Clinical Trial Protocol: THR-1442-C-458

Study Title:	A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of Exenatide on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin in Healthy Subjects
Study Number:	THR-1442-C-458
Study Phase:	1
Product Name:	Bexagliflozin tablets
IND Number:	103822103822
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:	Roger Albright 185 Cambridge Street, Boston, MA 02114 Phone: 617-643-5696 Fax: 617-643-8203 Email: ralbright@ccib.mgh.harvard.edu
Medical Monitor:	Mason W. Freeman, M.D. Translational Medicine Group, MGH 185 Cambridge Street, Boston, MA 02114 Phone: 617-724-7704 Fax: 617-643-8203 Email: freeman@molbio.mgh.harvard.edu

	Date
Protocol V1.0:	19 April 2017

Confidentiality Statement

SYNOPSIS

Sponsor: Theracos Sub, LLC

Name of Finished Product: Bexagliflozin tablets

Name of Active Ingredient: Bexagliflozin

Name of Inactive Ingredients: Polyethylene oxide, glyceryl behenate, lactose monohydrate, poloxamer, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.

Name of Reference Therapy: Byetta ®

Name of Active Ingredient of Reference Therapy: Exenatide

Name of Inactive Ingredients: metacresol, mannitol, glacial acetic acid, and sodium acetate trihydrate in water for injection.

Study Title:

A Phase 1, Open-label, Randomized, Two-period, Two-treatment, Crossover Study to Evaluate the Effect of Exenatide on the Pharmacokinetics (PK) and Pharmacodynamics (PD) of Bexagliflozin in Healthy Subjects.

Study Number: THR-1442-C-458

Study Phase: 1

Primary Objective:

To evaluate the effect of exenatide injection on the PK and PD of bexagliflozin.

Secondary Objective:

To assess the safety and tolerability of bexagliflozin when it is used in combination with exenatide.

Study Design:

This is a phase 1, single center, open-label, 2 × 2 crossover study designed to assess the effects of exenatide injection on the PK and PD of orally administered bexagliflozin tablets. Approximately 20 eligible healthy subjects will be randomly assigned to one of the two groups (1 or 2) with up to 10 subjects per group. Each group will receive both the 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 in Group 1 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast, and subjects in Group 2 will receive subcutaneous injection dose of exenatide at 10 μg twice a day (bid) with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals. In Treatment Period 2, subjects in Group 1 will receive subcutaneous injection dose of exenatide at 10 μg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals and subjects in Group 2 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast.

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

periods.

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 at each period at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose.

Urine samples for PD (urinary glucose excretion) analysis will be collected at each period in 12 h batches at pre-dose (h -12 to 0), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

Study Population:

Approximately 20 healthy subjects are planned.

Diagnosis and Main Criteria for Inclusion:

1. Male and female subjects who are between the ages of 18 and 65 years, inclusive, in good health based on medical history, physical examination (PE), electrocardiogram (ECG) and routine laboratory tests.
2. Subjects with body-mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2, inclusive.
3. Subjects who are non-smokers for at least 3 months prior to screening.
4. Subjects with adequate venous access at multiple sites in both arms.
5. Subjects who are willing and able to be confined to the clinical research facility as required by the protocol.
6. Subjects who have the ability to comprehend and who are willing to provide written informed consent in accordance with institutional and regulatory guidelines.

Test Product; Dose; and Mode of Administration:

Bexagliflozin tablets, 20 mg, oral administration.

Reference Therapy; Dose; and Mode of Administration:

Byetta® (Exenatide), 10 μg, bid, subcutaneous injection.

Duration of Treatment:

This is a phase 1, two-period, two-treatment, crossover study. Subjects will be screened within 21 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 the treatments alternately, in a crossover fashion (two-period, two-treatment crossover design), with the two treatment periods separated by a 7-day washout period.

Pharmacokinetics Variables:

The following PK parameters of bexagliflozin will be determined after each subject is dosed with bexagliflozin alone or the combination of exenatide and bexagliflozin.

C_{max} Maximum observed plasma concentration

t_{max} Time of maximum observed plasma concentration

λ_z Terminal phase rate constant

$t_{1/2}$ Apparent terminal 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

AUC_{0-extr} % of $AUC_{0-\infty}$ due to extrapolation from t_{last} to infinity

Pharmacodynamics Assessments:

PD parameters include:

- Urinary glucose excretion (UGE)

Safety Assessments:

- Physical examinations (PE)
- Vital signs
- 12-lead ECG
- Clinical laboratory tests including blood chemistry and hematology parameters
- Urinalysis
- Adverse events

Statistical Methods:

Statistical analysis will be performed using Statistical Analysis Software SAS (SAS Institute Inc., USA). PK parameters of bexagliflozin will be calculated using non-compartmental analyses (NCA) of plasma concentration-time data. To assess the effect of co-administration of exenatide on the PK of bexagliflozin, 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 ratio of geometric means of PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) when bexagliflozin is dosed in combination with exenatide versus when dosed alone, 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}, AUC_{0-extr}, 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}.

Descriptive statistics on the PD parameters will also be performed. Descriptive statistics will be used to describe any differences in UGE values between treatment groups.

