Clinical Trial Protocol: THR-1442-C-481

Study Title:	A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of A High-Fat Meal on the Pharmacokinetics of Bexagliflozin in Healthy Subjects
Study Number:	THR-1442-C-481
Study Phase:	1
Product Name:	Bexagliflozin Tablets
Indication:	Type 2 Diabetes Mellitus
Investigators:	Single Center
Sponsor:	Theracos Sub, LLC.
Sponsor Contact:	Albert Collinson, Ph.D. Theracos Sub, LLC. 225 Cedar Hill Street, Suite 200, Marlborough, MA 01752 Phone: 508-688-4221
Sponsor's Protocol Representative:	Xiao-Yan Li, Ph.D. Translational Medicine Group Massachusetts General Hospital 185 Cambridge Street, Boston, MA 02114 Phone: 617-726-7960, Fax: 617-643-8203 Email: xli@ccib.mgh.harvard.edu
Medical Monitor:	Geoffrey Walford, M.D. Massachusetts General Hospital 185 Cambridge Street, Boston, MA 02114 Phone: 617-643-4986, Fax: 617-643-8203 E-mail: gwalford@partners.org.

	Date
Version 2:	20 May 2016

Confidentiality Statement

SYNOPSIS

Sponsor:

Theracos Sub, LLC.

Name of Finished Product:

Bexagliflozin Tablets

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.

Study Title:

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

Study Number:THR-1442-C-481

Study Phase: 1

Primary Objective:

- To evaluate the effect of a high-fat meal on the pharmacokinetics (PK) of bexagliflozin extended release tablets in healthy subjects.

Secondary Objectives:

- To evaluate the safety of bexagliflozin after a single oral dose in a fasted state and in a fed state in healthy subjects.
- To evaluate the effect of a high-fat meal on the potential pharmacodynamic activity of bexagliflozin by determining urinary glucose excretion in healthy subjects under fasted and fed conditions.

Study Design:

This is a phase 1, single center, open-label, 2 × 2 crossover study designed to assess the effects of a high-fat meal on the PK of orally administered bexagliflozin tablets, 20 mg. Following a ≥ 10-h overnight fast, eighteen (18) eligible healthy subjects will be assigned to two groups with an equal number (n=9) of subjects per group to receive a single oral dose of bexagliflozin tablets, 20 mg, in either a fasted state or 30 min after starting a high-fat meal. A washout period of at least 7 days will be used between the two treatment periods, after which, subjects will receive bexagliflozin tablets, 20 mg, in a fasted or fed state (high-fat), whichever state they had not received previously. The high-fat meal will be ingested in its entirety over an approximate 25-minute period, such that it is completed at least 5 minutes prior to the scheduled time of bexagliflozin dosing for the group receiving bexagliflozin with food. If a portion of the meal is not consumed, the reason and the amount of remaining food

will be recorded. No food should be allowed for at least 4 h after drug administration. Standard meals will be served to both groups 4 hour after dosing.

In treatment period 1, subjects will be admitted to the clinic on day 0, the day before dosing, and will stay in the clinic until 48-h post-dose. In treatment period 2, subjects will be admitted to the clinic on day 7, the day before dosing, and will stay in the clinic until 48-h post-dose. Blood samples for bexagliflozin plasma concentrations will be collected in each period at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose. Urine collection in 12 h batches will be performed at pre-dose (-12 to 0 h on day 0 and day 7), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

Clinical laboratory tests and safety monitoring will be conducted during both treatment periods.

Study Population:

Eighteen healthy subjects are planned to be enrolled and dosed.

Diagnosis and Main Criteria for Inclusion

1. Healthy subjects who are between the ages of 18 and 65 years, inclusive.
2. Subjects with body-mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2, inclusive.
3. Male subjects who are surgically sterile or male subjects who are not surgically sterile but who agree to refrain from donating sperm and use appropriate birth control such as the use of condoms when engaging in sexual intercourse for a period of 30 days after discharge from the clinic.
4. 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. Female subjects who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible if they test negative on the urine pregnancy test.
5. Subjects who are non-smokers for at least 3 months prior to screening.
6. Subjects with adequate venous access at multiple sites in both arms.

Test Product; Dose; and Mode of Administration:
Bexagliflozin tablets, 20 mg, oral administration.

Duration of Treatment:

Two single dose treatments with at least 7 days apart

Pharmacokinetic Variables:

The following PK parameters of bexagliflozin will be determined where feasible after each subject is dosed with bexagliflozin in a fasted state and 30 min after starting a high-fat meal.

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:

- Vital signs
- Clinical laboratory tests including blood chemistry and hematology parameters
- Urinalysis
- Adverse events
- Concomitant medication use

PD Assessment:

- UGE
- Urinary electrolytes, uric acid, and creatinine

Statistical Methods:

Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS Institute Inc., USA). PK parameters of bexagliflozin will be calculated by non-compartmental analysis (NCA) of plasma concentration-time data. Non-compartmental analysis will be performed using Phoenix® WinNonlin® 6.4 (Certara, USA). To assess the effect of a high-fat meal on the PK of bexagliflozin, an analyses of variance (ANOVA) using a linear mixed-effects model will be fitted to the natural logarithmic transformation of PK parameters of bexagliflozin (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 fed : fasted ratio of 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 terminal elimination half-life ($T_{1/2}$) 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}.

Descriptive statistics on the PD parameters will be also performed. The effect of high-fat meal on the cumulative UGE between subjects under fasted and fed conditions will be compared.

