Theracos Sub, LLC.

STATISTICAL ANALYSIS PLAN

A Phase 2b, Multi-center, Double-blind, Placebo-controlled, Dose Range Finding Study to Evaluate the Effect of Bexagliflozin Tablets on HbA1c in Subjects with Type 2 Diabetes Mellitus

THR-1442-C-449

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADA	American Diabetes Association
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CA	Calcium
CI	Confidence Interval
Cl	Chloride
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FPG	Fasting Plasma Glucose
GMI	Genital Mycotic Infection

Abbreviation	Full Term
HbA1c	Hemoglobin A1c
HCO_3	Bicarbonate
HDL-C	High-density Lipoprotein Cholesterol
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IWRS	Interactive Web Response System
K	Potassium
LDL-C	Low-density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MCHC	Mean Corpuscular Hemoglobin Concentration
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary of Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
Na	Sodium
NYHA	New York Health Association
OHA	Oral Hypoglycemic Agent
PK	Pharmacokinetic
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile

Abbreviation	Full Term
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides
TEAE	Treatment-Emergent Adverse Event
UN	Unstructured
UTI	Urinary Tract Infections
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

Study THR-1442-C-449 is a Phase 2b, multi-center, double-blind, placebo-controlled, dose range finding study. The goals of the study are to evaluate the efficacy and safety of once daily bexagliflozin at 5 mg, 10 mg and 20 mg strengths compared to placebo in either treatment-naïve type 2 diabetic subjects or subjects previously treated with one oral hypoglycemic agent (OHA) and to identify the optimal dose(s) for further clinical study.

The statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report (CSR) for Protocol THR-1442-C-449. The statistical methods and analyses described here are based on those presented in Section 9 of the study protocol (Version 2: 16 February 2015).

Blood samples for a population pharmacokinetic (PK) analysis will be collected and the required plasma concentration determined, however, the PK parameters will be assessed separately as a population PK analysis (i.e., the population PK analysis will not be described in this SAP).

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

Primary Objective

- To identify dose(s) of bexaglifloxin for further clinical study through the comparison of hemoglobin A1c (HbA1c) change from baseline in each active group that will receive bexagliflozin tablets, 5 mg, 10 mg or 20 mg, to the placebo group over 12 weeks of treatment

Secondary Objectives

- To assess the change in HbA1c over time
- To assess the efficacy of bexagliflozin in lowering fasting plasma glucose (FPG) as a function of time
- To assess the efficacy of bexagliflozin based on the proportion of subjects who reach the American Diabetes Association (ADA) and the Japan Diabetes Society target HbA1c of <7%
- To assess the effect of bexagliflozin on systolic and diastolic blood pressure over time

- To assess the effect of bexagliflozin on body weight over time
- To assess the safety of bexagliflozin in subjects with type 2 diabetes mellitus (T2DM)

Other Exploratory Objective

- Population PK evaluation of bexagliflozin plasma concentration

2.2 STUDY DESIGN

A brief summary of the main study design features and assessments to be performed is presented here. Refer to Section 3 of the study protocol for complete details.

This is a Phase 2b, multi-center, double-blind, placebo-controlled parallel group, dose range finding study of once daily bexagliflozin tablets in either treatment-naïve type 2 diabetes subjects or subjects previously treated with one OHA. Treatment-naïve subjects are those who have never received prescription anti-diabetic medications or who have received no more than 14 days of prescription medications for diabetes in the 12 weeks prior to enrollment. Subjects who meet all of the inclusion criteria, none of the exclusion criteria and who consent to participate in the study are eligible to be enrolled to complete a 6 to 10 week washout (only required if the subject is not treatment naïve), and a 2 week placebo run-in period prior to being randomized. Subjects who can adhere to the run-in medication dosing scheduled (i.e., miss no more than one dosage in 2 weeks) and who have HbA1c between 7 and 8.5% at baseline will be eligible for randomization. Eligible subjects will be randomized to receive oral bexagliflozin tablets, 5, 10, 20 mg or placebo, once daily for 12 weeks in an outpatient setting. Subjects will visit their study site at weeks 2, 6 and 12 for safety and efficacy evaluation, with a follow up visit at week 14.

2.2.1 Number of Subjects

Approximately 320 subjects will be randomized into this study, with approximately 80 subjects in the placebo group and 80 subjects in each of the three bexagliflozin treatment groups (5 mg, 10 mg and 20 mg).

The study will be conducted at multiple investigative sites 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 32 subjects. Activation of investigational sites will be centrally controlled by interactive web response system (IWRS). Subject randomization will be deactivated for all sites when the planned number of subjects is met. However, if a potential subject is in the washout period and wishes to participate in the study, the subject will be allowed to continue and, if eligible, to be randomized.

2.2.2 Randomization and Blinding Procedures

Eligible subjects, who sign the informed consent form (ICF), complete the run-in period and meet all inclusion/exclusion requirements will be randomized in a 1:1:1:1 ratio on Day 1 (Visit 1 – Treatment Phase) to receive investigational product according to a computer-generated randomization schedule. Subjects will be assigned to treatment groups in sequential order as they qualify for the study, using a centrally located and managed IWRS. Randomization will be stratified according to background anti-diabetic treatment status (treatment naïve or taking one OHA). Upon randomization, each subject will receive a subject randomization number and a drug kit assignment.

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. 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 the electronic case report form (eCRF) and the sponsor must be notified within 24 hours.

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 Data Safety Monitoring Board (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.

2.2.3 Efficacy Assessments

Efficacy assessments will include blood draws for a glycemic control laboratory panel, including HbA1c and FPG, body weight, and systolic and diastolic blood pressure (BP).

Blood samples for HbA1c and FPG will be obtained at Screening (Visit S1), Run-in (Visit S5), Treatment Period Visits 2, 3, 4 and Follow-up Visit 5. Body weight will be measured at Screening (Visit S1), Washout (Visit S2), Run-in (Visit S5), Treatment Period Visits 2, 3, 4 and Follow-up Visit 5. Supine, sitting and standing

BP measurements will be obtained at Screening (Visit S1), Run-in (Visits S4 and S5), Treatment Period Visits 2, 3, 4 and Follow-up Visit 5.

2.2.4 Safety Assessments

Adverse event (AE) occurrences will be recorded throughout the study. For non-serious AEs, documentation will start from the time the subject signs the ICF until the last scheduled contact. For serious adverse events (SAEs), documentation will start from the time the subject signs the ICF through 14 days after the last treatment, or for ongoing events, until the event is resolved or the subject is lost to follow-up. Careful evaluation and documentation of the following potential adverse events of special interest, as outlined in Sections 6.10.6 through 6.10.9 of the Protocol, will also occur throughout the study: urinary tract infections (UTIs), genital mycotic infections (GMIs), hepatotoxicity and hypoglycemia.