Date of Original Protocol: 19 April 2017

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
ATC	anatomic therapeutic chemical classification
AUC	area under the concentration-time curve
$AUC_{0\text{-}extr}$	% of $AUC_{0\text{-}\infty}$ due to extrapolation from T_{last} to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from Time 0 to Time t
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from Time 0 to infinity
ANOVA	analyses of variance
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
BLOQ	below the limit of quantitation
CFR	Code of Federal Regulations
CL/F	apparent clearance
C_{last}	observed concentration corresponding to t_{last}
C_{max}	maximum observed plasma drug concentration
CRF	case report form
CRO	contract research organization
CYP450	cytochrome P450
dL	deciliter
d	day
ECG	electrocardiogram
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1 RAs	glucagon-like peptide 1 receptor agonists
h	hour (s)
HBsAg	hepatitis B surface antigen
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
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

LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
NCA	non-compartmental analysis
OADs	oral antidiabetes drugs
Pgp	p-glycoprotein
PD	pharmacodynamics
PK	pharmacokinetics
PR	the period of time from the onset of the P wave to the beginning of the QRS complex
QRS	the QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram
QT	the 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
QTc	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.
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SC	subcutaneous
SGLT1	sodium glucose cotransporter 1
SGLT2	sodium glucose cotransporter 2
SOP	standard operating procedure
RBC	red blood cell (count)
$T_{½}$	apparent terminal half-life
TEAE	treatment emergent adverse event
T_{last}	time of last measurable concentration
T_{max}	time to maximum observed plasma concentration
T2DM	type 2 diabetes mellitus
TG	triglycerides
UTI	urinary tract infection
WOCBP	women of childbearing potential

1 INTRODUCTION

The renal Na+/glucose transport protein SGLT2 actively transports extracellular glucose into cells using the driving energy of the transmembrane electrochemical potential for sodium ions. Individuals with disruptions in SLC5A2, the gene encoding SGLT2, exhibit prominent glucosuria in the absence of significant co-morbidities (Santer, Kinner et al. 2003, Kothare, Seger et al. 2012); (van den Heuvel, Assink et al. 2002)). The excretion of glucose in the urine of diabetic subjects in amounts comparable or greater than that seen in individuals harboring loss of functions mutations in SGLT2 has the potential to improve both fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia.

Bexagliflozin, a candidate oral antidiabetic agent, is a potent and highly specific inhibitor of the SGLT2. Bexagliflozin elicits a prominent and predictable glucosuria as demonstrated in laboratory animals and in humans. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease. Patients with T2DM often require multiple drug therapy to control the hyperglycemia and other comorbidities. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) offer important benefits as monotherapies or in combination with other oral antidiabetes drugs (OADs), with low risk for hypoglycemia and significant weight loss by enhancing glucose-dependent insulin secretion, suppressing postprandial glucagon release, signaling satiety, and slowing gastric emptying.

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 were developed to provide greater than 75% release in approximately 8 h *in vitro*.

Exenatide is one of most commonly prescribed GLP-1 RAs and is administered subcutaneously (SC) twice daily (bid) for its relatively short half-life of 2.4 h. Exenatide is primarily eliminated by glomerular filtration and subsequent proteolytic degradation, thus, interactions involving cytochrome P450 (CYP450) isoenzymes or enzymes responsible for phase II metabolism are not expected. As enzymes responsible for phase II metabolism are responsible for the elimination of bexagliflozin, drug-drug interaction between bexagliflozin and exenatide is not expected ((U.S. Department of Health and Human Services February, 2012). However, because exenatide slows gastric emptying, the rate of absorption for concurrent orally administered medications may be altered (Hurren and Pinelli 2012) (Kothare, Seger et al. 2012). The objective of this study is to evaluate the effects of coadministering exenatide on the pharmacokinetics (PK) and pharmacodynamics (PD) of bexagliflozin tablets.

1.1 Bexagliflozin for the Treatment of Type 2 Diabetes Mellitus

Bexagliflozin is a highly specific inhibitor of sodium glucose cotransporter 2 (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.

1.1.1 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.

1.1.2 Summary of Clinical Data with Bexagliflozin

Following administration of bexagliflozin tablets in extended release formulations, t_{max} was reached between 3 to 5 h. A 20 mg bexagliflozin tablet produced exposure with a C_{max} of 176 ng/mL or 134 ng/mL and an AUC_{0-24} of 1199 ng·h/mL or 1087 ng·h/mL in healthy subjects when dosing was after or before 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 treatment study in which doses ranged from 5 mg/d to 50 mg/d and up to 96 weeks of treatment were evaluated. Detailed information of bexagliflozin clinical experience and potential risks for study subjects are provided in the Investigator's Brochure.