Date of Original Protocol(V1): 18 May 2016

Prepared in: Microsoft Word 2010

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALB	albumin
ALT	alanine aminotransferase
ANOVA	analyses of variance
AST	aspartate aminotransferase
ATC	anatomic therapeutic chemical classification
AUC	area under the time-concentration curve
AUC_{extr}	extrapolated area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from Time 0 to Time t
BLOQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatinine kinase
C_{last}	concentration corresponding to T_{last}
CL/F	apparent oral clearance
C_{max}	maximum observed plasma concentration
CRF	case report form
CRO	contract research organization
d	day
ECG	electrocardiogram
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
γ-GTP	gamma-glutamyl transferase
h	hour(s)
HBsAg	hepatitis B surface antigen
HCO_3	bicarbonate
Hct	hematocrit
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
Hgb	hemoglobin
HIV	human immunodeficiency virus
IC_{50}	concentration that produces 50% inhibition of response

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IR	immediate release
IRAE	immediately reportable adverse event
IRB	Institutional Review Board
K_2EDTA	potassium ethylenediaminetetraacetic acid
λ_z	terminal elimination phase rate constant
LDL-C	low density lipoprotein cholesterol
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
n	number
NCA	non compartmental analysis
OTC	over-the-counter
PD	pharmacodynamic
PE	physical examination
Pgp	p-glycoprotein
PK	pharmacokinetic
QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram
QT_C	The corrected QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RBC	red blood cell (count)
RR	respiration rate
SAE	serious adverse event
SD	standard deviation
SGLT1	sodium glucose cotransporter 1
SGLT2	sodium glucose cotransporter 2
SOP	standard operating procedure
$t_{1/2}$	apparent terminal elimination half-life
TBL	serum total bilirubin
TC	total cholesterol
TEAE	treatment emergent adverse events

TG	triglycerides
T_{last}	time of last measurable (positive) concentration
T_{max}	time of maximum observed plasma concentration
UGE	urinary glucose excretion
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9
ULN	upper limit of normal (value)
UTI	urinary tract infection
V_z/F	apparent volume of distribution
WBC	white blood cell (count)
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential
λ_z	Terminal elimination phase rate constant

1 INTRODUCTION

Bexagliflozin, a potent and selective renal Na+/glucose transport protein sodium glucose cotransporter 2 (SGLT2) inhibitor is being developed as a treatment for type 2 diabetes mellitus. The transport of glucose from the renal tubule into the tubular epithelial cells is facilitated by SGLT2 which is expressed primarily in the kidney in the early proximal tubule of the nephron (Washburn 2009). By inhibiting SGLT2, bexagliflozin blocks the reabsorption of filtered glucose, in turn promoting urinary glucose excretion and thereby reducing plasma glucose (Zhang, Welihinda et al. 2011).

Clinical pharmacokinetic (PK) studies have shown that the peak plasma bexagliflozin concentrations occurred between 3 to 5 h and thereafter declined in a biphasic manner with mean elimination half-life values ranging from 7.80 to 9.71 h. Bexagliflozin is cleared predominantly by metabolism to an inactive metabolite, bexagliflozin 3-O-glucuronide by the uridine diphosphate glucuronosyltransferase isoform 1A9 (UGT1A9) pathway. Extended release bexagliflozin tablet formulations are developed to provide greater than 75% release in approximately 8 h *in vitro*. The objective of this study is to evaluate the effects of a high-fat meal on the PK of extended release bexagliflozin tablets, 20 mg.

1.1 Bexagliflozin for the Treatment of Type 2 Diabetes Mellitus

Bexagliflozin is a highly specific inhibitor of SGLT2 with an *in vitro* IC_{50} of 2 nM or 0.9 ng/mL and a 2435-fold selectivity for human SGLT2 compared with sodium glucose cotransporter 1 (SGLT1). Details of the nonclinical and clinical findings are described in the Investigator's Brochure.

1.2 Summary of Nonclinical Data with Bexagliflozin

Bexagliflozin exhibits high permeability and is a potential Pgp (p-glycoprotein) substrate and inhibitor. It is not a significant inducer or inhibitor of cytochrome P450 isozymes and other transporters relevant for drug-drug interactions.

1.3 Summary of Clinical Data with Bexagliflozin

The early clinical studies have been conducted using immediate release (IR) products in capsules. Theracos has completed multiple phase 1 studies to evaluate safety, tolerability, pharmacokinetics (plasma exposure), pharmacodynamics (glucosuria), and drug metabolism in healthy subjects, patients with type 2 diabetes, and diabetic patients with renal impairment.

Following administration of bexagliflozin IR capsules, time of maximum observed plasma concentration (T_{max}) was reached within 1 to 3 h. The systemic exposure was dose proportional with a maximum observed plasma concentration (C_{max}) of 11 ng/mL per mg bexagliflozin and an area under the plasma concentration-time curve (AUC_{0-24}) of approximately 60 ng·h/mL per mg bexagliflozin in healthy or diabetic subjects. Following administration of bexagliflozin tablets in extended release formulations, T_{max} was reached between 3 to 5 h. The tablets produced dose proportional exposure with a C_{max} of 4 or 8

ng/mL per mg bexagliflozin and an AUC_{0-24} of 40 or 50 ng·h/mL per mg bexagliflozin in healthy subjects when dosing was before or after a meal, respectively.

The principal metabolites in humans are similar to those found in monkeys and are dominated by glucuronides of the parent compound, for which the AUC is >30% relative to parent bexagliflozin. Modest accumulation consistent with an extended half-life has been seen following multiple daily dosing. Following oral administration of radiolabeled bexagliflozin, >90% of the ingested radioactivity was recovered, 51% as fecal excretion and 41% as urinary excretion. In urine, bexagliflozin accounts for 1.5% of the dose; most of the radioactivity is excreted as bexagliflozin 3'-*O*-glucuronide. The largest fraction of the radioactivity in feces is due to bexagliflozin, accounting for about 30% of the administered dose.

