL of water at least 1 hour prior to drinking and 4 hours prior to eating.

5.4 Method of Assigning Subjects to Treatment Groups

A total of 18 healthy subjects who consent to participate in the study will be enrolled in the study. Subjects will be randomized to one of the two study groups (Group 1 and Group 2). Subjects who discontinue the study early due to safety issues will not be replaced.

- Group 1: Treatment A first, followed by Treatment B
- Group 2: Treatment B first, followed by Treatment A

5.5 Blinding

This is an open-label study.

5.6 Concomitant Therapy

The participants are not allowed to take any prescription or non-prescription drugs or dietary supplements with the exception of acetaminophen and topical medications at any time during 14 days prior to (first) drug administration and for the duration of each study period. Vitamins are prohibited for 7 days prior to first drug administration and for the duration of the study. No other concomitant medications are permitted with the exception of those required for treatment of an adverse event. Subjects may receive any medications for adverse events that are necessary to control or minimize the likelihood of more serious adverse events in the investigators' judgment.

Concomitant medications administered at the time of randomization and during the study are to be recorded on the case report form (CRF). The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. This documentation should continue until the end of the last study period. Medications that a subject receives after entering the study and prior to randomization must be recorded in the CRF.

5.7 Restrictions

5.7.1 Prior Therapy

No study subject shall have been dosed with any SGLT2 inhibitor within 3 months prior to the first dose of study medication, nor with an investigational drug within 30 days or 7 half-lives prior to first dose, or used any prescription medication or herbal supplements within 14 days or vitamins 7 days prior to the first dose of study medication.

5.7.2 Fluid and Food Intake

An overnight fast of at least 10 hours prior to dosing is required. Study drug(s) will be taken in the morning with approximately 240 mL of water prior to any drinking or eating. Water is permitted during the fasting period up to 1 hour before and after the administration of each study drug administration. Adequate hydration is encouraged during the study period. Food can be consumed 4 h after dosing.

5.7.3 Subject Activity Restrictions

Light physical activity is permitted. Subjects should not perform strenuous activity which could result in elevations of muscle creatine kinase levels within 72 h prior to first dose and through the end of the study. Smoking during the study is prohibited. Alcohol consumption is restricted for 24 hours prior to each clinic admission check-in. Subjects must refrain from smoking, or consuming alcohol, grapefruit, grapefruit juice or related products, or caffeine (including chocolate), during the duration of the study.

5.8 Treatment Compliance

To ensure compliance, all medication dosing will be supervised by the Investigator or qualified staff in the clinic. The exact times of medication dosing will be recorded in the CRFs, including a record of checks followed by hand mouth inspection.

5.9 Packaging and Labeling

5.9.1 Bexagliflozin

Bexagliflozin tablets, 20 mg, are packaged in high density polyethylene bottles sealed with a child resistant closure. The product is packaged with 90 tablets per bottle. Investigational product bottles will be labeled with protocol number, drug name and strength, lot number, sponsor's name, storage condition, and the investigational drug caution statement.

5.9.2 Digoxin

Digoxin tablets are packaged with 100 tablets per bottle. Digoxin bottles are labeled with drug name, strength, lot number, expiration date, storage and dispensation information and drug caution statement.

5.10 Storage and Accountability

All drug supplies should be stored in a secure area with access limited to authorized personnel. Bexagliflozin tablets should be stored below 30°C. Digoxin should be stored at 15° to 25°C in a dry place and protected from light, and dispensed according to label instructions. The sponsor will perform an ongoing inventory of study products. The responsible pharmacist must keep a careful inventory of drug shipments received and the number of tablets dispensed per study subject. A full reconciliation of drug inventory will be performed at the end of the study and the results of this inventory must be recorded in the Clinical Trial Material Inventory Logs and Accountability Logs. At study close out after the post-study inventory reconciliation is completed, empty and partially used bottles of bexagliflozin tablets will be returned to the originating IP depot for destruction. Digoxin bottles may be discarded according to the study sites' regulations for the disposal of investigational drug products.

6 STUDY PROCEDURES

6.1 Informed Consent

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

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

6.2 Medical History

The following information will be collected at the screening visit:

- Demographic information including age, sex, and race.
- Significant medical, surgical history (i.e. cholecystectomy, kidney transplant, etc.) and timeframe of the history relative to study screening, if applicable.
- Clinically significant history of allergy including drugs and latex.
- History of smoking in the last 6 months prior to first dose, and alcohol or drug dependence, or abuse in the last 12 months prior to first dose.
- Any blood donation within 56 days or blood component donation in the last 14 days prior to first dose.
- Use of any medications including OTC drugs or dietary supplements in the last 14 days prior to first dose. Use of any vitamins in the last 7 days prior to first dose.
- History of vaccination (except the flu vaccine) within 30 days prior to first dose.
- History of diagnosis with HIV, hepatitis B or hepatitis C.
- Use of any investigational drug in the previous 30 days or 7 half-lives prior to first dose, whichever time frame is longer.
- Prior exposure to bexagliflozin (or EGT0001474), or any other SGLT2 inhibitors in the last 3 months prior to first dose.
- Prior exposure to digoxin in the last 3 months prior to first dose.
- History of recurrent yeast or urinary tract infections or any such infections in the last 6 months prior to first dose.

