Clinical Trial Protocol: THR-1442-C-455

Study Title:	A Phase 1, Open-label, Parallel-group Study to Evaluate the Effect of Moderate Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin
Study Number:	THR-1442-C-455
Study Phase:	1
Product Name:	Bexagliflozin tablets
Sponsor:	Theracos Sub, LLC
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	Date
Protocol V1.1:	29 May 2018
Protocol V2.0	02 August 2018
Protocol V3.0	21 August 2018

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SYNOPSIS

Sponsor: Theracos Sub, LLC

Name of Finished Product: Bexagliflozin tablets, 20 mg

Name of Active Ingredient: Bexagliflozin

Name of Inactive Ingredient:

Polyethylene oxide, glyceryl behenate, lactose monohydrate, micronized poloxamer, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate

Study Title:

A Phase 1, Open-label, Parallel-group Study to Evaluate the Effect of Moderate Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin

Study Number:THR-1442-C-455

Study Phase: 1

Primary Objective:

- To evaluate the effect of moderate hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single oral dose of bexagliflozin tablets, 20 mg

Secondary Objective:

- To assess the safety and tolerability of bexagliflozin in subjects with moderate hepatic impairment

Study Design:

This is a phase 1, open-label, parallel-group study designed to assess the effects of moderate hepatic impairment on the PK and PD of orally administered bexagliflozin tablets, 20 mg. Approximately 16 subjects (eight with moderate hepatic impairment [Child-Pugh total score 7-9] and eight healthy, matched controls) will receive a single oral dose of bexagliflozin tablet, 20 mg.

Clinical laboratory tests and safety monitoring will be conducted during the treatment period and follow-up visit.

Blood samples for plasma concentrations of bexagliflozin will be collected at predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose.

Urine samples for PD analysis will be collected predose and in the following intervals after dosing: 0–12, 12–24, 24–36, and 36–48 h.

Plasma concentrations of bexagliflozin will be determined by validated liquid chromatography-mass spectrometry (LC-MS/MS) assays.

The unbound fraction of bexagliflozin will be determined at 24 h postdose and maximum plasma concentration for each subject by equilibrium dialysis.

For the schedule of events, see Appendix 1.

Study Population:

Approximately 16 subjects (eight with moderate hepatic impairment [Child-Pugh total score 7-9] and eight healthy, matched controls) are planned to be enrolled.

Eligible Subjects:

Prospective subjects must:

1. Be male or female adults between the age of 18 to 75 years (inclusive) at screening
2. Have a body-mass index (BMI) of 18.0 - 40.0 kg m^{-2} (inclusive) at screening
3. Have adequate venous access at multiple sites in both arms
4. Be willing and able to be confined to the clinical research facility as required by the protocol
5. Be able to comprehend the explanation of the informed consent and be willing to provide written informed consent in accordance with institutional and regulatory guidelines
6. Be diagnosed with moderate hepatic impairment with a Child-Pugh score 7 to 9 (classification in Appendix 2) and must be in stable general health apart from hepatic impairment and its related conditions **(for subjects in the hepatic impairment group only)**
7. Be in general good health with matching demographics and baseline characteristics to individual subjects in the hepatic impairment group by age (±10 years), weight (±10%), sex, and smoking status (**for subjects in the healthy control group only)**
8. Have no evidence of an active infection or be receiving any treatment with antibiotics at the time of screening **(for subjects in the healthy control group only)**

Duration of Treatment:

This is a single dose study. Selection and enrollment of study subjects will begin with those designated for the hepatic impairment group. A screening visit will be completed 2 to 28 days prior to study drug administration. Subjects will be admitted to the clinic the day before administration of the investigational product and will remain in the clinic for at least 48 h following administration. Subjects will return for an end-of-study examination within 13 days of the last pharmacokinetic sample collection. Each subject from the hepatic impairment group will be matched to a healthy comparator subject.

For details of the schedule and nature of the investigations, see the Schedule of Events in Appendix 1.

Pharmacokinetics Variables:

The following PK parameters for bexagliflozin will be determined:

C_{max} Maximum observed plasma concentration

T_{max} Time of maximum observed plasma concentration

λ_z Terminal elimination phase rate constant

$t_{½}$ Apparent terminal elimination half-life

CL/F Apparent oral clearance

V_z/F Apparent volume of distribution

AUC_{0-24} Area under the plasma concentration-time curve from the time of dosing to 24 h postdose

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

$AUC_{0-\infty}$ Extrapolated area under the plasma concentration-time curve from the time of dosing to infinity

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

f_u Unbound fraction, calculated as (free drug concentration)/(total drug concentration)

$C_{max, u}$ Maximum unbound plasma concentration

AUC_u Area under the unbound plasma concentration-time curve

Cl_u/F Apparent clearance relative to the unbound drug concentration

Pharmacodynamics Assessments:
PD parameters will be assessed before dosing and at the end of the treatment period.

The PD parameters will include:

- Urine glucose concentrations
- Creatine concentrations
- UGE
- Urinary glucose normalized by creatinine.

Safety Assessments:
Physical examinations (PE)

- Vital signs (VS)
- 12-lead electrocardiograms (ECG)
- Clinical laboratory tests including blood chemistry and hematology parameters
- Urinalyses
- Adverse events (AEs)
- Concomitant medication (CM) use

Statistical Methods:
Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS Institute Inc., USA). PK parameters for bexagliflozin will be calculated using non-compartmental analyses (NCA) of plasma concentration-time data. An analyses of variance (ANOVA) with a fixed effect corresponding to the hepatic function group will be fitted to the natural logarithmic transformation of the PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The 90% confidence intervals will be constructed for the ratio of geometric means of PK parameters (total and unbound C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The

apparent clearance relative to the unbound drug concentration (Cl_u/F) will be calculated as $Cl_u/F = Dose/AUC_u$.

Descriptive statistics of plasma concentration-time data will be summarized by hepatic function group and timepoint.

The PK parameters C_{max}, T_{max}, λ_z, $t_{1/2}$, CL/F, V_z/F. AUC_{0-t}, $AUC_{0-\infty}$, AUC_{extr}, $AUC_{u(0-t)}$ and $AUC_{u(0-\infty)}$ will be summarized by hepatic function group. Means, standard deviations, medians, ranges (min, max) and geometric means and coefficients of variation will be presented for all parameters will the exception of T_{max}. Medians and ranges will be presented for T_{max}.

The amount of UGE, and urinary glucose normalized by urinary creatinine will be calculated. Descriptive statistics will be used to describe any differences in these PD parameters between hepatic function groups.