The safety and tolerability of bexagliflozin in healthy or diabetic subjects was initially evaluated in a single-dose study of up to 100 mg, followed by a 4-week treatment study in which doses ranged from 5 mg/d to 50 mg/d. The most frequently occurring adverse events (AEs) were mild to moderate headache, pollakiuria, nausea, and fatigue. No symptomatic hypoglycemia was reported and no treatment-related adverse event led to discontinuation of treatment. Extended release tablets of 3 mg to 90 mg strengths were well tolerated in a Japanese population with few adverse events reported.

Detailed information of bexagliflozin clinical experience and potential risks for study subjects are provided in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of a high-fat meal on the pharmacokinetics of bexagliflozin extended release tablets in healthy subjects.

2.2 Secondary Objectives

To evaluate the safety of bexagliflozin after a single oral dose in fasted or fed state in healthy subjects.

To evaluate the effect of a high-fat meal on the potential pharmacodynamic activity of bexagliflozin by determining urinary glucose excretion in healthy subjects under fasted and fed conditions.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This single center, phase 1, open-label, 2 × 2 crossover study is designed to assess the effects of a high-fat meal on the PK of orally administered bexagliflozin tablets. Eighteen eligible healthy subjects will be randomized into two groups such that an equal number (n=9) of subjects will receive a single oral dose of a bexagliflozin tablets, 20 mg, with or without a meal on treatment day 1. Subjects randomized to receive bexagliflozin tablets with a high-fat meal on day 1 will receive a second dose of bexagliflozin tablets without a meal on treatment day 8 after an overnight fast. Subjects randomized to receive bexagliflozin tablets without a meal on treatment day 1 after an overnight fast will receive a second dose of bexagliflozin tablets with a high-fat meal on treatment day 8.

Bexagliflozin will be taken orally with 240 mL of water in the morning (approximately 8 a.m. to 10 a.m.). The time of dosing for a given subject will be the same (as far as practicalities permit) in both treatment periods.

The high-fat meal will follow the FDA guidance (Food Drug Administration 2002) on high-fat (50% of total caloric content of the meal) and high-caloric (800 to 1000 cal) content. An example of the high-fat meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

Subjects dosed in the fed state will receive an oral bexagliflozin tablets, 20 mg, 30 min after starting to consume a high-fat meal after an overnight fast. No additional food should be allowed for at least 4 h post-dose. Water will be allowed as desired except for one hour before and after drug administration. The meal will be ingested in its entirety over an approximate 25-minute period, such that it is completed at least 5 minutes prior to the scheduled time of bexagliflozin dosing for the fed state treatment. If a portion of the meal is not consumed, the reason and the amount of remaining food will be recorded. Subjects should receive standard meals scheduled at the same time in each period of the study.

Subjects dosed in the fasting state will receive an oral bexagliflozin tablets, 20 mg, after an overnight fast. No food should be allowed for at least 4 h post-dose. Water will be allowed as desired except for one hour before and after drug administration. Subjects should receive standard meals scheduled at the same time in each period of the study.

Subjects will be admitted to the clinic on day 0 and day 7, the day before dosing in each treatment period, and will stay in the clinic until 48-h post-dose. Standard meals will be served at the clinic during the stay. Blood samples (2 mL) for bexagliflozin plasma concentrations will be collected at 0 h (pre-dose), and at, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose (days 1-3 in treatment period 1 and days 8-10 in treatment period 2 respectively). Urine collection in 12 h batches will be performed at pre-dose (-12 to 0 h on day 0 and day 7), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

Clinical laboratory tests and safety monitoring will be conducted during both treatment periods.

For the Schedule of Events table, see Appendix 1. For the overall Dosing Schedule, see Table 1.

3.2 Rationale for Study Design

The PK profile of bexagliflozin formulated as an extended release product at 10 and 30 mg has been evaluated in an early clinical trial (THR-1442-C-445). The effects of dose administration in the fasted and fed states were assessed in healthy Japanese subjects for absorption, distribution, metabolism and excretion of bexagliflozin. Twelve subjects were randomized evenly to two dose groups (10 and 30 mg). Each group received first dose of bexagliflozin tablets under fed state on day 1, then after 7-day washout, subjects received second dose under fasted state. The administration of bexagliflozin at 10 and 30 mg with a standard meal resulted in increased average C_{max} (range 39% to 59% for bexagliflozin and 19% to 28% for bexagliflozin 3-O-glucuronide) and decreased half-life (range 23-40% for bexagliflozin and 10% to 21% for bexagliflozin 3-O-glucuronide). However, no meaningful change in the T_{max} of either analyte was observed. No effect of food on the overall systemic exposure [area under the plasma concentration-time curve (AUC)] of bexagliflozin and bexagliflozin 3-O-glucuronide was observed.

In general, meals that are high in total calories and fat content are more likely to affect the gastrointestinal physiology and thereby result in a maximal effect on the bioavailability of a drug substance. Therefore, a high-fat meal will be used in this study to evaluate the potential maximum effect of food on the PK of bexagliflozin tablets, 20 mg, which is the intended commercial product. The planned sample size in this crossover study will be powered to provide sufficient data for a statistical testing of food effect on the PK of bexagliflozin. The results will provide a guide for the timing of dosing relative to meals for this bexagliflozin product.

3.3 Study Duration and Dates

This is a phase 1, two-period, two-treatment, crossover study. Subjects will be screened within 28 days of the initiation of study drug dosing. Eligible subjects who consent to the study will be randomly assigned to 1 of 2 groups, each group will receive both treatments alternately, in a crossover fashion (two-period, two-treatment crossover design), with the two treatment periods separated by a 7-day washout period.