A complete physical examination will be performed at Screening (Visit S1) and at the Follow-up Visit 5. Unless clinically indicated, an abbreviated physical examination will be performed at Run-in (Visit S5) and Treatment Period Visit 4. Vital sign measurements (supine, sitting and standing blood pressure, pulse, temperature and respiratory rate) will be performed at Screening (Visit S1), Run-in (Visits S4 and S5) and Treatment Period Visits 2, 3, 4 and Follow-up Visit 5. A 12-lead electrocardiogram (ECG) will be conducted at Screening (Visit S1), Run-in (Visit S5), Treatment Period Visit 4, Follow-up Visit 5 and whenever clinically indicated. ECG measurements include RR interval, PR interval, QRS duration, QTcB, P wave axis and QRS axis, overall interpretation. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities.

Clinical laboratory tests, including hematology, serum chemistry and electrolytes, lipids, infectious disease testing, urine drug screen, urinalysis and urine pregnancy test [women of childbearing potential (WOCBP) only], will all be obtained at Screening (Visit S1). Hematology, serum chemistry and electrolytes samples will also be obtained at Run-in (Visit S5), Treatment Period Visits 2, 4 and Follow-up Visit 5. Serum lipids will be obtained at Run-in (Visit S5), Treatment Period Visit 4 and Follow-up Visit 5. Urinalysis and urine pregnancy test (WOCBP only) will be obtained at Washout (S2), Run-in (Visits S4 and S5), Treatment Period Visits 2, 3, 4 and Follow-up Visit 5.

2.2.5 Other Assessments

Other assessments include concomitant medication use throughout the study and compliance with study drug administration. Compliance is reviewed at each visit after investigational product has been dispensed. In addition, for subjects who fail to

complete the study (through follow-up) or treatment, the reason for study or treatment discontinuation will be recorded.

Blood samples for the population PK analysis will be drawn at Treatment Period Visits 2, 3 and 4.

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Table 1. Schedule of Events

	Screen -ing	Washout		Run-in		Treatment				Follow Up
Visit number	S1	S2	S3	S4	S5	V1	V2	V3	V4	V5
Time to Randomization (weeks)[1]	up to 15 weeks	-12 or -8	-10 or -6	-2	-0.5	0	2	6	12	14
Informed Consent	X									
Screening for I/E criteria	X	X			X					
Demographics and medical history	X									
Diet & exercise counseling[2]		X		X						
Physical exam[3]	X				X				X	X
Body weight	X	X			X		X	X	X	X
Diary & glucometer record review[4]			X	X	X	X	X	X	X	X
Start washout		X								
Dispense Run-in Medication				X						
Randomization						X				
Vital signs	X			X	X		X	X	X	X
ECG	X				X				X	X
Dispense study medication[5]						X				
Blood draw for clinical lab test[6]	X				X		X	X	X	X
Population PK sampling							X	X	X	
Urine collection[7]	X	X		X	X		X	X	X	X
AE		X	X	X	X	X	X	X	X	X
Con Med		X	X	X	X	X	X	X	X	X

[1] *Screening period may last up to 3 weeks; washout period will be 10 weeks for subjects on a TZD or 6 weeks for subjects on other OHA, which includes a clinic visit (S2) and a phone interview (S3); run-in period is to be 2 weeks (S4 to S5); the treatment period (V1 to V4) will be 12 weeks. A visit window of ± 3 days is allowed for all visits except visit V1. Visit V1 is to be scheduled at 3 days after visit S5 and can be extended to 5 days pending on HbA1c value availability.*

[2] *Counseling will be performed at S2 for washout and at S4 for treatment naïve subjects.*

[3] *A complete physical examination will be performed by the investigator at screening (S1) and at the termination visit (V5). Abbreviated physical examinations will be performed by the investigator at all other time points, unless clinically indicated. General assessment of the skin, heart, lungs and abdomen will be performed.*

[4] *Glucometer and diary will be dispensed to each enrolled subject at visit S2 (for subjects undergoing washout) or S4 (for subjects not undergoing washout), and subjects will be trained in glucometer use and SMBG recording. The SMBG record will be reviewed by the investigator at all subsequent visits.*

[5] *At visit V1, an investigational product kit will be dispensed; subjects should bring in their study medication to be checked on visits V2, V3, and V4.*

[6] *Blood sample collection and laboratory tests at designated visits are listed in Appendix 2 of the Protocol. A minimum fasting time of 10 h must be confirmed prior to blood draw.*

[7] *UPT is scheduled for all women at screening and for WOCBP thereafter.*

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher.

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in subject data listings. Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], first quartile [Q1], median, third quartile [Q3], minimum and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage.

Means, medians and confidence intervals (CIs) will be reported to one decimal place more than what is reported on the eCRF or by the laboratory/vendor. Standard deviations will be reported to two decimal places more than what is reported in the data. Interquartile range values (Q1 and Q3) and minimum and maximum values will be reported to the same number of decimal places displayed on the eCRF or by the laboratory/vendor.

P-values will be reported to four decimals.

3.1.3 Significance Level

Inferential treatment comparisons on efficacy endpoints will be declared statistically significant at the 0.050 level using two-tailed tests. There will be no adjustments made for multiple comparisons. Tests for interaction will be declared statistically significant at the 0.100 level.

All confidence intervals will be two-sided 95% CIs.

3.1.4 Multiplicity

The primary objective of this study is to identify the effect of bexagliflozin tablets in three strengths on the placebo-corrected change from baseline in HbA1c after 12 weeks of treatment. All secondary endpoints are considered exploratory and adjustment for multiple endpoints and multiple comparisons within each endpoint will not be performed.

3.1.5 Baseline and Change from Baseline

Baseline is defined as the last non-missing value obtained immediately prior to administration of the first dose. For each post-baseline value, change from baseline will be calculated by subtracting the baseline assessment value from the post-baseline assessment for each subject (i.e., post-baseline assessment – baseline assessment).

3.1.6 Study Day

Subjects will be randomized and the first dose of investigational product during the Treatment Period will be considered Day 1. Study day for event dates prior to randomization and first dose will be determined as Study Day = (Event Date – Treatment Period First Dose Date). Study day for events after randomization and treatment period first dose will be determined as Study Day = (Event Date – Treatment Period First Dose Date) + 1.

3.1.7 Handling of Missing/Incomplete Values

To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. However, if missing data are present for the primary efficacy endpoint, HbA1c, they will be handled using a multiple imputation approach, as a part of a sensitivity analysis, as described in Section 3.8.1 of the SAP. For all other endpoints, the missing data will not be imputed and only the observed data will be used for analyses. The number, timing, pattern, reason for and possible implications of missing values in efficacy and safety assessments will be investigated. The dropout patterns may be assessed by graphical methods (e.g., Kaplan-Meier plot for time to drop-out).

