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

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADA	American Diabetes Association
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CEC	Cardiovascular Endpoint Committee
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimating Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
GLP-1	Glucagon-like Peptide-1
GMI	Genital Mycotic Infection
GGT	Gamma Glutamyl Transferase
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
Hct	Hematocrit
HDL-C	High Density Lipoprotein Cholesterol
Hgb	Hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization

Abbreviation	Description
ITT	Intention to Treat
IVRS	Interactive Voice Randomization System
IWRS	Interactive Web Randomization System
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Event
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hematocrit
MCV	Mean Cell Volume
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial Infarction
Min	Minimum
mL	Milliliter
MMRM	Mixed Model Repeated Measures
N/A	Not Applicable
NA	Not Applicable
Na	Sodium
NCI	National Cancer Institute
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
QTc	Time between the start of the Q wave and the end of the T wave in the ECG, corrected for heart rate
RBC	Red Blood Cell

Abbreviation	Description
RR	Time between the start of one R wave and the start of the next R wave in the ECG
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
SS	Safety Set
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TLF	Table, Listing And Figure
UACR	Urine Albumin To Creatinine Ratio
UGE	Urine Glucose Excretion
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.

Serious adverse event data on adverse event form will be reported. Detailed serious adverse event follow-up data will be reported from ARGUS database and is not included in 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 subjects complete the planned 24 weeks of blinded study treatment and the subsequent follow-up period or terminate early from the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

To determine the placebo-adjusted treatment effect of bexagliflozin tablets, 20 mg on the change in HbA1c from baseline to week 24 in subjects with type 2 diabetes mellitus (T2DM) and inadequate glycemic control.

3.2. KEY SECONDARY OBJECTIVES

The key secondary efficacy objectives of this study are:

- To compare the effect of bexagliflozin to effect of placebo on the change in systolic blood pressure (SBP) from baseline to week 24
- To compare the effect of bexagliflozin to the effect of placebo on the change in body weight from baseline to week 24 in subjects with a BMI ≥ 25 kg/m^2

The other exploratory secondary efficacy objectives are:

- To compare the effect of bexagliflozin to the effect of placebo on the proportion of subjects with HbA1c of < 7% over time
- To compare the effect of bexagliflozin to the effect of placebo on change in HbA1c over Time
- To compare the effect of bexagliflozin to the effect of placebo on FPG over time

3.3. SAFETY OBJECTIVES

- To compare the safety of bexagliflozin to the safety of placebo in subjects with T2DM.
- To compare the effect of bexagliflozin to the effect of placebo on the incidence of adverse events (AE) of special interest. AEs of special interest include either upper or lower UTIs, GMI, hepatic toxicity, hypoglycemia, falls and fractures, cardiovascular events, malignancies, hypersensitivity reactions, hypotensive episodes, acid-base disorders, renal failure events, and amputations.
- To contribute major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo.

MACE+ is defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina.

3.4. BRIEF DESCRIPTION

THR-1442-C-450 is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. It is designed to compare the efficacy and safety of once daily oral administration of bexagliflozin tablets, 20 mg to bexagliflozin tablets, placebo, in treatment-naïve type 2 diabetic subjects or subjects previously treated with no more than one oral hypoglycemic agent (OHA).

All eligible subjects will start a 2 week placebo run-in period. Subjects who miss no more than one dose of the run-in medication, have fasting blood glucose values ≥ 250 mg/dL on no more than two consecutive days, and who, at the baseline visit (Visit V5), have an HbA1c level between 7 and 10.5% and a fasting glucose level < 250 mg/dL will be eligible for randomization.

Approximately 210 subjects will be randomly assigned to receive oral bexagliflozin tablets, 20 mg or placebo, in a 2:1 ratio once daily for 24 weeks in an out-patient setting. Subjects with uncontrolled hyperglycemia based on blood glucose levels may receive additional approved anti-diabetic medications. Treatment group assignment at the start of the treatment period will be stratified by HbA1c level at the start of the run-in period (7.0 to 8.5% or 8.6 to 10.5%) and background anti-diabetes treatment status (treatment naïve or not).

Each subject will be contacted by telephone at week 2 (Visit V7) for safety monitoring and will be instructed to return to the clinic at weeks 6, 12, 18, and 24 (Visits V8, V9, V10, V11) for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up visit at week 26 or two weeks after the last dose of investigational product if the subject terminates prior to week 24 (Visit V12).

