STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Theracos Sub, LLC.
Protocol Number:	THR-1442-C-455
IND Number:	103822
Investigational Drug:	Bexagliflozin Tablets
Indication:	Type 2 Diabetes Mellitus
Dosage Form/Strength:	Tablets/20 mg - Bexagliflozin

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

Last Revision Date: 31-May-2019

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CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

Revision Date**	Section(s) Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by*
			Sponsor, Everest
18-Jan-2019	Section 6.1.1; Section 8.3	Scheduled visit numbers updated in Table 4. Addition of hepatic impairment history.	YH, ME
01-Mar-2019	Section 6.1.1	Addition of procedure for results out-of -window.	YH, ME
01-Mar-2019	Sections 7.2 and 13	ISCV removed from analysis (not appropriate)	YH, ME
24 May, 2019	Section 5.3	Fix of PD population definition	ME

* ME = Michael Edwardes; YH = Yuan-Di Halvorsen

** Update the Last Revision Dates on the cover page and the document header.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analyses of variance
AST	aspartate aminotransferase
ATC	anatomic therapeutic class
AUC	area under the plasma concentration-time curve
AUC_{extr}	extrapolated area under the plasma concentration-time curve from t_{last} to infinity
AUC_{0-24}	area under the plasma concentration-time curve from the time of dosing (Time 0) to 24 hrs post-dose
$AUC_{0-\infty}$	area under the plasma concentration-time curve from the time of dosing (Time 0) to infinity
$AUC_{u\ (0-\infty)}$	area under the unbound plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration-time curve from the time of dosing (Time 0) to Time t
$AUC_{u\ (0-t)}$	area under the unbound plasma concentration-time curve from time 0 to time t
BLOQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
Ca	calcium
CI	confidence interval
Cl	chloride
C_{last}	concentration corresponding to T_{last}
CL/F	apparent oral clearance
CL_u/F	apparent clearance relative to unbound drug concentration
cm	centimeter

GLOSSARY OF ABBREVIATIONS

C_{max}	maximum observed plasma concentration
C_{maxu}	maximum unbound plasma concentration
cps	cycles per second
CRF	case report form
CV	coefficient of variation
DBP	diastolic blood pressure
dL	deciliter
DM	data management
ECG	electrocardiogram
f_u	Unbound fraction, calculated as (free drug concentration)/(total drug concentration)
hr	hour(s)
HbsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
Hgb	hemoglobin
HIV	human immmunodeficiency virus
ICF	informed consent form
INR	international normalized ration
IRAE	immediately reportable adverse event
K	potassium
kg	kilogram
KR	Kenward-Roger
L	liter
λ_z	terminal elimination phase rate constant

GLOSSARY OF ABBREVIATIONS

LC-MS/MS	liquid chromatography/mass spectrometry
LDL-C	low density lipoprotein cholesterol
LLN	lower limit of normal
LS	least square
max	maximum
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDMA	methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
msec	millisecond
Na	sodium
NCA	non compartmental analysis
NTR	not treatment related, includes unrelated
nUGE	creatinine normalized UGE
OTC	over the counter
PCP	phencyclidine
PCS	potentially clinically significant
PD	pharmacodynamic
PE	physical examination
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).

GLOSSARY OF ABBREVIATIONS

PT	preferred term
QA	quality assurance
QC	quality control
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 [$QT/(RR^{1/2})$]
RBC	red blood cell (count)
REML	restricted maximum likelihood
RR interval	intra-beat interval
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$T_{½}$	apparent terminal elimination half-life
TC	total cholesterol
TCA	tricyclic antidepressant
TEAE	treatment emergent adverse event
TG	triglycerides
T_{last}	time of last measurable (positive) concentration
TLF	table, listing, figure
T_{max}	time of maximum observed plasma concentration
TR	Treatment related - includes definitely, probably, possibly, and not likely related

GLOSSARY OF ABBREVIATIONS

T-wave	repolarization of the ventricles
UGE	urinary glucose excretion
ULN	upper limit of normal (value)
VS	vital sign
V_z/F	apparent volume of distribution
WBC	white blood cell (count)
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Theracos Sub, LLC protocol version 3.0 dated 21-Aug-2018. As with any SAP, the proposed methods and approaches to the data analysis should be deemed as flexible. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, the statistical analysis to a certain degree is iterative since much of the planning is based on assumptions that require verification. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

This SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the latest version of the protocol mentioned above and the final version of the annotated CRFs dated 11-SEP-2018.

