STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Theracos Sub, LLC.
Protocol Number:	THR-1442-C-458
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, Randomized, Two-Period, Two-treatment, Crossover Study to Evaluate the Effect of Exenatide on the Pharmacokinetics and Pharmacodynamics of Bexagliflozin in Healthy Subjects

Last Revision Date: 26-Jul-2017

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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.

TABLE OF CONTENTS

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	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
DDI	drug-drug interaction
dL	deciliter
DM	data management

Abbreviation	Term
ECG	electrocardiogram
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
NTR	not treatment related, includes unrelated
OHA	oral hypoglycemic agent
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.
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

Abbreviation	Term
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
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
T-wave	repolarization of the ventricles
UGE	urine 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 version 1.0 dated 19-Apr-2017. 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 12-JUN-2017.

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 9.4. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA version 20.0 or newer).

This is a phase 1, single-center, open-label, randomized, two-period, two-treatment crossover study to assess the effects of exenatide injection on the pharmacokinetics (PK) and pharmacodynamics (PD) of bexagliflozin in healthy subjects. A total of 20 eligible healthy subjects will be enrolled and assigned to one of the two groups, with up to 10 subjects per group. Each group will receive both the treatments alternatively, in a crossover fashion (two-period, two-treatment crossover design) with the two treatment periods separated by a 7-day washout period.

In Treatment Period 1, subjects in Group 1 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast, and subjects in Group 2 will receive a subcutaneous injection dose of exenatide at 10 µg twice a day (bid) with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by a second dosing of exenatide alone 1 h prior to evening meals. In Treatment Period 2, subjects in Group 1 will receive a subcutaneous injection dose of exenatide at 10 µg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 hr before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals and subjects in Group 2 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast.

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

2. STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

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

3. STUDY DESIGN

3.1 Study Design

This single center, phase 1, open-label, 2 x 2 crossover study is designed to assess the effects of exenatide injection on the PK and PD of orally administered bexagliflozin tablets. Approximately 20 eligible healthy subjects will be randomly assigned to one of the two groups (1 or 2) with up to 10 subjects per group. Each group will receive both the treatments alternately, in a crossover fashion (two-period, two-treatment crossover design), with the two treatment periods separated by a 7-day washout period. In Treatment Period 1, subjects in Group 1 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast, and subjects in Group 2 will receive subcutaneous injection dose of exenatide at 10 µg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by the second dosing of exenatide alone 1 h prior to evening meals. In Treatment Period 2, subjects in Group 1 will receive subcutaneous injection dose of exenatide at 10 µg bid with initial dosing 30 min prior to a single oral dose of bexagliflozin tablets, 20 mg, and 1 h before breakfast and followed by a second dosing of exenatide alone 1 h prior to evening meals and subjects in Group 2 will receive a single oral dose of bexagliflozin tablets, 20 mg, alone 30 min before breakfast.

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

In treatment period 1, subjects will be admitted to the clinic on day 0, the day before dosing, and will stay in the clinic until 48 h post dose. In treatment period 2, subjects will be admitted to the clinic on day 7, the day before dosing, and will stay in the clinic until 48 h post-dose. Blood samples for bexagliflozin plasma concentrations will be collected in each period at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose of bexagliflozin.

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

3.2 Randomization

A total of 20 healthy subjects will be enrolled and randomly assigned to group 1 or group 2 in a 1:1 ratio. Subjects who discontinue the study after randomization for non-safety related reasons may be replaced to ensure that the number of evaluable subjects in each group is not 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

The sample size for this study is not based upon formal statistical consideration. The sample size is considered adequate to characterize the PK of bexagliflozin, to assess potential drug-drug interactions, and to provide safety and tolerability data on bexagliflozin when administered with exenatide.

3.6 Schedule of Assessments and Study Procedures

Table 1. Schedule of Events

	Screening	Period 1					Period 2				
Study activity	**D -21 to -1**	**D 0**	**D1 pre-dose**	**D1 post-dose**	**D 2**	**D3**	**D7**	**D8 pre-dose**	**D8 post-dose**	**D 9**	**D10**
Medical history and ICF	X										
Screening for I/E criteria	X	X					X				
Physical exam[1]	X	X				X	X				X
Demographics	X										
Randomization		X									
Admission and discharge		X				X	X				X
Vital signs[2]	X	X	X	X		X	X	X	X		X
ECG[3]	X	X	X	X			X	X	X		X
Urinalysis[4]	X	X				X	X				X
Blood draw for clinical lab tests[5]	X	X				X	X				X
Blood sample for PK[6]			X	X	X	X		X	X	X	X
Urine collection[7]		X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X	X					X				
Adverse event and concomitant medication		X	X	X	X	X	X	X	X	X	X
Study termination											X

Abbreviations: D = day; ECG = electrocardiogram; 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 day10 prior to discharge. A partial PE will be performed on days 0, 3 and 7.
2. Vital signs include: pulse, body temperature, respiratory rate, systolic and diastolic blood pressure. Vital signs will be recorded at screening, on days 0, 1 (predose, 4 h postdose), 3 (48 h postdose), 7, 8 (predose, 4 h postdose), and 10 (48 h postdose), and when clinically indicated.
3. 12-lead ECG will be conducted after 10 min resting. ECG data will be recorded at screening, on days 0, 1 (predose, 4 h postdose), 7, 8 (predose, 4 h postdose), and 10 (48 h postdose), and when clinically indicated.
4. Urine samples will be collected at screening, on days 0, 7 and prior to discharge in each period. If urine is dipstick positive for leukocyte esterase or nitrites, sample is to be sent for microscopic evaluation and culture. Urine drug screen will be performed on screening visit and on day 7. If drug screening is conducted more than 5 days prior to dosing, screening shall be repeated.
5. Blood sample at the designated visits (screening, on days 0, 3, 7 and 10 for clinical chemistry and hematology parameters are listed in Table 2. Blood will be drawn after 10 h of fasting prior to breakfast (i.e. only water is allowed, no caloric intake).
6. Plasma samples for PK profile of bexagliflozin will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post-dose.
7. Urine for urinary glucose (PD) and creatinine will be collected at pre-dose (h -12 to 0), and at post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 48 h.

