STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Theracos Sub, LLC.
Protocol Number:	THR-1442-C-481
IND Number:	103822
Investigational Drug:	Bexagliflozin Tablets
Indication:	Type 2 Diabetes Mellitus
Drug Number:	
Dosage Form/Strength:	Tablets/20 mg

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

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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

* Provide person's initial and last name.
** 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
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
$AUC_{0-\infty}$	area under the plasma concentration-time curve from Time 0 to infinity
AUC_{0-t}	area under the plasma concentration-time curve from Time 0 to Time t
BLOQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Ca	calcium
Cl	creatinine chloride
C_{last}	concentration corresponding to T_{last}
CL/F	apparent oral clearance
cm	centimeter
C_{max}	maximum observed plasma concentration
CRF	case report form
CV	coefficient of variation
DBP	diastolic blood pressure
dL	deciliter
DM	data management
ECG	electrocardiogram

Abbreviation	Term
FDA	Food and Drug Administration
FPG	fasting plasma glucose
h	hour(s)
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
Hct	hematocrit
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
Hgb	hemoglobin
ICF	informed consent form
IRAE	immediately reportable adverse event
K	potassium
kg	kilogram
KR	Kenward-Roger
L	liter
λ_z	terminal elimination phase rate constant
LDL-C	low density lipoprotein cholesterol
LLN	lower limit of normal
LS	Least square
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute

Abbreviation	Term
mL	milliliter
msec	millisecond
Na	sodium
NCA	non compartmental analysis
OTC	over the counter
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).
PT	preferred term
QA	quality assurance
QC	quality control
QRS	The combination of three of the graphical deflections seen on a typical electrocardiogram.
RBC	red blood cell (count)
REML	restricted maximum likelihood
RR interval	intra-beat interval
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$T_{½}$	apparent terminal elimination half-life

Abbreviation	Term
TC	total cholesterol
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
T-wave	Repolarization of the ventricles
UGE	urinary glucose excretion
ULN	upper limit of normal (value)
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 THR-1442-C-481 version 2 dated 20-May 2016. 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 final version of the protocol mentioned above and the final version of the annotated CRFs dated 30-Jun-2016.

The SAP 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 9.3. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA version 19.0 or newer).

This is a single center, phase 1, open-label, 2 × 2 crossover study designed to assess the effects of a high-fat meal on the pharmacokinetics (PK) of orally administered bexagliflozin tablets. Approximately 18 eligible healthy subjects are planned to be randomized into two treatment groups such that an equal number (n = 9) of subjects will receive a single oral dose of 20 mg of bexagliflozin with or without a meal on treatment day 1. Subjects randomized to receive bexagliflozin with a high-fat meal on day 1 will receive a second dose of bexagliflozin without a meal on treatment day 8 after an overnight fast. Subjects randomized to receive bexagliflozin without a meal on treatment day 1 after an overnight fast will receive a second dose of bexagliflozin with a high-fat meal on treatment day 8.

(See Protocol Sections 3.1 to 3.3 for details).

2. STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

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

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

3. STUDY DESIGN

3.1 Study Design

This single center, phase 1, open-label, 2 × 2 crossover study is designed to assess the effects of a high-fat meal on the PK of orally administered bexagliflozin tablets. Eighteen (18) eligible healthy subjects will be randomized into two treatment groups such that an equal number (n = 9) of subjects will receive a single oral dose of 20 mg of bexagliflozin with or without a meal on treatment day 1. Subjects randomized to receive bexagliflozin tablets with a high-fat meal on day 1 will receive a second dose of bexagliflozin tablets without a meal on treatment day 8 after an overnight fast. Subjects randomized to receive bexagliflozin tablets without a meal on treatment day 1 after an overnight fast will receive a second dose of bexagliflozin tablets with a high-fat meal on treatment day 8.

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

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

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

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

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

Urine collection in 12 h batches will be performed at pre-dose (-12 to 0 h on day 1 and day 8), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

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

3.2 Randomization

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

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

For this Phase 1 food effect study, a sample size of 18 subjects is considered sufficient. The sample size for this study is not based upon formal statistical consideration. The sample size is considered adequate to characterize the PK of bexagliflozin, to assess potential food-drug interactions, and to provide safety and tolerability data on bexagliflozin when administered with food.

3.6 Schedule of Assessments and Study Procedures

Table 1. Schedule of Events

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

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

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

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, 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 Population 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 randomized subjects who receive at least one dose of the drug. Subjects will be analyzed according to the treatment received.

