Sponsor Name:	Theracos Sub, LLC
Protocol Number and Title:	THR-1442-C-480 A Phase 3, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Effects of Bexagliflozin versus Glimepiride in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin
Protocol Version and Date:	Version 3.0, 27 October 2016
INC Research Project Code:	1007777A
Author(s):	Fang Zhu, Principal Biostatistician
SAP Version:	Final Version 1.0
SAP Version Date:	24-Jun-2019

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
0.1	28-Jul-2016	Fang Zhu	Initial draft
0.2	3-Feb-2016	Fang Zhu	Update based on sponsor comments
0.3	1-Aug-2018	Fang Zhu	Update per SAP for THR-1442-C-419 and THR-1442-C-423
0.4	29-Jan-2019	Fang Zhu	Update per comments
0.5	14-Mar-2019	Fang Zhu	Update per comments
1.0	24-Jun-2019	Fang Zhu	Updates includes: 1. Correct WHO-DD version; 2. Update the offset in section 8.2.4 for subjects used rescue medication; 3. Add rule to compute compliance when some bottles dispensed are not returned; 4. Add EQ-5D-3L score.

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

APPROVALS	
INC Research	
Lead Biostatistician Fang Zhu Principal Biostatistician	24-Jun-2019 **Date** (dd-Mmm-yyyy)
Senior Reviewing Biostatistician Mike Ou Director, Biostatistics	25-Jun-2019 **Date** (dd-Mmm-yyyy)
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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
Max	Maximum
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hematocrit
MCV	Mean Cell Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial Infarction
Min	Minimum
mL	Milliliter
MMRM	Mixed Model Repeated Measures
MODY	Maturity-onset Diabetes of the Young
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

Abbreviation	Description
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
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
TZD	Thiazolidinedione
UACR	Urine Albumin To Creatinine Ratio
UGE	Urine Glucose Excretion
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
UTI	Urinary Tract Infection
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE

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

2.1. RESPONSIBILITIES

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

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

Adverse events that have met the seriousness criteria defined in the protocol are reported on the serious adverse event (SAE) forms using MediData RAVE platform. An SAE case, consists of the information reported in the SAE forms, subject characteristics documented in the case report forms (CRF), and additional source data such as a hospital discharge summary, is recorded in a validated ARGUS database which is managed by Covance. Any discrepancies in critical data fields of each SAE will be reconciled between the ARGUS and THR-1442-C-480 clinical database prior to database lock. The SAE coding, analyses and summaries are based on the final study data recorded in the clinical database. Detailed serious adverse event follow-up data will be reported from ARGUS database and not included this report.

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

2.2. TIMINGS OF ANALYSES

The final analysis of safety and efficacy is planned after all subjects have completed the 96 weeks of treatment period and a two-week post-dose follow-up period. The treatment assignment is blinded to all study personnel throughout the 96-week treatment and the two-week follow-up periods. The database will be cleaned and locked followed by the unblinding of subject treatment codes.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary efficacy objective of this trial is to demonstrate that bexagliflozin is non-inferior to glimepiride by evaluating the treatment effect on Hemoglobin A_{1C} (HbA_{1c}) reduction at week 60 in subjects whose type 2 diabetes mellitus (T2DM) is inadequately controlled by metformin.

3.2. SECONDARY OBJECTIVES

- To evaluate the treatment effect of bexagliflozin vs. glimepiride on the change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2 at week 60
- To evaluate the treatment effect of bexagliflozin vs. glimepiride on the change in systolic blood pressure (SBP) in subjects with baseline SBP ≥ 140 mmHg at week 60
- To evaluate the treatment effect of bexagliflozin vs. glimepiride on the difference in proportion of subjects with ≥1 severe or documented symptomatic hypoglycemia events over 96 weeks
- To evaluate if bexagliflozin is superior to glimepiride on HbA1c reduction at week 60

