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I confirm that I have reviewed this document and agree with the content.

APPROVALS	
INC Research	
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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
BP	Blood Pressure
CEC	Cardiovascular Endpoint Committee
CI	Confidence Interval
CRF	Case Report Form
DKA	Diabetic Ketoacidosis
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimating Glomerular Filtration Rate
ESA	Erythropoiesis-stimulating Agent
FMI	Fraction of Missing Information
FPG	Fasting Plasma Glucose
GMI	Genital Mycotic Infection
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HDL-C	High Density Lipoprotein Cholesterol
Hgb	Hemoglobin
ICH	International Conference on Harmonization
IP	Investigational products
ITT	Intention to Treat
IWRS	Interactive Web Randomization System

Abbreviation	Description
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Event
MAR	Missing at Random
Max	Maximum
MCAR	Missing Complete at Random
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hematocrit
MCV	Mean Cell Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial Infarction
Min	Minimum
mL	Milliliter
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not at Random
MODY	Maturity-onset Diabetes of the Young
N/A	Not Applicable
OHA	Oral Hypoglycemic Agent
PP	Per Protocol
PR	Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
PT	Preferred Term
QRS	Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram
RBC	Red Blood Cell
RR	Time between the start of one R wave and the start of the next R wave in the ECG

Abbreviation	Description
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGLT2	Sodium Glucose Linked Transporter 2
SI	Standard International System of Units
SMBG	Self-Monitored Blood Glucose
SOC	System Organ Class
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TLF	Table, Listing And Figure
TZD	Thiazolidinedione
UACR	Urine Albumin To Creatinine Ratio
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
UTI	Urinary Tract Infection
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Theracos has designed the study protocol and is responsible for the conduct of the study. INC Research is responsible for the development and validation of a clinical database using MediData RAVE platform.

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

Adverse events that have met the seriousness criteria defined in the protocol are reported on the serious adverse event (SAE) forms using MediData RAVE platform. An SAE case, consists of the information reported in the SAE forms, subject characteristics documented in the case report forms (CRF), and additional source data such as a hospital discharge summary, is recorded in a validated ARGUS database which is managed by Covance. Any discrepancies in critical data fields of each SAE will be reconciled between the AUGUS and THR-1442-C-448 clinical database prior to database lock. The SAE coding, analyses and summaries are based on the final study data recorded in the clinical database. Detailed serious adverse event follow-up data will be reported from ARGUS database and not included this report.

Theracos will perform review of all tables, figures and listings before the finalization.

2.2. TIMINGS OF ANALYSES

The final analysis of safety and efficacy is planned after all patients who complete the planned 24 weeks of blinded study treatment and the subsequent follow-up period or who have withdrawn from the study. At this time, the database will be cleaned and locked, and the treatment codes will be unblinded.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective is to determine the efficacy of bexagliflozin on lowering HbA1c in patients with T2DM and moderate renal impairment after 24 weeks of treatment.

3.2. SECONDARY OBJECTIVES

The key secondary objectives are:

- To assess the effect of bexagliflozin on the change in body weight at week 24 in subjects with baseline body mass index (BMI) ≥25 kg/m^2
- To assess the effect of bexagliflozin on the change in systolic blood pressure (SBP) at week 24 in subjects with baseline SBP ≥130 mmHg
- Change in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m^2 at week 24
- Change in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m^2 at week 24

Additional exploratory objectives are:

- Change in HbA1c over time in all subjects
- Proportion of subjects who reach target HbA1c of <7% over time
- Changes in fasting plasma glucose (FPG) over time
- Proportion of ≥ 5% reduction of body weight in subjects with baseline BMI ≥25 kg/m2 at week 24
- Change in body weight in all subjects over time
- Changes in SBP and diastolic BP over time in all subjects
- Change in albuminuria (urine albumin creatinine ratio [UACR]) from baseline to week 24 in all subjects and in subjects with baseline macroalbuminuria (UACR ≥300)

3.3. SAFETY OBJECTIVES

The safety objective is the evaluation of the safety of exposure to bexagliflozin for 24 weeks.

An additional safety objective of this study is the contribution major adverse cardiovascular events (MACE) to an eventual meta-analysis that is intended to exclude

excessive cardiovascular risks for subjects exposed to bexagliflozin compared to subjects exposed to placebo during the investigational phase of bexagliflozin.

3.4. OTHER OBJECTIVES

Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted and will include approximately 144 subjects.

3.5. BRIEF DESCRIPTION

THR-1442-C-448 is a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral administration of bexagliflozin at 20 mg versus placebo in subjects with T2DM, moderate renal impairment, and inadequate glycemic control.

Main eligibility criteria include: 1) male or female subjects with T2DM, 2) screening HbA1c of 7.0-10.5% (inclusive), and 3) estimated glomerular filtration rate (eGFR) based on serum creatinine at 2 different assessments ≥ 30 to < 60 mL/min/1.73 m^2 based on the serum creatinine at the screening visit and one additional time point between 1 and 12 months prior to screening (may be obtained from available medical records. The eGFR will be calculated by the modification of diet in renal disease study equation (MDRD). At the time of screening, the doses and frequency of all anti-diabetic medications must have been stable for 8 weeks.

All eligible subjects will enter a one week single blind, placebo run-in period to allow for diabetes education and optimization of compliance with diet and exercise recommendations. Subjects who are compliant in taking run-in medication (missing no more than one dose), have screening eGFR ≥ 30 to < 60 mL/min/1.73 m^2, and have stable GFR (no more than 20% change in eGFR between a historical value and the value determined at the screening visit V1) will be eligible for randomization and receive study drug.

Approximately 300 subjects will be randomly assigned in equal ratio to receive once daily bexagliflozin tablets, 20 mg or placebo, in equal ratio once daily for 24 weeks in an outpatient setting. Randomization will be stratified by screening HbA1c level (7.0 to 8.5% or 8.6 to 10.5%), screening anti-diabetic treatment regimen (insulin treated or other) and screening eGFR (30 - 44 mL/min/1.73 m^2 or 45 - 59 mL/min/1.73 m^2). At least 135 subjects in each of the eGFR groups must be enrolled.

Study subjects will have scheduled visits at weeks 2, 6, 12, 18, and 24 for safety and efficacy evaluation. At weeks 2 and 18, the visit will be conducted via phone interviews unless clinically necessary. A final follow up visit will be conducted at week 26 or two weeks after last dose of study drug if the subject terminates prior to Week 24.

An assessment of bexagliflozin population pharmacokinetics (PK) will also be conducted to include approximately 144 subjects. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

3.6. SUBJECT SELECTION

The study population will include approximately 300 subjects diagnosed with sub-optimally controlled T2DM who have moderate renal impairment. Eligible subjects who must be informed of the nature of the study and the potential risk and consent to participate in the study will be enrolled in clinical investigational sites in multiple countries.

3.6.1. Inclusion Criteria

Refer to protocol section 4.2 for inclusion criteria.

3.6.2. Exclusion Criteria

Refer to protocol section 4.3 for exclusion criteria.

3.7. DETERMINATION OF SAMPLE SIZE

Approximately 300 subjects will be randomized and equally allocated to receive bexagliflozin tablets, 20 mg, or placebo.

The sample size calculation for this study is based on a two group t-test with a two-sided significance at the 5% level and the following assumptions:

1) The placebo-corrected population mean change from baseline to Week 24 in HbA1c in the dose group of 20 mg will be -0.4%.