6.3 Physical Examination

The investigator or designated qualified individual will perform the PEs. A complete PE will be performed at screening and on the last day of Period 2 prior to discharge. Partial PEs will be performed on scheduled days as described in Appendix 1.

A complete PE will include measurement of body weight and height (height will be measured only at screening), general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, lungs, heart, abdomen, lymph nodes, and extremities. A partial PE will include body weight and an update of the general assessment of the skin, heart, lungs and abdomen.

6.4 Vital Signs

Vitals signs, including pulse, systolic and diastolic blood pressure (BP), respiration rate, and oral temperature, will be measured on scheduled visits as described in Appendix 1.

Vital signs should be measured prior to blood draws.

Pulse, systolic and diastolic BP should be measured in a seated position after a subject has been sitting for 5 minutes.

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

BP measures will be obtained using a calibrated sphygmomanometer or calibrated automated vitals machine.

6.5 Electrocardiography

A 12-lead electrocardiography (ECG) will be conducted as listed in Appendix 1 and whenever clinically indicated.

This procedure should be performed in the supine position after at least 5 minutes of rest. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities.

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

6.6 Clinical Laboratory Tests

6.6.1 Laboratory Parameters

Subjects will be in a seated, semi-recumbent or in a supine position during blood collection. Clinical blood chemistry and hematology tests will be performed at the scheduled visits (Appendix 1). Blood samples should be drawn after overnight fasting prior to breakfast. The details of the required laboratory tests are listed in Table 1.

Table 1. Required Laboratory Tests

Test Name		mL (sample)
Hematology		4.0 (blood)
Hematocrit	Mean corpuscular volume	
Hemoglobin	Platelet count	
Mean corpuscular hemoglobin	Red blood cell count	
Mean corpuscular hemoglobin concentration	White blood cell count with differential	
Serum Chemistry, Electrolytes and Lipids		8.5 (serum)
Albumin	Calcium	
Alanine aminotransferase (ALT)	Magnesium	
Aspartate aminotransferase (AST)	Phosphorus	
Blood urea nitrogen (BUN)	Potassium	
Glucose	Sodium	
Total Carbon Dioxide	Total bilirubin	
Creatinine	Direct bilirubin	
Chloride	Uric acid	
Total protein	Total cholesterol	
Low-density lipoprotein cholesterol, calculated	High-density lipoprotein cholesterol	
Triglycerides		
Urinalysis		20 (urine)
Appearance	Nitrite	
Bilirubin	pH	
Color	Protein	
Glucose	Specific gravity	
Ketones	Urobilinogen	
Microscopic examination of sediment	Leukocyte esterase	
Urine Drug Screen		10 (urine)
Amphetamines	Opiates	
Barbiturates	Benzodiazepines	
Cocaine Metabolites	Cannabinoids	
Cotinine		
Urine Pregnancy Test (Female only)		5 (urine)
Infectious Disease Testing		3.5 (serum)
Hepatitis B surface antigen (HBsAg)	Hepatitis C virus (HCV)	

6.6.2 Sample Collection, Storage, and Shipping

6.6.2.1 Hematology and Blood Chemistry

Blood samples for hematology and chemistry will be collected. Timing of the collection is described in Appendix 1.

6.6.2.2 Urinalysis

Clean-catch, midstream urine samples will be collected per schedule outlined in Section 7 and in Appendix 1. Dipstick urinalysis will be conducted. Microscopy will be obtained if the subject has a positive result on any of the dipstick tests that require microscopic follow-up to clarify their significance. If urine is dipstick positive for white blood cell (count) (WBC) or blood (except female subjects who are menstruating), urine sample will be sent for microscopic evaluation and culture. In addition, urinalysis will be performed from a clean-catch urine sample at any time in subjects with symptoms of UTI or pyelonephritis.

6.6.2.3 PK Plasma Sample Collection and Analysis

Whole venous blood samples of 3 mL will be collected from a peripheral vein in each period at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h post-dose of digoxin for Groups 1 and 2. Blood samples will be collected in tubes containing potassium ethylenediaminetetraacetic acid (K_2EDTA) and stored on ice until centrifuged under refrigeration for at least 5 min at 3,000 rpm. After centrifugation, plasma will be removed, divided into 2 aliquots of approximately 0.5 mL, frozen and stored at or below -20°C. Plasma should be processed and frozen within 2 h of blood collection. Processed frozen plasma samples will be transferred on dry ice to the analytical laboratory and will be stored at or below -20^{o}C until analysis.