1.2 Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and Exenatide

GLP-1 RAs are recommended as an option in patients with T2DM, typically as a second-line agent, particularly when weight loss or avoidance of hypoglycemia is a primary consideration in the therapeutic strategy. GLP-1 RAs reduce hyperglycemia and promote weight loss by enhancing glucose-dependent insulin secretion, suppressing postprandial glucagon release, signaling satiety, and slowing gastric emptying. In terms of safety, the most common adverse events seen in clinical trials with GLP-1 RAs are of gastrointestinal character; mainly nausea, vomiting and diarrhea. However, the incidence diminishes over time. Other identified risks include pancreatitis, immunogenicity, acute renal failure and

rapid weight loss. Exenatide is one of most widely prescribed GLP-1 RAs. It was approved in 2005 and is administered subcutaneously bid at a maximum approved dose in the United States of 10 µg. It is recommended to be taken within 60 minutes of the morning meal and within 60 minutes of the evening meal (approximately 6 hours or more apart).

After subcutaneous administration, exenatide is rapidly absorbed, usually reaching peak concentrations 2 h post administration. Peak plasma concentrations of exenatide after a 10 µg dose reach approximately 200 pg/mL. Exenatide is primarily eliminated by glomerular filtration and subsequent proteolytic degradation. After a single subcutaneous dose, it exhibits a short half-life of approximately 2.4 h. PK/PD modeling and empirical assessments from early clinical studies supported a twice daily dosing regimen. Because of its relatively short half-life, significant systemic accumulation is not observed with repeated twice-daily dosing.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the effect of exenatide injection on the PK and PD of bexagliflozin tablets.

2.2 Secondary Objective

- To assess the safety and tolerability of bexagliflozin tablets when it is administered in combination with exenatide injection.

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 exenatide injection on the PK and PD of orally administered bexagliflozin tablets. Approximately 20 eligible healthy subjects will be randomly assigned to one of the two groups (1 or 2) with up to 10 subjects per group. Each group will receive both the 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 in Group 1 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast, and subjects in Group 2 will receive subcutaneous injection dose of exenatide at 10 μg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals. In Treatment Period 2, subjects in Group 1 will receive subcutaneous injection dose of exenatide at 10 μg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals and subjects in Group 2 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast.

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

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 at each period at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose of bexagliflozin.

Urine samples for PD analysis will be collected at each period in 12 h batch at pre-dose (h -12 to 0), and at post-dose of bexagliflozin at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

Sampling time was determined based on previous pilot PK and PD studies.

For the schedule of study events table, see Appendix 1. For overall dosing schedule, see Table 1.

3.2 Rationale for Study Design and Control Group

The primary goal of the study is to assess the safety, tolerability, PK and PD of orally administered bexagliflozin tablets when it is concurrently administered with exenatide injection in healthy subjects.

This study is designed to be a two-period, two-treatment, crossover study with a 7-day washout period (>10 plasma apparent terminal elimination half-lives for both bexagliflozin and exenatide). The crossover study will allow direct comparison of two treatments in the

same subjects. Such an approach eliminates the influence of difference in subject characteristics seen in parallel group design. The primary route for excretion of exenatide is glomerular filtration and subsequent degradation of peptide bonds. Thus, drug interaction involving CYP450 and phase II enzymes are not expected between bexagliflozin and exenatide. However, because of slowing of gastric emptying, exenatide is expected to alter the absorption of orally administered concomitant medications especially when exenatide is administered prior to co-administered drug, typically resulting in a minor reduction of maximum plasma concentration (C_{max}) and a prolonged time of maximum concentration (t_{max}). Drug exposures are not expected to be significantly altered. In order to observe the maximal potential effect of exenatide on the absorption rate of bexagliflozin, bexagliflozin will be administered orally 30 min after subcutaneous exenatide injection, at 10 μg bid (the highest dose approved for use in the United States), meanwhile, the highest dose used (10 μg bid exenatide injection in the United States) or intended to be used (20 mg bexagliflozin tablets) clinically will be selected.

Previous studies showed that the PK parameters after multiple dosing were consistent with those after single doses for both bexagliflozin and exenatide. Thus a single oral dose of bexagliflozin tablets will be administered to healthy subjects in this study to evaluate the potential drug-drug interaction between bexagliflozin and exenatide. In this protocol, the effect of bexagliflozin on PK/PD of exenatide injection will not be measured since the PK of exenatide injection is unlikely to be affected by CYP450 and phase II enzymes involved pharmacokinetic interactions.

3.3 Study Duration and Dates

This is a phase 1, two-period, two-treatment, crossover study. Subjects will be screened within 21 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 the 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 postdose. 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 postdose. For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1.

4 STUDY POPULATION SELECTION

4.1 Study Population

Twenty (20) 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. Male and female subjects who are between the ages of 18 and 65 years, inclusive, in good health based on medical history, physical examination (PE), electrocardiogram (ECG) and routine laboratory tests.
2. Subjects with body-mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2, inclusive.
3. Subjects who are non-smokers for at least 3 months prior to screening.
4. Subjects with adequate venous access at multiple sites in both arms.
5. Subjects who are willing and able to be confined to the clinical research facility as required by the protocol.
6. 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 hypoglycemia.
4. Subjects with a history of alcohol or drug dependence in the last 12 months.
5. 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 of screening.
6. Subjects who have used prescription or over-the-counter (OTC) drugs within 14 days prior to the first dose.
7. Subjects who have used vitamin preparations or supplements (including St. John's Wort and ginseng) within 14 days prior to the first dose .
8. Subjects who are not willing to refrain from smoking, alcohol, grapefruit, grapefruit juice or related products, caffeine consumption (including chocolate), and strenuous exercise within 72 h prior to day 1 and through the end of the PK study.
9. Male subjects who do not agree to refrain from donating sperm and use appropriate birth control methods including condoms with spermicide, female partner’s use of diaphragm with spermicide, or stable oral, implanted, or injected contraceptive hormones, or with an intrauterine device, or female partner is surgically sterile (i.e. have undergone partial

or full hysterectomy, or bilateral oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years), for a period of 30 days after discharge from the clinic.