2) The pooled standard deviation for the change from baseline to Week 24 in HbA1c for the active and placebo groups will be 1.0%.

Under the above assumptions, an estimated sample size of 133 evaluable subjects per treatment arm yields approximately 90% power to detect a treatment difference between bexagliflozin and placebo. A sample size of 150 per arm has been selected to account for a potential 12% drop-out and to allow adequate safety evaluation. The total sample size for this study will be 300 subjects.

3.8. TREATMENT ASSIGNMENT & BLINDING

3.8.1. Treatment Assignment

The study will be conducted at investigative sites in multiple countries and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but each site will be capped at 30 randomized subjects per site. Activation of investigational sites in each country will be centrally controlled by an Interactive Web Response System (IWRS).

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized to receive investigational product. The treatment period for each study subject will start at randomization. Approximately 300 eligible patients will be randomized at the end of the run-in period in a 1:1 ratio to receive once daily bexagliflozin tablets for 24 weeks. Randomization will be stratified by HbA1c level (7.0 to 8.5% or 8.6 to 10.5%), screening anti-diabetic treatment regimen (insulin treated or not) and screening eGFR (30-44 or 45-59 mL/min/1.73 m^2).

Subject randomization will be deactivated for all sites when the planned number of subjects is met. However, if a potential subject is in run-in period already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized.

3.8.2. Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the cardiovascular adjudication committee members will be blinded to the study medication. Upon randomization, each subject will receive a subject randomization number and a drug kit assigned to the subject. To maintain blinding of the individual treatment assignment, the results of urinary glucose testing will not be made available to any study personnel or subjects.

If knowledge of the treatment is needed to manage the subject's condition, the investigator will contact the IWRS to obtain the treatment assignment. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded on CRF and the sponsor must be notified within 24 h.

A designated statistician who is not involved with the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies.

The treatment assignment will continue to be withheld from the cardiovascular adjudication committee members until all global investigational studies are completed and a meta-analysis to assess cardiovascular risk is conducted.

3.9. ADMINISTRATION OF STUDY MEDICATION

The following investigational products (IP) will be used for oral administration:

- Bexagliflozin tablets, 20 mg: tablets containing 20 mg of bexagliflozin
- Bexagliflozin tablets, placebo: tablets containing no bexagliflozin

Dosing with bexagliflozin tablets, 20 mg or placebo, will be based on randomized assignment. All study subjects will be instructed to self-administer tablets once daily in the morning prior to eating or drinking; the medication should be taken with water. There will be no change of dose during the treatment period.

On the day of each scheduled clinic visit, subjects must fast for a minimum of 8 hours prior to the collection of blood samples. During the fasting period, only water will be permitted.

3.10. STUDY PROCEDURES AND FLOWCHART

The activities that must be performed at each clinic visit listed below are presented in Table 1.

Table 1 Schedule of Events

Procedure	Screening	Run-in	Treatment						Follow-up
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Time to Randomization	**3 days -3 weeks to V2**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**26**
Informed Consent	X								
Screening for I/E Criteria	X		X						
Medical History	X								
Diet and Exercise Counseling		X							
Physical Examination			X						
Abbreviated Physical Examination	X					X		X	X
Weight	X		X		X	X		X	X
Vital Signs	X		X		X	X		X	X
Electrocardiography	X							X	
Diary and Glucometer Record Review			X	X	X	X	X	X	X
Dispensing Run-in Drug		X							
Randomization			X						
Dispensing Investigational Product			X			X			
Adverse Events & DKA Assessments		X	X	X	X	X	X	X	X
Concomitant Medication Assessments		X	X	X	X	X	X	X	X
Hematology	X		X		X	X		X	X
Serum Chemistry and Electrolytes	X		X		X	X		X	X
Glycemic Control	X		X		X	X		X	X
Serum Lipids	X		X			X		X	X
Urinalysis	X		X		X	X		X	X
UACR	X		X					X	X
Urine Pregnancy Test (WOCBP)	X		X		X	X		X	X
Population PK sampling					X	X			

A visit window of ± 3 days is allowed for all visits except Visit 3. V3 is the day of randomization and the basis for the visit window.

The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of proper fasting practice. A subject must be queried to assess compliance with a minimum of 8 hours fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for a minimal of 8 h, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting.

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

- Change from baseline to week 24 in HbA1c

4.2. SECONDARY EFFICACY ENDPOINTS

The key secondary endpoints are:

- Change from baseline to week 24 in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2
- Change from baseline to week 24 in SBP in subjects with baseline SBP ≥ 130 mmHg from baseline
- Change from baseline to week 24 in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m^2
- Change from baseline to week 24 in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m^2

Other Efficacy Endpoints

- Change in HbA1c over time in all subjects
- Proportion of subjects who reach target HbA1c of <7% over time
- Changes in FPG over time
- Proportion of ≥ 5% reduction of body weight in subjects with baseline BMI ≥25 kg/m^2 at week 24
- Change in body weight in all subjects over time
- Changes in SBP and diastolic BP over time in all subjects
- Change in albuminuria (urine albumin creatinine ratio or UACR) categories at week 24 in all subjects and in subjects with baseline macroalbuminuria (UACR ≥300)

4.3. SAFETY ENDPOINTS

- Adverse events (AE), including AE of special interest (urinary tract infections [UTI], genital mycotic infection [GMI], diuretic effects, hepatotoxicity, hypoglycemia, MACE, fractures, malignancy, hypersensitivity reactions,

hypotensive episodes, acid-base disorders, diabetic ketoacidosis [DKA], renal failure events and amputations)

- Laboratory testing, including hematology, serum chemistry, urinalysis, urinary electrolytes and creatinine
- 12-lead ECG
- Vital signs
- Physical examination
- Concomitant medication use

4.4. OTHER ENDPOINTS

- Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled).

5. ANALYSIS SETS

5.1. SCREENED ANALYSIS SET

The Screened Analysis Set will include all subjects who have signed the informed consent forms and completed the eligibility screening prior to randomization. The screened analysis set will consist of both enrolled subjects and subjects who do not meet the eligibility criteria. This set will be used for summaries of subject disposition.

5.2. SAFETY ANALYSIS SET

All subjects who are randomized and take at least one dose of the double-blind IPs will be included in the Safety Analysis Set. Safety analyses will be based on the treatment that a subject takes upon randomization. The Safety Analysis Set is the primary analysis set for safety evaluation.

5.3. INTENTION-TO-TREAT ANALYSIS SET

All subjects who are randomized will be included in the Intention-to-Treat (ITT) Analysis Set. All analyses of the ITT Analysis Set will be based on each subject's randomized assigned treatment. The ITT analysis set will serve as the primary set for the efficacy analyses.

5.4. PER PROTOCOL ANALYSIS SET

The Per Protocol (PP) Analysis Set will include all subjects in the ITT Analysis Set who meet the study eligibility requirements and have no major protocol deviations that affect the validity of the efficacy measurements. Detailed protocol deviations that may result in subject or visit exclusion from the PP Analysis Set are described in Section 5.5. The PP Analysis Set will serve as the secondary set for efficacy assessment.

5.5. PROTOCOL DEVIATIONS

Protocol deviations will be captured during the study conduct. Some of the examples of major deviations that may result in subject exclusion from the PP Analysis Set are given in Table 2. The list of deviations will be reviewed before unblinding and major protocol deviations that, in the opinion of the medical monitor, could affect the primary and secondary variables will be determined.

Table 2 Some Possible Types of Major Protocol Deviations That Lead to Subject or Visit Exclusion from PP analysis set.