Rules for handling missing dates are outlined within applicable sections.

3.1.8 Methods of Pooling Data

Pooling of subjects from different study centers may be done to ensure a sufficient number of subjects per treatment arm for analyses that include study center as a model effect. Therefore, pooling will be done in the case where there is at least one study center with fewer than 5 subjects in the per protocol analysis set per treatment arm. Study centers will be pooled based on geographical region (i.e., closest geographical site) within each country. Study center pooling will be determined during a blinded review of the data prior to database lock.

3.1.9 Analysis Visit Windows

Visit windows for study conduct are specified in footnote 1 of Table 1: Schedule of Events. Treatment period visits are planned for Day 1, Randomization (V1: Week 0),

Day 15 (V2: Week 2), Day 43 (V3: Week 6) and Day 85 (V4: Week 12). There is also a scheduled follow-up visit at Day 99 (V5: Week 14). A visit window of ±3 days is allowed for all visits except for Week 0. Week 0 (Study Day 1, Randomization) is to be scheduled at 3 days after the last run-in visit (Visit S5) and can be extended to 5 days pending on HbA1c value availability.

For any unscheduled visits, Table 2 will be used to map the unscheduled assessments to the analysis visits prior to selection of records for analysis

Table 2: Nominal (Targeted) Time Points and Analysis Visit Windows

Assessment	Nominal (Targeted) Time Point	Analysis Visit Window (Interval in Study Days)
Baseline Assessments	Week 0 (Study Day 1)	≤ Day 1
Post-Baseline Assessments	Week 2 (Study Day 15)	Day 8 through Day 22
	Week 6 (Study Day 43)	Day 36 through Day 50
	Week 12 (Study Day 85)	Day 78 through Day 92
	Week 14 (Study Day 99)	Day 93 through Day 105

After mapping the data to the analysis visits, the following rules will apply unless otherwise 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 first record will be selected.
- If a subject has no record in an analysis window, the subject will be considered missing at that time point.

For subjects withdrawing early, the end of study data (early termination visit) will be mapped according to the analysis visit windows in Table 2 for summarization and analysis. However, if the visit does not fall within any of the analysis visit windows then the visit will be mapped to the next scheduled time point.

3.2 Analysis Populations and Subgroups

3.2.1 Definition of Analysis Populations

All Enrolled

All subjects who signed an informed consent form will be included in the all enrolled analysis set.

Full Analysis Set

All subjects who are randomized, take at least one dose of double-blind study medication, and have at least one post-randomization HbA1c measurement will be included in the full analysis set. All analyses of the full analysis set will be based on each subject's randomized assigned treatment.

Intent-to-Treat Analysis Set

All subjects who are randomized will be included in the intent-to-treat analysis set. All analyses of the intent-to-treat analysis set will be based on each subject's randomized assigned treatment.

Safety Analysis Set

All subjects who are randomized and take at least one dose of double-blind study medication will be included in the safety analysis set. Safety analyses will be based on the medication that was actually dispensed to each subject.

Per Protocol Analysis Set

The per protocol (PP) analysis set will include all subjects in the full analysis set who meet the study eligibility requirements as defined in Section 4 of the study protocol and have no major protocol deviations that affect the validity of the efficacy measurements. All analyses of the per protocol analysis set will be based on each subject's randomized assigned treatment. Major protocol deviations are defined as:

- Study drug compliance <80%
- Missing baseline or Week 12 HbA1c measurement
- Received prohibited medication including SGLT2 inhibitor, insulin or GLP-1 receptor agonists
- Randomization error
- Inappropriate unblinding (i.e., blind was broken (requested in IWRS) in absence of medical emergency or blind broken by unauthorized site personnel)
- Subject was dispensed with incorrect study medication

Subject exclusions will be determined on a case-by-case basis during a blinded review of the data prior to database lock. In addition, a blinded review of concomitant medications will be performed to further identify any other potential restricted medications.

3.2.2 Definition of Subgroups

Consistency of treatment effects across country (USA versus Japan) will be examined through the addition of a treatment-by-country interaction term to the statistical model for the primary efficacy endpoint. This is described in Section 3.8.1 of the SAP. No other subgroup analyses are planned.

3.3 Analysis Variables

3.3.1 Primary Efficacy Variable

- Change in HbA1c from baseline to Week 12

3.3.2 Secondary Efficacy Variables

- Change in HbA1c from baseline over time
- Change in FPG from baseline over time
- Percentage of subjects with HbA1c <7% post-baseline
- Change in systolic and diastolic blood pressure from baseline over time
- Change in body weight from baseline over time

3.3.3 Safety Variables

- Incidence of adverse events
- Percentage of subjects with a hypoglycemic event post-baseline
- Change in clinical laboratory parameters from baseline to each post-baseline assessment
- Shift in clinical laboratory parameters from baseline to each post-baseline assessment
- Change in vital sign measurements from baseline to each post-baseline assessment
- Change in ECG parameters from baseline to each post-baseline assessment

3.3.4 Other Variables

- Incidence of discontinuations and reasons for discontinuations from the study and, separately, from treatment
- Incidence of concomitant medications used

- Number of weeks on study drug
- Percentage of study drug taken relative to the planned dose

3.4 Subjects Disposition and Evaluability

3.4.1 Subject Disposition

Subject disposition will be summarized overall (all subjects) and then separately by country (USA and Japan). The overall number of subjects screened will be presented. The number of subjects randomized to treatment (intent-to-treat analysis set) and the number of subjects evaluated for safety (safety analysis set) will be presented by treatment group and overall. The number and percentage of subjects evaluated for efficacy (full and per protocol analysis sets) will be presented by treatment group and overall. The numbers and percentages of subjects completing and not completing the study through follow-up as well as the reasons for study discontinuations will be tabulated by treatment group and overall. In addition, the number and percentage of subjects completing and not completing treatment through week 12 as well as reasons for treatment discontinuations will be presented by treatment group and overall.

The demographic information for screen failures and run-in failures as well as reasons for their failures will be listed.

Screen failures are subjects who sign the informed consent but who have failed screening (e.g., subject did not meet eligibility criteria, subject withdrew consent) at Screening (Visit S1), Washout (Visit S2) or at the Phone Interview (Visit S3). Subjects who did not have study medication dispensed at the start of the Run-in Period (Visit S4) are also considered screen failures.

A run-in failure is defined as a subject who signs the informed consent but is deemed ineligible for the study (e.g., subject did not meet entry criteria, subject withdrew consent) after start of the Run-in Period but prior to randomization (Visit S5).

3.4.2 Protocol Deviations

All protocol deviations will be shown in a subject listing by treatment group. Subjects with major deviations identified as exclusions from the per-protocol analysis set will be indicated in the listing.