Date of Version 1.1: 29 May 2018

Date of Version 2.0: 02 August 2018

Date of Version 3.0: 21 August 2018

SUMMARY OF CHANGES

Location	Modification
Revision in Version 1.1	
4.3 Exclusion Criteria, 21, pg. 22	A history of vitamin preparation… To. If destined for the healthy control group, a history of vitamin preparation…
6.2 Medical History, pg. 26	Medication history including prescription, OTC drugs, and vitamin preparation or supplement use (including St. John's Wort and ginseng) within 7 days or 5 half-lives of the drug, whichever is longer, prior to D0. Added. (for subjects in the healthy control group only)
Appendix 1, pg. 51 Table Footnote	Correction in footnote 6 of: Plasma samples for PK profile of EGT0002149… To. Plasma samples for PK profile of **bexagliflozin**…
Revision in Version 2.0	
4.3 Exclusion Criteria, page 22	Exclusion criteria # 2, 7, 8, 9, 15, 17, 19, and 28 are revised to better represent the population with hepatic impairment.
Revision in Version 3.0	
4.3 Exclusion criterion #7, page 22	Exclusion criterion #7 was changed from QTc > 500 ms to QTc > 480 ms (corrected by Bazett's formula)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the plasma concentration-time curve
AUC_{extr}	% of $AUC_{0-\infty}$ due to extrapolation from t_{last} to infinity
AUC_{0-24}	Area under the plasma concentration-time curve from the time of dosing to 24 h postdose
$AUC_{0-\infty}$	Extrapolated area under the plasma concentration-time curve from the time of dosing to infinity
AUC_{0-t} (AUC_{last})	Area under the plasma concentration-time curve from the time of dosing to the time of last quantifiable plasma concentration
AUC_u	area under the unbound plasma concentration-time curve
BMI	body mass index
BLOQ	below limit of quantification
BP	blood pressure
BUN	blood urea nitrogen
C_{max}	maximum observed plasma concentration
$C_{max,u}$	maximum unbound plasma concentration
C_{last}	concentration corresponding to T_{last}
CL/F	apparent oral clearance
CL_u	apparent clearance relative to the unbound drug concentration
CM	concomitant medication
CRF	case report form
CV	coefficient of variation
CYP	cytochrome P450
D0	day zero
ECG	electrocardiogram
EOS	End of study
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
f_u	unbound fraction
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
INR	International Normalized Ratio
IRAE	immediately reportable adverse event

IRB	Institutional Review Board
IR	Immediate release
λ_z	terminal elimination phase rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	modification of diet in renal disease study equation
NCA	non-compartmental analysis
nUGE	Normative UGE
OTC	over-the-counter
PD	pharmacodynamic
PE	physical examination
P-gp	p-glycoprotein
PK	pharmacokinetic
PR	The period that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization).
PT	preferred term
QRS	The combination of three of the graphical deflections seen on a typical electrocardiogram.
QT	Time from electrocardiogram Q wave to the end of the T wave corresponding to the electrical system
QTcB	QT corrected using Bazetts formula [$QT/(RR^{1/2})$]
RR interval	intra-beat interval
SAE	serious adverse event
SAS	statistical analysis software
SD	standard deviation
SGLT1	sodium glucose cotransporter 1
SGLT2	sodium glucose cotransporter 2
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
$t_{1/2}$	terminal elimination half life
t_{last}	time of last measurable concentration
T_{max}	time of maximum observed plasma concentration
T2DM	type 2 diabetes mellitus
UGE	urinary glucose excretion
ULN	upper limit of normal
UGT	uridine diphosphate glucuronosyltransferases
UTI	urinary tract infection
V_z/F	apparent volume of distribution
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

Bexagliflozin is a potent and selective inhibitor of human sodium-glucose linked transporter 2 (SGLT2). The clinical pharmacology of bexagliflozin is largely consistent with the expected consequences of SGLT2 inhibition. The primary pharmacodynamic effect is a glucosuria that increases with glomerular filtration rate and plasma glucose concentration. Effects secondary to diuresis, possible natriuresis, and caloric wasting, including reductions in blood pressure and body weight, have been observed. Consistent with clinical observations that individuals genetically deficient for SGLT2 are euglycemic and normotensive to slightly hypotensive, inhibition of SGLT2 function does not appear to confer a risk of hypoglycemia or of significant hypotension. Mild hemoconcentration associated with volume depletion attributed to the diuretic effect has been observed. Slight elevations in blood urea nitrogen (BUN) and creatinine, and corresponding inferred decreases in estimated glomerular filtration rate (eGFR), have typically accompanied the pharmacodynamic response and are considered to be consistent with diuresis and metabolic shifts favoring protein catabolism. Moderate reductions in plasma urate and small increases in LDL cholesterol concentration that appear to be class effects have yet to be explained.

Bexagliflozin tablets, 20 mg, are blue caplet-shaped film-coated tablets with a gastroretentive mechanism based on mucoadhesion. Peak plasma bexagliflozin concentrations are observed 3 to 5 h after dosing and thereafter decline in a biphasic manner with mean elimination half-life values ranging from 7.8 to 9.7 h. Bexagliflozin is extensively metabolized, predominantly to a 3'-*O*-glucuronide, but also to a mixture of additional glucuronides and oxidation products. .

The relative contributions of different organs to metabolism of bexagliflozin are not known. Cytochrome P450 oxidases are found in intestine, kidney and liver, with the latter usually considered the most important site for xenobiotic oxidation. Glucuronidation is principally carried out in the kidney and liver. Because high amounts of [^{14}C]-bexagliflozin have been observed in the kidney in rats and renal recirculation of the compounds appears likely, a significant renal contribution cannot be excluded.

Metabolism represents the primary pathway for the clearance of bexagliflozin accounting for > 60% of the administered drug and is primarily via glucuronidation (hepatic and extra-hepatic) by uridine diphosphate glucuronyl transferase (UGT1A9) to form a major inactive metabolite (EGT0002149), which accounted for 32.2% of systemic exposure of the parent drug. Less than 2.0% of the administered bexagliflozin dose is recovered in the urine as unchanged drug and most of the radioactivity excreted in urine was associated with EGT0002149, accounting for 30.1% of the administered dose. No glucuronides were found in feces, but the possibility of action of microbial glucuronidases could not be excluded. (THR-1442-C-410).

ICH guidelines recommend that the consequences of diminished hepatic function for the metabolism of new molecular entities be studied if hepatic metabolism and/or excretion accounts for > 20% of the absorbed agent(Industry, 2003). Because bexagliflozin is extensively metabolized and the sites of metabolism are unknown, the sponsor has chosen to

undertake an investigation of the pharmacokinetics of bexagliflozin in subjects with differing degrees of liver dysfunction.

1.1 Summary of Nonclinical Data for Bexagliflozin

Bexagliflozin is highly (97%) bound to protein in human plasma. The degree of binding is minimally reduced in plasma from subjects with moderate to severe renal impairment. It is a high solubility, low permeability class III BCS agent and is not a significant inducer or inhibitor of cytochrome P450 isozymes and transporters relevant for drug-drug interactions. It is a substrate for P-gp but does not affect the pharmacokinetics of digoxin, a drug with a narrow therapeutic window that is strongly affected by P-gp inhibition.

The potential adverse effects of bexagliflozin have been evaluated in standard safety pharmacology, genotoxicity, repeated-dose toxicity and reproductive toxicity studies. Based on findings in rats and monkeys, the potential limiting adverse effects in human subjects have been predicted to involve the gastrointestinal (GI) tract and to manifest as diarrhea and gastric irritation. Animals given high daily doses of bexagliflozin have also experienced adverse effects involving the respiratory system, liver, kidney, heart and bone marrow. Chronic toxicity studies have produced similar toxicity profiles with additional microvacuolation of renal cortical cells in monkeys. This microscopic pathology occurred without clinical chemistry correlates, and the effects generally reversed during the recovery phase.

In rats, bexagliflozin did not affect fertility or reproductive performance by either sex at doses representing approximately 600 times the expected clinical exposure. Bexagliflozin produced maternal toxicity but did not affect embryo/fetal viability, growth or development at dose levels up to 200 mg kg^{-1} day^{-1} (in rats) or 150 mg kg^{-1} day^{-1} (in rabbits). Maternal toxicity was observed at $\geq$ 40 mg kg^{-1} day^{-1} from mid- to late gestation, and litter size and average pup weight were slightly lower at 200 mg kg^{-1} day^{-1}. Bexagliflozin did not affect neuromuscular development or reproductive system development in F_1 rats. Based on these results, bexagliflozin administered during pregnancy and the nursing period was considered non-toxic for offspring.

In a juvenile toxicity study, bexagliflozin up to 100 mg kg^{-1} day^{-1} was administered to rats from postnatal days 21 through 49 and produced > 300 × the expected C_{max} and > 600 × the expected AUC of the intended dose of 20 mg in adult humans. The 4-week daily dosing was well tolerated with the main findings related to effects on kidney and bone, including renal pelvic dilatation, a narrower mean femur width in males and a wider mean femur width and narrower mean tibia width in females.