Category	Criteria	Exclusion
Inclusion/Exclusion Criteria		
Ineligible subject is enrolled	- Subjects not satisfying HbA1c inclusion criteria - Subjects not satisfying eGFR inclusion criteria (inclusion #4 and #7) - Treated with SGLT2 within 3 months of screening	Subject exclusion
Prior or Concomitant Medication Restrictions		
Use of another SGLT2 inhibitor	Use of an SGLT2 inhibitor as the rescue medication for hyperglycemia	Visit exclusion [exclude data post SGLT2 starts]
Use of new Diuretic medication	Initiate of new diuretic medication within 12 weeks of randomization	Visit exclusion [exclude data post initiation of a new diuretic]
Randomization/Blinding		
Unblinding	Blind was broken (requested in IWRS)	Visit exclusion [exclude data post blind broken]
Dosing Non-Compliance	-Subject missed more than 50% of the investigational product doses between week 12 and week 24	Subject exclusion

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

Statistical methodology and analyses are in accordance with the principles outlined by the ICH E9 guidelines. All statistical analyses will be conducted using SAS statistical software version 9.3 or higher.

Tables, listings and figures (TLFs) will be produced in accordance with the principles outlined by the ICH E3 guidelines. For most summary statistics, data will be analyzed by the following treatment groups: Bexagliflozin 20 mg and Placebo. All available data will be presented in the subject listings.

Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage of subjects for categorical and ordinal variables, unless otherwise specified.

Unless otherwise specified, all tests will be two-sided using a 0.05 level of significance. All confidence intervals (CIs) will be two-sided 95% CIs.

The analysis visit window will be assigned to data collection. One selected data point per visit will appear in summary tables and figures. Refer to section 6.4 for details. All visit assessment data will be included in shift tables and will appear in the subject listings.

6.2. KEY DEFINITIONS

6.2.1. Baseline Values

For safety endpoints, baseline is defined as the last non-missing measurement prior to the first dose of double-blind IP. For baseline demographics and efficacy endpoints, baseline is defined as the last non-missing value before the randomization date. These endpoints include HbA1c values, sitting SBP, height, body weight, BMI, FPG, eGFR, and UACR.

6.2.2. First Dose Date

Two “first dose dates” will be required, one for the Run-In period and one for the double-blind treatment period. The first dose date for the Run-In period will be the date of administration of the first dose of single-blind placebo tablets during the Run-In period. The first dose date for the double-blind treatment period will be the date that the first dose of randomized, double-blind study drug is administered. Both

first dose dates will be obtained from the CRF. Study analyses will use the double-blind treatment period first dose date.

6.2.3. Study Day

Study Day is the number of days starting from the first administration of double-blind study drug, which is counted as Study Day 1. If the assessment date is after the date of the first double-blind medication, the study day is calculated as date of assessment - date of the first dose administration+1. If the assessment date is prior to the date of the first double-blind medication, the study day is calculated as date of assessment - date of the first dose administration.

6.2.4. Duration

Duration of double-blind treatment will be determined as Double-Blind Duration = Double-Blind Last Dose Date minus Double-Blind First Dose Date plus 1. Duration of Run-In period will be determined as Last Dose Date in the run-in period minus First Dose Date in the run-in period plus 1.

6.2.5. End of Study

The end of study is defined as the date of final contact as entered on the End-of-Study page of the CRF. Any missing date of last contact on the End-of-Study CRF will be imputed as the date of last contact recorded in the database.

6.2.6. Patient Years

Patient years are calculated as sum of the duration of double-blind treatment / 365.24 of all subjects in the specified analysis set and treatment arm. This is used as the denominator of the computation of incidence rate.

6.3. MISSING DATA

The handling of missing or incomplete data is described for each endpoint and data type (as needed) in Sections 7 to 10.

6.4. ANALYSIS VISIT WINDOWS

Table 3 shows how data will be mapped to analysis visits prior to selection of records for analysis. All post-baseline visits, including unscheduled and early termination visits, will be mapped. After mapping the data to the analysis visits, the following rules will apply unless other handling is specified for a particular analysis.

- If multiple records are available within a single analysis visit window, the record closest to the planned assessment day will be selected for analysis.
- If 2 records are equidistant from the target day, then the later record will be selected.
- If a subject has no record in an analysis window, the subject will be considered missing at that visit.

Table 3 Analysis Visit Windows

Study Day Window	Scheduled day	Scheduled Visit/Week
Day 1 - 63	Day 42	Visit 8/Week 6
Day 64 – 125	Day 84	Visit 9/Week 12
>= Day 126	Last Dose Date + 1, or Day 168, whichever is earlier	Visit 11/Week 24

* Week 24 is the end of treatment visit for those subjects completing the study per protocol. For endpoint of lab, vital sign, and ECG, the first collection after assigned Week 24 and > 7 days from Week 24 visit will be considered as Week 26 visit. All lab, vital sign, and ECG data summary will base on the mapped visit.

6.5. POOLING OF CENTERS

Subjects will not be pooled based on site size, but rather by region, to ensure a sufficient number of subjects per treatment arm in both the ITT and PP sets for analysis that contain region as a model effect. The tables below show which countries comprise each of the regions to be used in analysis.

Region	**Country**
Europe	France
	Spain
North America	United States
Asia	Japan

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition data will be listed. A disposition table will present, by treatment group and overall, the number and/or percentage of subjects who signed the informed consent and entered the study (i.e., were screened, screen failed prior to Run-in, screen failed during the Run-in, and randomized), complete the study drug, discontinued study drug, completed the study, and discontinued from the study after randomization. The reasons for early withdrawal after randomization will be summarized.

Assignment to the analysis sets (Safety, ITT, and PP) will be summarized.

7.2. SUBJECT ELIGIBLITY AND PROTOCOL DEVIATIONS

All subjects, including screen failure subjects, who violate the Inclusion/ exclusion criteria will be listed. Reason for screen failure will be summarized.

Deviations that could affect the primary and secondary variables will be considered when determining a subject's eligibility for the PP Analysis Set. The number and percent of subjects who had any major deviation and each type of major protocol deviation will be tabulated for the ITT Analysis Set. All deviation term and class will be listed.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics include age, gender, race, ethnicity, and country and region of investigational site. Baseline characteristics will include baseline HbA1c values, blood pressure, height, body weight, BMI, FPG, eGFR, eGFR baseline groups (<45 or ≥45 mL/min/1.73m^2), UACR, duration of diabetes from diagnosis to the date of informed consent, and prior anti-diabetic treatment status at screening. Baseline will be defined as the last non-missing value prior to randomization. Randomization stratification related factors will be summarized based on data collected on CRF or by lab. They include screening HbA1c groups (7.0 to 8.5% vs. 8.6 to 10.5%), screening anti-diabetic treatment status (insulin treated, other), screening eGFR values, and screening eGFR groups (30-44 or 45-59 mL/min/1.73m^2). Stratification factors from IWRS will be summarized if they are not consistent with CRF or lab values. Summary descriptive statistics by treatment will include counts and percentages for discrete variables and estimation of means, standard deviations, medians, inter-quartile range (Q1, Q3), minimum, and maximum for continuous variables. Subjects' baseline

demographic and personal baseline characteristics will be summarized by treatment group and overall for subjects in the Safety, ITT, and PP Analysis Set. Subject age will be the age at date of inform consent collected from CRF.

Demographics data and randomization stratification factors will be presented in a data listing. Prior treatment will be listed along with all medications.