3.5. SUBJECT SELECTION

The study will enroll both male and female subjects with T2DM. If treatment naïve, they must have an HbA1c at the screening visit of between 7% and 10.5%. Alternatively, prospective subjects may be eligible if at the time of the screening visit they are being treated with one OHA, have an HbA1c of between 6.5% and 10.0% and are willing to complete a 6-week washout. Individuals taking thiazolidinediones are not eligible for the study. A candidate will be considered treatment-naïve if he or she has received no more than 14 days of prescription medication for diabetes in the 12 weeks prior to screening.

3.5.1. Inclusion Criteria

Refer to protocol section 4.2 for inclusion criteria.

3.5.2. Exclusion Criteria

Refer to protocol section 4.3 for exclusion criteria.

3.6. DETERMINATION OF SAMPLE SIZE

Approximately 210 subjects will be randomized 2:1 to bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo. The sample size calculation for this study was based on a two group t-test with a two-sided significance test at the 5% level and the following assumptions:

1. The difference in mean change from baseline to week 24 in HbA1c in the bexagliflozin group compared to that of the placebo group will be -0.5%.

2. The standard deviation for the difference in mean change from baseline to week 24 in HbA1c between the bexagliflozin group and the placebo group will be 1.0%.

Under the above assumptions, an estimated sample size of 128 and 64 evaluable subjects in the bexagliflozin and placebo arms, respectively, yielded a 90% power that bexagliflozin treatment will be found to be significantly different from placebo. To account for an estimated drop-out rate of approximately 10%, the study design anticipates randomizing 140 and 70 subjects in the bexagliflozin and placebo arm, respectively.

3.7. TREATMENT ASSIGNMENT & BLINDING

3.7.1. Treatment Assignment

Eligible subjects who complete the run-in period and meet all study inclusion/exclusion requirements will be randomized in a 2:1 ratio to receive once daily bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo, during the 24-week treatment period. Subjects will be assigned to treatment groups in sequential order as they qualify for the study, using a centrally located and managed Interactive Web Response System (IWRS). Randomization will be stratified according to HbA1c measured at the last assessment prior to randomization (Visit V5) (HbA1c at 7.0 to 8.5% or 8.6 to 10.5%) and background anti-diabetic treatment status (treatment-naïve or on treatment).

Potential study subjects will be screened and assigned a subject number. Once all screening procedures are completed and the study eligibility is confirmed by the investigator, the randomization numbers will be allocated to subjects within the

appropriate treatment group by the randomization system. Once a screening or randomization number has been assigned, it will not be re-used in any event. No subjects will be randomized into the study more than once. If a randomization number has been allocated incorrectly, no attempt will be made to remedy the error once study medication has been dispensed. The subject will continue with the randomization number and study medication. The study staff will notify the Sponsor Contact as soon as the error is discovered without disclosing the study medication administered. Admission of subsequent eligible subjects will continue using the next unallocated number in the sequence.

The study will be conducted at multiple investigative sites and will likely involve a variable numbers of subjects at each site. Enrollment will be on a competitive basis but each site will be capped at 21 randomized subjects. However, when a site reaches 21 randomized subjects, if a potential subject at that site is in washout or run in already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized. Subject randomization will be deactivated for all sites when the planned number of subjects has been enrolled. However, if a potential subject is in washout or run in already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized.

3.7.2. Blinding

This is a double-blind placebo-controlled study. The sponsor, investigators, study coordinators, pharmacists, study subjects, and the cardiovascular endpoint committee (CEC) 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 assignments, central laboratory glucose urinalysis data will not be made available to any study personnel or subjects.

If knowledge of the test substance 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 in the case report form (CRF) and the sponsor must be notified within 24 hours.

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

3.8. ADMINISTRATION OF STUDY MEDICATION

The following investigational products will be used for oral administration:

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

Bexagliflozin tablets, 20 mg or placebo, should be taken with 250 mL of water in the morning prior to eating or drinking.

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 with 250 mL of water in the morning prior to eating or drinking. There will be no change of dose during the 24-week treatment period.

On the day of each scheduled clinic visit, subjects must fast for approximately 10 hours prior to the collection of blood samples. On the day of each scheduled clinic visit, bexagliflozin tablets should be taken with water in the morning prior to eating or drinking (as above) and prior to the collection of blood samples. During the fasting period, only water will be permitted.