This document details the analysis of the data collected in the study and the presentation of the results of the analyses. The table, listing, and figure (TLF) shells are displayed in a companion document which provides information on the layout of the data displays.

All statistical analyses will be performed using SAS® version 9.4. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA version 21.0 or newer). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

This is a phase 1, open-label, parallel-group study designed to evaluate the effect of moderate hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (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.

The Child-Pugh grading system will be used to assess the severity and prognosis of hepatic disease. The study population will be comprised of male and 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 3.

For each enrolled subject with liver dysfunction a matched control subject (healthy subject) of similar age (±10 years), weight (±10%), sex, and smoking status will be enrolled.

Blood samples to characterize the PK profile of bexagliflozin will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hrs post-dose.

Urine samples for PD analysis will be collected at pre-dose (-12 to 0 hr), and in the following intervals post-dose 0–12, 12–24, 24–36, and 36–48 hrs.

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

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

(See Protocol Sections 3.1 to 3.3 for additional details).

2. STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

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

3. STUDY DESIGN

3.1 Study Design

This is a phase 1, open-label, parallel-group study. Subjects will be screened within 28 days of the initiation of study drug dosing. Eligible subjects who consent to participate in the study will receive a single oral dose of bexagliflozin tablets, 20 mg, and then will be kept under close medical surveillance at the trial center for at least 48 hrs following drug administration. Subjects will return for an end-of-study examination within 13 days of the last PK sample collection.

Blood samples for characterization of the PK profile of bexagliflozin will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hrs after oral administration of bexagliflozin.

Urine samples for PD analysis will be collected prior to dosing (-12 to 0 h) and in the following intervals after dosing: 0–12, 12–24, 24–36, and 36–48 hrs.

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

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

3.2 Randomization

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

3.3 Hypothesis Testing

No formal statistical hypothesis testing will be conducted for this study.

3.4 Interim Analysis

There will be no interim analysis conducted.

3.5 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 differences between healthy and hepatic impairment subjects.

3.6 Schedule of Assessments and Study Procedures

Table 1. Schedule of Events

Study activity	Screening		In-Clinic				Follow-up
	D -28 to -1	D0	D1 pre-dose	D1 post-dose	D2	D3	D15 ± 1 day
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 termination[8]							X

Abbreviations: D = day; ECG = electrocardiogram; ICF = informed consent form; I/E = inclusion/exclusion; PD = pharmacodynamic; PK = pharmacokinetic.

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 the 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), 48 h (day 3) postdose and at the follow up visit.
3. 12-lead ECG will be conducted after 5 mins of resting. ECG data will be recorded at screening, on day 1 at predose and at 4 h postdose and day 3, and at the follow up visit and when clinically indicated.
4. A clean sample will 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 the 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 the PK profile of bexagliflozin will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose.
7. Urine for PD will be collected at pre-dose (h -12 to 0), and during the following intervals post-dose 0-12, 12–24, 24–36, and 36–48 h.
8. If early withdrawal occurs, activities scheduled for the follow up visit should be conducted. Reasons for all withdrawals should be recorded on the CRF.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance (QA) procedures for the study data, statistical programming and analyses are described in Everest's Standard Operating Procedures (SOPs). Detailed data management (DM) procedures are documented in the Data Management Plan (DMP), Data Validation Check Specifications, and Data Review Plan. Detailed statistical and programming quality control (QC) and QA procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized, and protocol violations will be identified and decisions for inclusion and exclusion of subjects from the PK and PD Populations will be made prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

Three subject populations will be evaluated during this study and are defined as follows:

5.1 Safety Population

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

5.2 Pharmacokinetic Population

The PK Population will include all subjects who have been dispensed study drug and who have received study drug and provided an observation for ≥1 primary PK endpoints, and without major protocol violations. The PK Population will be used to summarize the PK parameters.