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 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 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. Subjects will be analyzed according to the treatment received.

5.3 Pharmacodynamic Population

The PD Population will include all randomized subjects who receive study drug and have had 0-12 hr and 12 to 24 hr urine collection from which to calculate 24-hour UGE following dosing. The PD Population will be used to summarize the PD parameters. Subjects will be analyzed according to the treatment received.

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)

- 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)
  - QTcF interval (msec)
- Medical history and baseline conditions
- 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	-21 to -1	-21 to -1
2	Day 0	0	0
3	Day 1	1	1
4	Day 2	2	2
5	Day 3	3-5	3
6	Day 7	7	7
7	Day 8	8	8
8	Day 9	9	9
9	Day 10	10-12	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 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 in each period at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h post dose.

Urine samples for PD analysis will be collected in 12 hr intervals.

Urine collection in 12 h batches will be performed at pre-dose (-12 to 0 h), and post-dose at 0 to 12 h, 12 to 24 h, 24 to 36 h, and 36 to 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 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. Urine drug screen
4. Vital signs
5. ECG
6. Physical examination
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

Subjects who gave consent to participate in the study will be randomly assigned to 1 of the 2 groups. Subjects in each group will be randomly assigned to receive 1 of 2 treatment regimens in a crossover fashion with 2 treatment periods separated by a washout period of at least 7 days. Refer to Table 1 under Section 3.6.

In order to observe the maximal potential effect of exenatide on the absorption rate of bexagliflozin, bexagliflozin will be administered orally 30 min after subcutaneous exenatide injection, at 10 µg bid (the highest dose approved for use in the United States), meanwhile, the highest dose used (10 µg bid exenatide

injection in the United States) or intended to be used (20 mg bexagliflozin tablets) clinically will be selected.

6.3.3 Adverse Events (AEs)

Adverse events will be collected and coded using version 20.0 (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 second dose, the AE(s) will be assigned to the first treatment. If the AE(s) onset date-time or date occurs after the second dose, the AE(s) 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.

6.3.3.1 Treatment-Emergent AE (TEAE)

An adverse event is considered treatment-emergent if it occurs after bexagliflozin and/or exenatide administration and 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)

An IRAE is 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 case report form (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 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.

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 listings regardless the completeness of the onset dates.

6.3.4 Laboratory Data

Clinical laboratory tests on hematology, serum chemistry, electrolytes, and lipids 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
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)
Total carbon dioxide	Total bilirubin
Creatinine	Direct bilirubin
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	Leukocyte esterase
Occult blood	
Urine Collection	
Glucose	Creatinine
Urine Drug Screen	

Amphetamines	Opiates
Barbiturates	Benzodiazepines
Cocaine Metabolites	Cannabinoids
Cotinine	
Pregnancy Test	
Infectious Disease Testing	
Hepatitis B Surface Antigen (HbsAg)	Hepatitis C virus (HCV)
HIV	

6.3.5 Vital Signs

Vital signs include pulse (beats/min), SBP and DBP (mmHg), oral temperature (^{o}C) 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.

6.3.9 Concomitant Medications/Treatments

Concomitant medications administered at the time of randomization and during the study will be recorded on the 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 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, 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 (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 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 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-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% 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/λ_z.

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

To assess the effect of co-administration of exenatide 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 ratio of the least squares (LS) geometric means of PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), when bexagliflozin is dosed in combination with exenatide versus when dosed alone, with 80-125% defined as the lack of interaction boundaries.

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 by Subject Number, Treatment Period, and Treatment will be provided.

Refer to Appendix 2 for the SAS code.

7.3 Pharmacodynamic Analyses

Urinary glucose excretion will be determined as a PD parameter at baseline and up to 48 hours.

Descriptive statistics of glucose concentrations, creatinine concentrations, UGE, and urinary glucose/urinary creatinine 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 PD parameters, UGE and UGE normalized by urinary creatinine, including UGE_{t1-t2}, in 12 hour and 24 hour increments, and total 24-hour and 48-hour UGE, will be determined. UGE_{t1-t2} (g) will be derived from urine volume (V_{t1-t2}, mL) x glucose concentration (mg/dL)/100/1000.

UGE normalized by urinary creatinine will be derived by dividing the UGE for each interval by the corresponding urinary creatinine concentration.

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 randomized 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 treatment 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 randomized, treated, completed, and those who discontinued early from the study. 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. These tabulations will include the number of subjects dosed, completed, and those who discontinued early from the study along with the corresponding primary reasons for early termination.

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

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 treatment, and by treatment sequence, for both the Safety and PK Populations 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 history and baseline conditions will be summarized by treatment sequence and listed. 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 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 20.0 (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, QT interval, and QTcB interval) will be summarized by changes from baseline values by treatment and treatment 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

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 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	$Change_t = Value_t - Value_{Baseline}$

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.