3.3. EXPLORATORY EFFICACY OBJECTIVES:

- To assess the treatment effect of bexagliflozin vs. glimepiride on the change in the proportion of subjects achieving HbA1c < 7.0% over time
- To assess the treatment effect of bexagliflozin vs. glimepiride on the change in HbA1c over time
- To assess the treatment effect of bexagliflozin vs. glimepiride on the change in fasting plasma glucose (FPG) over time
- To assess the treatment effect of bexagliflozin vs. glimepiride on the change in SBP over time
- To assess the treatment effect of bexagliflozin vs. glimepiride on the change in body weight over time
- To assess the treatment effect of bexagliflozin vs. glimepiride on the difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over time

3.4. SAFETY OBJECTIVES

- To compare the effects of bexagliflozin vs. glimepiride on the incidence of adverse events of interest. Adverse events of interest are urinary tract infections (UTI), pyelonephritis urosepsis, genital mycotic infections (GMI), diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, major adverse cardiovascular events (MACE), fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis, rash, and renal failure events

- To compare the effects of bexagliflozin vs. glimepiride on general safety assessments including treatment emergent adverse events, clinical laboratory events, 12-lead electrocardiograms (ECG) parameters, physical examinations, vital signs including orthostatic blood pressure, and use of concomitant medications

3.5. OTHER OBJECTIVES

- To compare the effects of bexagliflozin and glimepiride on health-related quality of life using a validated instrument EQ-5D-3L

3.6. BRIEF DESCRIPTION

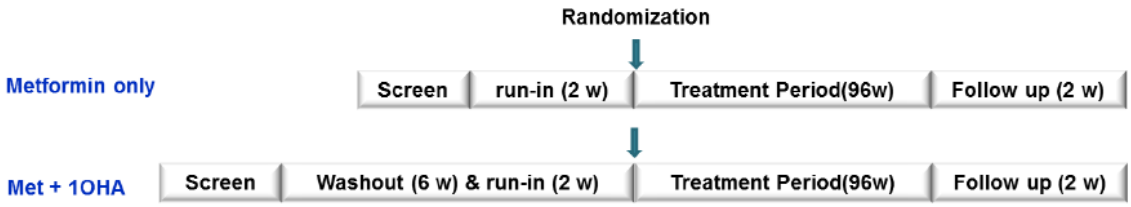
THR-1442-C-480 is a phase 3, multi-center, randomized, double-blind, active-controlled study and aims to demonstrate that bexagliflozin is non-inferior to glimepiride as add-on therapy in subjects whose T2DM is not adequately controlled by metformin treatment. The primary efficacy endpoint is the change in HbA_{1c} from baseline at week 60. The study will enroll T2DM patients who are treated with only metformin (metformin-only) or who are treated with metformin and one additional oral hypoglycemic agent (metformin-and-oral hypoglycemic agent [OHA]).

All subjects must have taken metformin at a stable dose of ≥ 1500 mg/day for ≥ 8 weeks prior to screening. Subjects can be eligible for the metformin-only treated group if they have received < 14 days of any other antidiabetic medications in the 8 weeks prior to screening. Subjects can be eligible for the metformin-and-OHA treated group if they have received ≥ 14 days of no more than 1 other OHA in the 8 weeks prior to screening; subjects taking any other antidiabetic medication (in addition to metformin and the 1 OHA) for < 14 days in the 8 weeks prior to screening are allowed.

A total of 420 subjects who meet all the inclusion criteria, none of the exclusion criteria, and who consent to participate in the study are eligible for study enrollment. Metformin-and-OHA treated subjects will undergo a 6-week washout of the non-metformin OHA prior to the start of run-in. Subjects who complete the 2-week run-in and who meet all eligibility criteria will be randomized in a 1:1 ratio to receive

once daily double-blind treatment of either active bexagliflozin tablets with placebo glimepiride capsules (Group 1) or placebo bexagliflozin tablets and active glimepiride capsules (Group 2). Active treatment in Group 1 will be bexagliflozin tablets, 20 mg. Active treatment in Group 2 will be glimepiride capsules, 2, 4, or 6 mg. Study subjects will continue receiving open-labeled metformin background medication during the entire study at a stable dose and frequency. The treatment period will last 96 weeks and be conducted in an outpatient setting (Figure 1).

Figure 1 Study Design



3.7. SUBJECT SELECTION

The study population will include approximately 420 subjects whose T2DM is inadequately controlled by metformin and who meet all of the inclusion criteria, none of the exclusion criteria. Clinical sites in the North America and Europe are anticipated to recruit subjects. Clinical sites in other continents may also participate in the trial.