5.2 Pharmacokinetic Population

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

5.3 Pharmacodynamic Population

The PD Population will include all randomized subjects who have PD parameter data available in both treatment periods. 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:

- Weight (kg)
- Height (cm)
- Vital signs

- systolic blood pressure (SBP, mmHg)
- diastolic blood pressure (DBP, mmHg)
- oral temperature (^{o}C)
- pulse (beats per minute)
- respiration rate

- Electrocardiogram (ECG) parameters
  - RR interval (msec)
  - PR interval (msec)
  - QRS duration (msec)
  - QT interval (msec)
- Medical and surgical history
- Clinical laboratory tests
- Prior and concomitant medication
- Physical examination

6.1.1 Study Day and Visit Window Definitions

Table 2. Time Windows for Safety Assessments

Time Windows for Safety Assessments			
Scheduled Visit Number	**Visit (label)**	**Time Interval (day)**	**Target Time Point (day)**
1	Screening	-28 to -1	-28 to -1
2	Day 1	1	1
3	Day 2	2	2
4	Day 3	3-6	3
5	Day 7	7	7
6	Day 8	8	8
7	Day 9	9	9
8	Day 10	10	10

Data obtained during unscheduled visits will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in Section 6.1.1. Safety data obtained during unscheduled time points will be allocated to the scheduled time point corresponding to the time window in which they fall. 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 or time point, the non-missing assessment closest to target time point will be selected for analysis.

6.2 Pharmacokinetics/Pharmacodynamics

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

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

Blood samples for bexagliflozin plasma concentrations will be collected in each period at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post dose.

Urine samples will be collected in 12 hr intervals to evaluate the mean UGE.

Urine collection in 12 h batches will be performed at pre-dose (-12 to 0 h on Day 1 and Day 8), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h in each treatment period.

6.3 Safety

Safety analysis will be performed on the Safety Population.

The safety profile of bexagliflozin under fasting and fed (high-fat, high-calorie) conditions will be assessed through the recording, reporting, and analyzing of adverse events, clinical evaluations, and laboratory tests.

Safety variables include the following:

1. Adverse events
2. Clinical laboratory measurements – serum chemistry, hematology, and urinalysis
3. Vital signs
4. ECG
5. Physical examination
6. Pregnancy test
7. 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

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

6.3.3 Adverse Events (AEs)

Adverse events will be collected and coded using version 19.0 (or newer) of MedDRA. Analysis of adverse events will be carried out on the Safety Population. All adverse events 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 treatment. If the AE(s) onset date-time or date occurs after the first dose up until right before the next dose, the AE(s) will be assigned to the first treatment. Any AE(s) that occur after the second dose up until study termination will be assigned to the second treatment.

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

If an AE becomes serious during the course of the study, the initial AE will be reported with an end date equal to the start date of the serious adverse event (SAE) and outcome ‘did not resolve’. The SAE start date will be the date the AE became serious.

6.3.3.1 Treatment-Emergent AE (TEAE)

An adverse event is considered treatment-emergent if the date of onset is on or after the date of first 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 6.9 of the study protocol.

6.3.3.3 Immediately Reportable AE (IRAE)

Any serious adverse event or any adverse event that necessitates discontinuation of the study drug.

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) more than once during the study will be counted only once in the number of subjects with that event.
3. A subject having experienced the same event (AE preferred term) more than once during the study with a different severity or seriousness, it will be counted only once with the worst grade and seriousness respectively.
4. A subject having experienced the same event (AE preferred term) more than once during the study with a different causal relationship to the study drug, it 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 CRF. The intensity of an adverse experience will be graded as “Mild”, “Moderate”, and “Severe” using the criteria specified in Section 6.9 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 6.9 of the study protocol.

6.3.3.7 AE with Irregular Start/End Dates

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

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

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

If a partial date is reported for the end of an adverse event and the adverse event 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 medication 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 of the adverse event.
2. The month and year 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.

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

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

6.3.4 Laboratory Data

Clinical laboratory tests on hematology, serum chemistry and electrolytes, serum lipids, 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 4 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
Serum Chemistry and Electrolytes	
Albumin (ALB)	Calcium (Ca)
Alanine aminotransferase (ALT)	Magnesium
Aspartate aminotransferase (AST)	Phosphorus
Blood urea nitrogen (BUN)	Potassium (K)
Glucose	Sodium (Na)
Bicarbonate (HCO_3)	Total bilirubin
Creatinine Chloride (Cl)	Direct bilirubin
Total protein	Uric acid
Serum lipids	
Total cholesterol (TC)	Low-density lipoprotein cholesterol (LDL-C), calculated
High-density lipoprotein cholesterol (HDL-C)	
Triglycerides (TG)	
Urinalysis	
Appearance	Nitrite
Bilirubin	Occult blood
Colour	pH
Glucose	Protein
Ketones	Specific gravity
Microscopic examination of sediment	Urobilinogen
	Leukocyte esterase
Urine Collection	
Glucose	Potassium
Creatinine	Calcium
Sodium	Uric acid

6.3.5 Vital Signs

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

Vital sign changes from baseline will be summarized by treatment.