5.3 Pharmacodynamic Population

The PD Population will include all subjects without major protocol violations who have been dispensed study drug and who have received study drug and who have had pre-dose urine collection and at least a postdose 0-12 hr urine sample collected. The PD Population will be used to summarize the PD parameters.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographic and Baseline Characteristics

Demographic variables consist of the following:

- Age in years (continuous) derived as the integer value of (informed consent date – date of birth + 1)/365.25
- Sex
- Race
- Ethnicity

Baseline characteristics consist of the following:

- Body mass index (BMI) (kg m^{-2})
- Weight (kg)

- Smoking status (non-smoker, current smoker, former smoker)
- Height (cm)
- Vital signs (VS)
  - systolic blood pressure (SBP, mmHg)
  - diastolic blood pressure (DBP, mmHg)
  - oral cavity temperature (°C)
  - pulse (beats per minute)
  - respiration rate (breaths/min)
- Electrocardiogram (ECG) parameters
  - RR interval (msec)
  - PR interval (msec)
  - QRS duration/interval (msec)
  - QT interval (msec)
  - QTcB interval (msec) (corrected by Bazett's formula)
- Medical history and baseline conditions
- Clinical laboratory test values
- Prior and concomitant medication
- Physical examination (PE)

6.1.1 Study Day and Visit Window Definitions

Table 4. Time Windows for Safety Assessments

Time Windows for Safety Assessments			
Scheduled Visit Number	**Visit (label)**	**Time Interval (day)**	**Nominal Target Time Point (day)**
1	Screening	-28 to -1	-28 to -1
2	Day 0	0	0
3	Day 1	Day 1 pre-dose	Day 1 pre-dose
3	Day 1	Day 1 post-dose	Day 1, 4 hrs post-dose
4	Day 2	2	2
5	Day 3	3	3
6	Day 15	15 ± 1 day	15

Data obtained during unscheduled visits will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in Table 4. Data will be analyzed based on the nominal visits and nominal time points. If the data from the nominal visit or time point is missing, data from unscheduled visits for the same nominal visit or time point will be used. If multiple unscheduled assessments fall in the same visit window, the latest assessment will be selected for analysis.

If there are multiple unscheduled visits within the interval of 15 ± 1 day the latest unscheduled visit within this window will be used. If there are multiple unscheduled visits outside of the time interval of 15 ±1 day, and there is no visit in the interval 15 ±1 day, the visit closest to the interval of 15 ± 1 will be used.

6.2 Pharmacokinetics/Pharmacodynamics

Pharmacokinetic/pharmacodynamic analysis will be performed on the PK and PD Populations respectively

Plasma samples will be analyzed for bexagliflozin concentrations using a validated method.

Blood samples for PK analysis will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post dose.

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

6.3 Safety

Safety analysis will be performed on the Safety Population.

The safety profile of bexagliflozin will be assessed through the recording, reporting, and analyzing of AEs, clinical evaluations (PE results, VS results, ECG results), and clinical laboratory testing.

Safety variables include the following:

1. AEs
2. Clinical laboratory measurements – serum chemistry, hematology, and urinalysis
3. Urine drug screen
4. VS
5. ECG
6. PE
7. Pregnancy test
8. Concomitant medications/treatments

6.3.1 Study Day and Visit Window Definitions

Refer to Section 6.1.1 for details.

6.3.2 Extent of Exposure to Study Medication

This is a single dose study. Subjects will receive a single dose of 20 mg of bexagliflozin.

6.3.3 Adverse Events (AEs)

Adverse events will be collected and coded using version 21.0 (or newer) of MedDRA. Analysis of AEs will be carried out on the Safety Population. All AEs will be included in the individual subject data listings. Only treatment emergent adverse events (TEAEs) will be tabulated in summary tables. The incidence of TEAEs will be presented by hepatic function group.

If the AE(s) onset date-time or date occurs after the dose of bexagliflozin up until the end of the study, the AE(s) will be assigned to bexagliflozin.

All adverse events will be assessed by the investigator(s) with respect to severity, relationship to study drug and seriousness.

6.3.3.1 Treatment-Emergent AE (TEAE)

An adverse event is considered treatment-emergent if it occurs after treatment with the study drug, and if the date of onset is on or after the date of the dose of study medication, or worsens during the treatment period (intensity/severity grades worsen).

6.3.3.2 Serious Adverse Events (SAE)

AEs will be categorized as serious or non-serious using the definition specified in Section 6.7 of the study protocol.

6.3.3.3 Immediately Reportable AE (IRAE)

An IRAE is any serious adverse event that is reported within 24 hrs of the site being aware of the event.