3.7.1. Inclusion Criteria

Refer to protocol Section 4.2 for a list of inclusion criteria.

3.7.2. Exclusion Criteria

Refer to protocol section 4.3 for a list of exclusion criteria.

3.8. DETERMINATION OF SAMPLE SIZE

An approximate total of 420 subjects will be randomized and equally allocated to receive:

- bexagliflozin tablets, 20 mg and glimepiride, placebo capsules (referred to as bexagliflozin group in this document)
- bexagliflozin tablets, placebo and glimepiride capsules, 2 mg, 4 mg, or 6 mg (referred to as glimepiride group in this document).

The sample size calculation for this study is based on a two group t-test with a one-sided significance at the 0.025 level and the following assumptions:

- The non-inferiority limit (margin) for mean change from baseline to week 60 in HbA_{1c} comparing bexagliflozin group to glimepiride group will be 0.35%
- The standard deviation for the change from baseline to week 60 in HbA_{1c} for bexagliflozin group and glimepiride group will be 1.0%

Under the above assumptions, an estimated sample size of 172 subjects is needed in each treatment arm to determine non-inferiority of bexagliflozin to glimepiride with respect to change in HbA_{1c} at week 60 from baseline. This estimation is based on a one-sided t-test with 90% power at a 0.025 level of significance. A sample size of 210 per arm has been selected to account for approximate 18% drop-out rate and to allow adequate safety evaluation. The total sample size for this study will be 420 subjects.

3.9. TREATMENT ASSIGNMENT & BLINDING

3.9.1. Treatment Assignment

The study will be conducted at multiple investigative sites and will likely involve various numbers of subjects at each site. The study will have a competitive enrollment but the number of randomized subjects from each site will be capped at 40. Activation of investigational sites will be centrally controlled by an 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 wash-out already and wishes to continue with the study, the subject will be allowed to continue and, if eligible, to be randomized.

Eligible subjects who have completed the wash-out of oral hypoglycemic agent other than metformin and have met all study inclusion/exclusion requirements are to be randomized in a 1:1 ratio to receive active bexagliflozin with placebo glimepiride or active glimepiride with placebo bexagliflozin. Subjects will be assigned to treatment groups in sequential order as they qualify for the study. Randomization will be stratified according to baseline (Visit V5) HbA_{1c} (< 8.5% or ≥ 8.5%), treatment background

(metformin-only or metformin-and-OHA), and Visit V5 eGFR (≥ 90 or < 90 and ≥ 60 mL/min/1.73 m^2).

3.9.2. Blinding

This is a double-blind, double dummy study. The sponsor, investigators, study coordinators, pharmacists, study subjects, the cardiovascular adjudication committee and the diabetic ketoacidosis committee 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 test substance is needed to manage a 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 case report form (CRF) 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 and 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 and diabetic ketoacidosis adjudication committee members until all global investigational studies are completed and final analyses to assess cardiovascular and ketoacidosis risks are conducted.

3.10. 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

Active comparator will be:

- Glimepiride capsules, 2 mg: capsules containing 2 mg of glimepiride
- Glimepiride capsules, 4 mg: capsules containing 4 mg of glimepiride
- Glimepiride capsules, 6 mg: capsules containing 6 mg of glimepiride
- Glimepiride capsules, placebo: capsules containing no glimepiride

Bexagliflozin tablets, 20 mg or placebo, should be taken with 250 mL of water in the morning prior to eating or drinking. On the day of scheduled clinic visits when there is

fasting and blood is to be drawn, administration of bexagliflozin should be delayed until after blood is drawn and taken in the clinic or at home prior to the first meal with 250 mL of water.

Glimepiride capsules, 2, 4 or 6 mg or placebo, should be taken once daily with the first meal. On the day of scheduled clinic visits when there is fasting and blood is to be drawn, administration of glimepiride shall be withheld until the first meal.