In treatment period 1, subjects will be admitted to the clinic on day 0, the day before dosing, and will stay in the clinic until 48 h post-dose. In treatment period 2, subjects will be admitted to the clinic on day 7, the day before dosing, and will stay in the clinic until 48 h post-dose. The scheduled visits and procedures for each visit are provided in Appendix 1.

4 STUDY POPULATION SELECTION

4.1 Study Population

Eighteen eligible 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 18-65 years of age inclusive with body-mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2, inclusive.
2. Male subjects who are surgically sterile or male subjects who are not surgically sterile must agree to refrain from donating sperm and use appropriate birth control such as the use of condoms when engaging in sexual intercourse for a period of 30 days after discharge from the clinic.
3. 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.
4. Female subjects who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible if they test negative on the urine pregnancy test.
5. Subjects who are non-smokers for at least 3 months prior to screening.
6. Subjects with adequate venous access at multiple sites in both arms.
7. Subjects who are willing and able to be confined to the clinical research facility as required by the protocol.
8. Subjects who have the ability to comprehend and willingness 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, including impairment of the central nervous system, circulatory system, respiratory system, blood/hematopoietic function system, gastrointestinal system, liver/kidney function, thyroid function, pituitary function and/or adrenal function.
2. Female subjects who are nursing or pregnant.
3. Subjects with a clinically significant history of allergy to drugs or latex.
4. Subjects with a history of alcohol or drug dependence in the last 12 months.
5. Subjects who had 400 mL of whole blood collected within four months or 200 mL of whole blood collected within one month of the screening test.
6. Subjects who had blood component collection within 14 days prior to the screening test.
7. Subjects who have used prescription or over-the-counter (OTC) drugs within 14 days prior to the first dose.

8. Subjects who have used vitamin preparations or supplements (including St. John's Wort and ginseng) within 14 days prior to the first dose.
9. Subjects who have undergone strenuous activity within 72 hours prior to Day 1 in each period.
10. Subjects who are unable (e.g., food intolerance) or unwilling to consume a high-fat breakfast within 25 minutes.
11. 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 of study drug in this trial.
12. Subjects who had previously received EGT0001474 or bexagliflozin, or any other SGLT2 inhibitors within 3 months from the screening.
13. Subjects whose screening electrocardiogram (ECG) demonstrates any one of the following: heart rate > 100 bpm, QRS > 120 msec, QTc > 470 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 that is not sinus rhythm, sinus bradycardia, or sinus arrhythmia.
14. Subjects whose sitting blood pressure is above 140/90 mmHg at screening.
15. Subjects who have a positive result of HBsAg antigen, HCV antibody, urinary drug or urinary cotinine test.
16. Subjects with known human immunodeficiency virus (HIV) disease.
17. Subjects with abnormal vital signs, laboratory values, symptoms or signs that are deemed clinically significant by the investigator.
18. Subjects who have had a febrile illness within 5 days prior to the first dose of study medication.
19. Subjects vaccinated within 30 days prior to the first dose of medication.
20. Detectable urine glucose at screening (trace or greater).
21. Subjects with eGFR < 90 mL/min/1.73 m^2 or a history of kidney transplant.
22. Subjects with digestion problems, including gastroesophageal reflux disease, irritable bowel syndrome, gastroparesis, and any other disorder deemed by the investigator to be clinically significant.

5 STUDY TREATMENTS

5.1 Study Drug

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*.

5.2 Treatments Administered

Subjects who consent to be in the study will be randomly assigned to 1 of 2 treatment groups. Each group will be dosed with bexagliflozin under a fasted state in one period and under a fed state (high fat, high calorie) in the other period. A single oral dose of bexagliflozin tablets, 20 mg, will be provided to subjects in each treatment period.

The detailed dosing schedule is shown in Table 1.

Table 1. Dosing Schedule

Subject Group	Treatment Period	Treatment Period 1 (Day 1)			Treatment Period 2 (Day 8)		
	Dosing Time (h)	-0.5	0	4	-0.5	0	4
Group 1	Bexagliflozin single oral dose		X			X	
	*Meal	X		X			X
Group 2	Bexagliflozin single oral dose		X			X	
	*Meal			X	X		X

*High-fat meal will be provided at time -0.5 h, while standard meal will be provided at other times.

5.3 Selection and Timing of Dose for Each Subject

Dosing order with bexagliflozin alone or in combination with food will be based on randomized assignment. Results from previous clinical trials indicate that doses of 1.7 mg to 100 mg of bexagliflozin are well tolerated and the planned dose of bexagliflozin tablets, 20 mg, produced significant glucosuria and is not expected to produce serious drug-related adverse events.

- **Bexagliflozin alone**: After an overnight fast of at least 10 h, a bexagliflozin tablets, 20 mg, will be administered 4 h prior to the first meal of the day with 240 mL of water.
- **Co-administration of bexagliflozin with food**: After an overnight fast of at least 10 h, a bexagliflozin tablets, 20 mg, will be administered 30 min after starting to consume a high-fat meal with 240 mL water.

If for some reason, a portion of the water is not consumed, the reason and the amount of remaining water will be recorded.

5.4 Method of Assigning Subjects to Treatment Groups

A sufficient number of subjects will be screened to ensure that up to 18 subjects will be randomized. Eligible subjects will be randomly assigned to group 1 or group 2 in a 1:1 ratio. Subjects who discontinue the study after randomization for non-safety related reasons may be replaced to ensure that the number of evaluable subjects in each group should not be less than 8.

5.5 Blinding

This is an open-label study. There is no blinding process in this protocol.

5.6 Concomitant Therapy

The participants are not allowed to take any prescription or non-prescription drugs, vitamins, or dietary supplements at any time during 14 days prior to (first) drug administration and for the duration of each study period. 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 1 week from the end of the last study product dosing. 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 screening, nor an investigational drug within 30 days or 7 half-lives, or used any prescription medication or herbal supplements within 14 days prior to the first dose of study medication.