3.5 Demographics and Baseline Characteristics

If the full and intent-to-treat analysis sets are different from the safety analysis set then demographic and baseline characteristic analyses will be repeated using the full and intent-to-treat analysis sets.

3.5.1 Demographics

Subject demographics including age, gender, race, ethnicity, country and study center will be summarized by treatment group and overall for the safety analysis set.

Descriptive statistics will be provided for age (years). Frequencies and percentages will be tabulated for gender, race, ethnicity, country and study center.

3.5.2 Screening Characteristics

Subject baseline characteristics including screening body weight, height and body mass index (BMI) will be summarized by treatment group and overall for the safety analysis set.

Descriptive statistics will be provided for screening body weight (kg), height (cm) and BMI (kg/m^2).

3.5.3 Disease Characteristics

Subject disease characteristics including prior anti-diabetic treatment status, disease duration since diagnosis and episodes of symptomatic hypoglycemia per week will be summarized by treatment group and overall for the safety analysis set.

Descriptive statistics will be provided for disease duration since diagnosis (years). Disease duration is based on the year of first diagnosis and the year of informed consent signature (i.e., year of informed consent signature – year of first diagnosis). A value of 0 year means that the subject was diagnosed in the same year when informed consent was signed. Frequencies and percentages will be tabulated for prior anti-diabetic treatment status (whether treatment naïve or not) and for how many episodes of symptomatic hypoglycemia per week a subject experienced on average over the past year (0, 1, 2, 3 and more than 3).

3.5.4 Medical History

All significant medical and surgical history conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 17.0) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Medical and surgical history conditions will be included in a subject data listing. Type 2

diabetes history and cardiovascular disease history will also be included in subject data listings.

3.6 Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD, Version B2 June 2014). A concomitant medication is defined as any medication that the subject has taken prior to enrollment and that the subject is expected to continue to take for some portion of the study as well as any medication other than the double-blind study medication that the subject takes during the course of the study. Medications used for controlling hypoglycemia will be recorded as concomitant medications in the eCRF.

Medications started prior to administration of the double-blind study medication will be identified as prior medications and included in a subject data listing only. Medications ongoing during the treatment period or started on or after administration of double-blind study medication will be summarized for the safety analysis set. The number and percentage of subjects who took at least one medication during the double-blind period as well as the number and percentage of subjects who took each type of medication will be presented for each treatment group and all active treatment groups combined. Medications will be listed according to their WHO-DD anatomic therapeutic chemical (ATC) class level 4 and preferred drug name within ATC class level 4 by decreasing frequency of incidence for all active treatment groups combined.

- Rescue Medications

  Any medication given to treat hyperglycemia is considered a rescue therapy only if it is continued for 2 weeks or longer. Rescue medications will be identified by review of concomitant medication data, specifically the WHO-DD preferred drug name, indication field and duration of use (start and stop dates), during a blinded review of the data prior to database lock. Missing or partial start and stop dates for rescue medications taken during the double-blind treatment period are not expected, however if there are missing or partial start dates for rescue medications the same rules for handling missing or partial adverse event start dates will be applied (see Section 3.9.1). Missing or partial stop dates for rescue medications will not be imputed. Unless it is obvious from review of the partial stop date that the medication given to treat hyperglycemia could not have continued for 2 weeks or longer, it will be considered a rescue medication. Medications given to treat hyperglycemia with missing stop dates will be considered rescue medications.

Time to administration of first rescue medications will be summarized for the safety analysis set. Time to rescue medication use is derived by [(date of rescue medication – date of first study medication dose) +1 day] / 7. The number and percentage of subjects who took at least one rescue medication during the double-blind period as well as the number and percentage of subjects who took their first rescue medication during the intervals of <=2 weeks, >2 weeks - <=6 weeks, >6 weeks - <=12 weeks and > 12 weeks from administration of first double-blind study drug will be tabulated by treatment group and all active treatment groups combined.

3.7 Treatment Compliance and Exposure

3.7.1 Compliance with Study Treatment

Compliance rates during the treatment period will be derived with the following formula:

100*((Total number of tablets dispensed – Total number of tablets returned) / (Expected number of tablets to be taken over a subject's extent of exposure in days))

Expected number of tablets to be taken over a subject's extent of exposure is based on the date of first study medication dose and the date of last study medication dose [i.e., (date of last study medication dose – date of first study medication dose) +1]. If a subject is lost to follow-up, and therefore does not have a date of last study medication dose, the last visit date will be used as the date of last study dose to determine the expected number of tablets to be taken and it will be assumed that the subject did not take any tablets since the last visit date.

Compliance rates will be presented for the safety analysis set using summary statistics and percentage for the frequency distributions (0-<20%, 20-<40%, 40-<60%, 60-<80%, 80-<100%, 100-≤120%) by treatment group and overall.

3.7.2 Exposure to Study Treatment

Treatment duration (weeks on treatment) will be described in the safety analysis set using summary statistics. Treatment duration will be calculated as follows: [(date of last study medication dose – date of first study medication dose) + 1 day] / 7. Summaries will also include the number and percentage of subjects who were exposed for at least 2, >2 - ≤6, >6 - ≤12, and >12 - ≤13 weeks.

If the last dose date is unknown, the date of the last visit will be used.

3.8 Efficacy Analysis

Unless otherwise specified, all efficacy analyses will be performed using the full analysis set.

3.8.1 Primary Efficacy Endpoint(s)

The primary endpoint is HbA1c change from baseline through 12 weeks, and the primary analysis is based on the available data and data obtained after rescue will be excluded and considered missing. Mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA) with baseline HbA1c as a covariate will be fit to the available data, incorporating all visits at which HbA1c was measured for each subject including scheduled visits at Weeks 2, 6, and 12 as well as unscheduled visits for measurements of HbA1c. Treatment (placebo, 5 mg, 10 mg, 20 mg), study center, prior anti-diabetic treatment status, study visit and treatment-by-visit interaction will be applied as fixed effects and subject as a random effect.

A normal distribution will be assumed for the built-in probability distribution. Model assumption will be checked. An unstructured (UN) within-subject covariance structure will also be assumed. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Sample SAS code for this analysis is as follows:

```
proc mixed data=temp method=reml covtest;
      class subject visit treat prior center;
      model change = visit treat prior center baseline visit*treat /
      solution ddfm=KENWARDROGER;
      repeated visit / subject=subject type=un;
      lsmeans visit*treat / diff=all cl alpha=0.05;
run;
```

In the case that this covariance matrix is not an appropriate estimate, other covariance structures (e.g., compound symmetry) will be considered and ultimately determined through graphical tools (i.e., plot of changes in covariance and correlation among residuals on the same subject over lag between times of observation) and information criteria [e.g., Akaike's Information Criteria (AIC)].

Descriptive statistics will be presented for the observed measurements as well as for change from baseline by treatment group and visit overall (all subjects) and by country.