6.3.3.4 Adverse Events Counting Rules

1. A subject with more than one different AE in a particular system organ class (SOC) will be counted only once in the total of subjects experiencing adverse events in that particular SOC.
2. A subject having experienced the same event (AE preferred term [PT]) more than once during the study will be counted only once in the number of subjects with that event.
3. For a subject who experienced the same event (AE preferred term) more than once during the study with a different severity or seriousness, the AE will be counted only once with the worst grade and seriousness respectively.
4. For a subject who experienced the same event (AE preferred term) more than once during the study with a different causal relationship to the study drug, the AE will be counted only once by considering the most-related documented degree of relationship.

6.3.3.5 AE Severity

Adverse events will be graded on a 3-point scale and reported as indicated on the case report form (CRF). The intensity of an adverse experience will be graded as Grade 1 “Mild”, Grade 2 “Moderate”, and Grade 3 “Severe” using the criteria specified in Section 6.7 of the study protocol.

6.3.3.6 Relationship to the Investigational Medicinal Product

The relationship of an AE to dosing will be assessed as “Definite”, “Probable”, “Possible”, “Not Likely”, or Unrelated using the criteria specified in Section 6.7 of the study protocol.

6.3.3.7 AE with Irregular Start/End Dates or Times

Partial dates or times may be imputed when appropriate. Imputed dates will be used to determine Study Day.

If a partial date and/or time is reported for the start of an AE, a complete date and time will be imputed by the following algorithm:

1. Only the year is reported: If the subject started receiving study drug in the previous year, then January 1 will be used as the starting date of the event. If the subject started receiving study drug in the year reported, then the date of the first dose of study drug will be used as the start date of the event.

2. The month and year is reported: If the subject started receiving study drug prior to the month and year reported, then the first day of the month will be used as the starting date of the event. If the subject started receiving study drug during the month and year reported, then the date of the first dose of study drug will be used as the start date of the event.
3. Time is not reported: If the event date, or imputed date (from rule 1 or 2), is on the same date as study drug start, then time of start of the drug will be used as the start time. For other dates or imputed dates, 12 AM (00:00) will be imputed as the start time.

If a partial date is reported for the end of an AE and the AE is not continuing, a complete date will be imputed by the following algorithm:

1. Only the year is reported: If the subject started receiving study drug in the previous year, then the date of final study contact with the subject will be used as the end of the adverse event. If the subject started receiving study drug in the year reported, then the earlier of December 31 or the date of final study contact with the subject will be used as the end date of the AE.
2. The month and year is reported: The earlier of the last date of the month or the date of final contact with the subject will be used as the end of the AE.
3. Time is not reported: Impute 23:59.

The above rules are subject to logical sense, for example, imputed start date should be on or prior to imputed end date, and end time must equal or exceed start time, if on the same date and end time should equal or exceed start time on the same date.

All AEs will be included in the listings regardless the completeness of the onset dates.

6.3.4 Laboratory Data

Clinical laboratory tests on hematology, serum chemistry, and urinalysis will be performed according to the schedule in Section 3.6. Investigators will assess whether there are any clinically significant abnormalities and record the abnormality on medical history or AE forms.

Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Abnormal Values

Based upon laboratory normal ranges, laboratory test results will be categorized according to the normal range as low, normal and high. Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

Table 3 Clinical Laboratory Tests

Hematology	
Hematocrit (Hct)	Mean corpuscular volume (MCV)
Hemoglobin (Hgb)	Platelet count
Mean corpuscular hemoglobin (MCH)	Red blood cell (RBC) count
Mean corpuscular hemoglobin concentration (MCHC)	White blood cell (WBC) count with differential
International normalized ration (INR)	
Serum Chemistry, Electrolytes, and Lipids	
Albumin (ALB)	Calcium (Ca)
Alanine aminotransferase (ALT)	Magnesium
Aspartate aminotransferase (AST)	Phosphorus
Blood urea nitrogen (BUN)	Potassium (K)
Glucose	Sodium (Na)
Bicarbonate	Total bilirubin
Creatinine	Direct bilirubin
Creatinine kinase	Alkaline Phosphatase (ALP)
Chloride (Cl)	Uric acid
Total protein	Low-density lipoprotein cholesterol (LDL-C), calculated
Total cholesterol (TC)	
High-density lipoprotein cholesterol (HDL-C)	
Triglycerides (TG)	
Urinalysis	
Appearance	Nitrite
Bilirubin	pH
Color	Protein
Glucose	Specific gravity
Ketones	Urobilinogen
Microscopic examination of sediment (performed if protein, leukocyte esterase, nitrite, or blood is positive)	Leukocyte esterase
Occult blood	
Urine Collection	
Glucose	Creatinine
Urine Drug Screen	