Plasma concentrations of digoxin will be determined at Covance by validated liquid chromatography - mass spectrometry (LC-MS/MS) method, with lower limit of quantitation (LLOQ) of 0.05 ng/mL for digoxin.

6.7 Adverse Events Assessments

Adverse Event (AE*)*: Any untoward medical occurrence in clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment.

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

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

- results in death,
- is life-threatening *(NOTE:* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event and 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 an important medical event.

An important medical event is an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. 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.

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

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

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

Hypoglycemia will be defined as any fasting plasma glucose (FPG) value < 70 mg/dL and documented as described in Section 6.7.4.4.

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

An increase in creatinine from baseline by 0.5 mg/dL or more will be reported as a laboratory adverse event.

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

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

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

3 = Severe: inability to work or perform normal daily activity

Investigational Product Causality: The site and database should ask for the causality relative to the study compound. Relationship of an adverse event to dosing will be assessed as follows:

Definite: There is a reasonable causal relationship between the investigational product and the AE when the event responds to withdrawal of the investigational product (dechallenge), and recurs with administration of the investigational product (rechallenge).

Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Possible: There is a reasonable causal relationship between the investigational product and the AE. Dechallenge is lacking or unclear.

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

Unrelated: There is no temporal or causal relationship to investigational product administration.

6.7.1 Collecting and Reporting Adverse Events

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

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

6.7.2 Immediately Reportable Adverse Events

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

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

Subjects experiencing an SAE should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal, or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

6.7.3 Pregnancy

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

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

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

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

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

If a subject or investigator suspects that the subject may be pregnant prior to investigational product administration, the investigational product administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the investigational product and must not remain in or be enrolled in the study.

The investigator must notify the Medical Monitor within 3 working days of the receipt of information that any female subject who has become pregnant.

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

6.7.4 Follow-up of Adverse Events

6.7.4.1 Follow-up of Non-serious Adverse Events

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

6.7.4.2 Follow-up of Post-Study Serious Adverse Events

SAEs that are identified on the last scheduled contact must be recorded on the AE CRF page and reported to Theracos according to the reporting procedures outlined in Section 6.7.1. These may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these subjects until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to Theracos until the event has been resolved.

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the Medical Monitor or the sponsor's designated personnel. These 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 subjects with 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 14 days after discharge from the study.

6.7.4.3 Hepatotoxicity

Any clinically significant increase in hepatic enzymes and specifically ALT or AST $\geq$ 3x ULN requires immediate repeat test within 48 to 72 h to confirm the hepatic enzyme elevation. Study medication should be stopped and the event should be reported as an adverse event within the CRF if the enzyme elevation is confirmed or worsening. Potential contributors to hepatic enzyme elevation should be evaluated by the investigator. The investigator is encouraged to consult with the Medical Monitor regarding ongoing diagnostic workup.

Investigational product should be permanently discontinued if any of the following criteria is met:

- 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%).

6.7.4.4 Hypoglycemia

Hypoglycemia will be recorded under 5 categories:

- Critical hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. All such events should be recorded as serious adverse events in the CRF.
- 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).
- Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
- Probable symptomatic hypoglycemia: An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (3.9 mmol/L).
- Relative hypoglycemia: An event during which the person 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).

If a subject experiences symptomatic hypoglycemia, confirmed by point-of-care glucose monitoring at the time of symptoms with a blood sugar level < 70 mg/dL (3.9 mmol/L), the subject should be treated with 15 to 20 grams of oral glucose or simple carbohydrate (glucose tablets, raisins, orange juice, glucose-containing soda, or soft sugar candies).

If a subject with symptomatic hypoglycemia is unable to self-administer glucose tablets, candies, or glucose-containing solutions, then the appropriate study staff should administer 50% IV Dextrose as soon as possible. If IV Dextrose is unable to be administered, an injection of 1.0 mg of glucagon should be administered intramuscularly or subcutaneously, and the injection may need to be repeated after 15 minutes depending on the response.

Blood glucose monitoring will be done by appropriate study staff using a point-of-care glucose monitor beginning at the time of hypoglycemia detection and continue every fifteen minutes, or more frequently if required, until that time that the subject's level of alertness has returned to appropriate levels and point-of-care glucose levels are above 70 mg/dL.

6.8 Concomitant Medication Assessments

A concomitant medication is any medication the subject enters the trial taking and is expected to continue taking for some portion of the trial, as well as any medication the subject takes during the course of the trial. 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 are discharged.

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 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.

Concomitant medications administered during the study are to be recorded on the CRF. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. This documentation should continue until discharge from the study.

6.9 Removal of Subjects from the Trial or Discontinuation of Investigational Product

The investigator must emphasize to potential subjects the importance of continued participation for the full duration of the trial during the informed consent process. Participation in the study is voluntary. A participant has the right to withdraw from the study at any moment for any reason. The investigator will be informed immediately.