Least squares (LS) means and the corresponding standard errors (SE) of the change from baseline over time will be presented by treatment. In addition, the time profile of these LS mean and SE values will be presented graphically.

Least squares means and the corresponding standard errors for the difference in the changes from baseline over time between each bexagliflozin dose group and placebo will also be presented. Two-sided 95% CIs for the difference in these changes between each active dose and placebo will be generated. P-values from the model effects and key comparisons (i.e., treatment difference at Week 12) will be presented.

- Sensitivity Analyses

  The same MMRM model and methods as outlined above for the primary analysis will be repeated using the per protocol analysis set.

  Missing Data

  The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following sensitivity analyses will be performed on the primary efficacy variable for the full analysis set:

  1) HbA1c values collected after start of rescue medication will be considered missing. Missing HbA1c data (for Weeks 2, 6, or 12) will be imputed through multiple imputation (MI) linear regression methods which assumes a monotone missing data pattern. If the missing data pattern does not follow a monotone missing data then the Markov Chain Monte Carlo (MCMC) method will be used. The covariates to be included in the imputation linear regression model are treatment, center, age, gender, race, BMI, prior anti-diabetic treatment status as well as previous visit HbA1c values. A total of 10 imputed datasets will be generated and then analyzed using the MMRM methods as outlined above for the primary analysis. The point and variance estimates from each of these 10 analyses will be calculated. These analyses results will be combined across the 10 datasets using the standard techniques for multiple imputed data sets through SAS PROC MIANALYZE in order to yield overall treatment comparison results on imputed data.

  2) Missing HbA1c data will be imputed through last observation carried forward (LOCF), where a subject's prior post-baseline non-missing observation will be imputed for any missing post-baseline visit for which there is a prior non-missing value, and then analyzed using the MMRM methods as outlined above for the primary analysis. HbA1c values collected after the start of rescue medication will be considered missing.

  3) HbA1c values collected after the start of rescue medication will NOT be considered missing, and the MMRM methods as outlined above for the primary analysis will be re-performed.

Dropout patterns may be assessed by graphical methods (e.g., Kaplan-Meier plot for time to drop-out).

- Tests for Interaction

  For the primary efficacy model, specifically the MMRM ANCOVA model, a test for a significant treatment-by-baseline interaction will be performed in a separate model. If the treatment-by-baseline interaction is significant at an alpha=0.100, then an analysis of variance (ANOVA) model will be used instead, removing the baseline covariate.

  A treatment-by-study center interaction term will be added to the MMRM ANCOVA (or ANOVA) model used for the analyses of the primary efficacy variable. If a statistically significant treatment-by-study center interaction effect is observed at a 0.100 level, then separate analyses may be performed for each study center.

  A treatment-by-country interaction term will be added to the MMRM ANCOVA (or ANOVA) model used for the analyses of the primary efficacy variable. A statistically significant treatment-by-country interaction effect will be declared at the 0.100 level. Separate analyses will be performed for each country.

  Note that significant interactions, if only quantitative (and not qualitative) in nature, will not necessarily preclude data being pooled across the baseline covariate or across study centers for the primary analysis.

- Dose Response

  A dose response analysis on the change from baseline in HbA1c to Week 12 for the full analysis set will be conducted. Mean change from baseline in HbA1c to Week 12 (on vertical axis) will be presented graphically by dose group (on horizontal axis). Assessments of linear and quadratic dose-response trends across dose groups will be constructed using the MMRM ANCOVA model used for the primary efficacy analysis with appropriate orthogonal polynomial contrasts. P-values for each orthogonal polynomial contrast will be presented. To account for the unequal spacing of the dose levels (0, 5, 10 and 20), the coefficients to be used for the contrasts are as follows:

Linear:	-0.591608	-0.253546	0.0845154	0.7606388
Quadratic:	0.5640761	-0.322329	-0.644658	0.4029115

  The coefficients are derived based on the statistical method from Robson, D.S. 1959: A simple method for constructing orthogonal polynomials when the independent variable is unequally spaced. Biometrics 15(2): 187-191.

Additional models may be considered if the dose response curve appears to be highly influenced by any single dose group.

3.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints, fasting plasma glucose, sitting systolic and diastolic blood pressure and weight, will be analyzed using the same MMRM ANCOVA model used for the primary efficacy analysis on the full analysis set. In addition, for each secondary efficacy endpoint, the least squares means and standard errors of the change from baseline over time by treatment group will be presented graphically. Sensitivity analyses will not be performed on the secondary efficacy endpoints.

For each subject, post-baseline HbA1c values will be reviewed and subjects with at least one post-baseline HbA1c value <7% will be flagged. HbA1c values obtained after start of rescue medication will be excluded from this analysis. The number and percentage of subjects with at least one HbA1c value <7% will be summarized by treatment group for the full analysis set. A logistic model will be used to characterize treatment differences in the proportions of subjects with at least one post-baseline HbA1c value <7%. For this model, the dependent variable will take values of 1='<7%' or 0='≥7%' and the predictor variables will include treatment, study center, baseline HbA1c and prior anti-diabetic treatment status. Odds ratio for the treatment difference versus placebo, its 95% confidence interval and the associated p-value will be presented.

3.9 Safety Analysis

Safety analyses will be conducted using the safety analysis set.

3.9.1 Adverse Events

All adverse events will be coded using the MedDRA Version 17.0 and will be classified by MedDRA SOC and PT. Analyses of adverse events will be performed using the safety analysis set.

AEs that started on or after the first dose of study medication or worsened after the first dose of study medication are considered treatment-emergent AEs (TEAEs). TEAEs will be assigned to the run-in period or the double-blind period in the same manner. TEAEs occurring during the run-in period will be listed only.

For all summaries, SOCs and PTs within SOC will be presented by decreasing frequency of incidence for all active treatment groups combined.

Handling of Missing or Partial Start Dates for Adverse Events

Rules for handling incomplete or missing adverse event start dates are addressed below (stop dates will not be imputed). Once implemented, the adverse event start date will be used to identify treatment-emergent adverse events for both run-in and double-blind treatment periods.

In the unusual case that the month portion of an adverse event start date is missing but the day portion is not missing, the day portion will be assumed to be missing. Likewise, in the case where the year portion of an adverse event start date is missing but the month and/or day portion is not missing, the month and/or day portion will be assumed to be missing. All missing portion(s) of the date will be handled using the same rules:

- In the event that the day portion (and only the day portion) of the date is missing:
    - If the adverse event started in the same month and year as the first dose date, the adverse event start date will be assumed to be the first dose date.
    - Otherwise, the adverse event start date will be assumed to be the last day of the given month and year, e.g., XX–DEC-2005 would be 31-DEC-2005 where XX represents an unknown day.
- In the event that the day and month portions (and only the day and month portions) of the date are missing:
    - If the adverse event started in the same year as the first dose date, the adverse event start date will be assumed to be the first dose date.
    - Otherwise, the adverse event start date will be assumed to be last month and day of the given year, e.g., XX–XXX-2005 would be 31-DEC-2005 where XX represents an unknown day and XXX represents an unknown month.
- In the event that the day, month, and year portions of the adverse event start date are missing, it will be assumed to be the first dose date.
- If the adverse event start date has been imputed using the rules above, then the adverse event start date must be compared with the adverse event stop date to ensure the logical ordering of dates. If the imputed adverse event start date is after the non-missing adverse event stop date, then the imputed start date will be reset as the stop date.