3.9. STUDY PROCEDURES AND FLOWCHART

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

A visit window of ± 3 days is allowed for all visits except Visit 6. V6 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 an approximately 10 hours fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for approximately 10 hours, the subject must return as soon as can be arranged (within 1 week) to provide a specimen after proper fasting. Blood samples will be transported to the central lab for analysis.

Table 1 Schedule of Events

Procedure	Screen -ing	Washout		Run In		Treatment Period						Follow -Up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Time to Randomization Visit (weeks)	-11	-8	-6	-2	-0.5	0	2	6	12	18	24	26
Informed Consent	X											
Screening or Confirmation for I/E Criteria	X	X			X							
Medical History	X											
Diet and Exercise Counseling		X		X								
Physical Examination					X							X
Abbreviated Physical Examination	X										X	
Vital Signs	X				X			X	X	X	X	X
Electrocardiography	X				X						X	X
Hematology	X				X			X	X	X	X	X
Serum Chemistry and Electrolytes	X				X			X	X	X	X	X
Glycemic Control	X				X			X	X	X	X	X
Serum Lipids	X				X				X		X	X
Urinalysis	X				X			X	X	X	X	X
Infectious Disease Testing	X											
UACR	X				X						X	
Urine Pregnancy Test (all women)	X											
Urine Pregnancy Test (WOCBP)					X			X	X	X	X	X
Diary and Glucometer Dispensation		X		X								
Dispensing Run-in Drug				X								
Diary and Glucometer Record Review			X	X	X	X	X	X	X	X	X	X

Procedure	Screen -ing	Washout		Run In		Treatment Period						Follow -Up
Dispensing Investigational Product						X			X			
Adverse Events & DKA Assessments		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessments		X	X	X	X	X	X	X	X	X	X	X

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

- Change in HbA1c from baseline to week 24 in subjects with type 2 diabetes mellitus (T2DM) and inadequate glycemic control

4.2. SECONDARY EFFICACY ENDPOINTS

The key secondary efficacy endpoints include:

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

The exploratory secondary efficacy endpoints include:

- Change from baseline in HbA1c over time
- Proportion of subjects with HbA1c of < 7% over time
- Change from baseline FPG over time

4.3. SAFETY ENDPOINTS

- AEs
- AE of special interest
- Clinical laboratory results
- Physical exam results
- Vital signs
- ECG results
- Medication use

5. ANALYSIS SETS

5.1. SCREENED ANALYSIS SET

The screened analysis set will include all subjects screened for eligibility prior to randomization. The screened population will include screen failures. Unless specified otherwise, this population will be used for subject listings and for summaries of subject disposition.

5.2. SAFETY ANALYSIS SET

All subjects who are randomized and have taken at least one dose of double-blind study medication will be included in the Safety Analysis Set. Safety analyses will be based on the first medication kit that was dispensed to a subject. 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 the randomization schedule. 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 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 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 monitoring visits. Major protocol deviations that could affect the primary and secondary variables, in the opinion of the medical monitor, will be considered when determining a subject's eligibility for the PP population.

Table **2** describes some possible types of major protocol deviations. All protocol deviations will be reviewed and determined as major or minor before database lock.

Table 2 Some Possible Types of Major Protocol Deviations

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; Placebo; and total of all treatment groups. All available data from subjects who signed an informed consent 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 statistical tests will be two-tailed 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.

No data imputation will be applied for missing values, unless otherwise specified.

6.2. KEY DEFINITIONS

6.2.1. Baseline Values

For safety endpoints, baseline is defined as the last non-missing value before the first dose of double-blind study medication. For baseline demographics and efficacy endpoints, baseline is defined as the last non-missing value before the randomization date.

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 eCRF. 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 Duration = 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 eCRF. Any missing date of last contact on the End-of-Study eCRF will be imputed as the date of last contact recorded in the database.

6.3. MISSING DATA

The handling of missing or incomplete data is described for each endpoint and data type (as needed) in Section 7 to 9.

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 – 105	Day 84	Visit 9/Week 12
Day 106 - 147	Day 126	Visit 10/Week 18
>= Day 148	Last Dose Date + 1	Visit 11/Week 24

* Week 24 is the end of treatment visit for those subjects completing the study per protocol. For safety 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.

6.5. POOLING OF CENTERS

Subjects will not be pooled based on site size, but rather by country, to ensure a sufficient number of subjects per treatment arm in both ITT and PP populations for analysis that contain country as a model effect. Pooling by country will not be performed if the number of subjects at Canadian sites comprises less than 5% of enrolled subjects. Otherwise, pooling by country will be performed.