Amphetamines	Opiates
Barbiturates	Benzodiazepines
Cocaine Metabolites	Cannabinoids
MDMA	Methamphetamine
TCA	Methadone
PCP	OXY
Alcohol	
Pregnancy Test - Urine	
Infectious Disease Testing (measured at screening only)	
Hepatitis B Surface Antigen (HbsAg)	Hepatitis C virus (HCV)
Human Immunodeficiency Virus antibody (HIV)	

6.3.5 Vital Signs

Vital signs include pulse (beats/min), SBP and DBP (mmHg), oral temperature (°C) and respiration rate (breaths/min).

Vital sign changes from baseline will be summarized by hepatic function group.

Baseline values are those measured at last evaluation prior to administration of study drug.

Change from baseline to time point t, denoted $Change_t$, will be calculated as:

$Change_t = Value_t - Value_{Baseline}$.

6.3.6 Electrocardiogram

ECG parameters, including the RR interval (intra-beat interval), PR interval (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]), QRS interval, QT interval (the corrected QT interval is the measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle), and QTcB interval will be measured according to the study assessment schedule as specified in Section 3.6. Each ECG will be assessed by the Investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave (repolarization of the ventricles) abnormalities. Baseline ECGs will be defined as the last evaluation performed prior to the administration of study drug.

ECG changes from baseline will be summarized by hepatic function group.

Change from baseline to time point t, denoted $Change_t$, will be calculated as:

$Change_t = Value_t - Value_{Baseline}$.

6.3.7 Physical Examination

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

Physical examination results will be presented in individual subject data listings.

6.3.8 Pregnancy Test

Only pregnancies considered by the investigator as related to study treatment (e.g., resulting from an interaction between study drug and a contraceptive medication) are considered AEs unto themselves.

6.3.9 Concomitant Medications/Treatments

Concomitant medications administered during the study will be recorded on the CRF. The medication name, indication, dose, unit, frequency, route of administration, start/stop date(s) and time(s) of administration and reason for administration will be recorded. If the concomitant medication is ongoing this will be documented on the CRF. This documentation should continue until discharge from the study.

A concomitant medication is any medication the subject enters the trial taking and is expected to continue taking for some portion of the trial, as well as any medication other than the investigational product that the subject takes during the course of the trial. All prescription and over-the-counter (OTC) medications (non-prescription drugs), including vitamins and herbal supplements, that subjects receive during the trial must be documented on the CRF. This documentation will continue until the subjects are discharged.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

All prior and concomitant medication will be presented in individual subject data listings.

For medications with incomplete dates or times, imputation will be used to convert to a complete date and time. Imputed dates will be used to determine Study Day.

Partial medication start dates and times will be imputed as follows:

1. Only the year is reported: If the subject started to receive study drug in the year reported, then the date of the first dose of study drug will be used as the starting date of the medication. Otherwise, January 1 will be used as the start date of the medication.
2. The month and year is reported: If the subject started to receive study drug during the month and year reported, then the date of first dose of study drug will be used as the starting date of the medication. Otherwise, the first day of the month will be used as the start date of the medication.
3. Time is not reported: If the medication start date, or imputed date (from rule 1 or 2), is on the same date as study drug start, then time of start of the study drug will be used as the start time. For other dates or imputed dates, 12 AM (00:00) will be imputed as the start time.

Partial medication end dates and times will be imputed for non-ongoing medications as follows:

1. Only the year is reported: If the subject stopped to receive study drug in the year reported, then the date of the last dose of study drug will be used as the end date of the medication. Otherwise, December 31 will be used as the end of the medication.
2. The month and year is reported: If the subject stopped to receive study drug during the month and year reported, then the date of last dose of study drug will be used as the end date of the medication. Otherwise, the last day of the month will be used as the end of the medication.
3. Time is not reported: Impute 23:59.

The above rules are subject to logical sense, for example, imputed start date should be on or prior to imputed end date.

Verbatim terms will be coded and assigned a preferred (PT) term and an ATC (anatomic therapeutic class) term.

7. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

7.1 General Considerations

The PK Population will be used for PK analyses. The PD Population will be used for PD analyses.