3.9.1.1 Overall Summary of AEs

An overall summary of TEAEs will be presented by treatment group and for all active treatment groups combined. The number and percentage of subjects who experienced

at least one TEAE, at least one severe TEAE, at least one treatment-related TEAE, at least one serious TEAE, at least one treatment-related serious TEAE, at least one TEAE leading to study drug discontinuation, at least one TEAE leading to study withdrawal and at least one TEAE leading to death will be displayed. Treatment-related TEAEs are events with a study drug causality of 'possible', 'probable' or 'definite.'

3.9.1.2 AE Incidences

The incidence of TEAEs will be presented by treatment group and for all active treatment groups combined. The number and percentage of subjects who experienced at least one TEAE as well as the number and percentage of subjects who experienced each specific SOC and PT will be presented. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject. Similarly, if a subject has more than one occurrence of the same PT within a SOC, the subject will be counted only once in that SOC.

A summary table by PT will be presented using the same methods as described above for the by SOC and PT summary table.

All TEAEs will be included in a subject listing.

3.9.1.3 Maximum Severity

The incidence of TEAEs will be presented by maximum severity and by treatment group and for all active treatment groups combined. For this analysis, if a subject experiences more than one occurrence of the same PT, the subject will be counted only once under the maximum severity at which it was experienced (mild, moderate, severe). TEAEs with missing severity will be counted as severe.

3.9.1.4 Related AEs

The incidence of drug-related TEAEs will be presented by treatment group and for all active treatment groups combined. Related TEAEs are those with a 'possible', 'probable' or 'definite' relationship to treatment. TEAEs with missing relationship will be counted as related. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject. Similarly, if a subject has more than one occurrence of the same PT within a SOC, the subject will be counted only once in that SOC.

3.9.1.5 Deaths, Serious AEs and AEs That Led to Discontinuation

Subject data listings of fatal AEs, serious AEs, AEs that led to treatment discontinuation and AEs that led to study withdrawal will be presented.

3.9.1.6 AEs of Special Interest

Adverse events of special interest include the following categories:

- Genital mycotic infections
- Urinary tract infections including urosepsis and pyelonephritis
- Diuretic effects including hypovolemia
- Hypotension episodes
- Hepatotoxicity
- Major Adverse Cardiovascular Event (MACE)
- Hypoglycemia
- Falls and fractures
- Malignancies
- Hypersensitivity reactions
- Acid-base disorders
- Renal failure events

All AEs of special interest will be identified by appropriate MedDRA preferred term during a blinded review of the data.

The incidence of TEAEs of special interest by treatment group and for all active treatment groups combined will be presented separately for each category. The number and percentage of subjects who experienced at least one TEAE of special interest as well as the number and percentage of subjects who experienced each specific SOC and PT will be presented. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject. Similarly, if a subject has more than one occurrence of the same PT within a SOC, the subject will be counted only once in that SOC.

3.9.1.7 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.

Subjects will be dichotomized into two categories, having a hypoglycemic event during the double-blind period (i.e., meeting one of the above categories) or not having a hypoglycemic event during the double-blind period. The number and percentage of subjects in each category will be summarized by treatment group for the safety analysis set. For this analysis, if a subject experiences more than one occurrence of a hypoglycemic event, the subject will be counted only once under the maximum severity at which it was experienced ('relative', 'probable symptomatic', 'asymptomatic', 'documented symptomatic', 'severe'). A logistic model will be used to characterize treatment differences in the proportions of subjects with at least one hypoglycemic event. For this model, the dependent variable will take values of 1='Event' or 0='No Event' and the predictor variables will include treatment, study center, baseline FPG and prior anti-diabetic treatment status Odds ratio for the treatment difference versus placebo, its 95% confidence interval and the associated p-value will be presented.

3.9.2 Clinical Laboratory Evaluation

A list of clinical laboratory tests is given in Table 3.

Table 3. List of Laboratory Tests

Hematology	- Hematocrit - Hemoglobin - Mean corpuscular hemoglobin - Mean corpuscular hemoglobin concentration (MCHC)	- Mean corpuscular volume - Platelet count - Red blood cell (RBC) count - White blood cell (WBC) count with differential
Serum Chemistry and Electrolytes	- Albumin - 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
Glycemic Control	- Fasting plasma glucose (FPG) - Hemoglobin A1c (HbA1c)	
Serum Lipids	- Total cholesterol (TC) - High-density lipoprotein cholesterol (HDL-C) - Triglycerides (TG)	- Low-density lipoprotein cholesterol (LDL-C), calculated - LDL-C, direct5
Urinalysis[1]	- Appearance - Bilirubin	- Nitrite - Occult blood

	- Color - Glucose - Ketones	- pH - Protein - Specific gravity - Urobilinogen - Leukocyte esterase
Urine Drug Screen[1]	- Amphetamines - Barbiturates - Cocaine Metabolites	- Opiates - Benzodiazepines - Cannabinoids
Infectious Disease Testing[1]	- HBsAg	- HCV

[1] Urinalysis, urine drug screen parameters and infectious disease testing parameters will be listed only.

Continuous laboratory data will be examined for trends using descriptive statistics of changes from baseline to each planned post-baseline visit. These data will also be categorized as low, normal or high based on the reference ranges of the central laboratory. The number and percentage of subjects with indicated shifts relative to the laboratory normal ranges (low, normal, high) in their results from baseline to each post-baseline visit will be presented by category for all applicable laboratory parameters listed in Table 3. The analyses will be performed using the safety analysis set and presented by treatment group.

A separate listing for all clinically significant laboratory abnormalities will be provided.

3.9.3 Vital Signs

Descriptive statistics will be presented for orthostatic systolic and diastolic blood pressure (mmHg), orthostatic pulse (beats per minute), systolic and diastolic blood pressure (mmHg), pulse (beats per minute), temperature (Celsius) and respiratory rate (breaths/min) at each visit. For each parameter, descriptive statistics on the change from baseline to each planned post-baseline visit will be presented by treatment group for the safety analysis set.

Orthostatic systolic and diastolic blood pressure will be calculated as supine measurement – standing measurement. Orthostatic pulse will be calculated as supine measurement – standing measurement.