Studies of rodents dosed daily with bexagliflozin for approximately 2 years (mice) or 1.5 – 2 years (rats) did not produce evidence of an oncogenic effect. There was no statistically significant increase in the incidence of any tumor type in any tissue for either sex. Based on the expected AUC of the intended human dose of 20 mg in the extended release tablet formulation, the exposure provided safety margins ranging from 149 × (males) to 202 × (females) for mice and from 52 × (males) to 88 × (females) for rats. The duration of the rat

study was briefer than intended due to an unanticipated increase in mortality affecting all male rat cohorts (including vehicle) in a dose-dependent manner

1.2 Summary of Clinical Data for Bexagliflozin

CLINICAL PHARMACOKINETICS AND METABOLISM

Following administration of bexagliflozin extended release tablets, time to reach maximum observed concentration (T_{max}) has typically been observed between 2 and 4 h. The tablets produce dose-proportional exposure with a C_{max} of 6.4 ng mL^{-1} mg^{-1} bexagliflozin and an AUC_{0-t} of 45 ng h mg^{-1} mL^{-1} in healthy subjects. A food effect has been observed, with a delayed T_{max} of 5 h following dosing in the fed state compared to 3.5 h following dosing in the fasted state. Following dosing in the fed state, the C_{max} has been found to be 31% greater than the C_{max} following dosing in the fasted state, without substantial change in AUC. In light of the perceived wide safety margins, the increase in C_{max} has not been considered to represent a meaningful hazard and dosing in either prandial state has been thought likely to elicit similar pharmacological effects and to pose comparable risks.

The principal metabolites in humans are similar to those found in monkeys and dominated by glucuronides of the parent compound, for which the AUC has been < 35% relative to parent compound in most studies. All metabolites were reduced in abundance relative to the parent species following administration of the sustained release formulation.

All of the glucuronides have negligible pharmacologic activity *in vitro,* and are present in monkeys, in approximately the same proportion as in humans. The total contribution of metabolites to the pharmacology of bexagliflozin is estimated to be less than 1% based on *in vitro* activity measurements and the proportion of metabolites in plasma.

Following oral administration of radiolabeled bexagliflozin, 91.6% of the ingested radioactivity was recovered, 51.1% as fecal excretion and 40.5% as urinary excretion. In urine, bexagliflozin accounted for 1.5% of the dose; most of the radioactivity was excreted as the 3'-*O*-glucuronide (EGT0002149). The largest fraction of the radioactivity in feces was due to bexagliflozin, accounting for about 28.7% of the administered dose. Disposition of radiolabel could be accounted for by known metabolites and only 0.27% of the input radioactivity could not be identified, approximately equally divided between one species each in urine and feces.

The PK of bexagliflozin and its principal metabolites was determined in subjects with T2DM and renal impairment. Absorption of bexagliflozin was not affected by diminished renal function. Reduced clearance due to renal impairment resulted in systemic exposure that increased as the glomerular filtration rate (GFR) decreases. Increases in AUC of 34% and 54% were observed in subjects with moderate and severe impairment, respectively, compared to the AUC measured in subjects with normal renal function. Exposure to the main metabolite, the glucuronide EGT0002149, increased up to 2.2-fold in subjects with severe renal impairment. Given the moderate increase in exposure and wide safety margins for bexagliflozin, dose adjustment for individuals with mild to moderate renal impairment has not been expected to be necessary.

Bexagliflozin exposure has been moderately affected by co-administration of the commonly co-prescribed oral hypoglycemic agents metformin, glimepiride and sitagliptin. An increase in glimepiride exposure upon co-administration with bexagliflozin has been observed although the increase has not been deemed clinically significant. Administration of bexagliflozin 30 minutes after injection of exenatide, a glucagon-like peptide-1 (GLP-1) agonist, results in delayed absorption and an approximately 50% increase in systemic exposure to bexagliflozin. A decrease in exposure has been observed following co-administration with rifampin, an inducer of xenobiotic metabolism. Although bexagliflozin is a P-gp substrate, the pharmacokinetics of the P-gp substrate digoxin have been unaffected by co-administration of the extended release formulation to healthy subjects. Adjustment of the bexagliflozin dose to compensate for drug-drug interactions is not expected to be necessary in general.

PHARMACODYNAMICS AND EFFICACY OF BEXAGLIFLOZIN IN HUMANS

Dose-titration studies have shown that the primary pharmacodynamic effect, urinary glucose excretion (UGE), can be described in both healthy and diabetic subjects by a simple logistic equation. The median effective dose (ED_{50}) is estimated to be 3.6 mg in healthy subjects and 1.2 mg in diabetic subjects. From this, a 20 mg dose is expected to produce 85% or 94% of the theoretical maximum UGE in healthy or diabetic subjects, respectively. After a single dose of bexagliflozin, diabetic subjects have exhibited significant glucosuria and experienced meaningful reductions in fasting plasma glucose (FPG). Healthy and diabetic subjects have also experienced a moderate diuretic effect. The dose-related glucosurias observed in Japanese and American populations have been similar in magnitude.

Although bexagliflozin is a potent glucosuric agent, hypoglycemia and hypotension have not been observed in the setting of monotherapy. All reports of hypoglycemia and hypotension have occurred in the context of additional anti-diabetic or anti-hypertensive agents. Insulin and insulin secretagogues of the sulfonylurea class have been frequently implicated in bexagliflozin-associated hypoglycemia.

SAFETY INFORMATION FROM HUMAN EXPOSURE

Bexagliflozin has been well tolerated whether administered as immediate release capsules or extended release tablets. The proportion of subjects who have experienced any treatment-emergent adverse event (AE) has been comparable between active and placebo arms. The most frequently occurring AEs (> 5%) have been urinary tract infections and hypoglycemia. For both types of event, the rate has been higher in the combined placebo group than in the combined bexagliflozin groups (of all strengths). Similarly, taking all completed studies into consideration, a higher percentage of subjects in the placebo or comparator groups have experienced serious adverse events (SAEs) than subjects in the bexagliflozin treatment groups, taking all dosage levels combined. Neither death nor serious adverse event has been observed in any of the phase 1 clinical pharmacology studies. Deaths have occurred in multiple phase 2 and 3 studies, particularly in a large, ongoing cardiovascular safety study.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of moderate hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single oral dose of bexagliflozin tablets, 20 mg

2.2 Secondary Objective

To assess the safety and tolerability of bexagliflozin in subjects with moderate hepatic impairment.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Approximately 16 subjects (eight with moderate hepatic impairment [Child-Pugh total score 7-9] and eight healthy, matched controls) will be enrolled.

The Child-Pugh grading system will be used to assess the severity and prognosis of hepatic disease. Male or female subjects with hepatic impairment conforming to the Child-Pugh classification of B (Child-Pugh total score 7-9) based on the Child-Pugh scoring method described in Appendix 2 will be enrolled. For each enrolled subject with liver dysfunction a matching control subject (healthy subject) with similar age (±10 years), weight (±10%), sex, and smoking status will be enrolled.

Each subject will take a single bexagliflozin tablet, 20 mg, with 240 mL of water in the morning (approximately 8 a.m. to 10 a.m.) after an overnight fast. Food will be withheld for at least 2 h postdose. Water will be allowed as desired except for one hour before and after drug administration.

Blood samples for determining the plasma concentrations of bexagliflozin will be collected at predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose.

Urine samples for PD analysis will be collected predose and in the following intervals after dosing: 0–12, 12–24, 24–36, and 36–48 h.