7.4. MEDICAL HISTORY

Significant medical and surgical history, including dates of diagnoses and procedures and whether the condition is ongoing, if applicable, will be collected. Each condition will be recorded as a verbatim term, date of onset, date resolved, and a checkbox that indicates ongoing conditions. Significant surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 or higher.

Medical and surgical history will be summarized for the Safety Analysis Set by treatment group, system organ class (SOC), and MedDRA preferred term (PT), overall. Subject data will be listed.

Subject renal, diabetes and cardiovascular diseases history will be summarized for all categorical variables by frequency and percentage. Listing will be provided.

7.5. MEDICATION

All prescription and over-the-counter medications, including vitamins and herbal supplements, that subjects receive during the trial must be documented on the CRF. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. This documentation should continue through the treatment period and the follow up period.

All medication will be coded using the World Health Organization Drug Dictionary (WHO-DD) version March 2016 or higher. Preferred drug name, Anatomical/ Therapeutic/ Chemical (ATC) class will be reported for inclusion in the database.

Medication summaries based on ATC level 2 and the preferred drug names will be produced for the Safety Analysis Set. The summaries will present, by treatment group, the frequency and percentage of subjects who used any medication in an ATC class, or any medication based on a single preferred drug name. Medication summaries will be sorted by descending total frequency of ATC class and by PT within ATC class. Subjects will be counted only once for each medication class and each preferred drug name.

For subject listings, medications will be reported based on ATC class and PT; multiple medications for an individual subject will be listed by start date and then by stop date, from earliest to latest medications.

7.5.1. Prior Medication

Any medication with a start date prior to or on first dose date for the double-blind treatment period will be considered a prior medication. If the entire start date of a given medication is missing, then the medication will be considered as prior medication.

No summary for prior medication will be presented. Prior and concomitant medications will be presented together on a single listing. The listing will be ordered by subject number and medication start/end dates. Prior medication will be flagged.

7.5.2. Concomitant Medication

A concomitant medication is any medication that starts prior to double-blind treatment period and continue into double-blind treatment period, or started after the first dose of double-blind treatment. All medications or treatment for controlling hyperglycemia will be recorded as concomitant medications in CRF. In the case of completely missing stop date, medication will be assumed to be concomitant.

Concomitant medications will be presented in a summary table as well as in a subject listing.

7.5.3. Rescue Medication

Rescue medication is any new anti-hyperglycemic medication that a subject starts taking during the double-blind treatment period or an increase in dose of the anti-hyperglycemic medication that the subject has been taking and continued for more than 2 weeks. Rescue medications will be summarized in a separate table and flagged in the same listing.

Independent blinded medical reviewers will identify the rescue medication before the study is unblinded. Adjudication process and definition of dose intensification and relaxation will be specified in a separate adjudication plan (Appendix 21.1).

8. EFFICACY

Efficacy data include HbA1c, FPG, body weight, SBP, DBP, and albuminuria.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy hypothesis is that bexagliflozin reduces HbA1c after 24 weeks of treatment when compared to placebo.

8.1.1. Primary Efficacy Analysis

Let $\mu_{Bexagliflozon}$ and μ_{PBO} represent the mean changes from baseline in HbA1c at Week 24 for bexagliflozin and placebo arms, respectively. The following hypotheses will be tested:

$$H_0: \mu_{Bexagliflozon} = \mu_{PBO} \text{ versus } H_1: \mu_{Bexagliflozon} \neq \mu_{PBO}$$

This hypothesis will be tested based on ITT analysis set using all observed data and a mixed model repeated measures (MMRM) approach. Treatment, visit, treatment-by-visit, region, screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (<45 or ≥45 mL/min/1.73m^2) will be applied as fixed effects. Baseline HbA1c will be used as covariate. The analysis will evaluate the mean change from baseline in HbA1c over the 24-week double-blind treatment period. An unstructured covariance will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the model with the unstructured covariance structure does not converge, an autoregressive (1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from the analysis.

Based on the MMRM model, the treatment and treatment-by-visit interaction terms allow for comparisons of the treatment groups at each visit. Least squares (LS) mean treatment differences between the bexagliflozin group and the placebo group at week 24 will be estimated from the model with the corresponding p-values and their two-sided 95 % CIs presented. Sample SAS code will be provided in Appendix 21.2.

Descriptive statistics (n, mean, Q1, median, Q3, SD, minimum, and maximum) will be reported by treatment group and visit, along with the least squares means, differences between LS means, a 2-sided 95% confidence interval for each difference, p-values from the model effects. In addition, the LS means with standard errors of the change from baseline over time and difference between treatment groups with 95% will be presented graphically for the ITT Analysis Set.

For supportive analyses, the primary efficacy endpoint will be analyzed with observed available data using the PP analysis set in a similar manner as above. LS means over time will also be presented graphically.

8.1.2. Sensitivity Analyses

Randomized subjects who withdraw consent to participate in the study will not be replaced. The early termination rate is estimated to be 12%. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct.

To investigate the possible implications of missing values in efficacy assessments, the number, timing, pattern, and reason for the missing value will be summarized. If there are missing values for the primary analysis, only available data will be analyzed and data obtained after rescue will not be excluded. To account for subjects for whom the post-baseline endpoint (ie, at the time when the last post-baseline double-blind assessment was performed) occurs at a time point before Week 24, a MMRM approach will be used as the primary method. It is assumed that the majority of the missing values will be one of the following:

- "Missing Completely at Random (MCAR)" (ie, probability of an observation being missing does not depend on observed or unobserved measurements) or

- "Missing at Random (MAR)" (ie, probability of an observation being missing depends only on observed measurements)

In such situations, likelihood-base methods like MMRM are appropriate.

The dropout patterns will be assessed by a Kaplan-Meier plot of time to discontinuation by treatment group to assess whether they differ between treatment groups.

For our primary analysis, it is assumed that a majority of the missing values will be MCAR or MAR. In such situations, likelihood-base methods like MMRM are appropriate and widely accepted in superiority trials (Little et al, 2002). This will be considered the primary analysis. Sensitivity analyses will be performed as:

1. Missing HbA1c data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will not be considered missing.

2. Missing HbA1c data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.

3. HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be re-performed.

4. Missing HbA1c data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard MI techniques; HbA1c values collected after the start of rescue medication will be considered missing.

For sensitivity analysis 1 and 4, data will be imputed in the framework of a pattern mixture model (PMM) with placebo-based pattern imputation for missing visits. The method described here is based on methodology described by Little and Yau (1996) and extended in a PharmaSUG paper by Ratitch and O'Kelly (2011). The concept for the imputation used here is that subjects who drop out of the study from the active treated arms will exhibit the same evolution of the disease under study as those subjects assigned to the placebo arm. It is assumed, as well, that subjects who discontinue from the placebo arm would have the same evolution of the disease as those subjects on the placebo arm who remained in the study. The three-step approach outlined below will be followed (Ratitch B and O'Kelly M, 2011):

1. Non-monotone (intermediate visits) missing data will be imputed first using the Monte Carlo Markov Chain method under the MAR assumption in all treatment arms (using the MCMC statement in PROC MI). Multiple chains option (CHAIN=MULTIPLE option in the MCMC statement of PROC MI) will be used. For the non-monotone imputation of the HbA1c missing data, a multivariate normal model will be used including variables for the HbA1c at baseline and all post-baseline visits within each treatment group.