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 Day -14 to Day -1 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. A separate table will display the number of subjects who met eligibility criteria at screening and washout period but withdrew prior to randomization (non-randomized subjects) with a summary of the reasons for withdrawal prior to randomization.

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 population. 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.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics include age, gender, race, ethnicity and country of investigational site. Baseline characteristics will include HbA1c, blood pressure, body weight, BMI, FPG, duration of diabetes from diagnosis to the date of informed consent, and stratification factors including HbA1c values at V5 and background anti-diabetic treatment status (treatment naïve or not). 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 calculated as:

Age at Study day 1 = (date of informed consent - date of birth + 1) / 365.25 and round down to complete years.

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.

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 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. Changes from baseline anti-hypertensive therapy and their rationale must be recorded in the CRF.

All medication will be coded using the World Health Organization Drug Dictionary (WHO-DD) version March 2016. 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 the subject has been taking prior to the first dose of double blind study medication and that the subject is expected to continue to take for some portion of the study treatment period, as well as any medication other than the investigational product that the subject takes during the course of the study treatment period. In the case of completely missing stop date, medication will be assumed to be concomitant. A medication can be both prior and concomitant.

The medications or treatment for controlling hypoglycemia must be recorded as concomitant medications in the CRF. Any medication given to treat hyperglycemia and continued for more than 2 weeks during the treatment period is considered a rescue therapy and should be recorded in the concomitant medication log. All medication given to treat hyperglycemia will be recorded in CRF.

Concomitant medications will be presented in a summary table as well as in a subject listing. Rescue medications will be summarized in a separate table and flag in the same listing.

8. EFFICACY

Efficacy data include HbA1c, FPG, body weight, and blood pressure. All changes from baseline will be calculated as the post-treatment value minus the last non-missing assessment before randomization (Visit V5). All continuous efficacy data will be summarized for observed and change values by treatment and visit. Proportion of subjects with HbA1c of < 7% will be summarized by frequency and proportion by treatment and visit.

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. The MMRM model will include terms for background anti-diabetes treatment status (treatment naïve or not), treatment, visit, treatment-by-visit interaction and the baseline HbA1c value as a fixed effect covariate. Country will be used as a fixed effect if pooling by country is used. 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, and over week 6 to week 24. 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 1.

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 population.

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.

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 10%. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct, but if data are missing for the primary endpoints, the number, timing, pattern, and reason for the missing value will be summarized. The reason for missing value will be evaluated to investigate possible implications of missing values in efficacy assessments. The dropout patterns will be assessed by Kaplan-Meier plots, if applicable, to assess whether they differ between treatment groups. 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" (ie, probability of an observation being missing does not depend on observed or unobserved measurements) or

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

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

Sensitivity analyses will be performed as:

1. A multiple imputation method will be used to impute missing observations (including observations obtained after rescue medication) in the ITT Analysis Set prior to carrying out the MMRM analysis. All intermediate missing, drop-out, and data after rescue medication will be imputed.

2. A multiple imputation method will be used to impute missing observations (not including observations obtained after rescue medication) in the ITT Analysis Set prior to carrying out the MMRM analysis. All intermediate missing and drop-out will be imputed.

Observed data after rescue medication will be used in the MMRM analysis and not considered missing.

3. A last observation carried forward (LOCF) method will be used to impute the missing observations in the ITT Analysis Set. Subjects who are rescued before Week 24 will have their HbA1c recorded at the time of rescue and carried forward.

For sensitivity analysis 1 and 2, 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 Missing at Random (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 background anti-diabetes treatment status (treatment naïve or not) 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 1.

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, the observed data and the imputed values will be analyzed using the same MMRM model. Model will include terms for background anti-diabetes treatment status (treatment naïve or not), treatment, 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.

8.1.3. Subgroups

The primary efficacy endpoint will be summarized and analyzed by the following subgroups:

- Age (<65 years or ≥65 years)
- Gender (male or female)
- Race (white or caucasian; black or African-American; other)
- Baseline HbA1c (7.0% to 8.5% or 8.6% to 10.5%)
- Background anti-diabetic treatment status (treatment-naïve or on treatment)

- Country (USA or Canada)

8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

The key secondary efficacy endpoints include:

- Change in SBP from baseline to week 24.
- Change in body weight from baseline to week 24 in subject with BMI≥ 25 kg/m^2

The exploratory efficacy endpoints include:

- Change from baseline in HbA1c over time
- Proportion of subjects with HbA1c of < 7% over time
- Change from baseline FPG over time.