5.7.2 Fluid and Food Intake

An overnight fast of at least 10 h prior to dosing is required. For the fasting state treatment group, oral intake of food (standard meals) will be restricted for 4 h following administration of bexagliflozin.

The fed state treatment will consist of a bexagliflozin tablet, 20 mg, taken 30 min after subjects start to consume a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800–1000 cal) meal after an overnight fast.

Each dose will be administered with 240 mL tap water. Food intake will be forbidden during the first 4 h post dosing. Water can be allowed as desired except for one hour before and after drug administration

Subjects are expected to consume 100% of the high-fat meal and 240 mL of water provided. If a portion of the meal and water is not consumed, the reason and the amount of remaining meal and water will be recorded.

Subjects should receive standard meals scheduled at the same time in each period of the study.

5.7.3 Subject Activity Restrictions

Light physical activity is permitted. Subjects should not perform strenuous activity during the clinical stay and during the washout period as this could result in elevations of muscle creatinine kinase (CK) levels. Smoking during the study is prohibited.

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

Investigational product will be provided to the pharmacist or designated site personnel in bottles of 90 tablets enclosed with a child-resistant cap. The pharmacist or designated site personnel will dispense the investigational products for each subject according to randomization assignment.

5.10 Storage and Accountability

Bexagliflozin tablets should be stored at controlled room temperature, 15 to 30°C (59 to 86°F) in a secure area with access limited to authorized personnel. The drug storage facility must comply with the medication storage instructions. The trial staff must record the amount of investigational product dispensed to each subject in the dosing record. 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 Drug Accountability Form. All unused drug must be returned to a sponsor-designated depot after drug accounting is verified by the sponsor or its designee.

6 STUDY PROCEDURES

6.1 Informed Consent

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 Conference on 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 and whether childbearing potential if female.
- Significant medical, surgical history and timeframe of the history relative to study screening, if applicable.
- Clinically significant history of allergy including drugs and latex.
- History of smoking, alcohol or drug dependence, or abuse in the last 12 months.
- Any blood donation or blood component donation within 4 months.
- Use of any medications including over the counter drugs, vitamins, or dietary supplements within 14 days.
- History of vaccination within 30 days prior to the first dose of study medication.
- History of diagnosis with HIV, hepatitis B or hepatitis C.
- Use of any investigational drug in the previous 30 days or 7 half-lives, whichever is longer.
- Prior exposure to bexagliflozin (or EGT0001474), or any other SGLT2 inhibitors within 3 months from the screening.

6.3 Physical Examination

The investigator or designated qualified individual will perform the physical examinations (PEs). A complete physical examination will be performed at screening and at the termination visit. Partial physical examinations will be performed at scheduled visits.

A complete physical examination will include measurement of body weight and height (height will be measured only at screening), general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, lungs, heart, abdomen, lymph nodes, and extremities. A partial physical examination 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) in a seated position will be obtained after a subject has been sitting for 5 min, respiration rate (RR), and oral temperature, will be measured at the scheduled visits described in Appendix 1. BP measures will be obtained using a calibrated sphygmomanometer.

Vital signs should be measured prior to blood draws.

Respiration rate should be measured after at least 5 min of rest. Devices designed to measure BP from the finger or wrist may not be used.

6.5 Electrocardiography and Continuous Telemetry Monitoring

6.5.1 12-Lead Electrocardiograms

A 12-lead electrocardiogram (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 10 min 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 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 or supine position during blood collection. Clinical blood chemistry and hematology 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 2.

Table 2. Required Laboratory Tests

Test Name		Blood or urine Vol. (mL)
Hematology		3 (blood)
Hematocrit (Hct)	Mean corpuscular volume (MCV)	
Hemoglobin (Hgb)	Platelet count	
Mean corpuscular hemoglobin (MCH)	Red blood cell (RBC) count	
Mean corpuscular hemoglobin concentration (MCHC)	White blood cell (WBC) count with differential	
Serum Chemistry and Electrolytes		10 (serum)
Albumin (ALB)	Calcium (Ca)	
Alanine aminotransferase (ALT)	Magnesium	
Aspartate aminotransferase (AST)	Phosphorus	
Blood urea nitrogen (BUN)	Potassium (K)	
Glucose	Sodium (Na)	
Bicarbonate (HCO_3)	Total bilirubin	
Creatinine Chloride (Cl)	Direct bilirubin	
Total protein	Uric acid	
Serum Lipids		6 (serum)
Total cholesterol (TC)	Low-density lipoprotein cholesterol (LDL-C), calculated	
High-density lipoprotein cholesterol (HDL-C)		
Triglycerides (TG)		
Urinalysis		10 (urine)
Appearance	Nitrite	
Bilirubin	Occult blood	
Color	pH	
Glucose	Protein	
Ketones	Specific gravity	
Microscopic examination of sediment	Urobilinogen	
	Leukocyte esterase	
Urine Collection (in 12-h batches)		
Glucose	Potassium	All (urine)
Creatinine	Calcium	
Sodium	Uric acid	
Urine drug screen		10 (urine)
Amphetamines	Opiates	
Barbiturates	Benzodiazepines	
Cocaine Metabolites	Cannabinoids	
Cotinine		
Urine pregnancy test		2 (urine)
Infectious Disease Testing		6 (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 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. In addition, urinalysis will be performed from clean catch urine sample at any time in subjects with symptoms of urinary tract infection (UTI) or pyelonephritis.