10. Female subjects of childbearing potential who are not willing to use an adequate methods of contraception including bilateral tubal ligation, intrauterine device, diaphragm with spermicide and male partner's use of male condom with spermicide, and to not become pregnant for the duration of the study. Female subjects who are surgically sterile (partial or full hysterectomy, or bilateral oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible if they test negative on the pregnancy test.
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 have previously received exenatide ,or any other GLP-1 RAs within three months from the screening or subjects who have had any GLP-1 RA and suffered an adverse reaction due to the medication.
13. Subjects who had previously received EGT0001474 or EGT0001442, or any other SGLT2 inhibitors within 3 months from the screening.
14. Subjects whose screening electrocardiogram (ECG) demonstrates any one of the following: heart rate > 100 bpm, QRS > 120 msec, QTc > 470 msec (corrected by Fridericia'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 clinically significant arrhythmia.
15. 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 blood pressure is 140/90 +/-5 mmHg at the discretion of the Investigator.
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 human immunodeficiency virus (HIV) infection.
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 (with the exception of the flu vaccine) prior to the first dose of investigational drug.
20. Subjects with a history of acute or chronic pancreatitis or gall stones.
21. Positive urine glucose at screening.
22. Subjects with estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m2 or a history of kidney transplant.
23. 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 TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 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*.

5.1.2 Exenatide

Subcutaneous exenatide injection at 10 μg/dose bid in a 2.4 mL prefilled pen that is procured from a licensed manufacturer.

5.2 Treatment(s) Administered

Approximately 20 eligible healthy subjects will be randomly assigned to one of the two groups (1 or 2) with up to 10 subjects per group. Each group will receive both the 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 in Group 1 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast, and subjects in Group 2 will receive subcutaneous injection dose of exenatide at 10 μg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals. In Treatment Period 2, subjects in Group 1 will receive subcutaneous injection dose of exenatide at 10 μg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals and subjects in Group 2 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast.

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**	**0.5**	**1**	**4-6**	**9**	**10**	**0**	**0.5**	**1**	**4-6**	**9**	**10**
Group 1	Bexagliflozin tablets, 20 mg Single oral dose		X						X				
	Exenatide at 10 µg bid SC							X				X	
	Meal			X	X		X			X	X		X
Group 2	Bexagliflozin tablets, 20 mg Single oral dose		X						X				
	Exenatide at 10 µg bid SC	X				X							
	Meal			X	X		X			X	X		X

5.3 Selection and Timing of Dose for Each Subject

Dosing order with bexagliflozin alone or in combination with exenatide will be based on randomized assignment. Results from pre-clinical data and previous clinical trials indicate that the doses of 1.7 mg to 100 mg bexagliflozin are well tolerated and the planned dose of 20 mg bexagliflozin tablets produced significant glucosuria and is not expected to produce serious drug-related adverse events. Subcutaneous exenatide at 10 μg bid is the recommended clinical dose in patients with T2DM.

- **Bexagliflozin alone**: After an overnight fast of at least 10 h, 20 mg bexagliflozin tablets will be administered 30 min before the first meal of the day with 240 mL of water.
- **Co-administration of bexagliflozin tablets and exenatide**: After an overnight fast of at least 10 h, subcutaneous exenatide at 10 μg bid will be administered 30 min prior to a single oral dose of bexagliflozin and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals.

5.4 Method of Assigning Subjects to Treatment Groups

Twenty 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-labeled 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. Intermittent use of up to 2 grams per day of acetaminophen may be administered if approved by the Investigator or designee. 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, dates of administration and reason for administration must be recorded. 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 treated with any SGLT2 inhibitors within 3 months prior to the screening, or 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. Bexagliflozin tablets will be taken in the morning with 240 mL of water prior to any drinking or eating.

Water can be allowed as desired except for one hour before and after drug administration. Water can be allowed during breakfast on D1 and D8.

5.7.3 Subject Activity Restrictions

Light physical activity is permitted. Subjects should not perform strenuous activity as this could result in elevations of muscle creatine kinase 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

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 Exenatide

Exenatide in its Byetta form will be supplied as a sterile solution for subcutaneous injection containing 250 μg/mL exenatide. The subcutaneous injection (do not inject into a vein or muscle) of Byetta will be given under the skin of upper arm. The package will be provided as 10 μg per dose, 60 doses, 2.4 mL prefilled pen. The pens are not to be shared with other subjects. A new needle will be provided for each injection of exenatide.