Plasma concentrations of bexagliflozin will be determined by validated liquid chromatography-mass spectrometry (LC-MS/MS) methods.

The unbound fraction of bexagliflozin will be determined at 24 h postdose (or earlier if the 24 h postdose sample has a concentration below the limit of quantitation) and at the maximum plasma concentration for each subject by equilibrium dialysis.

Clinical laboratory tests and safety monitoring will be conducted during the treatment period and at the follow-up visit. The study event table is provided in Appendix 1.

3.2 Rationale for Study Design and Control Group

3.2.1 Rationale for Study Design

Pharmacokinetic studies are used to identify special subgroups of patients for whom an alternative dosing regimen may be indicated for efficacy and/or safety reasons. Liver dysfunction of all types, from transient injury to acute liver failure, are common in adult populations. Through a variety of oxidative and conjugative metabolic pathways, the liver is involved in the clearance of many drugs. In addition, the liver directly excretes xenobiotic compounds and their metabolites into bile. Because the liver produces the majority of protein in plasma, hepatic failure can also affect plasma protein binding, which can influence the distribution or elimination of protein-bound drugs.

In this study, the PK, PD and safety profile produced by a single oral dose of bexagliflozin tablets, 20 mg, will be compared between patients with moderate hepatic impairment and demographically matched subjects with normal hepatic function.

3.2.2 Rationale for Dose Selection

Bexagliflozin produces a dose-dependent and saturable UGE in healthy volunteers and diabetic subjects. A population PD model has predicted that bexagliflozin tablets, 20 mg, produced 85% and 94% of the maximal UGE in healthy and diabetic subjects, respectively. Bexagliflozin has consistently demonstrated wide safety margins in clinical and nonclinical studies. .

A single-dose study is considered sufficient since previous studies show bexagliflozin exhibit linear and time-independent pharmacokinetics (THR100-CLR-002).

3.2.3 Rationale for PK and PD Sampling Time Points

Plasma and urine samples will be collected for 48 hours after dosing. The excretion of total radioactivity in urine occurred principally in the first 48 h following oral dose of [^{14}C] - bexagliflozin in humans (THR-1442-C-410).

3.3 Study Duration and Dates

This is a single dose study. Selection and enrollment of study subjects will begin with those designated for the hepatic impairment group. A screening visit will be completed 2 to 28 days prior to study drug administration. Subjects will be admitted to the clinic the day before administration of the investigational product and will remain in the clinic for at least 48 h following administration. Subjects will return for an end-of-study examination within 13 days of the last pharmacokinetic sample collection. Each subject from the hepatic impairment group will be matched to a healthy comparator subject. 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

The study population comprise eight subjects with hepatic impairment conforming to the Child-Pugh class B (Child-Pugh total score 7-9) and eight control subjects (healthy subjects with normal hepatic function). Each healthy control subject will be matched with an individual subject in the hepatic impairment group by age (±10 years), weight (±10%), sex, and smoking status.

Eligible subjects who consent to participate in the study will be enrolled in clinical investigational sites in the United States. Study subjects will be informed of the purpose and potential risks of participation in the study.

4.2 Inclusion Criteria

Prospective subjects must:

1. Be male or female adults between the age of 18 to 75 years (inclusive) at screening
2. Have a body-mass index (BMI) of 18.0 - 40.0 kg m^{-2} (inclusive) at screening
3. Have adequate venous access at multiple sites in both arms
4. Be willing and able to be confined to the clinical research facility as required by the protocol
5. Be able to comprehend the explanation of the informed consent and be willing to provide written informed consent in accordance with institutional and regulatory guidelines
6. Be diagnosed with moderate hepatic impairment with a Child-Pugh score 7 to 9 (classification in Appendix 2) and must be in stable general health apart from hepatic impairment and its related conditions **(for subjects in the hepatic impairment group only)**
7. Be in general good health with matching demographics and baseline characteristics to individual subjects in the hepatic impairment group by age (±10 years), weight (±10%), sex, and smoking status (**for subjects in the healthy control group only)**
8. Have no evidence of an active infection or be receiving any treatment with antibiotics at the time of screening **(for subjects in the healthy control group only)**

4.3 Exclusion Criteria

Subjects who have any of the following attributes will be excluded from the study:

1. A clinically significant history of allergy to drugs or latex (at the investigator's discretion)
2. A positive alcohol or drug result based on urine sample or breathalyzer testing at screening or at clinic admission (D0). A subject may be eligible upon medical monitor

review and approval if the positive urine drug test is from stable dose of prescription medication

3. A record of donation of 400 mL of whole blood within two months, 200 mL of whole blood within one month, or blood components or plasma within 14 days prior to D0.
4. A history of exposure to an investigational drug within 30 days or 5 half-lives of the investigational drug prior to D0, whichever is longer
5. A history of exposure to any SGLT2 inhibitor within 3 months prior to D0 or participation in previous bexagliflozin clinical trials
6. A history of exposure to probenecid, rifampin or any potential strong UGT1A9 inducers or inhibitors within 2 months of D0
7. A clinically significantly abnormal screening ECG that includes but is not limited to: heart rate <40 or >110 bpm, QRS > 160 ms, QTc > 480 ms (corrected by Bazett's formula), or any clinically significant arrhythmia including Mobitz type II 2nd Degree Heartblock, and bifascicular block.
8. If destined for the hepatic impairment group, a seated systolic blood pressure <80 or > 160, confirmed by repeat or diastolic blood pressure of < 40 or >100
9. If destined for the healthy control group, a seated systolic blood pressure <90 or > 140, confirmed by repeat or diastolic blood pressure of < 40 or > 90
10. A history of HIV infection or a positive titer for human immunodeficiency virus (HIV) antibody
11. A history of vaccination (with the exception of the flu vaccine) within 30 days prior to D0
12. An estimated glomerular filtration rate (eGFR) < 60 mL min^{-1} per 1.73 m^2 as calculated by the modification of diet in renal disease study equation (MDRD), at screening
13. Severe or moderate renal dysfunction or a history of kidney, other organ, bone marrow or stem cell transplant
14. If male, refusing to refrain from donating sperm or use of appropriate birth control when engaging in sexual intercourse for the duration of the study and a period of 14 days after discharge from the clinic. Appropriate birth control methods include condoms with spermicide, female partner's use of diaphragm with spermicide, female partner's use of stable oral, implanted, or injected contraceptive hormones or an intrauterine device. Male subjects who are surgically sterile are eligible
15. If female and of childbearing potential, refusing to use an adequate method of contraception to avoid prevent pregnancy for the duration of the study and a period of 14 days after discharge from the clinic. Adequate methods of contraception for female subjects of childbearing potential include bilateral tubal ligation, intrauterine device, diaphragm with spermicide and male partner's use of male condom with spermicide. Female subjects who are surgically sterile (i.e. have undergone full hysterectomy, or bilateral oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible. All females must have negative pregnancy test at screen and at admission
16. Unwilling to forgo consumption of grapefruit and grapefruit products from 7 days prior to D0 through discharge from the clinic

17. Pre-existing thrombocytopenia (platelet blood count < 30,000 platelets) at screening or other clinically significant findings in CBC
18. A history of current febrile illness, hepatocellular carcinoma, acute liver disease, severe hepatic encephalopathy, or biliary liver cirrhosis
19. A history of significant acute medical illness (new conditions, exacerbation of preexisting conditions or major surgery within 4 weeks of study drug administration), active alcoholic hepatitis, current or recent (within 2months before D0) history of significant gastrointestinal disease
20. Clinical evidence of severe ascites, as judged by the investigator
21. A history of surgical portosystemic shunt
22. If destined for the healthy control group, a history of vitamin preparation or supplement use (including St. John's Wort and ginseng) within 7 days prior to D0, or caffeine and xanthine containing foods/beverages within 48 h prior to D0
23. If destined for the hepatic impairment group, a history of any new prescription medication within 30 days prior to D0
24. If destined for the hepatic impairment group, a history of fluctuating or rapidly deteriorating hepatic function or the production of widely varying or worsening clinical and/or laboratory signs of hepatic impairment within the screening period
25. If destined for the healthy control group, a history of prescription or over-the-counter (OTC) drug use within 7 days or 5 half-lives of the drug, whichever is longer, prior to D0
26. If destined for the healthy control group, a history of liver disease or liver injury as indicated by an alanine aminotransferase (ALT), aspartate aminotransferase (AST), > 2.5 × the upper limit of normal (ULN) at screening, or serum bilirubin > 1.5 × ULN
27. If destined for the healthy control group, evidence of HBV or HCV infection.
28. Any other serious medical condition that, in the opinion of the investigator, would pose a significant risk to the subject or interfere with the interpretation of safety, PK, or PD data.