6.6.2.3 Urine Collection

Pre-dose urine samples must be collected from -12 to 0 h for baseline measurement, immediately after which subjects will empty their bladders. Post dose urine will be collected without preservative in four (4) batches: 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h collections. Urine must be refrigerated at 2-8^{o}C during collection. After collection, the total volume of each batch and collection time will be recorded. A 20 mL aliquot will be prepared from well mixed urine collections. The samples will be analyzed for urinary glucose (PD), uric acid, creatinine, and electrolytes.

6.6.2.4 Plasma Sample Collection for PK

Whole venous blood samples of 2 mL will be collected from a peripheral vein in each period at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose. Samples will be placed in tubes containing potassium ethylenediaminetetraacetic acid (K_2EDTA) and stored on ice until centrifuged under refrigeration for at least 10 min at 3,000 rpm. After centrifugation, plasma will be removed and stored frozen in 3 aliquots of 200 µL at or below -20°C. Processed frozen plasma samples will be transferred on dry ice to the analytical laboratory and will be stored at or below -20^{o}C until analysis.

6.6.2.5 Blood and Urine Volume and Frequency for PK/PD and Safety Assessment

The total volume and number of sampling times for blood and urine collections are outlined in Table 3.

Table 3. Blood and Urine Samples

Test	Volume/sample (mL)	No. of Samples	Total	Storage
Blood				
Hematology	3	6	18	
Chemistry	16	6	96	
Infectious Disease Testing	6	1	6	
PK	2	28	56	≤ -20^{o}C

Table 3. Blood and Urine Samples

Test	Volume/sample (mL)	No. of Samples	Total	Storage
Urine Collection				
Urinalysis	10	6	60	+4°C
PD	20	10	200	+4°C
Urine Drug Screen	10	1	10	
Urine Pregnancy Test	2	1	2	+4°C

Total blood volume required in each subject: 176 mL; total urine volume required in each subject: 272 mL.

6.7 Pharmacokinetic Assessments

A non-compartmental analysis (NCA) will be used to calculate the PK parameters of bexagliflozin using the software Phoenix® WinNonlin® 6.4 (Certara, USA). From the plasma bexagliflozin 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.

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 above 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 below the limit of quantitation (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 bexagliflozin by Treatment and Timepoint will be provided. A listing of plasma concentrations by SubjectID, Treatment Period and Timepoint will also be provided.

6.8 Pharmacodynamic Assessment

Urinary glucose excretion will be determined as the pharmacodynamic (PD) parameter at baseline (day 0 and day 7), and up to 48 h postdose (days 1-3 and 8-10). The effect of high-fat meal will be evaluated by comparing the mean cumulative urinary glucose excretion (UGE) between subjects under fasted and fed conditions. Potential effects on urinary creatinine, uric acid, sodium, potassium, and calcium will also be analyzed.

6.9 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 a medicinal product, whether or not considered related to the medicinal 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; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- 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 study drug.

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 an abnormal change from baseline for that subject, this is considered an AE.

Hypoglycemia will be defined as any FPG (fasting plasma glucose) value < 70 mg/dL and documented as described in Section 6.9.4.4.

Any increase in liver function tests (AST, aspartate 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 not iced, 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.

Study Drug 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 study drug and the AE when the event responds to withdrawal of the study drug (dechallenge), and recurs with rechallenge by administration of the study drug.

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

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

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

Unrelated: There is not a temporal or causal relationship to study-drug administration.

6.9.1 Collecting and Reporting Adverse Events

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

In addition, 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.

6.9.2 Immediately Reportable Adverse Events

The investigator must report any serious adverse event (SAE), by telephone, email, or fax, to Theracos or its representative immediately after the investigator becomes aware of the event. An immediately reportable adverse event (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 study drug (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.

6.9.3 Pregnancy

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

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

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

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

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

If a subject or investigator suspects that the subject may be pregnant prior to investigational product administration, the investigational product administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the investigational product and must not remain 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. This reporting requirement will continue until 4 weeks after the last investigational product exposure.

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

6.9.4 Follow-up of Adverse Events

6.9.4.1 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.

6.9.4.2 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 6.9.1. 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 study drug, 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.

6.9.4.3 Hepatotoxicity

Any clinically significant increase in hepatic enzymes and specifically ALT or AST ≥ 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.

Study drug should be permanently discontinued if any of the following criteria is met:

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

6.9.4.4 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 with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg/dL (3.9 mmol/L).

6.10 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 (ATC) and preferred name will be produced. A listing of concomitant medications will include all medications taken by any subjects during the course of the study.

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.

6.11 Removal of Subjects from the Trial or Study Drug

The investigator must emphasize to potential subjects the importance of continued participation for the full duration of the trial during the informed consent process. 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 study drug 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 THR-1442-C-481 trial for any of the following reasons:

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

6.12 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.

Determination of urinary glucose is a non-invasive and quantitative method that allows immediate assessment of the pharmacodynamic effects of an SGLT2 inhibitor. The excreted glucose is dose dependent, saturable, and correlates with lowering of fasting plasma glucose and of hemoglobin A1c based on data from bexagliflozin studies and other SGLT2 inhibitors.

7 STUDY ACTIVITIES

7.1 Screening (Days -28 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.
- Medical history and demographic information obtained.
- Perform a physical examination, including height and weight measurements as described in Section 6.3.
- Vital signs collected 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.
- 12-lead ECG taken in the supine position after at least 10 min of rest as described in Section 6.5.
- Clean-catch, mid-stream urine will be collected for urinalysis as described in Section 6.6.2.2. If urine is dipstick positive for leukocyte esterase or nitrites, sample is to be sent for microscopic evaluation and culture.
- Urine screen for drug abuse and cotinine. If the drug screen is conducted more than 5 days pre-dose, the drug screen must be repeated prior to dosing. Drug abuse testing includes amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.
- Women will receive urine pregnancy test.
- Blood will be drawn for hematology, serum chemistry, and serology as detailed in Section 6.6.2.1.
- The inclusion/exclusion criteria will be evaluated based on the information collected at the screening examination.