2. After the non-monotone missing data have been imputed, the remaining monotone missing data will be imputed under the Missing Not at Random (MNAR) assumption that subjects who withdraw from the bexagliflozin group will have correlations with future (post-withdrawal) visits similar to subjects in the placebo group, adjusted for baseline covariates and observed outcomes prior to withdrawal. Monotone missing data of withdrawn subjects from the placebo group will be imputed under the MAR assumption and will follow the pattern of placebo completers. In other words, monotone missing values of the HbA1c will be imputed for all subjects who withdrew from the study (regardless of treatment group) using an imputation model at each time point estimated from subjects with available data in the placebo group only. A regression imputation model for the HbA1c at each time point t will include explanatory variables including

screening anti-diabetic treatment regimen [insulin treated or other], baseline eGFR [<45 or ≥45 mL/min/1.73m^2]), region and HbA1c at all previous time points, including baseline. Data from bexagliflozin group with time t data observed will not be used to impute time point t. Imputations will be performed using a sequence of regression-based imputations (using PROC MI statement MONOTONE REG) for each post-baseline time point as described in (Ratitch B and O'Kelly M, 2011).

3. Imputed data in each of the multiple imputed datasets will be analyzed using the same mixed model for repeated measures as in the primary analysis. The results from all imputed datasets will be combined using the Rubin's combination rule (PROC MIANALYZE).

The sample SAS codes can be found in Appendix 21.2.

The number of imputation will be determined using the method described by White, et.al., 2011. We will use Bodner's approximation to estimate the fraction of missing information (FMI) as the proportion of the incomplete cases in the data. Since the parameter of interest is the mean changes from baseline in HbA1c at Week 24 for bexagliflozin and placebo groups, FMI will be approximated using the proportion of subjects missing Week 24 values. As indicated by Bodner, this is a very conservative approach and will work with FMI≤0.5. The number of imputations m will be determined to provide sufficient level of reproducibility using formula:
$m \geq 100 \times FMI$
as recommended by White. The Monte Carlo error of the P-value using m imputation datasets will be approximately 0.01 when the true P-value is 0.05, and 0.02 when the true P-value is 0.1.

At least 10 datasets will be imputed. We will examine the FMI estimated from the combined results. If it is much larger than our initial approximation, a considerable volatility is observed from the imputed datasets. In this case, we will increase the number of m using the estimated FMI.

For sensitivity analysis using LOCF, all observed data and the imputed values will be analyzed using MMRM model. Model will include terms for screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (<45 or ≥45 mL/min/1.73m^2), region, treatment, visit, treatment-by-visit, and the baseline HbA1c value as a fixed effect covariate. LS mean treatment differences between the bexagliflozin group and the placebo group will be estimated from the model with the corresponding p-values and their two-sided 95 % CIs presented.

Sensitivity analysis will be conducted for ITT Analysis Set. If > 5% subjects in either treatment arm had major protocol deviation that cause exclusion from PP analysis set, sensitivity analysis will be repeated for PP Analysis Set.

8.1.3. Subgroups

Both descriptive and model comparison for the primary analysis will be repeated by subgroups. The nominal p-value will be presented without adjustment to the multiple comparisons. They are not used for inferential purpose. The subgroups include:

- Age (<65 years or ≥65 years)
- Gender (male or female)
- Race (3 largest race groups or other)
- Baseline HbA1c (7.0% to 8.5% or 8.6% to 10.5%)
- Screening anti-diabetic treatment regimen (insulin treated or other)
- Baseline eGFR (30-44 mL/min/1.73m^2 or 45-59 mL/min/1.73m^2)
- Region (North America, EU, or Asia)

8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

The key secondary efficacy endpoints include:

- Change from baseline to week 24 in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2
- Change from baseline to week 24 in SBP in subjects with baseline SBP ≥ 130 mmHg from baseline
- Change in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m^2 at week 24
- Change in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m^2 at week 24

The exploratory efficacy endpoints include:

- Change in HbA1c over time in all subjects
- Proportion of subjects who reach target HbA1c of <7% over time
- Changes in fasting plasma glucose (FPG) over time
- Proportion of ≥ 5% reduction of body weight in subjects with baseline BMI ≥25 kg/m^2 at week 24
- Change in body weight in all subjects over time

- Changes in SBP and diastolic BP over time in all subjects
- UACR categories at week 24 in all subjects and in subjects with baseline macroalbuminuria (UACR ≥300)

8.2.1. Key secondary efficacy endpoints and analyses

The primary superiority test on lowering of HbA1c at week 24 from baseline for bexagliflozin when compared to placebo will be conducted at 0.05 significance level. If it is significant, the hierarchical testing strategy will be followed to preserve experiment-wide type I error of 0.05. The key secondary efficacy end points will be tested in the order:

1. Superiority test of the change in body weight in subjects with baseline BMI ≥ 25 kg/m^2 at week 24 in the bexagliflozin group compared to the placebo group
2. Superiority test of the change in systolic blood pressure (SBP) over time in subjects with SBP ≥ 130 mmHg in the bexagliflozin group compared to the placebo group
3. Superiority test of the change in HbA1c at week 24 in subjects with eGFR 45 to 59 mL/min/1.73m^2 in the bexagliflozin group compared to the placebo group
4. Superiority test of the change in HbA1c at week 24 in subjects with eGFR 30 to 44 mL/min/1.73m^2 in the bexagliflozin group compared to the placebo group

These key secondary endpoints will only be tested sequentially when significant treatment differences are established for the primary efficacy endpoint in the comparisons between the bexagliflozin and placebo groups.

Analysis for key secondary endpoints will be based on the ITT Analysis Set and repeated for the PP Analysis Set.

8.2.1.1. Change in body weight from baseline to week 24 in subjects with a BMI ≥ 25 kg/m^2

This will be tested if the change from baseline body weight is significantly different between bexagliflozin and placebo groups based on ITT analysis set for subject with a baseline BMI ≥ 25 kg/m^2. The comparison of change in body weight between randomized treatments at week 24 will be carried out using similar MMRM ANCOVA model stated in section 8.1.1. Treatment, visit, treatment-by-visit, region, baseline HbA1c level as continuous variable, screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (<45 or ≥45 mL/min/1.73m^2) will be applied as fixed effects. Corresponding baseline weight value will be used as additional covariate. Treatment comparison p-values and difference at week 24 will be estimated from the

model, with the two-sided 95 % CIs of the treatment difference also presented. If the primary hypothesis is not significant, the nominal p-value will not be used for inferential purposes. The most conservative sensitivity analysis, sensitivity analysis #4 in section 8.1.2, multiple imputations with values after rescue medication considered as missing, will be repeated in ITT analysis set.

8.2.1.2. Change in SBP from baseline to week 24 in subjects with baseline systolic blood pressure ≥ 130 mmHg

This will be tested if the primary and the first key secondary efficacy endpoints are significant. Change from baseline in sitting SBP at week 24 will be analyzed using the same MMRM ANCOVA model stated in section 8.1.1. The corresponding baseline SBP value will be used as additional covariate. Treatment comparison p-values and difference at week 24 will be estimated from the model, with the two-sided 95 % CIs of the treatment difference also presented. The most conservative sensitivity analysis, sensitivity analysis #4 in section 8.1.2, multiple imputations with values after rescue medication considered as missing, will be repeated in ITT analysis set.

8.2.1.3. Change in HbA1c from baseline to week 24 by eGFR status

They will be tested following the hierarchical order specified in section 8.2. They will be analyzed using the same MMRM ANCOVA model stated in section 8.1.1.