The investigator has the right to terminate participation of a subject in case it is difficult to obtain blood samples, in case of violation of the protocol or in case of severe or serious adverse events.

In case a subject withdraws from the study, the study monitor will be informed immediately. If there is a medical reason for withdrawal, the volunteer should remain under the supervision of the medical investigator until satisfactory health returns.

Subjects who discontinue the active dosing phase of the study due to adverse event(s) or other safety concerns will not be replaced.

When the decision is made to discontinue a subject's participation in the study, no further investigational product medication should be administered. Every attempt should be made to complete all required study evaluations and procedures. Reasons for all withdrawals should be recorded on the CRF.

The investigator may withdraw a subject from the THR-1442-C-443 trial for any of the following reasons:

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

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

6.10 Appropriateness of Measurements

PK and safety parameters in this protocol are standard assessments and are widely used and generally recognized as reliable, accurate, and relevant measurements.

7 STUDY ACTIVITIES

7.1 Screening (Days –14 to -1)

During the screening period, the following information will be gathered and the indicated procedures will be performed:

- Explain the content of informed consent to the subject and collect signed informed consent
- Obtain medical history and demographic information
- Perform a complete physical examination, including height and weight measurements as described in Section 6.3.
- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest as described in Section 6.4
- Conduct 12-lead ECG in the supine position after at least 5 min of rest as described in Section 6.5
- Collect clean-catch urine for urinalysis
- Conduct urine screen for use of drugs including amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids
- Conduct urine pregnancy test for all female subjects
- Draw blood for hematology, serum chemistry, electrolytes and lipids and serology as detailed in Section 6.6
- Evaluate inclusion/exclusion criteria based on the information collected at the screening examination

7.2 Group 1

7.2.1 Period 1

DAY 0

- Admit eligible subjects to Phase I unit
- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Perform abbreviated physical examination as described in Section 6.3.
- Conduct urine pregnancy test for all female subjects
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 1

- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct urinalysis on clean-catch urine pre-dose
- Re-confirm eligibility criteria prior to randomization based on results for clinical lab tests from Day 0 and vital signs, ECG and urinalysis results from Day 1 pre-dose
- Randomization of subjects
- Administer bexagliflozin to subjects as described in Section 5.3
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 2

- Administer bexagliflozin to subjects as described in Section 5.3
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 3

- Draw blood for hematology, serum chemistry, electrolytes and lipids pre-dose
- Conduct urinalysis on clean-catch urine pre-dose
- Perform abbreviated physical examination pre-dose
- Collect vital signs collected including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, pre-dose, 4 and 8 h post-dose
- Administer both bexagliflozin and digoxin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 4

- Administer bexagliflozin to subjects as described in Section 5.3
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, 24 h post-dose digoxin
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 5 TO DAY 7

- Administer bexagliflozin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 8

- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Administer bexagliflozin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure in the sitting position after at least 5 min of rest as described in Section 6.4
- Conduct urinalysis on clean-catch urine
- Assess adverse events and record concomitant medications as described in Section 6.7
- Discharge subjects after all study activities are completed

For subjects who are terminated from the study for any reason after dosing, all activities for the study termination day except for PK sample collection must be completed. The reason for termination must be entered onto the case report form.

7.2.2 Period 2

DAY 18

- Admit Group 1 subjects to the Phase 1 clinic
- Perform abbreviated physical examination as described in Section 6.3
- Conduct urine pregnancy test for all female subjects
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 19

- Draw blood for hematology, serum chemistry, electrolytes and lipids pre-dose
- Conduct urinalysis on clean-catch urine pre-dose
- Perform abbreviated physical examination pre-dose
- Collect vital signs collected including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, pre-dose, 4 and 8 h post-dose

- Administer digoxin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 20

- Conduct 12-lead ECG in the supine position after at least 5 min of rest, 24 h post-dose digoxin
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 21 TO DAY 23

- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 24

- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure in the sitting position after at least 5 min of rest as described in Section 6.4
- Conduct urinalysis on clean-catch urine
- Conduct 12-lead ECG in the supine position after at least 5 min of rest as described in Section 6.5
- Perform a full physical examination as described in Section 6.3
- Assess adverse events and record concomitant medications as described in Section 6.7
- Discharge subjects after all study activities are completed

For subjects who are terminated from the study for any reason after dosing, all activities for the study termination day except for PK sample collection must be completed. The reason for termination must be entered onto the case report form.