8.2.1. Key secondary efficacy endpoints and analyses

A hierarchical testing procedure will be applied to these endpoints in the sequence provided above. 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. The sensitivity analyses stated in Section 8.1.2 will be performed on all key secondary endpoints.

8.2.1.1. Change in SBP from baseline to week 24

This will be tested if the primary efficacy endpoint is significant. Change from baseline in sitting SBP at week 24 will be analyzed using the MMRM ANCOVA model with unstructured covariance assumption. The model will include terms for treatment, visit, treatment-by-visit interaction, baseline HbA1c and background anti diabetes treatment status as fixed effects and the corresponding baseline SBP value as an additional fixed effect 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 model does not converge with the unstructured correlation assumption, an autoregressive (1) model will be used.

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

This will be tested if the primary efficacy endpoint and the key secondary endpoint-change from baseline SBP are significantly different between bexagliflozin and placebo groups based on ITT analysis set. The comparison of change in body weight between randomized treatments at week 24 will be carried out using the ANCOVA model. The model will include terms for treatment, background anti diabetes treatment status and baseline HbA1c as fixed effects, and the corresponding baseline weight value as an additional fixed effect 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.

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, and in FPG over time

These endpoints will be analyzed using similar MMRM ANCOVA models as for the key secondary efficacy endpoint, Section **Error! Reference source not found.**. The treatment-by-visit interaction term will be removed if it is not significant. Of interest in the MMRM ANCOVA model is the difference between treatments on these endpoints across all post-baseline time points. Also, changes from baseline for each endpoint will be estimated and analyzed at each study visit using this MMRM model. Specifically, for each endpoint, treatment difference in least squares means will be estimated by visit from the model with the corresponding p-values and the two-sided 95% CIs of the difference between treatments.

8.2.2.2. Proportions of subjects with HbA1c of < 7% over time

This endpoint will be analyzed using generalized estimating equation logistic regression. The treatment-by-visit interaction term will be removed if not significant. An unstructured correlation structure will be used (or autoregressive(1) if the model with the unstructured structure does not converge). Of interest is the difference between treatments across all post-baseline time points. Also, odds ratios will be estimated from the model with the corresponding p-values and their two-sided 95% CIs presented at each 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. Sample SAS code will be provided in Appendix 1.

9. SAFETY

All analyses described in this section will be performed separately for each part of the study. 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, standard deviations, medians, inter-quartile range, 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 received 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. If the date of last dose is unknown, this date will be estimated using the last study drug return date, if available; otherwise, the date of the last completed visit will be used. Total dose received will be calculated as number of tablets dispensed – number of tablets returned.

Summary statistics for treatment duration (in weeks) and total dose received, as well as a frequency summary of treatment duration categories (e.g., < 1, 1 - < 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 dispensed – 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 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 serious adverse events (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

A treatment-emergent adverse event (TEAE) is defined as an AE that begin 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 bexagliflozin 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). The onset day will be missing if the start date is missing or partially missing.

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:

- All TEAEs
- All TEAEs at least possibly related to bexagliflozin
- Serious AEs
- AEs leading to treatment discontinuation
- AEs leading to death.

Additional information will be collected for diabetic ketoacidosis (DKA). These data will be listed.

9.3.3. AE of Special Interest

AE of special interest include urinary tract infection (UTI), genital mycotic infection (GMI), diuretic effects, hepatotoxicity, cardiovascular events, hypoglycemia, fracture, malignancy, hypersensitivity reactions, hypotensive episodes, acid-base disorders, renal failure events, and amputations. These AEs of special interest, except for cardiovascular events 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. Cardiovascular events, hypoglycemia events by severity, and amputations will be summarized separately.

9.3.3.1. AE of special interest identified by 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. Each category of events will be displayed in a separate listing.

9.3.3.2. Hypoglycemic 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. Major Adverse Cardiovascular Events

Cardiovascular events considered as MACE by investigator will be submitted to an independent 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. The number, percentage and incidence rate per 100 patient years of suspected MACE and adjudicated MACE will by summarized for each treatment group. Adjudicated MACE will be further summarized by PTs.

9.3.3.4. 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.