8.2.2. Exploratory secondary efficacy endpoints and analyses

All endpoints in this section are exploratory. No sensitivity analyses and adjustment for multiple comparisons will be conducted. Nominal p-values will be used to examine any trends in these endpoints.

8.2.2.1. Changes from baseline in HbA1c, body weight, SBP, diastolic BP, FPG, and albuminauria over time

The schedule of HbA1c, body weight, SBP, diastolic BP, and FPG over time can be found in Table 1. The absolute value and change from baseline during the double-blind treatment period will be summarized by descriptive statistics at each visit. Change from baseline in HbA1c will be analyzed as part of primary efficacy analysis. The change from baseline in body weight, SBP, and FPG will be analyzed using the MMRM ANCOVA model from primary analysis as a template (Section 8.1.1). The fixed effect will include region, baseline HbA1c level as continuous variable, screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (<45 or ≥45 mL/min/1.73m^2), treatment, visit, and treatment-by-visit. The appropriate baseline values will be used as covariate. LS means for each treatment and the difference between treatments will be estimated at each visit. The

corresponding p-values will also be presented.

All values for follow-up visits will be listed.

8.2.2.2. Change in albuminuria from baseline to week 24

Descriptive statistics for geometric mean, geometric coefficient of variation (gCV), median, Q1, Q3, minimum, and maximum of UACR values will be presented at baseline, and week 24 for all subjects and for baseline macroalbuminuria subjects (>300 mg/g). UACR data is left-skewed and will be natural log transformed first. Change in log transformed UACR from baseline to week 24 will be analyzed by ANCOVA model. The fixed effect will include region, baseline HbA1c level as continuous variable, screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (<45 or ≥45 mL/min/1.73m^2), and treatment. The log transformed baseline values will be used as covariate. Analysis will be repeated for baseline macroalbuminuria subjects. LS means for each treatment and the difference between treatments will be estimated at week 24. The adjusted geometric mean ratio of relative change from baseline in UACR (the ratio of the week 24 geometric mean and baseline geometric mean) and the corresponding two sided 95 % CI by treatment group will be calculated as the antilog of the LS mean and 95 % CI of log transformed values, converted to percentage. The adjusted geometric mean ratios of relative change from baseline in UACR for bexagliflozin vs. placebo (ratio of the two ratios obtained from previous steps) and their 95% CI will be calculated as the antilog of the LS mean differences and their 95% CI. Sample SAS code will be provided in Appendix 21.2.

8.2.2.3. Proportions of subjects with HbA1c of < 7% over time and proportion of ≥ 5% reduction of body weight in subjects with baseline BMI≥25 kg/m^2 at week 24

Summary on the proportion of subjects achieving HbA1c < 7% at each visit and the proportion of ≥ 5% reduction of body weight during each visit interval will be presented over time. They will be analyzed using generalized estimating equation (GEE) logistic regression. The fixed effect will include region, baseline HbA1c level, screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (<45 or ≥45 mL/min/1.73m^2), treatment, visit, and treatment-by-visit. An unstructured correlation structure will be used (or autoregressive [1] if the model with the unstructured structure does not converge). The LS mean proportion for each treatment will be estimated at each post-baseline visit. The odds ratios of bexagliflozin group over the placebo group at each visit and across all post-baseline time points will be estimated from LS means based on the model with the corresponding p-values and their two-sided 95 % CIs presented. Similar method will be used for analyzing proportion of subjects with body weight reduction ≥ 5% in subjects with baseline BMI≥ 25 mg/m^2. Baseline body weight will be added to the model as a

covariate. Sample SAS code will be provided in Appendix.

9. SAFETY

The analysis population used for safety analyses will be the Safety Analysis Set. Safety data include AEs; physical examination results; vital signs, including blood pressures; ECG results; and clinical laboratory results, including serum chemistry, hematology, serum lipids, and urinalysis.

Observed data will be summarized by treatment group as counts and percentages for discrete variables and means, SDs, medians, minimum, and maximum for continuous variables. All subjects who are randomized and receive at least one dose of double-blind study medication will be included in the safety analysis. All safety data will be presented in by-subject listings and included in the clinical trial report.

9.1. EXTENT OF EXPOSURE

Study drug exposure will include:

- Treatment duration by treatment group
- Total dose taken by treatment group

Treatment duration of tablets (in weeks) is calculated as (the date of the last dose of study drug – the date of the first dose of study drug + 1) / 7 and rounded to 1 decimal place.

The specific definitions of the first dose and last dose dates of study drug are given below:

- First dose date: The date of the first dose of study treatment during the double-blind treatment period obtained from the study drug exposure CRF.
- Last dose date: The date of the last dose of study medication in the 24 week treatment period for subjects who have completed the study or discontinued early.

Total dose taken will be calculated as number of tablets dispensed – number of tablets returned. If any of the bottles dispensed is not returned, it will not be possible to compute the total dose received. In this case, the number of tablets taken will be considered as missing. Summary statistics for total dose taken will be provided by treatment group for the double-blind treatment period.

Summary statistics for treatment duration (in weeks) and a frequency summary of treatment duration categories (e.g., >=1 Day, >=6 weeks), will be provided.

9.2. TREATMENT COMPLIANCE

Subjects will be provided with dosing instructions each time study medication is dispensed. Subjects will also be instructed to bring their medication with them to every visit. During the run-in period, subjects will be considered compliant in investigational product administration by missing no more than one dose of run-in medication. Subjects who are not compliant during the run-in period will be excluded from randomization.

At each visit the study staff will review the self-monitored blood glucose (SMBG) control diary, glucometer data and medication use with the subject and record the drug consumption in the CRF. Reasons for non-adherence will also be recorded in the protocol deviation log if applicable.

Compliance in the run-in and double-blind phase is calculated for as follows:

- Percent compliance = (number of tablets taken / number of tablets should have taken) x 100.
- Number of tablets taken = number of tablets – number of tablets returned.
- Number of tablets should have taken = (number of tablets supposed to take in a day) x (number of exposure days).
- Number of exposure days = last dose date – first dose date + 1.

If any of the bottles dispensed is not returned, it will not be possible to compute the compliance. In this case, the number of tablets taken and compliance will be considered as missing. Summary statistics for tablet or capsule compliance (%) will be provided by treatment group for the double-blind treatment period. A frequency summary of compliance will also be presented with the following categories: < 75%, 75% -< 100%, 100%- ≤ 120%, and > 120%.

9.3. ADVERSE EVENTS

Adverse events will be collected and recorded from the time a subject signs the informed consent form (ICF) to the last scheduled contact. And new SAE reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the investigational product, should be reported to the sponsor or designated personnel. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined study period (i.e., up to last scheduled contact). The investigator should follow SAEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor until the event

has been resolved. This study requires that subjects be actively monitored for SAEs for at least 4 weeks after the last treatment.

For all AEs, preferred AE terms and system organ class (SOC) will be coded using terminology from the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or higher.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins after the first administration of double-blind study medication or existing AEs that worsen after the first dose of double-blind study medication. All reported AEs will be listed, but only TEAEs will be summarized in tables.

Drug-related AEs will be considered those to be possibly, probably and definitely related to IP administration based on the investigators assessment.

Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs and PTs within SOCs presented in descending order of subject incidence.

9.3.1. Derived Data

AE onset day is calculated as (date of AE start – date of double-blind first dose + 1) if it is after the first dose of study drug. AE onset day is calculated as (date of AE start – date of double-blind first dose) if it is before the first dose of study drug.