7.3 Group 2

7.3.1 Period 1

DAY 0

- Admit eligible subjects to the Phase 1 clinic

- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Perform abbreviated physical examination as described in Section 6.3
- Conduct urine pregnancy test for all female subjects
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 1

- Conduct urinalysis on clean-catch urine pre-dose
- Perform abbreviated physical examination pre-dose
- Collect vital signs collected including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, pre-dose, 4 and 8 h post-dose
- Re-confirm eligibility criteria prior to randomization based on results for clinical lab tests from Day 0 and vital signs, ECG and urinalysis results from Day 1 pre-dose
- Randomization of subjects
- Administer digoxin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 2

- Conduct 12-lead ECG in the supine position after at least 5 min of rest, 24 h post-dose digoxin
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 3 TO DAY 5

- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 6

- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure in the sitting position after at least 5 min of rest as described in Section 6.4

- Conduct urinalysis on clean-catch urine
- Assess adverse events and record concomitant medications as described in Section 6.7
- Discharge subjects after all study activities are completed

For subjects who are terminated from the study for any reason after dosing, all activities for the study termination day except for PK sample collection must be completed. The reason for termination must be entered onto the case report form.

7.3.2 Period 2

DAY 14

- Admit Group 2 subjects to Phase I unit
- Perform abbreviated physical examination as described in Section 6.3
- Conduct urine pregnancy test for all female subjects
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 15

- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, pre-dose and 4 h post-dose
- Conduct urinalysis on clean-catch urine pre-dose
- Administer bexagliflozin to subjects as described in Section 5.3
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 16

- Administer bexagliflozin to subjects as described in Section 5.3
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 17

- Draw blood for hematology, serum chemistry, electrolytes and lipids pre-dose
- Conduct urinalysis on clean-catch urine pre-dose
- Perform abbreviated physical examination pre-dose
- Collect vital signs collected including pulse, temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest, pre-dose and 4 h post-dose

- Conduct 12-lead ECG in the supine position after at least 5 min of rest, pre-dose, 4 and 8 h post-dose
- Administer both bexagliflozin and digoxin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 18

- Administer bexagliflozin to subjects as described in Section 5.3
- Conduct 12-lead ECG in the supine position after at least 5 min of rest, 24 h post-dose digoxin
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 19 TO DAY 21

- Administer bexagliflozin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Assess adverse events and record concomitant medications as described in Section 6.7

DAY 22

- Draw blood for hematology, serum chemistry, electrolytes and lipids as detailed in Section 6.6
- Administer bexagliflozin to subjects as described in Section 5.3
- Collect plasma samples for PK analysis as detailed in Section 6.6
- Collect vital signs including pulse, temperature, respiratory rate, and blood pressure in the sitting position after at least 5 min of rest as described in Section 6.4
- Conduct urinalysis on clean-catch urine
- Conduct 12-lead ECG in the supine position after at least 5 min of rest as described in Section 6.5
- Perform a full physical examination as described in Section 6.3
- Assess adverse events and record concomitant medications as described in Section 6.7
- Discharge subjects after all study activities are completed

For subjects who are terminated from the study for any reason after dosing, all activities for the study termination day except for PK sample collection must be completed. The reason for termination must be entered onto the case report form.

7.4 Follow-up Procedures or Early Termination

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

8 QUALITY CONTROL AND ASSURANCE

The clinical research facility will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be 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 procedure (SOPs) of the contract research organization (CRO) and the sponsor. Review procedures will be implemented at the CRO for all documents that are generated in relation to the study.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical evaluation of PK parameters will be conducted by the designated CRO. A detailed Statistical and Analytical Plan will be generated prior to any PK statistical analysis of the data. Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS, USA). Non-compartmental analysis will be performed using Phoenix®WinNonlin® 6.4 (Certara, USA).

9.2 Determination of Sample Size

The sample size for this study is not based upon formal statistical consideration. The sample size is considered adequate to characterize the PK of digoxin, to assess potential drug-drug interactions and to provide safety and tolerability data on the compound when administered either alone or with bexagliflozin.

9.3 Analysis Populations

9.3.1 Safety Population

The Safety Population will include all randomized subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment received.

9.3.2 PK Population

The PK Population will include all randomized subjects who receive at least one dose of study drug and who have sufficient plasma digoxin measurements to derive PK parameters following dosing. The PK Population will be used to summarize the PK parameters.

9.4 Demographics and Baseline Characteristics

Baseline characteristics will be summarized for all subjects in the Safety and PK Populations. Descriptive statistics will be performed.

9.5 Pharmacokinetic Analysis

9.5.1 Calculation of Pharmacokinetic Parameters

A non-compartmental analysis will be used to calculate the PK parameters of digoxin when administered alone or with bexagliflozin using the software Phoenix® WinNonlin® 6.4 (Certara, USA). From the plasma digoxin concentration-time data, the following PK parameters will be estimated for each subject where feasible.

C_{max}: Maximum observed plasma concentration

T_{max}: Time of maximum observed plasma concentration

λ_z: Terminal elimination phase rate constant

$T_{½}$: Apparent terminal elimination half life

CL/F: Apparent oral clearance

V_z/F: Apparent volume of distribution

AUC_{0-t}: Area under the plasma concentration-time curve from Time 0 to Time t (time of last quantifiable plasma concentration)

$AUC_{0-\infty}$: Area under the plasma concentration-time curve from Time 0 to infinity

C_{max} and T_{max} will be obtained directly from experimental observations. If multiple maxima occur at equal concentrations, the first temporal value will be taken as the C_{max} and T_{max}.