5.10 Storage and Accountability

Bexagliflozin tablets should be stored below 30°C in a secure area with access limited to authorized personnel. 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 Drug Accountability Form. Partially used bottles may be discarded after use according to the study sites' regulations for the disposal of investigational drug substances at study close out, after the drug accountability form is completed.

Prior to first use, exenatide (Byetta) must be stored refrigerated at 36ºF to 46ºF (2ºC to 8ºC). After first use, exenatide can be kept at a temperature not to exceed 77ºF (25ºC). Do not freeze. Use exenatide (Byetta) only if it is clear, colorless and contains no particles. Do not use exenatide if it has been frozen. Exenatide should be protected from light. The pen should be discarded 30 days after first use, even if some drug remains in the pen.

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects will be informed of the nature and purpose of the study and their written informed consent will be obtained during the pre-study screening procedures conducted within three weeks prior to the first dosing day. A copy of the Informed Consent Forms, including subject information, will be provided to each subject.

6.2 Medical History

The following information will be collected at the screening period:

- Demographic information including age, sex, and race
- Significant medical, surgical history and timeframe of the history relative to study screening, if applicable
- History or knowledge of allergy including drugs and latex
- History of smoking, alcohol or drug dependence or abuse
- Any blood donation or blood component donation within 14 days
- Use of any medications including over the counter drugs, vitamins, or dietary supplements within a month
- History of vaccination within 30 days prior to the first dose of study medication
- History of diagnosis with HIV, hepatitis B or hepatitis C
- History of acute or chronic pancreatitis or gall stones
- Use of any investigational drug in the previous 30 days or seven half-lives, whichever is longer
- Prior exposure to EGT0001442 (or EGT0001474) or exenatide

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 or calibrated automated vitals machine.

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

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, semi-recumbent 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. The details of the required laboratory tests are listed in Table 2.

Table 2. Required Laboratory Tests

Test Name		Blood or urine Vol. (mL)	Shipment
Hematology		3 (blood)	Ambient
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		5 (serum)	Ambient
Albumin (ALB)	Calcium (Ca)		
Alanine aminotransferase (ALT)	Magnesium		
Aspartate aminotransferase (AST)	Phosphorus		
Blood urea nitrogen (BUN)	Potassium (K)		
Glucose	Sodium (Na)		
Bicarbonate (Total CO_2)	Total bilirubin		
Creatinine	Direct bilirubin		
Chloride (Cl)	Uric acid		
Total protein			
Serum Lipids			Ambient
Total cholesterol (TC)	Low-density lipoprotein cholesterol (LDL-C), calculated		
High-density lipoprotein cholesterol (HDL-C)			
Triglycerides (TG)			
Urinalysis		10 (urine)	Ambient
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			
Creatinine			
Urine Drug Screen		10 (urine)	Ambient
Amphetamines	Opiates		
Barbiturates	Benzodiazepines		
Cocaine Metabolites	Cannabinoids		
Cotinine			
Pregnancy Test (female only)			
Infectious Disease Testing		5 (serum)	
HBsAg	HCV		
HIV			

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 Schedule of Events (see 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 leukocytes esterase or nitrites 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 for PD (UGE)

Pre-dose urine samples must be collected from -12 to 0 h for baseline measurement of UGE. Post-dose urine will be collected without preservative in four 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 to 8^{o}C during collection. After collection, the total volume of each batch and collection time will be recorded. Aliquots will be prepared from well mixed collections for the PD of bexagliflozin.

6.6.2.4 Plasma Sample Collection for PK

Whole venous blood samples of 3 mL will be collected from a peripheral vein at each period at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose of bexagliflozin. 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 aliquot 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 outline in Table 3.

Table 3. Blood and Urine Samples

Test	Volume/sample (mL)	No. of Samples	Total	Storage
Blood				
Hematology	3	5	15	
Chemistry	5	5	25	
Infectious Disease Testing	5	1	5	
PK	3	30	90	≤ -20°C
Urine Collection (12 h batches)				
PD	All	10	All	+4°C
Total blood volume required in each subject: 135 mL				

6.7 Pharmacokinetic Assessments

A non-compartmental pharmacokinetic analysis (WinNonlin 6.4, Pharsight Corp., Certara, USA) will be used to calculate the PK parameters for each subject to determine the PK parameters of bexagliflozin.

C_{max} Maximum plasma concentration

t_{max} Time of maximum plasma concentration

λ_z Terminal phase rate constant

$t_{1/2}$ Apparent terminal 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

AUC_{0-extr} % of $AUC_{0-\infty}$ due to extrapolation from t_{last} to infinity

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

The apparent terminal 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 rule, using actual elapsed time values. If the actual time of sample collection is not available the nominal time may be used for the purposes of 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.

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

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

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

Descriptive statistics for the plasma concentrations of bexagliflozin by Treatment and Timepoint will be provided. A listing of plasma concentrations by Subject, Treatment Period and Timepoint will also be provided.

6.8 Pharmacodynamic Assessment

Urinary glucose excretion (UGE) will be determined as the PD parameter. Urinary creatinine will be determined to calculate the creatinine normalized UGE.

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.

S*erious 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 an abnormal 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 6.9.4.4.