5 STUDY TREATMENTS

5.1 Study Drug

Bexagliflozin tablets, 20 mg, are prolonged release, 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 tablets exhibit a > 75% release of drug substance by 8 hours in simulated gastric fluid *in vitro*.

5.2 Treatments Administered

Subjects who consent to participate and meet all inclusion/exclusion criteria will receive a single oral dose of bexagliflozin tablets, 20 mg.

5.3 Selection and Timing of Dose for Each Subject

Subjects in the hepatic impairment group will be dosed first. Control subjects will be enrolled after at least one subject in the hepatic impairment group is enrolled. Each control subject will be matched with individual subject in hepatic impairment group. Each subject will receive a single oral dose of bexagliflozin tablets, 20 mg, with 240 mL of water on Day 1 (D1) after an overnight fast of at least 10 h.

5.4 Method of Assigning Subjects to Treatment Groups and Sequences

This is an open-label, parallel-group study. An adequate number of male or female subjects with moderate hepatic impairment [Child-Pugh total score 7-9] will be enrolled to obtain eight evaluable subjects. Another adequate number of healthy subjects with normal hepatic function will be enrolled to obtain at least 8 evaluable subjects who are matched with the subjects in the moderate hepatic impairment group individually for age (±10 years), weight (±10%), sex, and smoking status.

Subjects who withdraw early for safety reasons will not be replaced.

5.5 Blinding

This is an open-labeled study.

5.6 Concomitant Therapy

Participants in the healthy control group will be prohibited from taking any prescription or OTC drugs, supplements, or vitamins 7 days prior to D0, as well as for the duration of the study. Subjects in the hepatic impairment group must not have changed the dose or frequency of administration of any prescription medications for 30 days prior to D0.

Medications may be prescribed for management of an adverse event (AE). Subjects may receive any medications for AEs that are necessary to treat the event or minimize the

likelihood of having serious adverse events (SAEs) in the investigators' judgment. Concomitant medications administered during the study are to be recorded on the case report form (CRF). The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration shall be recorded. This documentation shall continue until the end of the study.

5.7 Restrictions

5.7.1 Prior Therapy

No study subject shall have been dosed with any SGLT2 inhibitor within 3 months prior to D0, nor with an investigational drug within 30 days or 5 half-lives. No subject shall have previously participated in a bexagliflozin clinical trial. No subject in the control group shall have taken any OTC drugs, vitamins, or supplements 7 days prior to D0 or shall have consumed caffeine or similar methylxanthine-containing foods/beverages (tea, hot chocolate, energy drinks) within 48 h prior to D0. Subjects in the hepatic impairment group must not have changed the dose or frequency of administration of any prescription medications for 30 days prior to D0.

5.7.2 Fluid and Food Intake

Bexagliflozin will be administered to subjects after an overnight fast of at least 10 h with approximately 240 mL water. Subjects should fast at least 8 h prior to any safety laboratory collection. Water will be allowed as desired except for one hour before and after drug administration.

5.7.3 Subject Activity Restrictions

Alcohol consumption is restricted for 72 hours prior to D0 and throughout the study.

5.8 Treatment Compliance

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

5.9 Packaging and Labeling

Bexagliflozin tablets, 20 mg, are packaged in high-density polyethylene bottles sealed with a child resistant closure. The product is packaged in 90 count bottles.

Investigational product bottles will be labeled with the protocol number, drug name and strength, lot number, sponsor's name, storage condition, and the investigational drug caution statement.

5.10 Storage and Accountability

Bexagliflozin tablets will be stored below 30°C (86°F) in a secure area with access limited to authorized personnel. The pharmacist shall maintain an inventory of bexagliflozin product and the number of tablets dispensed per study subject. A reconciliation of drug inventory will be performed at the end of the study and the results of this inventory shall be recorded in the Drug Consumption Form (or equivalent). Empty, partially used and unused bottles must be returned to the depot for destruction at study close out, after the Drug Consumption Form (or equivalent) is completed.

6 STUDY PROCEDURES

6.1 Informed Consent

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

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

6.2 Medical History

The following information will be collected at the screening visit:

- Demographic information including age, sex, and race.
- Significant medical and surgical history with documentation of the dates relative to the time of study screening, if applicable.
- History of clinically significant allergies including to drugs and latex.
- History of smoking.
- History of blood donation within two months or blood components or plasma donation in the 14 days prior to D0.
- History of vaccination within 30 days prior to D0.
- History of diagnosis of HIV.
- History of severe or moderate renal dysfunction or a history of kidney, other organ, bone marrow or stem cell transplant.
- History of Hepatitis B, or Hepatitis C virus infection.
- History of exposure to any investigational drug in the previous 30 days or 5 half-lives prior to D0, whichever is longer.
- History of exposure to any SGLT2 inhibitors in the last 3 months prior to D0.
- History of participation in any bexagliflozin clinical trial.
- Medication history including prescription, OTC drugs, and vitamin preparation or supplement use (including St. John’s Wort and ginseng) within 7 days or 5 half-lives of

the drug, whichever is longer, prior to D0 **(for subjects in the healthy control group only)**.

- A history of any change in dose or frequency of dosing of prescription medication within 30 days prior to D0 **(for subjects in hepatic impairment group only)**

6.3 Physical Examination

The investigator or designated qualified individual will perform the PEs. A complete PE will be performed at screening, and on clinic admission (D0). A partial PE will be performed on day 1, and at follow up visit as described in Appendix 1.

A complete PE will include body weight, height and general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, lungs, heart, abdomen, lymph nodes, and extremities. A partial PE will include a general assessment of the skin, heart, lungs and abdomen.

6.4 Vital Signs

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

Vital signs, including pulse, systolic and diastolic BP, shall be measured prior to blood draws and after a subject has been sitting for 5 minutes.

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

BP measurements will be obtained using a calibrated manual or oscillometric sphygmomanometer.

6.5 Electrocardiography

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

The data should be collected from the subject in the supine position after at least 5 minutes of rest. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT. Each ECG shall 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 shall ascertain if the abnormality represents a clinically significant change from the screening ECG for that individual subject. This determination, however, need not 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, the finding shall be 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 tests will be performed at the scheduled visits (Appendix 1). Blood samples shall be drawn after overnight fasting (at least 8 h). The details of the required laboratory tests are listed in Table 1.