The apparent terminal elimination half-life, $T_{1/2}$, where determinable, will be calculated as the natural log of 2 divided by the terminal phase rate constant, λ_z. The number of data points included in the regression will be determined by visual inspection, but a minimum of three data points in the terminal phase, excluding C_{max}, is required to estimate λ_z. In order for the selection to take place the adjusted r^2 value reported in Phoenix®WinNonlin® must be ≥ 0.7.

AUC_{0-t} and $AUC_{0-\infty}$ will be calculated using the linear trapezoidal linear interpolation method, using actual elapsed time values. If the actual collection time is unknown the nominal collection time may be used for the purposes of PK parameter estimation. For the purpose of calculating AUC, all missing values will be treated as missing in the PK analysis and excluded from analysis except when they occur at pre-dose where they will be set to zero. All values that were below the limit of quantitation (BLOQ) prior to T_{max} will be set to zero. BLOQ values that occur after T_{max} will be set to missing. When ≥ 2 consecutive plasma concentrations BLOQ are encountered after T_{max}, these and all subsequent values will be excluded from the analysis.

$AUC_{0-\infty}$ will be calculated according to the following equation:

$AUC_{0-\infty} = AUC_{last} + (C_{last} / \lambda_z)$, where C_{last} is the last temporal quantifiable plasma concentration corresponding to T_{last}.

The proportion of $AUC_{0-\infty}$ due to extrapolation (AUC_{extr}) will be calculated and expressed as a percentage. $AUC_{0-\infty}$ values will be considered unreliable estimates if the AUC_{extr} is greater than 20%.

CL/F will be calculated as Dose/$AUC_{0-\infty}$.

Vz/F will be calculated as Dose/($\lambda_z \times AUC_{0-\infty}$).

$T_{½}$ will be calculated as $0.693/\lambda_z$.

Descriptive statistics for the plasma concentrations of digoxin by Treatment, Timepoint and Sex/Gender will be provided. A listing of plasma concentrations by Subject Number, Treatment Period, Timepoint and Sex/Gender will also be provided.

9.5.2 Statistical Analysis

To assess the effect of bexagliflozin on the PK of digoxin, an analyses of variance (ANOVA) using a linear mixed-effects model will be fitted to the natural logarithmic transformation of PK parameters of digoxin (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The linear mixed-effects model will include subject as a random effect, and treatment, period, and sequence as fixed effects. The 90% confidence intervals will be constructed for digoxin administered with bexagliflozin to digoxin alone ratio of the least squares (LS) geometric means of PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), with 80-125% defined as the lack of interaction boundaries.

Descriptive statistics for the PK parameters C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, CL/F, V_z/F, λ_z, and $T_{1/2}$ will be tabulated by treatment. Means, standard deviations, medians, ranges (min, max) and geometric means and coefficients of variation will be presented for all PK parameters with the exception of T_{max}. Medians and ranges will be presented for T_{max}.

A listing of derived PK parameters of bexagliflozin by Subject ID, Period and Sex/Gender will be provided.

9.6 Safety Analysis

Safety data will include AEs, PE results, vital signs, ECG results, and clinical lab results, including serum chemistry, hematology, and urinalysis. Observed data will be described as counts and percentages for discrete variables and estimation of means, standard deviations (SDs), medians, inter-quartile range, minimum and maximum for continuous metrics. All subjects in the Safety Population will be included in the safety analyses. All safety data will be presented in by-subject listings and included in the clinical trial report.

9.6.1 Adverse Events

Adverse events will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting adverse events will be determined by relationship to treatment and by severity of the event. Drug-related adverse events will be considered those to be possibly related to bexagliflozin administration.

Adverse event listings will be provided for the following subsets:

- all treatment emergent AEs (TEAEs).
- all TEAEs at least possibly related to bexagliflozin.
- serious TEAEs (if any).
- TEAEs leading to study discontinuation (if any).

AEs are dosing emergent if they occur on or after bexagliflozin administration. TEAEs will be considered at least possibly related to bexagliflozin based on the investigator's assessment. Only TEAEs will be tabulated in summary tables. If the AE(s) onset date-time or date occurs after the first dose up until right before the next dose, the AE(s) will be assigned

to the first treatment. Any AE(s) that occur after the second dose up until the follow-up visit will be assigned to the second treatment.

Tabulations will display TEAEs by severity and relationship to bexagliflozin.

9.6.2 Hypoglycemia

Hypoglycemia as defined in Section 6.7.4.4 will be presented in listings and summarized.

9.6.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory metrics are measured at baseline (pre-dose measurement of each period) and during the treatment periods (Appendix 1). These variables include vital signs (blood pressure, respiration, temperature), clinical laboratory results (see Section 6.6 for a complete list), and ECGs.