Any increase in liver function tests (AST, 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.

6.9.1 Collecting and Reporting Adverse Events

The investigator or designee will periodically assess subjects for the occurrence of adverse events. To avoid bias in collecting information about adverse events, the investigator or designee 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 or designee must report any serious adverse event (SAE), by telephone, email, or fax, to Theracos or its representative immediately after the investigator or study staff 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 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.

6.9.3 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 or designated study staff immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle).

If a subject, investigator or designee 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 or designee must notify the Medical Monitor within 3 working days of the receipt of information that any female subject who has become pregnant.

The investigator or designee 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 or designee 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 or designee 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 or designee 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 or designee should continue to report any significant follow-up information to the Sponsor until the event has been resolved.

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.

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

- ALT or AST > 8xULN,
- ALT or AST > 3xULN and (total bilirubin > 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 subjects report 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 either intramuscularly or subcutaneously a single injection of 1.0 mg of glucagon. A single dose of glucagon should restore consciousness within approximately fifteen minutes. Failure to correct hypoglycemia within this timeframe or observation by appropriate study staff of profound low sugar with accompanying coma or seizure will be treated by intravenous infusion of 5% dextrose.

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.

6.10 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 other than the investigational product that 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 or designee 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-458 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 parameters and safety assessments used in this study 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 PD effects of an SGLT2 inhibitor.

7 STUDY ACTIVITIES

7.1 Screening Visit (Days -21 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 complete 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 will be conducted 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, Cotinine and cannabinoids.
- All female subjects will receive 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.
- All female subjects will receive pregnancy test.
- 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.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest.
- Urinalysis will be collected 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 drug screen will be performed if drug screening is conducted more than 5 days prior to dosing.

- Blood will be drawn for hematology, and serum chemistry
- 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.
- Pre-dose urine collection in 12 h batches at -12 h to 0 h (on day 1) before bexagliflozin dosing for baseline analysis of creatinine and glucose for UGE (PD) analysis as described in Section 6.6.2.2 and Section 6.6.2.3.
- Concomitant medications and adverse event information will be collected as appropriate

7.3 Day 1 Activities: Groups 1 and 2 Pre-dose

Pre-dose blood glucose levels will be determined using a point-of-care blood glucose monitor. If the blood glucose levels are below 70 mg/dL, the study drug will not be administered. For subjects with pre-dose blood glucose levels < 70 mg/dL, oral glucose solution will be administered and once the subject's blood glucose is > 70 mg/dL, the study drug will be administered.

On day 1 the following information will be gathered and the indicated procedures will be performed PREDOSE (prior to whichever drug is taken first):

- 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) before bexagliflozin dosing for baseline UGE analysis and analysis of creatinine as described in Section 6.6.2.3.
- 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: Group 1 Post-dose

On days 1 through 3 the following information will be gathered for group 1 subjects and the indicated procedures will be performed after dosing:

- Dosing with bexagliflozin tablets will occur 30 min before the start of the meal as detailed in Section 5.2.
- Record vital signs at 4 h (day 1) and 48 h (day 3) postdose of bexagliflozin.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest at 4 h (day 1) postdose of bexagliflozin.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 (day 2) and 48 h (day 3) postdose of bexagliflozin.
- 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 postdose of bexagliflozin for UGE analysis and analysis of creatinine as described in Section 6.6.2.3.

- Postdose concomitant medications and adverse event information is collected as appropriate.
- On day 3 perform a partial physical examination as described in Section 6.3.
- 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 to return to the clinical research unit on Day 7.

Subjects who are terminated from the study for any reason after dosing has started must have the information and procedures shown for day 10 collected and completed and the reason for termination entered onto the case report form.

7.5 Day 1 Through 3 Activities: Group 2 Post-dose

On days 1 through 3 the following information will be gathered for group 2 subjects and the indicated procedures will be performed after dosing:

- Dosing with first dose of subcutaneous exenatide 30 min prior to bexagliflozin tablets dosing will occur 1 h before the start of the breakfast as detailed in Section 5.2.
- Dosing with second dose of subcutaneous exenatide 12 h after the first dose will occur 1 h before the start of the evening meal as detailed in Section 5.2.
- Record vital signs at 4 h (day 1) and 48 h (day 3) postdose of bexagliflozin.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest at 4 h (day 1) postdose of bexagliflozin.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 (day 2) and 48 h (day 3) postdose of bexagliflozin.
- 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 postdose of bexagliflozin for UGE analysis and analysis of creatinine as described in Section 6.6.2.3.
- Postdose concomitant medications and adverse event information is collected as appropriate.
- On day 3 perform a partial physical examination as described in Section 6.3.
- 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 to return to the clinical research unit on Day 7.

Subjects who are terminated from the study for any reason after dosing has started must have the information and procedures shown for day 10 collected and completed and the reason for termination entered onto the case report form.

7.6 Day 7 Activities: Groups 1 and 2

Pre-dose blood glucose levels will be determined using a point-of-care blood glucose monitor. If the blood glucose levels are below 70 mg/dL, the study drug will not be administered. For subjects with pre-dose blood glucose levels < 70 mg/dL, oral glucose solution will be administered and once the subject's blood glucose is > 70 mg/dL, the study drug will be administered.