Table 1. Required Laboratory Tests

Test Name		mL (sample)
Hematology		8.5 (blood)
Hematocrit	Mean corpuscular volume	
Hemoglobin	Platelet count	
Mean corpuscular hemoglobin	Red blood cell count	
Mean corpuscular hemoglobin concentration	White blood cell count with differential	
International normalized ration (INR)		
Serum Chemistry, Electrolytes and Lipids		4.0 (blood)
Albumin	Calcium	
Alanine aminotransferase (ALT)	Magnesium	
Aspartate aminotransferase (AST)	Alkaline Phosphatase (ALP)	
Blood urea nitrogen (BUN)	Phosphorus	
Glucose	Potassium	
Bicarbonate	Sodium	
Creatinine	Total bilirubin	
Creatinine kinase	Direct bilirubin	
Chloride	Uric acid	
Total protein	Total cholesterol	
Low-density lipoprotein cholesterol, calculated	High-density lipoprotein cholesterol	
Triglycerides		
Urinalysis		20 (urine)
Appearance	Nitrite	
Bilirubin	pH	
Color	Occult blood	
Glucose	Protein	
Ketones	Specific gravity	
Microscopic examination will be performed if protein, leukocyte esterase, nitrite, or blood is positive	Urobilinogen	
	Leukocyte esterase	

Table 1. Required Laboratory Tests

Test Name		mL (sample)
Urine Drug Screen		10 (urine)
Amphetamines	Opiates	
Barbiturates	Benzodiazepines	
Cocaine Metabolites	Cannabinoids (THC)	
MDMA	Methamphetamine	
TCA	Methadone	
PCP	OXY	
	Alcohol	
Urine pregnancy test (Female only)		5.0 (urine)
Infectious Disease Testing (measured at screening only)		4.0 (blood)
Hepatitis B surface antigen (HBsAg)	Hepatitis C virus (HCV)	
Human Immunodeficiency Virus antibody (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 sample collection is described in Appendix 1.

6.6.2.2 Urinalysis

Clean-catch, midstream urine samples will be collected per the schedule outlined in Section 7 and in Appendix 1. Dipstick urinalysis will be conducted at the local laboratory. If protein, leukocyte esterase, nitrite or blood is positive in the dipstick analysis, a microscopic examination will be performed. If microscopic examination is suggestive, then a culture may be performed at the discretion of the investigator. In addition, unscheduled urinalysis will be performed from a clean-catch urine sample from subjects with symptoms of UTI or pyelonephritis.

6.6.2.3 Urine Collection for PD

Predose urine samples must be collected from -12 to 0 h for baseline measurement. Subjects will empty their bladders prior to dosing. Postdose urine will be collected without preservative in four (4) batches at 0-12, 12 to 24, 24 to 36, and 36 to 48 h after oral administration of bexagliflozin. Urine must be refrigerated at 2-8 °C during collection. After collection, the total volume of each batch and collection time will be recorded. A 20 mL aliquots of the urine at each batch will be prepared from well-mixed urine collections. One aliquot of the urine samples will be analyzed for urinary glucose and creatinine at the local lab (for PD analysis).

6.6.2.4 Plasma Sample Collection for PK

Whole venous blood samples of 6 mL will be collected from a peripheral vein at predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h after oral administration of bexagliflozin. Blood samples will be collected 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, divided into 3 aliquots of approximately 1.0 mL, frozen and stored at or below -20 °C. Plasma should be processed and frozen within 2 h of blood collection. Processed frozen plasma samples will be transferred on dry ice to the analytical laboratory and will be stored at or below -20 °C until LC-MS/MS analysis and protein binding determination.

6.6.3 Blood Volume and Frequency for PK and Safety Assessment

The approximately total volume and number of sampling times for blood collections are outlined in Table 2.

Table 2. Blood Samples

Test	Volume per sample (mL)	No. of Samples	Total*	Storage
Blood				
Hematology	8.5	5	42.5	4 °C
Chemistry and infectious disease testing	4	6	24	4 °C
Virology testing	7	1	7	4 °C
PK	6	15	90	-20 °C

*Total blood volume required in each subject: approximately 178.5 mL, including additional 15 mL blood for heparin locks for PK draws.

6.7 Adverse Events Assessments

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

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

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

- results in death,

- is life-threatening *(NOTE:* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event and does not refer to an event which hypothetically might have caused death if it were more severe.),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event.

An important medical event is an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

Hypoglycemia will be defined as any fasting plasma glucose (FPG) value ≤70 mg dL^{-1} and documented as described in Section 6.7.3.4.

Any clinical significant increase in hepatic enzymes and specifically ALT or AST > or = 3x ULN (for healthy control subjects), or AST or ALT >or = to 3x the subject's baseline values, whichever is greater will be considered a clinical laboratory adverse event.

An increase in creatinine from baseline by 0.5 mg dL^{-1} or more will be reported as a laboratory adverse event.

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

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

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

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

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

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

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

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

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

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

6.7.1 Collecting and Reporting Adverse Events

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

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

6.7.2 Immediately Reportable Adverse Events

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

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

6.7.3 Follow-up of Adverse Events

6.7.3.1 Follow-up of Non-serious Adverse Events

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

6.7.3.2 Follow-up of Post-Study Serious Adverse Events

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

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the Medical Monitor or the sponsor's designated personnel. These may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined study period (i.e., up to last scheduled contact). The investigator should follow subjects with SAEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the Sponsor until the event has been resolved. This study requires that subjects be actively monitored for SAEs for at least 14 days after discharge from the study.

6.7.3.3 Hepatotoxicity

Any clinical significant increase in hepatic enzymes and specifically ALT or AST > or = 3x ULN (for healthy control subjects), or AST or ALT >or = to 3x the subject's baseline values, whichever is greater, requires immediate repeat test within 48 to 72 h to confirm the hepatic enzyme elevation. 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.

6.7.3.4 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^{-1} (3.9 mmol L^{-1}).
- Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg dL^{-1} (3.9 mmol L^{-1}).
- 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^{-1} (3.9 mmol L^{-1}).
- Relative hypoglycemia: An event during which the person reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg dL^{-1} (3.9 mmol L^{-1}).

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^{-1} (3.9 mmol L^{-1}), the subject should be treated with 15 to 20 grams of oral glucose or simple carbohydrate (glucose tablets, raisins, orange juice, glucose-containing soda, or soft sugar candies).

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

Blood glucose monitoring will be done by appropriate study staff using a point-of-care glucose monitor beginning at the time of hypoglycemia detection and continue every fifteen minutes, or more frequently if required, until that time that the subject's level of alertness has returned to appropriate levels and point-of-care glucose levels are above 70 mg dL^{-1}.

6.8 Concomitant Medication Assessments

A concomitant medication is any medication the subject enters the trial taking and is expected to continue taking for some portion of the trial, as well as any medication the subject takes during the course of the trial. All prescription and over-the-counter medications,

including vitamins and herbal supplements, that subjects receive during the trial must be documented on the CRF. This documentation should continue until the subjects are discharged.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). A table of concomitant medications based on the anatomic therapeutic chemical (ATC) classification and preferred name will be produced. A listing of concomitant medications will include all medications taken by any subjects during the course of the study.

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

6.9 Removal of Subjects from the Trial

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

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

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

Subjects who withdraw from the study due to adverse event(s) or other safety concerns will not be replaced.

After a decision is made to withdraw a subject, 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 for any of the following reasons:

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

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

6.10 Appropriateness of Measurements

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

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 Study Screening (Day -28 to Day -1)

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

- The content of informed consent will be explained to the subject and the signed informed consent collected.
- Medical history and demographic information will be obtained.
- A complete physical examination will be conducted, including height and weight measurements as described in Section 6.3.
- Vital signs will be measured, including pulse, body temperature, respiratory rate, and blood pressure taken in the sitting position after at least 5 min of rest as described in Section 6.4.
- A 12-lead ECG will be taken in the supine position after at least 5 min of rest as described in Section 6.5.
- A clean-catch, mid-stream urine specimen will be collected for urinalysis as described in Section 6.6.2.2. A microscopic examination will be performed if protein, leukocyte esterase, nitrite or blood tests are positive. If the results of microscopic analysis are suggestive a culture may be performed at the investigator's discretion.
- A urine drug screen will be conducted for drugs of abuse. A urine (or breath) alcohol test will also be conducted.
- All female subjects will receive urine pregnancy test.
- Blood will be drawn for hematology, serum chemistry, and serology as detailed in Section 6.6.2.1.
- Subject conformance to inclusion/exclusion criteria will be evaluated based on the information collected at the screening examination.