7.2 Clinic Admission (Day 0)

- On day 0 the following information will be gathered and the indicated procedures will be performed:
- If screening was conducted more than five days prior to dosing, the inclusion and exclusion criteria must be confirmed and a urine drug screen performed.
- A partial physical examination must be performed as described in Section 6.3.
- If the subject is still eligible based on the study inclusion and exclusion criteria the subject will be admitted and randomized into the study.
- Concomitant medications and adverse event information will be collected as appropriate
- Pre-dose urine collection in 12 h batches at -12 h to 0 h (on day 0) for baseline analysis of electrolytes, uric acid and creatinine and for UGE (PD) analysis as described in Section 6.6.2.3.

7.3 Day 1 Activities (Pre-dose)

The following information will be gathered and the indicated procedures will be performed Pre-dose:

- Record vital signs pre-dose.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest pre-dose.
- Complete pre-dose urine collection at 0 h (-12 h to 0 h) for baseline UGE analysis and analysis of electrolytes, uric acid and creatinine analysis as described in Section 6.6.2.3.
- Urine sample will be prepared for pre-dose urinalysis as described in Section 6.6.2.2. If urine is dipstick positive for leukocyte esterase or nitrites, sample is to be sent for microscopic evaluation and culture.
- Pre-dose blood will be drawn for hematology, and serum chemistry as detailed in Section 6.6.2.1.
- Pre-dose plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4.
- Pre-dose concomitant medications and adverse event information collected as appropriate.

7.4 Day 1 Through 3 Activities (Post-dose)

- For group 1 subjects, after an overnight fast of at least 10 h, bexagliflozin tablets, 20 mg, will be administered 30 min after the start of the high-fat meal as detailed in Section 5.2.
- For group 2 subjects, after an overnight fast of at least 10 h, bexagliflozin tablets, 20 mg, will be administered 4 h prior to the first meal of the day as detailed in Section 5.2.
- Record vital signs at 4 h (day 1) and 48 h (day 3) post-dose.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest at 4 h (day 1) post-dose.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 (day 2) and 48 h (day 3).
- Urine collection in 12 h batches at 0 to 12 h and 12 to 24 h, 24 to 36 h and 36 to 48 h for analysis of electrolytes, uric acid and creatinine and for UGE (PD) analysis as described in Section 6.6.2.3.
- Post-dose concomitant medications and adverse event information is collected as appropriate.
- On day 3 urine will be collected as described in Section 6.6.2.2 for urinalysis.
- On day 3 blood will be drawn for hematology and serum chemistry as detailed in Section 6.6.2.1.
- After completion of all day 3 activities the subject will be discharged and scheduled for day 8 (period 2) of the study.

Subjects who are terminated from the study for any reason after dosing has started must have the information and procedures shown for day 8 collected and completed and the reason for termination entered onto the case report form.

7.5 Day 7 Activities

On day 7 the following information will be gathered and the indicated procedures will be performed:

- If the subject is still eligible based on the study inclusion and exclusion criteria, the subject will be admitted for the cross-over phase of the study.
- Concomitant medications and adverse event information will be collected as appropriate.

Pre-dose urine collection in 12 h batches at -12 h to 0 h (day 1) for baseline analysis of electrolytes, uric acid and creatinine and for UGE (PD) analysis as described in Section 6.6.2.3. Subjects who are terminated from the study at this time must have the reason for termination entered onto the case report form.

7.6 Day 8 Activities (Pre-dose)

On day 8 the following information will be gathered and the indicated procedures will be performed Pre-dose:

- Record vital signs pre-dose.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest pre-dose.
- Complete pre-dose urine collection at 0 h (-12 h to 0 h) for baseline UGE analysis and analysis of electrolytes, uric acid and creatinine analysis as described in Section 6.6.2.3
- Urine will be collected pre-dose as described in Section 6.6.2.2 for urinalysis.
- Pre-dose blood will be drawn for hematology and serum chemistry as detailed in Section 6.6.2.1.
- Pre-dose plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4.
- Concomitant medications and adverse event information is collected as appropriate.

7.7 Day 8 through 10 Activities (Post-dose)

- For group 1 subjects, after an overnight fast of at least 10 h, bexagliflozin tablets, 20 mg, will be administered 4 h prior to the first meal of the day as detailed in Section 5.2.
- For group 2 subjects, after an overnight fast of at least 10 h, bexagliflozin tablets, 20 mg, will be administered 30 min after the start of the high-fat meal as detailed in Section 5.2.
- Record vital signs at 4 h (day 8) and 48 h (day 10) post-dose.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest at 4h (day 8) and 48 h (day 10) post-dose.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 (day 9), 36 (day 9) and 48 h (day 10).
- Urine collection in 12 h batches at 0 to 12 h and 12 to 24 h, 24 to 36 h and 36 to 48 h for analysis of electrolytes, uric acid and creatinine and for UGE (PD) analysis as described in Section 6.6.2.3.Concomitant medications and adverse event information is collected as appropriate.

- On day 10 perform a physical examination as described in Section 6.3.
- On day 10, urine will be collected as described in Section 6.6.2.2 for urinalysis.
- On day 10, blood will be drawn for hematology and serum chemistry as detailed in Section 6.6.2.1.
- After completion of all day 10 activities the subject will be discharged. A follow up visit may be scheduled on day 15 if clinically indicated. If a subject who withdraws consent prior to completion of all study activities, a follow up visit may be scheduled if clinically indicated.

7.8 Early Termination or Follow-up Procedures

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, serum chemistry, and glycemic control). 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 initiation of the study. Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS Institute Inc., 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 bexagliflozin, to assess potential food-drug interactions, and to provide safety and tolerability data on bexagliflozin when administered with food (Food and Drug Administration 2002).