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.
- Record vital signs.
- Perform 12-lead ECG taken in the supine position after at least 10 min of rest.
- Urine drug screen and clean catch urinalysis will be collected 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.
- All female subjects will receive pregnancy test.
- Blood will be drawn for hematology, and serum chemistry
- Perform a partial physical examination as described in Section 6.3.
- Pre-dose urine collection in 12 h batches at -12 h to 0 h (on day 1) before bexagliflozin dosing for baseline analysis of creatinine and glucose for UGE (PD) analysis as described in Section 6.6.2.2 and Section 6.6.2.3.
- Concomitant medications and adverse event information will be collected as appropriate.

7.7 Day 8 Activities: Groups 1 and 2 Pre-dose

On day 8 the following information will be gathered and the indicated procedures will be performed PREDOSE:

- 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) before bexagliflozin dosing for baseline UGE analysis and analysis of creatinine as described in Section 6.6.2.3.
- 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.

7.8 Day 8 through 10 Activities: Group 1 Post-dose

On days 8 through 10 the following information will be gathered for group 1 and the indicated procedures will be performed after dosing:

- Dosing with first dose of subcutaneous exenatide 30 min prior to bexagliflozin tablets dosing will occur 1 h before the start of the breakfast as detailed in Section 5.2.
- Dosing with second dose of subcutaneous exenatide 12 h after the first dose will occur 1 h before the start of the evening meal as detailed in Section 5.2.
- Record vital signs at 4 h (day 8) and 48 h (day 10) postdose of bexagliflozin.
- 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) postdose of bexagliflozin.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 (day 9), 36 (day 9) and 48 h (day 10) postdose of bexagliflozin.
- Urine collection in 12 h batches at 0 to 12 h and 12 to 24 h (day 8), 24 to 36 h and 36 to 48 h (day 10) for analysis of creatinine and glucose 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 10 perform a complete 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 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.

Subjects who are terminated from the study for any reason after dosing has started must have the information and procedures shown for day 10 collected and completed and the reason for termination entered onto the case report form.

7.9 Day 8 through 10 Activities: Group 2 Post-dose

On days 8 through 10 the following information will be gathered for group 2 and the indicated procedures will be performed after dosing:

- Dosing with bexagliflozin tablets will occur 30 min before the start of the meal as detailed in Section 5.2.
- Record vital signs at 4 h (day 8) and 48 h (day 10) postdose of bexagliflozin.
- 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) postdose of bexagliflozin.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 (day 9), 36 (day 9) and 48 h (day 10) postdose of bexagliflozin.

- Urine collection in 12 h batches at 0 to 12 h and 12 to 24 h (day 8), 24 to 36 h and 36 to 48 h (day 10) postdose of bexagliflozin for analysis of creatinine and glucose 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 10 perform a complete 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 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.

Subjects who are terminated from the study for any reason after dosing has started must have the information and procedures shown for day 10 collected and completed and the reason for termination entered onto the case report form.

7.10 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, urinalysis 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 pharmacokinetic and pharmacodynamic 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 (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 drug-drug interactions and to provide safety and tolerability data on bexagliflozin when administered with exenatide.

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.

PD: The PD population will include all randomized subjects who receive study drug and will have had at least 2 batches of 12 h urine collection from which to calculate UGE measurement following dosing. The PD population will be used to summarize the PD parameters.

9.4 Demographics and Baseline Characteristics

Baseline characteristics will be descriptively summarized for all subjects in the safety and the PK or PD populations. No statistical tests will be performed.

9.5 Statistical Analysis of Pharmacokinetic Variables

To assess the effect of co-administration of exenatide on the PK of bexagliflozin, 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 ratio of the least squares (LS) geometric means of PK parameters (C_{max}, AUC_{0-t} and

$AUC_{0-\infty}$) when bexagliflozin is dosed in combination with exenatide versus when dosed alone, 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}, $AUC_{0-extr,}$ CL/F, Vz/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 Subject and Treatment Period will be provided.

9.6 Pharmacodynamic Assessments

UGE and urinary creatinine will be assessed before first dosing and at the end of each treatment period.

UGE, including UGE_{t1-t2} and the total 0-24, 24-48 and 0-48 h UGE, will be determined. UGE_{t1-t2} (mg) will be derived from urine volume (V_{t1-t2} , mL) × glucose concentration (mg/dL) ÷ 100. Parameters normalized for urinary creatinine excretion will also be determined. UGE_{0-12h} , UGE_{12-24h} , UGE_{24-36h}, UGE_{36-48h} and the total 48 h UGE will be listed and presented in by subject listing and in summary tables for each group.

UGE in 12 h intervals up to 48 h post-dose, including the baseline, will be graphically presented against the corresponding treatment, bexagliflozin alone, and combination with exenatide.

The descriptive statistics will be used to describe any differences in UGE values between treatment groups.

9.7 Safety Analysis

Safety data 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.