9.4. LABORATORY EVALUATIONS

Laboratory tests will include hematology panel, chemistry panel, serum lipids, and urinalysis testing. Hematology, chemistry, serum lipids, and urinalysis will be performed at the following time points: at the screening visit (Week - 11), on baseline visit (Day -3 to -5), and at week 6, 12, 18, 24, and 26. Serum lipids will be performed at the screening visit (Week - 11), on baseline visit (Day -3 to -5), and on week 12, 24, and 26. Renal functional testing by UACR will be determined at the screening visit, on baseline visit and at week 24. 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 an approximately 10-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 10 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 triglycerides are >350 mg/dL, a reflex test will be performed based on direct LDL measurement. 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 triglycerides > 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 values, only take the direct LDL.

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 prior to Day 1. Change from baseline for all continuous parameters will be calculated as the post-baseline value minus the baseline value. All continues variables will be summarized by number of subjects [n], mean, SD, Q1, median, Q3, minimum and maximum and categorical

variables will be summarized by frequency and percentage.

All scheduled and unscheduled results will be considered in tables that assess maximum grade or toxicity.

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, and serum lipids, columns will be included for normal ranges and individual abnormal laboratory values will be flagged and clinical significance will be indicated. A listing for the microscopic examination will be provided for subjects who have a positive result from the urinalysis dipstick evaluation.

Table 4 List of Laboratory Tests

Test Name (sample volume)		
Hematology (2 mL blood)		
• Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC)	• Mean corpuscular volume (MCV) • White blood cell (WBC) count with differential	• Red blood cell (RBC) count • Hematocrit (Hct) • Hemoglobin (Hgb) • Platelet count
Serum Chemistry and Electrolytes (3 mL serum)		
• Albumin (ALB) • ALT • AST • Blood urea nitrogen (BUN) • Creatinine • Uric acid	• Calcium (Ca) • Magnesium • Phosphorus • Potassium (K) • Sodium (Na) • Total Protein	• Glucose • Bicarbonate (HCO_3) • Chloride (Cl) • Total bilirubin • Direct bilirubin
Glycemic Control (2 mL plasma, 2 mL blood)		
• FPG	• HbA1c	
Serum Lipids		
• Total cholesterol (TC) • High-density lipoprotein cholesterol (HDL-C)	• Low-density lipoprotein cholesterol (LDL-C), calculated, or • LDL-C, direct	• Triglycerides (TG)
Infectious Disease Testing (3 mL serum)		
• Hepatitis B surface antigen (HBsAg)	• Hepatitis C virus (HCV)	
Urinalysis		
• Appearance • Bilirubin • Color • Glucose (blinded) • Ketones	• Microscopic examination of sediment • Nitrite • Leukocyte esterase • Occult blood	• pH • Protein • Specific gravity • Urobilinogen
Renal Functional Test		
• UACR		
Urine Pregnancy Test		

9.5. VITAL SIGNS

Vital signs will be measured at the screening visit (Week -11), on baseline visit (Day -3 to -5), and at week 6, 12, 18, 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 nominal visit using descriptive statistics (n, mean and median, standard deviation, Q1, and Q3, minimum and maximum). For BP, supine, sitting, standing, and orthostatic BP will be summarized. 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 (Week - 11), on baseline visit (Day -3 to -5), at week 24, and at week 26. 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 baseline from scheduled visits will be summarized with descriptive statistics 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 (Day -3 to -5) and at week 26. 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 1 (Week -11) and at week 24, 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. INTERIM ANALYSES

No interim analyses are planned.

11. 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.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There is no change from analysis planned in protocol.

13. REFERENCE LIST

Little, R., Yau, L. Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. Biometrics, 1996; 52: 1324—1333.

Ratitch, B., O'Kelly, M. Implementation of Pattern-Mixture Models using Standard SAS/STAT Procedures. Pharmasug 2011 – Paper SP04, PHARMASUG.

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.

14. 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
Standard deviation (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 population 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 result divided by 2 will be used (e.g., < 10 and ≤ 10 becomes 5) 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.

14.1. 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

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- 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 8.
- 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.

14.2.2. Headers

- All output should have the following header at the top left of each page:
  Theracos Sub, LLC
  Protocol Number: THR-1442-C-450
- 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.

14.2.3. 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

14.2.4. 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).

14.2.5. Body of the Data Display

14.2.5.1. 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.

14.2.5.2. 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, 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 descending 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.

14.2.5.3. 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

14.2.5.4. 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.

14.2.6. 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').

15. 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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Attachment 1: Planned Table Shells

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20. APPENDICES