All vital sign results will be included in a subject listing.

3.9.4 ECG

Descriptive statistics will be presented for RR interval (msec), PR interval (msec), QRS duration (msec), QTcB (msec), P wave axis (degrees) and QRS axis (degrees) for each planned visit. For each parameter, descriptive statistics on change from baseline to each post-baseline visit will be presented by treatment group for the safety analysis set.

All ECG findings will be included in a subject listing.

3.9.5 Physical Examination and Body Weight

Physical exam findings and body weight will be included in a subject listing.

3.10 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established to review unblinded safety data on a regular basis and to make appropriate recommendations regarding the conduct of the trial. The study drug assignment will remain blinded to the sponsor, study team, investigators, study coordinators, pharmacists and study subjects for the course of the study. A designated unblinded statistical programming team at PROMETRIKA that is not involved with study operations will prepare the unblinded tables and listings. The selected tables and listings to be provided to IDMC members have a single asterisk (*) next to the table or listing title in Section 5 of this SAP.

4 Programming Specifications

It is suggested that computer-generated table output adhere to the following specifications.

1. Unless otherwise specified, all computer-generated tables and listings should be produced in landscape mode using SAS® ODS to create RTF output which can be imported by Microsoft® Word in table format. All output should have the following two-line header at the upper left margin:

   ```
   Theracos Sub, LLC.
   THR-1442-C-449
   ```

   and the following header at the upper right margin:

   ```
   Page x of y
   ```

2. Each table should be identified by in a sequential numeric order, and the table designation should be centered above the title. A decimal system within the numeric numbering (i.e., x.y and x.y.z) should be used to identify tables, listings and figures with related contents. The title is centered in initial capital characters and should include the analysis set analyzed (e.g. Safety Analysis Set). The title and table designation are single-spaced, but are separated from the table by at least a double space.

   ```
                                   Table No.

                            First Line of Title
                      Second Line of Title (if needed)
                            Analysis Set Analyzed
   ```

3. Column headings should be in proper case.
4. For variables with numeric values, include “unit” in column heading when appropriate.
5. Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table. All output should have at least the footnote about the program name and date of the program run.

   ```
   [1] Footnote 1
   [2] Footnote 2
   [3] Footnote 3

   PROGRAM: program file name                          DDMMMYYYY HH:MM
   ```

6. Unless specified otherwise, all data listings should be sorted by subject number with the study center, and by visit date within subject, where appropriate.
7. For tables that summarize categorical (discrete) data, a Missing category should be added to any parameters for which information is not available for any subject.

8. Unless otherwise specified, the estimated mean, median, first and third quartiles (Q1 and Q3, respectively) for a set of values should be printed out to one more decimal place than the raw (observed) data and rounded appropriately. Standard errors (or standard deviations) should be printed out to two additional decimal places than the raw (observed) data and rounded appropriately. For example, for age (with raw data in whole years):

```
n                    xx
Mean (SD)       xx.x (xx.xx)
Median              xx.x
Q1, Q3           xx.x, xx.x
Min, Max           xx, xx
```

9. The p-values will be printed in the tables rounded appropriately to 4 decimal places and formatted as '0.xxxx'. P-values less than 0.0001 will be formatted in the tables as '<0.0001'.
10. All fractional numeric values should be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3).
11. Unless otherwise specified, percentage values should be printed with one digit to the right of the decimal point (e.g., 12.8, 5.4).
12. Missing descriptive statistics due to non-estimability in tables, as well as missing data in subject listings should be represented 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.
13. Dates printed as a result in the table, listing, or graph should be printed in SAS DATE9. format ("DDMONYYYY": 01 JUL 2002). Missing portions of dates should be represented on subject listings as dashes (-- JUL 1999). Dates that are missing because they are not applicable for the subject should be listed as "N/A", unless otherwise specified.

5 List of Tables, Figures and Listings

5.1 List of Tables

Table Number	Table Title	Analysis Set
Disposition, Demographics, Baseline Characteristics, Compliance and Exposure		
14.1.1*	Subject Disposition	All Enrolled Subjects
14.1.2.1*	Demographics, Screening and Disease Characteristics	Safety Analysis Set
14.1.2.2#	Demographics, Screening and Disease Characteristics	Intent-to-Treat Analysis Set
14.1.2.3#	Demographics, Screening and Disease Characteristics	Full Analysis Set
14.1.3.1	Summary of Concomitant Medications	Safety Analysis Set
14.1.3.2	Summary of Rescue Medications for Hyperglycemia	Safety Analysis Set
14.1.4	Summary of Study Treatment Duration and Compliance	Safety Analysis Set
Primary Endpoints		
14.2.1.1.1*	Summary of HbA1c (%) by Visit: Observed and Changes from Baseline	Full Analysis Set
14.2.1.1.2	Summary of HbA1c (%) by Visit: Observed and Changes from Baseline	Per Protocol Analysis Set
14.2.1.2.1	Mixed Model Repeated-Measure (MMRM) Analysis of HbA1c (%): Change from Baseline and Dose Response, Overall Model for Primary Analysis and Sensitivity Analyses	
14.2.1.2.2	Least Squares Summary Mixed Model Repeated-Measures (MMRM) Analysis of HbA1c (%): Change from Baseline, Excluding HbA1c Data Obtained After Rescue Medication (Primary Analysis)	Full Analysis Set
14.2.1.2.3	Least Squares Summary Mixed Model Repeated-Measures (MMRM) Analysis of HbA1c (%): Change from Baseline, Using Multiple Imputation (Sensitivity Analysis 1)	Full Analysis Set

Table Number	Table Title	Analysis Set
14.2.1.2.4	Least Squares Summary Mixed Model Repeated-Measures (MMRM) Analysis of HbA1c (%): Change from Baseline, Using Last Observation Carried Forward (Sensitivity Analysis 2)	Full Analysis Set
14.2.1.2.5	Least Squares Summary Mixed Model Repeated-Measures (MMRM) Analysis of HbA1c (%): Change from Baseline, HbA1c Data Obtained After Rescue Medication Considered (Sensitivity Analysis 3)	Full Analysis Set
14.2.1.2.6	Least Squares Summary Mixed Model Repeated-Measures (MMRM) Analysis of HbA1c (%): Change from Baseline, Excluding HbA1c Data Obtained After Rescue Medication Considered (Sensitivity Analysis 4)	Per Protocol Analysis Set
Secondary Endpoints		
14.2.2.1*	Summary of Fasting Plasma Glucose (mmol/L) by Visit: Observed and Change from Baseline	Full Analysis Set
14.2.2.2	Mixed Model Repeated-Measure (MMRM) Analysis of Fasting Plasma Glucose (mmol/L): Change from Baseline	Full Analysis Set
14.2.2.3	Least Squares Summary Mixed Model Repeated-Measure (MMRM) Analysis of Fasting Plasma Glucose (mmol/L): Change from Baseline	Full Analysis Set
14.2.3.1	Summary of Sitting Systolic Blood Pressure (mmHg) by Visit: Observed and Change from Baseline	Full Analysis Set
14.2.3.2	Mixed Model Repeated-Measure (MMRM) Analysis of Sitting Systolic Blood Pressure (mmHg): Change from Baseline	Full Analysis Set