9.7.1 Adverse Events

Adverse events will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). In treatment period 1, 10 subjects in group 1 will receive a single oral dose of 20 mg bexagliflozin and in treatment period 2 another 10 subjects will receive the same dosing. As a result, a total of 20 subjects will receive a single oral dose of bexagliflozin alone. Likewise, a total of 20 subjects will receive a co-administration of bexagliflozin and exenatide. The number and percentage of subjects

reporting adverse events will be determined by relationship to dosing and by severity of the event. Drug-related adverse events will be considered those to be at least possibly related to bexagliflozin and/or exenatide administration.

Adverse event listings will be provided for the following subsets:

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

AEs are treatment emergent if they occur on or after bexagliflozin and/or exenatide administration. TEAEs will be considered at least possibly related to bexagliflozin or exenatide 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 and/or exenatide.

9.7.2 Hypoglycemia

Hypoglycemia as defined in Section 6.9.4.4 will be presented in listings and summarized.

9.7.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory metrics are measured at baseline and during the treatment. 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.

9.7.4 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.

9.8 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 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 Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) Part 50 and the International Conference for Harmonisation (ICH) Good Clinical Practices (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 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

Hurren, K. M. and N. R. Pinelli (2012). "Drug-drug interactions with glucagon-like peptide-1 receptor agonists." Ann Pharmacother **46**(5): 710-717.

Kothare, P. A., M. E. Seger, J. Northrup, K. Mace, M. I. Mitchell and H. Linnebjerg (2012). "Effect of exenatide on the pharmacokinetics of a combination oral contraceptive in healthy women: an open-label, randomised, crossover trial." BMC Clin Pharmacol **12**: 8.

Santer, R., M. Kinner, C. L. Lassen, R. Schneppenheim, P. Eggert, M. Bald, J. Brodehl, M. Daschner, J. H. Ehrich, M. Kemper, S. Li Volti, T. Neuhaus, F. Skovby, P. G. Swift, J. Schaub and D. Klaerke (2003). "Molecular analysis of the SGLT2 gene in patients with renal glucosuria." J Am Soc Nephrol **14**(11): 2873-2882.

U.S. Department of Health and Human Services, F. a. D. A., Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (February, 2012). "Guidance for Industry Drug Interaction Studies Study Design, Data Analysis, Implications: Population Pharmacokinetics."

van den Heuvel, L. P., K. Assink, M. Willemsen and L. Monnens (2002). "Autosomal recessive renal glucosuria attributable to a mutation in the sodium glucose cotransporter (SGLT2)." Hum Genet **111**(6): 544-547.

Appendix 1 Schedule of Events

Study activity	Screening		Period 1				Period 2				
	D -21 to -1	D 0	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	X	X					X				
Physical exam[1]	X	X				X	X				X
Demographics	X										
Randomization		X									
Admission and discharge		X				X	X				X
Vital signs[2]	X	X	X	X		X	X	X	X		X
ECG[3]	X	X	X	X			X	X	X		X
Urinalysis[4]	X	X				X	X				X
Blood draw for clinical lab tests[5]	X	X				X	X				X
Blood sample for PK[6]			X	X	X	X		X	X	X	X
Urine collection[7]		X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X	X					X				
Adverse event and concomitant medication		X	X	X	X	X	X	X	X	X	X
Study termination											X

[1] 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 day10 prior to discharge. A partial PE will be performed on days 0, 3 and 7.

[2] Vital signs include: pulse, body temperature, respiratory rate, systolic and diastolic blood pressure. Vital signs will be recorded at screening, on days 0, 1 (predose, 4 h postdose), 3 (48 h postdose), 7, 8 (predose, 4 h postdose), and 10 (48 h postdose), and when clinically indicated.

[3] 12-lead ECG will be conducted after 10 min resting. ECG data will be recorded at screening, on days 0, 1 (predose, 4 h postdose), 7, 8 (predose, 4 h postdose), and 10 (48 h postdose), and when clinically indicated.

[4] Urine samples will be collected at screening, on days 0, 7 and prior to discharge in each period. 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 and on day 7. If drug screening is conducted more than 5 days prior to dosing, screening shall be repeated.

[5] Blood sample at the designated visits (screening, on days 0, 3, 7 and 10 for clinical chemistry and hematology parameters are listed in Table 2. Blood will be drawn after 10 h of fasting prior to breakfast (i.e. only water is allowed, no caloric intake)

[6] Plasma samples for PK profile of bexagliflozin will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose.

[7] Urine for urinary glucose (PD) and creatinine will be collected at pre-dose (h -12 to 0), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

Appendix 2 Sponsor Signatures

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

Study Number: THR-1442-C-458

Final Date: 19 April 2017

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

Signed: _____ Date: 19 April 2017

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

Signed: _____ Date: 19 April 2017

Yuan-Di Halvorsen, Ph.D.
Project Leader
Consultant for Theracos Sub, LLC

Signed: _____ Date: 19 April 2017

Mason W. Freeman, M.D.
Medical Monitor
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 Exenatide on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin Tablets in Healthy Subjects.
Study Number:	THR-1442-C-458
Final Date:	19 April 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:_____

Kelly Whitehurst, MD
Covance CRU
617 Oakley Street
Evansville, IN 47710
(812) 474-5000