9.3 Analysis Populations

Statistical analysis populations will include:

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

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

9.4 Demographics and Baseline Characteristics

Baseline characteristics including demographics, physical examination, ECG parameters, and safety laboratory values will be summarized for all subjects in the Safety and the PK Populations. Descriptive statistics will be performed.

9.5 Statistical Analysis of Pharmacokinetic Variables

To assess the effect of a high-fat meal on the PK of bexagliflozin, an analyses of variance (ANOVA) using a linear mixed-effects model will be fitted to the natural logarithmic transformation of PK parameters of bexagliflozin (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 fed: fasted 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 terminal elimination half-life ($T_{1/2}$) 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 SubjectID and Treatment Period will be provided.

Descriptive statistics on the PD parameters will be also performed. The effect of high-fat meal on the cumulative UGE between subjects under fasted and fed conditions will be compared.

9.6 Safety Analysis

Safety data will include adverse events (AEs), physical exam 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 6.9.4.4 will be presented in listings and summarized.

9.6.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory metrics are measured at baseline 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. In addition, all serum biochemistry, hematology, and urinalysis data outside the reference ranges will be summarized by parameter.

Laboratory data will be summarized using Low-Normal-High shift tables. 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.

9.7 Interim Analysis

There will be no interim analysis conducted.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

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

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

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

10.3 Ethical Conduct of the Study

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor and investigator follow Good Clinical Practice (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/IEC or sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment should be submitted to the 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 and CRO's draft informed consent form. The sponsor will review the investigator's draft informed consent form prior to submission to the IRB/IEC and the final IRB/IEC 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 Ethics Committee or IRB the written approval or favorable opinion of the informed-consent form and any other written information to be provided to subjects. The written approval of the IRB/IEC together with the approved subject information/ informed consent forms must be filed. The informed consent form must contain all elements required by the FDA under 21 CFR 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 study drug. The study investigator is obliged to provide the sponsor with complete test results and all data developed in this study. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission. To ensure compliance with current ICH guidelines, data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the sponsor, and the IRB/IEC for each study site.

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

10.6 Study Monitoring

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

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

10.7 Case Report Forms and Study Records

For each subject consented, a case report form (CRF), in 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/IEC 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

Food Drug Administration, H. H. S. (2002). "Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies."

Washburn, W. N. (2009). "Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents." Expert Opin Ther Pat **19**(11): 1485-1499.

Zhang, W., A. Welihinda, J. Mechanic, H. Ding, L. Zhu, Y. Lu, Z. Deng, Z. Sheng, B. Lv, Y. Chen, J. Y. Roberge, B. Seed and Y. X. Wang (2011). "EGT1442, a potent and selective SGLT2 inhibitor, attenuates blood glucose and HbA(1c) levels in db/db mice and prolongs the survival of stroke-prone rats." Pharmacol Res **63**(4): 284-293.

Appendix 1 Schedule of Events

	Screening		Period 1				Period 2				
Study activity	**D -28 to -1**	**D0**	**D1 pre-dose**	**D1 post-dose**	**D2**	**D3**	**D7**	**D8 pre-dose**	**D8 post-dose**	**D9**	**D10**
Medical history and ICF	X										
Screening for I/E criteria[1]	X	X					X				
Physical exam[2]	X	X									X
Demographics	X										
Randomization		X									
Admission and discharge		X				X	X				X
Vital signs[3]	X		X	X		X		X	X		X
ECG[4]	X		X	X				X	X		X
Urinalysis[5]	X		X			X		X			X
Blood draw for clinical lab tests[6]	X		X			X		X			X
Blood sample for PK[7]			X	X	X	X		X	X	X	X
Urine Collection[8]		X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test	X										
Adverse event and concomitant medication		X	X	X	X	X	X	X	X	X	X
Study termination											X

1. Subject compliance with inclusion and exclusion criteria will be verified at check-in of each period (on day 0 and day 7).
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 and day 10 prior to discharge.
3. Vital signs include: pulse, body temperature, respiration rate, systolic and diastolic blood pressure. On days 1 and 8, vital signs will be determined at pre-dose and at 4 h and 48 h (day 3 or 10) post-dose.
4. 12-lead ECG will be conducted after 10 min of rest. ECG data will be recorded at screening, on days 1 and 8 at pre-dose and at 4 h post-dose and when clinically indicated.
5. Clean sample to be collected at each visit. If urine is dipstick positive for leukocyte esterase or nitrites, sample is to be sent for microscopic evaluation and culture. Urine drug screen will be performed on screening visit only. If screening is conducted more than 5 days prior to dosing, drug screening shall be repeated.
6. Blood samples at the designated visits for clinical chemistry and hematology parameters are listed in Table 2.
7. Plasma samples for the PK profile of bexagliflozin will be collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose.
8. Urine collection for urinary glucose (PD), electrolytes, uric acid & creatinine are described in Section 6.6.2.3.

Appendix 2 Sponsor Signatures

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

Study Number: THR-1442-C-481

Final Date: 20 May 2016

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: Xiaoyan Li Date: 23MAY2016

Xiao-Yan Li, Ph.D.
Protocol Originator
Massachusetts General Hospital

Signed: Date: 23 MAY 2016

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

Appendix 3 Investigator's Signature

Study Title:	A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of A High-Fat Meal on the Pharmacokinetics of Bexagliflozin in Healthy Subjects
Study Number:	THR-1442-C-481
Final Date:	20 May 2016

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: 5/23/16

Robert Williams, MD
Investigator
DaVita Clinical Research
11750 West 2nd Place, Suite 300, MOB#1
Lakewood, CO 80228