7.2 Day 0 (D0) (Clinic Admission)

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

- A complete PE will be performed as described in Section 6.3.
- Inclusion and exclusion criteria will be evaluated.
- A urine drug screen will be conducted for drugs of abuse. A urine (or breath) alcohol test will also be conducted.
- All female subjects will receive a urine pregnancy test.
- A urine sample will be collected for predose urinalysis as described in Section 6.6.2.2. If the urine specimen is positive for protein, leukocyte esterase, blood or nitrites, a sample is to be sent for microscopic evaluation. If the results of microscopic analysis are suggestive, a culture may be performed at the investigator's discretion.

- Predose blood will be drawn for hematology and serum chemistry as detailed in Section 6.6.2.1.
- If the subject is still eligible based on the study inclusion and exclusion criteria, the subject will be admitted to the study.
- Predose urine will be collected until 0 h (-12 h to 0 h batch) for PD analysis as described in Section 6.6.2.3.
- Concomitant medications and adverse event information will be collected as appropriate.

7.3 Day 1 (D1) (Dosing Day): Predose

- A partial PE will be performed as described in Section 6.3.
- Vital signs will be recorded predose.
- A 12-lead ECG will be taken in the supine position after at least 5 min of rest predose, as described in Section 6.5.
- A predose urine will be collected until 0 h (-12 h to 0 h batch) for PD analysis as described in Section 6.6.2.3.
- A urine sample will be collected for predose urinalysis as described in Section 6.6.2.2. If the urine specimen is positive for protein, leukocyte esterase, blood or nitrites, a sample is to be sent for microscopic evaluation. If the results of microscopic analysis are suggestive then a culture may be performed at the investigator's discretion.
- Predose blood will be drawn for hematology, and serum chemistry as detailed in Section 6.6.2.1.
- Predose plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4.
- Predose concomitant medications and adverse event information will be collected as appropriate.

7.4 Day 1 (D1) Dosing

- Subjects will receive a single dose of bexagliflozin tablets, 20 mg, with approximately 240 mL water after an overnight fast of at least 10 h as detailed in Section 5.3.

7.5 Day 1 (D1) Postdose

- Vital signs will be recorded at 4 h post-oral dose.
- A 12-lead ECG will be taken in the supine position after at least 5 min of rest at 4 h postdose.
- Urine samples for PD analysis will be collected at 0-12 h and 12-24 h after oral administration of bexagliflozin, as described in Section 6.6.2.3.
- Blood samples for PK samples will be collected at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 h after oral administration of bexagliflozin.

- Postdose concomitant medications and adverse event information will be collected as appropriate.

7.6 Day 2 (D2)

- Vital signs will be recorded at 24 h post-oral dose.
- Urine samples for PD analysis will be collected at 12-24 h, 24-36 h and 36-48 h after oral administration of bexagliflozin, as described in Section 6.6.2.3.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 24 and 36 h postdose.
- Postdose concomitant medications and adverse event information will be collected as appropriate.

7.7 Day 3 (D3)

- A 12-lead ECG will be taken at 48 h postdose in the supine position after at least 5 min of rest as described in Section 6.5.
- Vital signs will be recorded at 48 h postdose.
- Urine samples for PD analysis will be collected at 36-48 h after oral administration of bexagliflozin, as described in Section 6.6.2.3.
- Urine will be collected for urinalysis as described in Section 6.6.2.2.
- Blood will be drawn for hematology and serum chemistry as detailed in Section 6.6.2.1.
- Plasma samples will be drawn for PK analysis as detailed in Section 6.6.2.4 at 48 h postdose
- Postdose concomitant medications and adverse event information will be collected as appropriate.
- The subject will be discharged after completion of all activities

For subjects who are terminated from the study for any reason after dosing, all activities for Day 15 (D15) ± 1 day except for PK and PD sample collection must be completed. The reason for termination must be entered into the case report form.

7.8 Day 15 (D15) ± 1 day Activities

On day 15 (±1 day), the following information will be gathered and the indicated procedures will be performed after dosing:

- PA partial physical examination will be performed as described in Section 6.3.
- Vital signs will be recorded as indicated in Section 6.4.
- A 12-lead ECG will be recorded in the supine position after at least 5 min of rest.
- Urine will be collected as described in Section 6.6.2.2 for urinalysis.

- All female subjects will receive a urine pregnancy test.
- Blood will be drawn for hematology and serum chemistry as detailed in Section 6.6.2.1.
- Concomitant medications and adverse event information will be collected as appropriate.

7.9 Early Termination Procedures

Subjects who withdraw consent and have received investigational product should have a follow-up examination, including a partial physical examination, and undergo collection of vital signs, ECG data, urine pregnancy test outcomes (female only), and samples for clinical laboratory tests (hematology, serum chemistry, and urinalysis). 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 ensure 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 clinical research organization (CRO) and the sponsor. Review procedures will be implemented at the CRO for all documents that are generated in relation to the study.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical evaluation of PK and PD parameters will be conducted by the designated CRO. A detailed Statistical Analysis Plan will be generated prior to any PK/PD statistical analysis of the data. Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS, USA). Non-compartmental analysis (NCA) will be performed using Phoenix®WinNonlin® 6.4 or later (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 detect clinically relevant PK or PD differences between healthy and hepatic impairment subjects.

9.3 Analysis Populations

9.3.1 Safety Population

The Safety Population will include all subjects who are dispensed study drug. Subjects will be analyzed according to the respective hepatic function group.

9.3.2 PK Population

The PK Population will include all subjects without major protocol violations who are dispensed study drug and who provide an observation for ≥ 1 primary pharmacokinetic endpoint. The PK Population will be used to summarize the PK parameters.

9.3.3 PD Population

The PD Population will include all subjects without major protocol violations who are dispensed study drug and who produce at least the first 12 h postdose urine. The PD Population will be used to summarize the PD parameters.

9.4 Demographics and Baseline Characteristics

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

9.5 Pharmacokinetic Analysis

9.5.1 Calculation of Pharmacokinetic Variables

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

C_{max} Maximum observed plasma concentration

T_{max} Time of maximum observed plasma concentration

λ_z Terminal elimination phase rate constant

$t_{½}$ Apparent terminal elimination half-life

CL/F Apparent oral clearance

V_z/F Apparent volume of distribution

AUC_{0-24} Area under the plasma concentration-time curve from the time of dosing to 24 h postdose

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

$AUC_{0-\infty}$ Extrapolated area under the plasma concentration-time curve from the time of dosing to infinity

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

f_u Unbound fraction, calculated as (free drug concentration)/(total drug concentration)

$C_{max, u}$ Maximum unbound plasma concentration

AUC_u Area under the unbound plasma concentration-time curve

Cl_u/F Apparent clearance relative to the unbound drug concentration

C_{max} and T_{max} will be obtained directly from experimental observations. If two or more concentrations are equal and maximum, the first will be taken as the T_{max}.

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

AUC_{0-t}, AUC_{0-24} and $AUC_{0-\infty}$ will be calculated using the linear trapezoidal linear interpolation method, using actual elapsed time values. If the actual collection time is unknown, the nominal collection time may be used for the purposes of PK parameter estimation. For the purpose of calculating AUC, all missing values will be treated as missing in the PK analysis and excluded from analysis except when they occur at predose, in which case they will be set to zero. All values that are below the limit of quantitation (BLOQ) prior to T_{max} will be set to zero. BLOQ values that occur after T_{max} will be considered missing. When ≥ 2 consecutive plasma concentrations that are BLOQ are encountered after T_{max}, these and all subsequent values will be excluded from the analysis.