9.3.2. Data Summarization

AE summary tables are listed below:

- An overall summary of the number and percentage of subjects reporting any TEAEs, serious TEAEs, treatment-related TEAEs, serious treatment-related TEAE, any TEAEs leading to treatment discontinuation, any TEAEs leading to subject discontinuation and TEAEs leading to death.
- TEAEs overall and by SOC and PT
- TEAEs by severity, overall and by SOC and PT
- Serious TEAEs, overall and by system organ class and preferred term
- TEAEs by relationship to study treatment, overall and by system organ class and preferred term
- TEAEs leading to treatment discontinuation, overall and by SOC and PT

- TEAEs leading to study discontinuation, overall and by SOC and PT

- Most common TEAEs. Most common TEAEs are defined as TEAEs that occur in > 5% of the subjects in either of the treatment groups.

For summary tables, subjects having more than 1 event with the same PT will be counted once for that term. Subjects having more than 1 event with the same SOC will be counted once for each event and once for that SOC. For tabulations by severity, only a subject's most severe event within the category (e.g. overall, SOC, PT) will be counted; similarly, for tabulations by relationship, only a subject's most related event within a category will be counted. The denominator for percentages will be the number of subjects in the Safety Analysis Set for the given treatment group (i.e., the N's for the columns).

Listings will be provided for all AEs and the following subsets:

- Serious AEs
- AEs leading to treatment discontinuation
- AEs leading to death.

9.3.3. AE of Special Interest

AE of special interest include UTI, GMI, diuretic effects, hepatotoxicity, MACE, hypoglycemia, fracture, malignancy, hypersensitivity reactions, hypotensive episodes, acid base disorders, DKA, renal failure events, and amputations. The AEs of special interest, except for MACE and amputations, will be prospectively identified based on the MedDRA PTs in the AEs log by a medical expert prior to the data base lock and unblinding of the individual subject treatment assignment. The list of AEs of special interest will be confirmed in a peer review process. Adjudicated MACE will be summarized in the same AE of special interest table. Hypoglycemia events by severity, and amputations will be summarized separately. Additional information will be collected for DKA. These data will be listed if available.

9.3.3.1. AE of special interest identified by PTs

Cardiovascular events considered as MACE by investigator will be submitted to an independent Cardiovascular Endpoint Committee (CEC) for adjudication. The events of interest include cardiovascular mortality, MI, stroke, hospitalization for acute coronary syndromes, urgent revascularization procedures, and other possible serious cardiovascular events. Other AE of special interest will be identified from the PTs. The number and percentage of subjects experiencing these TEAEs of special interest will be summarized for each treatment group by type of event. The incidence rate of AE of special interest per 100 patient years will also be summarized. It will be

calculated as total number of AEs / total patient years in specific treatment arm (or total) * 100. Each category of events will be displayed in a separate listing.

9.3.3.2. Hypoglycemia Events

Hypoglycemic event categories include:

Category	Description
Severe	Assistance required and blood glucose ≤70 mg/dL or no value available but responded to glucose treatment
Documented Symptomatic	Blood glucose ≤70 mg/dL and typical symptoms of hypoglycemia
Asymptomatic	Blood glucose ≤70 mg/dL and no typical symptoms of hypoglycemia
Probable Symptomatic	Typical symptoms of hypoglycemia and no value available but responded to glucose treatment
Relative	Typical symptoms of hypoglycemia and blood glucose >70 mg/dL

While each event meeting the criteria above will be entered into the hypoglycemia log, only critical (severe) hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia will be entered as AEs.

The number and percentage will be summarized by treatment for:

- Each category of hypoglycemic events;
- Any severe or documented hypoglycemic events.

9.3.3.3. Revascularization and Amputations

Revascularization and amputations information are collected in a separate form. Frequency and percentage will be summarized for:

- Type of procedures –cardiovascular related or amputation
- Subjects with any amputation
- Conditions that resulted in amputation
- Location of amputation

Only procedures performed after the first dose of double-blind study drug will be summarized.

9.3.3.4. Renal Failure Events

Frequency and percentage of subjects will be summarized for:

- Any acute kidney event;
- Acute kidney event by stage of disease. If a subject has multiple events, the highest stage will be summarized.

All instances of acute kidney event and their stage will be listed.

9.4. LABORATORY EVALUATIONS

Laboratory tests will include hematology panel, chemistry panel, serum lipids, and urinalysis testing. Hematology, chemistry, and urinalysis will be performed at the following time points: at the screening visit, on baseline visit (week 0), and at weeks 12, 24, and 26. Serum lipids will be performed at the screening visit, on baseline visit (week 0), and on weeks 12, 24, and 26. The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of proper fasting practice. A subject must be queried to assess compliance with a minimum of 8-hour fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for approximately 8 hours, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting. A list of laboratory tests is included in Table 4.

Low density lipoprotein cholesterol (LDL-C) will be calculated by the Friedewald equation. If triglycerides are > 400 mg/dL, the calculated LDL-C value is invalid by this equation and will be set as missing. Direct LDL-C will be determined in subjects whose triglycerides are > 350 mg/dL at screening visit. All subsequent LDL-C of these subjects will be determined by the same direct LDL-C measurements only. If the triglycerides are >350, a reflex test will be performed based on direct LDL measurement. In that case, two values will be reported but only the direct LDL-C will be used for the analysis as the screening value. The following algorithm will be used to obtain LDL-C values for the analyses:

1. Select subjects (based on the SI unit) who had screening triglycerides >3.4 or >350 based on the conventional unit
2. Take the LDL – direct measurement values only, throughout the study visits for those subjects
3. If screening trig > 350 and no direct LDL-C values have been determined, take the calculated.

Among those subjects who have screening triglycerides >350 and have both calculated and direct LDL-C values, only take the direct LDL-C.

Urinalysis microscopy will be conducted if the subject has a positive result on the leukocyte esterase or nitrite dipstick tests to clarify the significance of the finding. Results of glucose measurement in the urinalysis must be suppressed from the

laboratory reports so the sponsor, investigators, study coordinators, pharmacists, study subjects, and the CEC members will remain blinded to the dosing assignment.

The baseline value will be the latest value obtained on or prior to Day 1. Change from baseline for all continuous parameters will be calculated as the post-baseline value minus the baseline value.

Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum and maximum) for continuous variables, and frequency and percentage of subjects for categorical and ordinal variables

Observed values (in SI units) and change from baseline over time will be summarized by treatment group. Laboratory data will be classified as low, normal, or high relative to the parameter's reference range. Laboratory abnormalities for each treatment will also be summarized with shift tables for selected parameters.

All laboratory data will be listed. For hematology, chemistry, including serum lipids, columns will be included for normal ranges and individual abnormal laboratory values will be flagged and clinical significance will be indicated. Listing for urinalysis will include the microscopic examination provided for subjects who have a positive result from the urinalysis dipstick evaluation.