3.11. 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

	Screening	Wash-out		Run-in		Efficacy Assessment									Safety Extension			Follow-up
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Time to Randomization Visit (wk)	-11	-8	-6	-2	-0.5	0	2	4	6	12	24	36	48	60	72	84	96	98
Off-site phone visit			X													X		
Informed Consent	X																	
EQ-5D-3L						X					X			X			X	
Screening for I/E criteria	X	X			X													
Demographics and medical history	X																	
Diet & exercise counseling		X		X														
Physical exam					X									X				X
Abbreviated physical exam	X								X		X	X	X		X		X	
Record height	X																	
Record body weight	X				X				X	X	X	X	X	X	X		X	X
Dispense diary & glucometer		X		X														
Diary & glucometer record review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Start wash-out		X																
Dispense Run-in Medication				X														
Randomization						X												
Vital signs	X			X	X		X	X	X	X	X	X	X	X	X		X	X
ECG	X				X						X			X			X	
Discontinue non-metformin OHA		X																
Dispense bexagliflozin						X				X	X	X	X	X	X			
Dispense glimepiride						X	X	X	X	X	X	X	X	X	X			

	Screening	Wash-out		Run-in		Efficacy Assessment									Safety Extension			Follow-up
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Time to Randomization Visit (wk)	-11	-8	-6	-2	-0.5	0	2	4	6	12	24	36	48	60	72	84	96	98
Blood draw for clinical lab test	X				X				X	X	X	X	X	X	X		X	X
Urine collection	X				X				X	X	X	X	X	X	X		X	X
AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Med		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X				X				X		X		X	X			X	X
Serum chemistry electrolytes	X				X				X		X		X	X			X	X
Fasting Plasma Glucose	X				X				X	X	X	X	X	X	X		X	X
HbA_{1c}	X				X					X	X	X	X	X	X		X	X
Lipids	X				X						X			X			X	X
Urinalysis	X				X				X	X	X	X	X	X	X		X	X
Urine pregnancy test (UPT)	X				X				X	X	X	X	X	X	X		X	X

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

- Change from baseline to week 60 in HbA_{1c} compared to glimepiride

4.2. SECONDARY EFFICACY ENDPOINTS

- Change from baseline to week 60 in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2
- Change from baseline to week 60 in SBP in subjects with baseline SBP ≥ 140 mmHg
- Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks
- Change from baseline to week 60 in HbA_{1c}

4.3. OTHER EFFICACY ENDPOINTS

- Change over time in proportion of subjects achieving HbA_{1c} < 7.0%
- Change over time in body weight
- Change over time in FPG
- Change over time in SBP
- Change over time in HbA_{1c}
- Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over time

4.4. SAFETY ENDPOINTS

- Adverse events of interest are UTI, pyelonephritis urosepsis, GMI, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, MACE, fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis, rash, and renal failure events
- Laboratory testing, including hematology, serum chemistry, and urinalysis
- Physical examination
- 12-lead ECG
- Vital signs
- Concomitant medication use

4.5. OTHER ENDPOINTS

- Health-related quality of life instrument, EQ-5D-3L

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 summaries of subject disposition.

5.2. 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 taken first. The Safety Analysis Set is the primary analysis set for safety evaluation.

5.3. INTENTION-TO-TREAT ANALYSIS SET

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

5.4. PER PROTOCOL ANALYSIS SET

The Per Protocol (PP) Analysis Set will include all subjects in the ITT Analysis Set who meet the study eligibility requirements and have no major protocol deviations that affect the validity of the efficacy measurements. Detailed protocol deviations that may result in subject 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 and recorded in CRF. Deviation will be classified into each of the 9 categories: enrollment criteria, non-compliance, laboratory, dosing, visit schedule, visit/procedure requirement, concomitant medication, informed consent, and other. Date and details of the deviation will be recorded. The list of deviation will be reviewed before unblinding and major protocol deviations that, in the opinion of the medical monitor, will be determined in the ongoing bases. The list of major protocol deviations will be further reviewed before database lock in the unblinded fashion and the deviations that could affect the primary and secondary variables will be determined. Some possible types of major protocol deviations are showing in Table 2.