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

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

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

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

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

$t_{½}$ will be calculated as 0.693/λ_z.

9.5.2 Statistical Analysis of Pharmacokinetic Variables

Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS Institute Inc., USA). PK parameters for bexagliflozin will be calculated using non-compartmental analyses (NCA) of plasma concentration-time data. An analyses of variance (ANOVA) with a fixed effect corresponding to the hepatic function group will be fitted to the natural logarithmic transformation of the PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The 90% confidence intervals will be constructed for the ratio of geometric means of PK parameters (total and unbound C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The apparent clearance relative to the unbound drug concentration (Cl_u/F) will be calculated as Cl_u/F = Dose/AUC_u.

Descriptive statistics of plasma concentration-time data will be summarized by hepatic function group and timepoint.

The PK parameters C_{max}, T_{max}, λ_z, $t_{1/2}$, CL/F, V_z/F. AUC_{0-t}, $AUC_{0-\infty}$, AUC_{extr}, $AUC_{u(0-t)}$ and $AUC_{u(0-\infty)}$ will be summarized by hepatic function group. Means, standard deviations, medians, ranges (min, max) and geometric means and coefficients of variation will be presented for all parameters will the exception of T_{max}. Medians and ranges will be presented for T_{max}.

9.6 Pharmacodynamic Analysis

The PD parameters, glucose concentrations, creatinine concentrations, UGE and UGE normalized by urinary creatinine, including UGE_{t1-t2} over specified time interval, and total 24-hour, 48-hour UGE, will be determined. UGE_{t1-t2} (mg) will be derived from urine volume (V_{t1-t2}, mL) × glucose concentration (mg dL^{-1}) / 100. UGE and nUGE will be listed and summarized by hepatic function group using descriptive statistics.

Reported predose values for PD data that are below the defined limit will be set to zero. Any missing values or values below the reported defined limit that appear after predose for PD data will be set to missing.

9.7 Safety Analysis

Safety data will include AEs, PE results, VS results, ECG results, and clinical lab results, including those of 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 study report (CSR).

9.7.1 Adverse Events

Adverse events will be mapped to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting adverse events will be determined by relationship to treatment and by severity of the event. Causality for AEs will be ascribed by the investigator according to the investigational product causality guidelines of section 6.7.

Adverse event listings will be provided for the following subsets:

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

AEs are dosing emergent if they occur on or after bexagliflozin administration. Causality for TEAEs will be ascribed by the investigator according to the investigational product causality guidelines of section 6.7. Only TEAEs will be tabulated in summary tables.

Tabulations will display TEAEs by severity and relationship to bexagliflozin.

9.7.2 Hypoglycemia

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

9.7.3 Clinical and Laboratory Events and Analyses

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

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

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

9.7.4 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.

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) Approval

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

10.3 Ethical Conduct of the Study

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

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

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

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

10.4 Subject Information and Consent

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

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

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

10.5 Subject Confidentiality

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

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

10.6 Study Monitoring

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

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

10.7 Case Report Forms and Study Records

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

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

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

10.8 Protocol Violations/Deviations

It is important to conduct the study according to the protocol. Protocol deviations will not be prospectively granted by the sponsor. If deviations occur, such as a visit or sampling window being missed, the investigator must decide whether to proceed, for example, whether or not to complete the visit or sample collection outside of the protocol-defined window. The sponsor's medical monitor must be notified immediately when protocol deviations are discovered so that a decision about whether to keep the subject in the study can be made.

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

Protocol violations must be reported in the final study report.

10.9 Access to Source Documentation

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

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

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

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

10.10 Retention of Data

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

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

10.11 Publication and Disclosure Policy

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

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

11 REFERENCES

US Food and Drug Administration. (2003). Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

Appendix 1 Schedule of Events

	Screening		In-Clinic				Follow-up
Study activity	**D -28 to -1**	**D0**	**D1 predose**	**D1 postdose**	**D2**	**D3**	**D15±1d**
Medical history and ICF	X						
Screening for I/E criteria	X	X					
Physical exam[1]	X	X	X				X
Demographics	X						
Admission and discharge		X				X	X
Vital signs[2]	X		X	X	X	X	X
ECG[3]	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	
Urine collection[7]		X	X	X	X	X	
Urine pregnancy test (Female only)	X	X					X
Adverse event and concomitant medication		X	X	X	X	X	X
Study completion[8]							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 on clinical admission (D0). A partial PE will be performed on day 1 and at follow up visit
2. Vital signs include pulse, body temperature, respiratory rate, systolic and diastolic blood pressure. Vital signs will be determined at predose and at 4 h, 24 h (day 2) and 48 h (day 3) postdose and at the follow up visit.
3. 12-lead ECG will be conducted after 5 min resting. ECG data will be recorded at screening, on day 1 at predose and at 4 h postdose and day 3, and at follow up visit on day 15 and when clinically indicated.
4. Clean sample to be collected at each visit. If urine dipstick is positive for protein, leukocyte esterase, blood or nitrites, a microscopic examination will be performed. If the microscopic exam is suggestive, a culture may be performed at the investigators discretion. Urine drug screen will be performed at screening visit and clinic admission (D0). Alcohol (via urine or breath) will be tested at clinic admission (D0) only.
5. Blood sample at the designated visits for clinical chemistry and hematology parameters are listed in Table 1. Infectious disease testing will be conducted at screening only.
6. Plasma samples for PK profile of bexagliflozin will be collected at predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose.
7. Urine for PD will be collected at predose (h -12 to 0), and at postdose at 0–12, 12–24, 24–36, and 36–48 h.
8. If early withdrawal occurs, activities scheduled for follow up visit should be conducted. Reasons for all withdrawals should be recorded on the CRF.

Appendix 2 The Child-Pugh Classification

Finding	Points Scored for Each Observed Finding		
	1	**2**	**3**
Encephalopathy[1]	None	1 or 2 (or suppressed with medication)	3 or 4 (or refractory)
Ascites[2]	Absent	Slight or Subject on 1 medication to control ascites	Moderate or Severe or Subject on 2 medications to control ascites
Bilirubin (mg dL^{-1})	<2	2 to 3	>3
Albumin (g dL^{-1})	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3

[1] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity

[2] Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation.
Slight: Ascites palpation doubtful
Moderate: Ascites detectable by palpation
Severe: Necessity of paracentesis, does not respond to medication treatment.

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe

Appendix 3 Sponsor Signatures

Study Title:	A Phase 1, Open-label, Parallel-group Study to Evaluate the Effect of Moderate Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin
Study Number:	THR-1442-C-455
Final Date:	21 August 2018

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: 21-Aug-2018

Xiao-Yan Li, Ph.D.
Sponsor Study Representative
Massachusetts General Hospital

Signed: _____ Date: 21 August 2018

Yuan-Di Halvorsen, Ph.D.
Sponsor Study Representative
Massachusetts General Hospital

Signed: _____ Date: 22 August 2018

J. Paul Lock, M.D.
Medical Monitor
Consultant for Theracos Sub, LLC

Appendix 4 Investigator's Signature

Study Title:	A Phase 1, Open-label, Parallel-group Study to Evaluate the Effect of Moderate Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin
Study Number:	THR-1442-C-455
Final Date:	21 August 2018

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: Mark Matson Date: 22 AUG 2018

Appendix 4 Investigator's Signature

Study Title:	A Phase 1, Open-label, Parallel-group Study to Evaluate the Effect of Moderate Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin
Study Number:	THR-1442-C-455
Final Date:	21 August 2018

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: Aug 22, 2018