Serum chemistry, hematology, and urinalysis (quantitative parameters) data will be summarized for each treatment period. Summaries for change from baseline will be presented for these laboratory tests.

ECG results will be summarized as changes from baseline in intervals. Abnormalities as well as changes from previous assessment will be listed.

9.6.4 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A by-subject listing of concomitant medications will include all medications taken during the study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

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

10.2 Institutional Review Board (IRB)

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

10.3 Ethical Conduct of the Study

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor and investigator follow Good Clinical Practice (GCP) Guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. An inspection by the sponsor representatives and/or their designee and/or healthy authority 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 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 head of the investigational site, IRB (via the head of the investigational site)/sponsor.

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

10.4 Subject Information and Consent

The investigator will draft the informed consent form based on the protocol. The sponsor will review the investigator's draft informed consent form prior to submission to the IRB and the final IRB approved document must be provided to the sponsor for regulatory purposes.

Prior to the beginning of the study, the investigator must have received from the 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 together with the approved subject information and informed consent forms must be filed. The informed consent form must contain all elements required by the Federal Drug Administration under 21 Code of Federal Regulations Part 50 and the ICH GCP Guidelines (E6), in addition to, any other elements required by regulations or institutional policy.

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

10.5 Subject Confidentiality

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

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

10.6 Study Monitoring

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

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

10.7 Case Report Forms and Study Records

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

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

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

10.8 Protocol Violations/Deviations

It is important to conduct the study according to the protocol. Protocol deviations will not be prospectively granted by the sponsor. If deviations occur, such as a visit or sampling window being missed, the investigator must decide whether to proceed, for example, whether or not to complete the visit or sample collection outside of the protocol-defined window. The sponsor's medical monitor must be notified immediately when protocol deviations are discovered 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 will there be such a departure without the sponsor's pre-approval. The nature and reasons for the protocol deviation will be recorded in the subject's CRF, and the principal investigator must notify the Sponsor.

Protocol violations must be reported in the final study report.

10.9 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 to inspect facilities and records relevant to this study.

The 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.

10.10 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.

10.11 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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Smith, T.W., Butler, V.P., Jr., and Haber, E. (1969). Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. The New England journal of medicine *281*, 1212-1216.

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Appendix 1 Schedule of Events

GROUP 1 SCHEDULE OF EVENTS

Evaluation	Screening	Period 1: Treatment A									Period 2: Treatment B						
Days to randomization (days)	-21 to -1	0	1	2	3	4	5	6	7	8	18	19	20	21	22	23	24
Medical history and ICF	X																
Demographics	X																
Review for I/E criteria[1]	X		X														
Physical exam[2]	X	X			X						X	X					X
Admission or discharge[3]		X								X	X						X
Randomization			X														
Administer bexagliflozin[4]			X	X	X	X	X	X	X	X							
Administer digoxin[4]					X							X					
Vital signs[5]	X		X		X					X		X					X
ECG[6]	X		X		X	X						X	X				X
Urinalysis[7]	X		X		X					X		X					X
Urine drug screening	X																
Urine pregnancy test (for females only)	X	X									X						
Blood draw for clinical lab tests[8]	X	X			X					X		X					X
Blood samples for PK[9]					X	X	X	X	X	X		X	X	X	X	X	X
Adverse event and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study termination																	X

[1] Eligibility criteria will be re-confirmed on Day 1 prior to randomization, based on results for clinical lab tests from Day 0 and vital signs, ECG and urinalysis results from Day 1 pre-dose.

[2] Weight and height will be recorded as part of the physical examination. Height will be recorded once at screening only. A complete physical exam (PE) will be performed at screening visit and the day of study termination, Day 24. A partial PE will be performed on Days 0, 3, 18 and 19. On Days 3 and 19, the PE will be performed prior to dosing.

[3] Group 1 subjects will be admitted to the clinic on Day 0, discharged on Day 8 for Period 1. For Period 2, subjects will be admitted on Day 18 and discharged on Day 24.

[4] See Appendix 2 for dosing schedule.

[5] Vital signs include pulse, body temperature, respiratory rate, and blood pressure after at least 5 minutes of rest. On Days 1, 3, and 19, vital signs will be measured pre-dose and 4 h post-dose.

[6] 12-lead ECG will be conducted after 5 min of rest. On Day 1, ECG will be recorded pre-dose and 4 h post-dose of bexagliflozin. On Days 3, 4, 19 and 20, ECG will be recorded at pre-dose and post-dose of digoxin at hours 4, 8 and 24. ECG will be recorded at additional time points when clinically indicated.

[7] Clean-catch urine will be collected for urinalysis on indicated days or if symptoms or signs suggestive of urinary tract infection are present. If urine is dipstick positive for WBC or blood (except female subjects who are menstruating), sample is to be sent for microscopic evaluation and culture. Urinalysis on Days 1, 3, and 19 will be done pre-dose.