Statistical, PK, and PD analyses will be performed by Everest Clinical Research. Statistical analysis will be performed using Statistical Analysis Software SAS for Windows® (SAS Institute Inc., USA). Non-compartmental analysis (NCA) will be performed using Phoenix® WinNonlin® 6.4 (Certara, USA) or later.

7.2 Pharmacokinetic Analyses

From the plasma concentration-time data, the following PK parameters will be estimated for each subject where feasible.

Table 7. Pharmacokinetic Parameters

Pharmacokinetic Parameters	
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 post-dose
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to time t (time of last quantifiable plasma concentration)
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{extr}	The proportion of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity, expressed as a %
C_{maxu}	Maximum unbound plasma concentration
$AUC_{u\ (0-t)}$	Area under the unbound plasma concentration-time curve from time 0 to time t
$AUC_{u\ (0-\infty)}$	Area under the unbound plasma concentration-time curve from time 0 to infinity
Cl_u/F	Apparent clearance relative to the unbound drug concentration

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

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

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

$AUC_{0-\infty} = AUC_{last} + (C_{last} / \lambda_z)$, 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% and will be excluded from summary tables but will be listed.

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 $0.693/\lambda_z$.

The fraction unbound (f_u) will be calculated as free drug concentration/total drug concentration.

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

Listings of plasma concentrations by Subject Number, hepatic function group, and timepoint will also be provided.

To assess the effect of moderate hepatic impairment on the PK of bexagliflozin, an analyses of variance (ANOVA) with a fixed effect corresponding to the hepatic function group (normal or moderate hepatic impairment) will be fitted to the natural logarithmic transformation of PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The 90% confidence intervals will be constructed for the ratio of least squares (LS) geometric means of PK parameters (total and unbound C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) for the moderate hepatic function group vs the normal group, with 80-125% defined as the boundaries for subjects in the PK Population.

The ratios of geometric least squares means and corresponding 90% confidence interval (CI) for the treatment comparison will be determined by exponentiating the mean differences between treatments on the logarithm scale.

The appropriateness of the mixed model will be assessed through residual analyses. Any modifications required due to poor fit will be reported and executed.

Refer to Appendix 2 for the SAS code.

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

A listing of bexagliflozin concentration-time data by Subject Number, hepatic function group and timepoint will be provided.

The PK parameters C_{max}, t_{max}, λ_z, $t_{1/2}$, CL/F, V_z/F, AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, AUC_{extr}, $AUC_{u\,(0-t)}$, $AUC_{u\,(0-\infty)}$, C_{maxu}, and Cl_u/F will be summarized by hepatic function group for bexagliflozin.

Descriptive statistics of total and unbound PK parameters will be summarized by hepatic function group for the PK Population.

Means, standard deviation (SD), 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}.

A listing of derived PK parameters of bexagliflozin for total and unbound bexagliflozin by Subject Number and hepatic function group will be provided.

Descriptive statistics for urinary glucose concentrations, urinary glucose excretion (UGE), urinary creatinine concentrations, and urinary glucose/creatinine by hepatic function group and collection interval will be summarized for the PD Population. Because concentration values that were below the limit of quantitation (BLOQ) prior to T_{max} will be set to zero, which cannot be included in calculation of a geometric mean, then geometric means and percent CV calculated for data including BLOQ values will be based only on the subjects with non-BLOQ data

A listing of urinary PD parameters will be provided by Subject Number, hepatic function group and collection interval.

Plasma protein bound and unbound bexagliflozin will be determined by an equilibrium dialysis method. The bexagliflozin unbound fraction will be calculated for each subject by dividing the bexagliflozin concentration in the dialysate by the bexagliflozin concentration in plasma. The unbound fraction from the plasma sample at the maximum plasma concentration will be used to calculate the unbound plasma concentration at each time point prior to 24 hrs for each individual subject. The unbound fraction from the plasma sample at 24 hrs postdose will be used to calculate the unbound plasma concentration at each time point at or after 24 hrs postdose for each subject. If the unbound fraction at 24 hrs is not available, the unbound fraction at the maximum plasma concentration will be used to calculate the unbound plasma concentration at all time points.

7.3 Pharmacodynamic Analyses

Urinary glucose excretion (UGE) and creatinine normalized UGE (nUGE) will be determined as PD parameters at baseline and up to 48 hours post-dose.