Baseline values are those measured at last evaluation prior to administration of study drug in each treatment period.

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 duration, and 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), 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 in each treatment period.

ECG changes from baseline will be summarized by treatment.

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. However, all pregnancies with an estimated conception date during the AE reporting period, must be recorded in the AE section of the eCRF. This applies to both pregnancies in female subjects and in female partners of male subjects.

6.3.9 Concomitant Medications/Treatments

Concomitant medications administered at the time of randomization and during the study will be recorded on the case report form (CRF). The medication name, indication, dose, unit, frequency, route of administration, date(s) of administration and reason for administration will be recorded. 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 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). A by-subject listing of concomitant medications will include all medications taken during the study.

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

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

Partial medication start dates 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 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 of the medication.

Partial medication end dates 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.

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 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 and PK 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).

7.2 Pharmacokinetic Analyses

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

Table 3. 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-t}	Area under the plasma concentration-time curve from time 0 to time t (time of last quantifiable plasma concentration)
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity

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

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

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

$AUC_{0-\infty}$ will be calculated 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%.

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 $0.693/\lambda_z$.

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

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

The ratios of geometric least squares means and corresponding 90% CI for the treatment comparison will be determined by exponentiating the mean differences between treatments on the logarithm scale. The intra-subject geometric CV%, $100\%*\sqrt{\exp(residual)-1}$, where residual = the residual variance component and where exp is the natural exponential function, will be reported.

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

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

A listing of derived PK parameters of bexagliflozin by Subject Number and Treatment Period will be provided.

Refer to Appendix 2 for the SAS code.

7.3 Pharmacodynamic Analyses

Descriptive statistics of glucose concentrations and UGE will be summarized by Treatment and Timepoint.

The quantity of glucose excreted in urine will be determined by multiplying the urine glucose concentration for each time interval by the volume of urine collected for the corresponding collection interval. The total 24-hour and 48-hour quantity of glucose excreted in urine will be calculated by adding the amounts collected during each interval.

PD data will also be reported in listings.

The effect of a high-fat meal will be evaluated by comparing the mean cumulative UGE between subjects under fasted and fed (high-fat, high-calorie conditions). Potential effects on urinary creatinine, uric acid, sodium, potassium, and calcium will also be analyzed.

8. STATISTICAL ANALYSIS

8.1 General Data Handling Rules and Definitions

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any randomized patient 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 9.3 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. 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 randomized, treated, not treated, completed, and those who discontinued early from the study along with the corresponding primary reasons for early termination. The number and percentage of randomized subjects who are included in the PK, Safety and PD Populations will also be tabulated.

Subject disposition by treatment and treatment sequence will also be summarized.

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

All subjects in the Safety Population will be listed.

8.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment and treatment sequence and listed.

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 and surgical history, physical examination, as well as prior and concomitant medications will be listed. Prior and concomitant medications will be listed with the drug names and ATC classification codes based on the data collected in the eCRF. The World Health Organization (WHO) Drug Dictionary, version March 2016 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Abnormalities in the subjects' medical and surgical histories will be coded using version 19.0 (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 treatment. 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 treatment. 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 related). Summary tables will be organized by SOC, then PT.

The following summaries will be presented for TEAEs:

- Overall Summary of TEAEs by Treatment
- Incidence of TEAEs by Treatment, System Organ Class and Preferred Term
- Incidence of Treatment Emergent Serious Adverse Events by Treatment, System Organ Class and Preferred Term

Subjects who prematurely discontinued due to TEAEs and subjects with serious TEAEs will be listed.

8.4.2 Laboratory Data

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will be summarized for each treatment. 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

Summary tables for vital signs 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 treatment.

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

8.4.4 Electrocardiogram (ECG)

ECG parameters (RR interval, PR interval, QRS duration and QT interval) will be summarized by changes from baseline values by treatment 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

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.

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 statistical analysis plan 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 9.3.

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	$Change_t = Value_t - Value_{Baseline}$

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 SEQ, SUBJ, PERIOD, and TRTP identifying SEQUENCE, SUBJECT, PERIOD and TREATMENT variables. "Y" denotes the response measure (log (AUC), log (CMAX)). "KR" denotes Kenward-Roger method. "CL" denotes confidence limits.** PROC MIXED METHOD=REML; CLASS SUBJ SEQ PERIOD TRTP; MODEL Y = SEQ PERIOD TRTP/ DDFM=KR; RANDOM SUBJ(SEQ); 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 REFERENCE RANGES AND CLINICALLY RELEVANT CHANGES FROM BASELINE FOR MARKED LABORATORY ABNORMALITIES

<To be inserted>

16. APPENDIX 4 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGs)

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