Table Number	Table Title	Analysis Set
14.2.3.3	Least Squares Summary Mixed Model Repeated-Measure (MMRM) Analysis of Sitting Systolic Blood Pressure (mmHg): Change from Baseline	Full Analysis Set
14.2.4.1	Summary of Sitting Diastolic Blood Pressure (mmHg) by Visit: Observed and Change from Baseline	Full Analysis Set
14.2.4.2	Mixed Model Repeated-Measure (MMRM) Analysis of Sitting Diastolic Blood Pressure (mmHg): Change from Baseline	Full Analysis Set
14.2.4.3	Least Squares Summary Mixed Model Repeated-Measure (MMRM) Analysis of Sitting Diastolic Blood Pressure (mmHg): Change from Baseline	Full Analysis Set
14.2.5.1	Summary of Body Weight (kg) by Visit: Observed and Change from Baseline	Full Analysis Set
14.2.5.2	Mixed Model Repeated-Measure (MMRM) Analysis of Body Weight (kg): Change from Baseline	Full Analysis Set
14.2.5.3	Least Squares Summary Mixed Model Repeated-Measure (MMRM) Analysis of Weight (kg): Change from Baseline	Full Analysis Set
14.2.6	Logistic Regression Analysis of Subject Achieving Post-baseline HbA1c <7%, Excluding HbA1c Data Obtained After Rescue Medication	Full Analysis Set
Safety Endpoints – Adverse Events		
14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	Safety Analysis Set
14.3.1.2	Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Analysis Set
14.3.1.3	Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum Severity	Safety Analysis Set

Table Number	Table Title	Analysis Set
14.3.1.4	Summary of Related Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Analysis Set
14.3.2	Summary of Treatment Emergent Adverse Events of Special Interest by MedDRA System Organ Class and Preferred Term	Safety Analysis Set
14.3.3	Summary of Hypoglycemic Events by Category and Logistic Regression Analysis of Subjects with a Post-baseline Hypoglycemic Event	Safety Analysis Set
Safety Endpoints – Clinical Laboratory		
14.3.4.1.1*	Summary of Hematology: Observed and Change from Baseline by Visit	Safety Analysis Set
14.3.4.1.2*	Shift from Baseline in Hematology Laboratory Parameters	Safety Analysis Set
14.3.4.2.1*	Summary of Serum Chemistry, Electrolytes, Glycemic Control and Serum Lipid Laboratory Parameters: Observed and Change from Baseline by Visit	Safety Analysis Set
14.3.4.2.2*	Shift from Baseline in Serum Chemistry, Electrolytes, Glycemic Control and Serum Lipid Laboratory Parameters	Safety Analysis Set
Safety Endpoints – Vital Signs and 12-Lead ECG		
14.3.5*	Summary of Vital Signs: Observed and Change from Baseline by Visit	Safety Analysis Set
14.3.6	Summary of 12-Lead Electrocardiogram: Observed and Change from Baseline by Visit	Safety Analysis Set

***** Table is to be provided to the IDMC. For Table 14.1.2.1, disease characteristics will not be included. For Table 14.3.4, only the following lab parameters will be included: ALT, AST, Creatinine, Bicarbonate and Hemoglobin. For Table 14.3.5, only orthostatic systolic and diastolic blood pressure will be included.
# Only performed if intent-to-treat analysis set and/or full analysis set are different from the safety analysis set.

5.2 List of Figures

Figure Number	Figure Title	Analysis Set
Primary Endpoints		
14.2.1.1	Mean HbA1c (+/- SE) over Time by Treatment Group	Full Analysis Set
14.2.1.2	Dose Response Analysis of HbA1c: Change from Baseline to Week 12	Full Analysis Set
Secondary Endpoints		
14.2.2.1	Mean FPG (+/- SE) over Time by Treatment Group	Full Analysis Set
14.2.2.2	Mean Sitting Systolic Blood Pressure (+/- SE) over Time by Treatment Group	Full Analysis Set
14.2.2.3	Mean Sitting Diastolic Blood Pressure (+/- SE) over Time by Treatment Group	Full Analysis Set
14.2.2.4	Mean Body Weight (+/- SE) over Time by Treatment Group	Full Analysis Set

5.3 List of Listings

Listing Number	Listing Title	Analysis Set
16.1.7	Subject Randomization Schedule and Treatment Assignments	
16.2.1*	Subject Disposition	All Subjects
16.2.2	Protocol Deviations	All Subjects
16.2.3.1	Informed Consent and Re-enrollment	All Subjects
16.2.3.2	Inclusion and Exclusion Criteria	All Subjects
16.2.4*	Demographics	All Subjects
16.2.5.1	Significant Medical and Surgical History	All Subjects
16.2.5.2*	Type 2 Diabetes and Cardiovascular Disease History	All Subjects
16.2.6.1	Study Drug Accountability	All Subjects
16.2.6.2	Study Drug Exposure and Compliance	All Subjects
16.2.7.1*#	Adverse Events	All Subjects
16.2.7.2#	Serious Adverse Events	All Subjects
16.2.7.3	Adverse Events Leading to Treatment Discontinuation	All Subjects
16.2.7.4	Adverse Events Leading to Study Discontinuation	All Subjects
16.2.7.5	Adverse Events Leading to Death	All Subjects
16.2.8.1	Clinical Laboratory Tests: Hematology	All Subjects
16.2.8.2	Clinical Laboratory Tests: Serum Chemistry, Electrolytes, Glycemic Control and Serum Lipids	All Subjects
16.2.8.3	Clinical Laboratory Tests: Urinalysis, Urine Drug Screen and Infectious Disease Testing	All Subjects
16.2.8.4	Clinically Significant Laboratory Abnormalities	All Subjects
16.2.9	Pregnancy Test	All Subjects
16.2.10	Vital Signs	All Subjects
16.2.11	12-Lead Electrocardiograms	All Subjects
16.2.12	Physical Examination and Body Weight	All Subjects
16.2.13	Concomitant Medications	All Subjects
16.2.14	Phone Interview	All Subjects
16.2.15	Blood Sample Collection for Population Pharmacokinetics	All Subjects
16.2.16	Hypoglycemic Events	All Subjects
16.2.17	Screen and Run-in Failures	All Subjects

* Listing is to be provided to the IDMC.

Adverse events from subjects who failed during run-in period will be included in this listing. The listing will be presented by run-in failures and randomized subjects.