$UGE_{t1\text{-}t2}$ (g) will be derived from urine volume and glucose concentration as follows:

[urine volume ($V_{t1\text{-}t2}$, mL) x glucose concentration (mg/dL)/100]/1000.

UGE normalized by urinary creatinine will be calculated as per below:

[urine volume ($V_{t1\text{-}t2}$, mL) x creatinine concentration (mg/dL)/100]/1000.

The total 24-hour and 48-hour quantity of glucose excreted in urine will be calculated by adding the amounts collected during each post-dose interval.

Descriptive statistics will be used to describe any differences in these PD parameters between treatment groups (normal hepatic function and moderate hepatic impairment).

For PD data, reported pre-dose values that are below the defined limit will be set to zero. Any missing values or values below the reported defined limit that appear after pre-dose for PD data (glucose, UGE, creatinine) will be set to missing. Because zero values cannot be included in calculation of a geometric mean, then geometric means and percent CV calculated for data including values below the defined limit will be based only on the subjects without such zero value data

PD data will also be reported in listings.

8. STATISTICAL ANALYSIS

8.1 General Data Handling Rules and Definitions

All data collected on CRFs will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any treated subject is found to be without valid documented informed consent, that subject's data will be excluded from the report, except as necessary to document the error.

All statistical analyses will be conducted using SAS version 9.4 or newer.

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by treatment and hepatic function group. Unless otherwise specified, the mean and median will be displayed to 1 more decimal place than the original data, and standard deviation will be displayed to two more decimal places than the original data. All frequencies will be rounded to 1 decimal place.

Missing data will be maintained as missing unless specified otherwise. For variables where missing data is imputed, the analysis dataset will contain one variable with the imputed value and the original variable with missing maintained as missing.

8.2 Subject Disposition

An overall disposition table for all subjects will be presented. This tabulation will include the number of subjects treated, completed, and those who withdraw study participation early. The number and percentage of subjects who are included in the PK, Safety and PD Populations will also be tabulated.

Subject disposition by site and hepatic function group will also be summarized for the Safety Population. These tabulations will include the number of subjects dosed, completed, and those who withdraw study participation early along with the corresponding primary reasons for early withdrawal.

Subjects in the Safety Population who prematurely discontinued from the study will be summarized by primary reason for early withdrawal.

Subject disposition will be listed for all subjects in the Safety Population.

8.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by site and by hepatic function group for both the Safety and PK Populations and listed for the Safety Population.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables. Frequency distributions (counts and percentages) will be presented for categorical variables.

Medical history and baseline conditions will be summarized by hepatic function group and for all subjects and listed for the Safety Population. Physical examination, as well as prior and concomitant medications, will also be listed. Prior and concomitant medications will be listed with the drug names and ATC classification codes based on the data collected in the electronic CRF. The World Health Organization Drug Dictionary (WHO-DD), version March 2018 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name and hepatic impairment history.

Abnormalities in the subjects' medical and surgical histories will be coded using version 21.0 (or newer) of MedDRA Medical Dictionary for Regulatory Activities, and summarized and listed.

8.4 Safety Analyses

Safety analyses will be performed using the Safety Population, unless otherwise specified.

Safety measurements will include AEs, clinical laboratory tests (i.e. serum chemistry, hematology and urinalysis), ECGs, physical exams and vital signs. All safety data will be summarized by hepatic function group. Baseline values for clinical laboratory tests, vital signs and ECGs will be defined as the last evaluation performed prior to administration of study drug.

8.4.1 Adverse Events

All AEs will be coded to system organ class (SOC), and preferred term (PT), using the latest Medical Dictionary for Regulatory Activities coding dictionary (version to be specified in the clinical study report). All reported AEs will be listed, but only TEAEs will be summarized.

The incidence of all TEAEs will be summarized by hepatic function group. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (definite > probable > possible > not likely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (e.g., considered treatment related [TR]). Summary tables will be organized by SOC, then PT.

The following summaries will be presented for TEAEs for each hepatic function group and for all subjects for selective summaries for the Safety Population.

- Overall Summary of TEAEs by hepatic function group
- Incidence of TEAEs by hepatic function group, system organ class, and preferred term
- Incidence of Treatment Emergent Serious Adverse Events by hepatic function group, system organ class, and preferred term

Subjects who prematurely withdraw due to TEAEs and subjects with serious TEAEs will be listed for the Safety Population.