Table 4 List of Laboratory Tests

Test Name		Blood or Urine Vol. (mL)	Shipment
Hematology -Hematocrit (Hct) -Hemoglobin (Hgb) -Mean corpuscular hemoglobin (MCH) -Mean corpuscular hemoglobin concentration (MCHC) -Platelet count	-Mean corpuscular volume (MCV) -Red cell distribution width (RDW) -Red blood cell (RBC) count -White blood cell (WBC) count with differential	2 (blood)	Ambient
Serum Chemistry and Electrolytes -Albumin (ALB) -Alanine aminotransferase (ALT) -Aspartate aminotransferase (AST) -Blood urea nitrogen (BUN) -Glucose -Bicarbonate (HCO_3) -Creatinine -Chloride (Cl) -Total protein	-Calcium (Ca) -Magnesium -Phosphorus -Potassium (K) -Sodium (Na) -Total bilirubin -Direct bilirubin -Uric acid	10 (serum)	Ambient
Glycemic Control -Fasting plasma glucose (FPG) -Hemoglobin A1c (HbA1c)		2 (plasma) 2 (blood)	Ambient
Serum Lipids -Total cholesterol (TC) -High-density lipoprotein cholesterol (HDL-C) -Triglycerides (TG)	-Low-density lipoprotein cholesterol (LDL-C), calculated -LDL-C, direct (if applicable)	6 (serum)	Ambient
Urinalysis -Appearance -Bilirubin -Color -Glucose -Ketones -Microscopic examination of sediment	-Nitrite -Occult blood -pH -Protein -Specific gravity -Urobilinogen -Leukocyte esterase	10 (urine)	Ambient
Urinary Albumin Assessment -UACR		2 (urine)	Ambient
Urine pregnancy test (WOCBP)		2 (urine)	Local
Population PK Sampling -Bexagliflozin plasma level		2 (plasma)	Frozen

9.5. VITAL SIGNS

Vital signs will be measured at the screening visit, baseline visit (Week 0), and at weeks 6, 12, 24, and 26. Measurements of vital signs will include measurement of supine, sitting and standing blood pressure (BP) measurements, and heart rate. Only the BP measured in the sitting position will be used to determine eligibility. Orthostatic systolic and diastolic BP will be calculated as supine measurement – standing measurement.

For BP, pulse rate, and respiration rate, observed values and change from baseline will be summarized by treatment group and visit using descriptive statistics (n, mean and median, SD, Q1, Q3, minimum, and maximum). BP summary will include supine, sitting, standing and orthostatic BP. Safety analysis set will be used for table summary. Subjects vital sign measurements, including scheduled and unscheduled visits, will be listed.

9.6. ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) will be conducted at the screening visit and at week 24. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT interval. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities or arrhythmia.

For each abnormal ECG result, the investigator shall ascertain if the observation represents a clinically significant change from the screening ECG for that individual subject (this determination, however, does not necessarily need to be made the first time an abnormal result is observed. The investigator may repeat the ECG to verify the results of the original result). If the ECG result is determined to be a clinically significant and abnormal change from baseline for that subject, it is considered an AE.

For the ECG parameters, observed values and change from screening from scheduled visits will be summarized with descriptive statistics (n, mean, SD, median, minimum and maximum) by treatment group and overall at each visit. The maximum change from baseline from scheduled visits will also be provided for ECG parameters.

For the ECG overall assessment, the number and percentage of subjects in each overall assessment category (normal, abnormal but not clinically significant, abnormal and clinically significant, missing) will be presented by treatment group and overall at each visit.

9.7. PHYSICAL EXAMINATION

A complete physical examination will be conducted at the baseline visit (Week 0). The examination will include measurement of body weight, and a general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, and extremities. An abbreviated physical examination will be conducted at screening visit and at weeks 12, 24, and 26 or clinically indicated. The examination will include body weight and height (height will be measured only at screening), and general assessment of the skin, heart, lungs and abdomen. Physical examination findings will be presented in a by-subject listing.

10. ANALYSIS OF PHARMACOKINETICS

PK analyses will be included in a separate population PK analysis plan.

11. INTERIM ANALYSES

No interim analyses are planned.

12. DATA AND SAFETY MONITORING BOARD

An independent data and safety monitoring board (DSMB) will review descriptive summaries of accumulating safety, subject disposition and limited efficacy data every 6 months, or a frequency recommended by the DSMB.

A designated statistician who is not involved with the study operation will hold the treatment codes. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies. The data outputs for this review will be created by an unblinded team. Personnel involved in the conduct of the study will not participate in the preparation of these outputs, receive the data, or participate in the unblinded portions of the DSMB meetings. More details will be provided for DSMB charter and DSMB SAP.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

In efficacy analysis in section 8, baseline eGFR categories, instead of screening eGFR, will be used as covariate and bases of subgroups analysis of key secondary analysis HbA1c in each eGFR groups. Albunimuria will be analyzed categorically, instead of change from baseline as continuous variable, due to some large outliers in the dataset.

14. REFERENCE LIST

Bodner TE. What improves with increased missing data imputations? Structural Equation Modeling: A Multidisciplinary Journal 2008; 15: 651—675.

White IR., Royston P., Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 2011; 30: 377—399.

15. PROGRAMMING CONSIDERATIONS

The following conventions will hold for programming of outputs:

- SAS® Version 9.3 or higher will be used for programming and production

- The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

- Patients in this study will be identified as "Subjects."

- Descriptive statistics will be displayed in the following order:

n
Mean
SD
Q1
Median
Q3
Minimum
Maximum

- Decimal places: For summary statistics, the minimum and maximum will be reported with the same number of decimal places as the collected measure, the mean, LS mean (if applicable) and median will have 1 more decimal place than the measure collected, and the SD and confidence interval (CI) will have 2 more decimal places than the collected measure. For frequency distributions, percentages will be reported to 1 decimal place. For p-values, 4 decimal places will be reported or the SAS® p-value format of "< 0.0001" or "> 0.9999" will be reported.

- Unless otherwise noted, the denominator for percentages is the number of subjects in the applicable analysis set and treatment group.

- If the frequency for a particular table cell is zero, then "0", properly aligned, will be displayed (i.e. "0 (0.0%)" will not be displayed.)

- Non-numeric values: Where variables are recorded using < (e.g., "< 10" or "≤ 10") the numeric portion of the resultwill be used (e.g., < 10 and ≤ 10 becomes 10) for summary; where variables are recorded using > (e.g., "> 10" or " ≥ 10") the numeric portion of the result will be used (e.g. > 10 and ≥ 10 become 10) for summary; the actual recorded results, (e.g. "< 10" or "> 10") will appear in listings.

15.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

15.2. TABLE, LISTING, AND FIGURE FORMAT

15.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 9
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 9.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- All output should have the following header at the top left of each page:
  Theracos Sub, LLC
  Protocol Number: THR-1442-C-448
- Draft or Final in top right corner.
- All output should have Page n of N at the top of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should

appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

15.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

15.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values will be presented in a separate comparison column (if applicable).
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be active treatment first, then placebo, followed by a total column (if applicable).

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

15.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified in mock-up shell, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Q1	XXX.X
Median	XXX.X
Q3	XXX.X

Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If the rounded percentage is 0.0, display as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for concomitant and rescue medications should be presented by treatment class with the highest occurrence in the total column in decreasing order. Tabular display of data for medical history and adverse event data should be presented by the SOC using internationally agreed order. Within the drug class and SOC, medical history (by preferred term), drugs (by ATC2 code), and adverse events (by preferred term) should be displayed in decreasing order in the total column. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated should be reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

15.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

16. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

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20. MOCK-UPS

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Attachment 3: Planned Figure Shells

21. APPENDIX

21.1. RESCUE MEDICATION ADJUDICATION PROCESS

Attachment 5: THR-1442-C-448 SAP rescue med review plan v1.0 20171115

21.2. SAS CODE USED IN THE ANALYSES

Attachment 4: SAS Code Used in the Analyses