[8] Blood for clinical chemistry and hematology will be drawn after a minimum of 10 h fasting prior to breakfast. Infectious disease testing will be conducted at screening only. Clinical lab test blood draw will be done pre-dose.

[9] PK plasma samples will be collected at the following time points: pre-dose of digoxin (0 h) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h post dose of digoxin.

GROUP 2 SCHEDULE OF EVENTS

Evaluation	Screening	Period 1: Treatment B							Period 2: Treatment A								
Days to randomization (days)	-21 to -1	0	1	2	3	4	5	6	14	15	16	17	18	19	20	21	22
Medical history and ICF	X																
Demographics	X																
Review for I/E criteria[1]	X		X														
Physical exam[2]	X	X	X						X			X					X
Admission or discharge[3]		X						X	X								X
Randomization			X														
Administer bexagliflozin[4]										X	X	X	X	X	X	X	X
Administer digoxin[4]			X									X					
Vital signs[5]	X		X					X		X		X					X
ECG[6]	X		X	X						X		X	X				X
Urinalysis[7]	X		X					X		X		X					X
Urine drug screening	X																
Urine pregnancy test (for females only)	X	X							X								
Blood draw for clinical lab tests[8]	X	X						X		X		X					X
Blood samples for PK[9]			X	X	X	X	X	X				X	X	X	X	X	X
Adverse event and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study termination																	X

1 Eligibility criteria will be re-confirmed on Day 1 prior to randomization, based on results for clinical lab tests from Day 0 and vital signs, ECG and urinalysis results from Day 1 pre-dose.

2 Weight and height will be recorded as part of the physical examination. Height will be recorded once at screening only. A complete physical exam (PE) will be performed at screening visit and the day of study termination, Day 22. A partial PE will be performed on Days 0, 1, 14, and 17. On Days 1 and 17, the PE will be performed prior to dosing.

3 Group 2 subjects will be admitted to the clinic on Day 0, discharged on Day 6 for Period 1. For Period 2, subjects will be admitted on Day 14 and discharged on Day 22.

4 See Appendix 2 for dosing schedule.

5 Vital signs include pulse, body temperature, respiratory rate, and blood pressure after at least 5 minutes of rest. On Days 1, 15, and 17, vital signs will be measured pre-dose and 4 h post-dose.

[6] 12-lead ECG will be conducted after 5 min of rest. On Day 15, ECG will be recorded pre-dose and 4 hr post-dose of bexagliflozin. On Days 1, 2, 17 and 18, ECG will be recorded at pre-dose and post-dose of digoxin at hours 4, 8 and 24. ECG will be recorded at additional time points when clinically indicated.

[7] Clean-catch urine will be collected for urinalysis on the indicated days, or if symptoms or signs suggestive of urinary tract infection are present. If urine is dipstick positive for WBC or blood (except female subjects who are menstruating), sample is to be sent for microscopic evaluation and culture. Urinalysis on Days 1, 15 and 17 will be done pre-dose.

[8] Blood for clinical chemistry and hematology will be drawn after a minimum of 10 h fasting prior to breakfast. Infectious disease testing will be conducted at screening only. Clinical lab test blood draw will be done pre-dose.

[9] PK plasma samples will be collected at the following time points: pre-dose of digoxin (0 h) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h post dose of digoxin.

Appendix 2 Dosing Schedule

		PERIOD 1								PERIOD 2					
		Treatment A								Treatment B					
	Day(s)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**19**	**20**	**21**	**22**	**23**	**24**
GROUP 1	**Bexagliflozin tablet, 20 mg**	X	X	X	X	X	X	X	X						
	Digoxin, 0.5 mg			X						X					

		Treatment B						Treatment A							
	Day(s)	**1**	**2**	**3**	**4**	**5**	**6**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
GROUP 2	**Bexagliflozin tablet, 20 mg**							X	X	X	X	X	X	X	X
	Digoxin, 0.5 mg	X								X					

Appendix 3 Sponsor Signatures

Study Title: A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of Bexagliflozin on the Pharmacokinetics of Digoxin in Healthy Subjects

Study Number: THR-1442-C-443

Final Date V2.0: 13 June 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: 13 June 2017

Annie L. Conery, Ph.D.
Protocol Originator
Massachusetts General Hospital

Signed: _____ Date: 13-JUN-2017

Xiaoyan Li, Ph.D.
PK Project Leader
Massachusetts General Hospital

Signed: _____ Date: 13-JUN-2017

Mason W. Freeman, M.D.
Medical Monitor
Massachusetts General Hospital
Consultant for Theracos Sub, LLC

Appendix 4 Investigator's Signature

Study Title:	A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of Bexagliflozin on the Pharmacokinetics of Digoxin in Healthy Subjects
Study Number:	THR-1442-C-443
Final Date V2.0:	13 June 2017

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

Signed: _____ Date: 13 Jun 2017

Melanie Fein, MD, CPI, DABFM
Principle Investigator/Medical Director
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