8.4.2 Laboratory Data

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will be summarized for subjects in the Safety Population. Summaries for change from baseline for hematology, chemistry, and urinalysis parameters will include descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) for values and change from baseline values for all continuous variables, and frequency counts and percentages for categorical variables, by treatment. Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

8.4.3 Vital Signs (VS)

Summary tables for VS data will include descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) for values and change from baseline values by hepatic function group.

A listing of VS results will be provided for all subjects in the Safety Population.

8.4.4 Electrocardiogram (ECG)

ECG parameters (RR interval, PR interval, QRS interval, QT interval, and QTcB interval) will be summarized by changes from baseline values by hepatic function group using descriptive statistics. For each parameter, only subjects who had both baseline and a post-baseline assessment will be included in the summary.

A listing of ECG results will be provided for all subjects in the Safety Population.

8.4.5 Physical examinations (PE)

Physical examination results will be presented in individual subject data listings.

8.4.6 Pregnancy Test

Pregnancy test results prior to treatment will be listed.

8.4.7 Protocol Deviations

All protocol deviations will be listed.

9. ANALYSES PERFORMED BEFORE DATABASE CLOSURE

No interim analyses are planned for this study.

10. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

Any changes to methods planned in this SAP will be documented in a revision to this statistical plan prior to database lock, or identified in the clinical study report.

11. STATISTICAL SOFTWARE

The statistical software to be used for generation of the tables, listings, and figures is SAS® version 9.4.

12. REFERENCES

Not Applicable.

13. APPENDIX 1 DATA HANDLING RULES

Category	Description	Data Handling Rules
Demographics	Age at informed consent	*Age = integer ([date of informed consent signed – date of birth + 1]/365.25)* *If in date of birth, only day is missing, it is imputed by 15th of the month of birth; both day and month are missing, it is imputed by July 1st of the year of birth.*
Baseline		*Baseline was defined as the last assessment made before the dose of the investigational product.*
Vital Signs/ECG/Lab	Change from baseline	$Change_t = Value_t - Value_{Baseline}$
PD	Data below the defined limit; Missing data	*For PD data, reported pre-dose values that are below the defined limit will be set to zero. Any missing values or values below the reported defined limit that appear after pre-dose for PD data (glucose, UGE, creatinine) will be set to missing.*
PK	Missing data	*For PK data, all missing values will be treated as missing in the PK analysis and excluded from analysis except when they occur at pre-dose where they will be set to zero. All values that were below the limit of quantitation (BLOQ) prior to T_{max} will be set to zero. BLOQ values that occur after T_{max} will be set to missing. When ≥ 2 consecutive plasma concentrations that are BLOQ are encountered after T_{max}, these and all subsequent values will be excluded from the analysis.*

14. APPENDIX 2 SAS CODE FOR STATISTICAL ANALYSES

This section will be completed after examining the existing data and prior to the final signoff of this SAP.

Test	Table/Figure	SAS Codes for Modeling
ANOVA using a linear mixed-effects model.	PK endpoints requiring ANOVA.	**Analysis using PROC MIXED in SAS with SUBJ as a random effect and HEPATIC FUNCTION GROUP as a fixed effect. "Y" denotes the response measure (log (AUC), log (CMAX)). "KR" denotes Kenward-Roger method. "CL" denotes confidence limits.** PROC MIXED METHOD=REML; CLASS SUBJ TRTP; MODEL Y = TRTP/ DDFM=KR; LSMEANS TRTP/ PDIFF CL ALPHA = 0.10; ESTIMATE 'T/R' TREAT -1 1/CL ALPHA = 0.1; RUN; **Anti-log transformation to obtain the geometric means. "GEO" denotes geometric and "LS" denotes least square.** DATA LSMEANS; SET LSMEAN; GEOLSMEAN = EXP(ESTIMATE); RUN; **Anti-log transformation to obtain the ratio of geometric means (point estimate) and 90% confidence interval (CI) – lower and upper bounds.** DATA DIFFS; SET ESTIMATE; RATIO = EXP(ESTIMATE)*100; LOWER = EXP(LOWER)*100; UPPER = EXP(UPPER) * 100; RUN;

15. APPENDIX 3 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)	<2	2 to 3	>3
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) 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 cps 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

16. APPENDIX 4 MOCKUP TABLES, LISTINGS, AND FIGURES (TLFS)

Mockup tables, listings, and figures are presented in a separate document.