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

Category	Criteria	Exclusion
Inclusion/Exclusion Criteria		
Ineligible subject is enrolled	- Subjects not satisfying HbA_{1c} 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, sulfonylurea, or additional metformin as the rescue medication for hyperglycemia	Visit exclusion [exclude data post rescue medication starts]
Randomization/Blinding		
Unblinding	Blind was broken (requested in IWRS)	Visit exclusion [exclude data post blind broken]
Dosing and Compliance		
Dosing Non-Compliance	Subject missed more than 20% of the investigational product doses for the 60 weeks of efficacy assessment period or missed more than 50% between week 48 and week 60	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; Glimepiride; and total of all treatment groups.

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.

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 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 subject who is dosed, baseline is defined as the last non-missing value on or prior to the first dose of double-blind study medication. For subject who is not dosed, baseline is defined as the last non-missing value on or prior to 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 CRF. Study analyses will use the double-blind treatment period first dose date.

6.2.3. Study Day

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

6.2.4. Duration

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

6.2.5. End of Study

The end of study is defined as the date of final contact as entered on the End-of-Study page of the CRF.

6.2.6. Patient Years

Patient years are calculated as sum of the duration from first dose of double-blind treatment to the end of study / 365.25 of all subjects in the specified analysis set and treatment arm. This is used as the denominator of the computation of incidence rate.

6.3. MISSING DATA

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

6.4. ANALYSIS VISIT WINDOWS

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

- If multiple records are available within a single analysis visit window, the record closest to the planned assessment day will be selected for analysis.

- If 2 records are equidistant from the target day, then the later record will be selected.
- If a subject has no record in an analysis window, the subject will be considered missing at that visit.

Table 3 Analysis Visit Windows

Data type	Study Day Window	Scheduled day	Scheduled Visit/Week
Body Weight, HbA_{1c}, Fasting Plasma Glucose, Lab data (including Lipids), EQ-5D-3L	Day 2 - 63	Day 42	Visit 9/Week 6
	Day 64 – 125	Day 84	Visit 10/Week 12
	Day 126 – 209	Day 168	Visit 11/Week 24
	Day 210 - 293	Day 252	Visit 12/Week 36
	Day 294 - 377	Day 336	Visit 13/Week 48
	Day 378 – 461	Day 420	Visit 14/Week 60
	Day 462 – 587	Day 504	Visit 15/Week 72
	> 587	Day 672	Visit 17/Week 96
Vital signs (except for height and weight	Day 2 - 21	Day 14	Visit 7/Week 2
	Day 22 - 35	Day 28	Visit 8/Week 4
	Day 36 - 63	Day 42	Visit 9/Week 6
	Day 64 – 125	Day 84	Visit 10/Week 12
	Day 126 – 209	Day 168	Visit 11/Week 24
	Day 210 - 293	Day 252	Visit 12/Week 36
	Day 294 - 377	Day 336	Visit 13/Week 48
	Day 378 – 461	Day 420	Visit 14/Week 60
	Day 462 – 587	Day 504	Visit 15/Week 72
	> 587	Day 672	Visit 17/Week 96
ECG	Day 2 - 294	Day 168	Visit 11/Week 24
	Day 295 – 546	Day 420	Visit 14/Week 60
	> 546	Day 672	Visit 17/Week 96

* Week 96 is the end of treatment visit for those subjects completing the study per protocol. For endpoint of lab and vital sign, the first collection after assigned Week 96 and > 7 days from Week 96 visit will be considered as Week 98 visit.

6.5. POOLING OF CENTERS

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

Region	Country
Europe	Germany
	Poland
	Spain
North America	United States

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 dosing, discontinued study drug dosing, completed the study, and discontinued from the study after randomization. The reasons for early withdrawal after randomization will be summarized.

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

7.2. SUBJECT ELIGIBILITY 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. All deviation term and class will be listed.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics include age, gender, race, ethnicity and country of investigational site. Baseline characteristics include baseline HbA_{1c} values, blood pressure, height, body weight, BMI, FPG, eGFR, eGFR at baseline categories (≥ 90 or < 90 mL/min/1.73 m^2), duration of diabetes from diagnosis to the date of informed consent, and prior anti-diabetic treatment status at screening (including type of therapy used [metformin, sulfonylurea, DPP-4 inhibitor, alpha-glucosidase inhibitor etc.]). Randomization stratification related factors will be summarized based on data collected on CRF or by lab. They include HbA_{1c} values at baseline (< 8.5% vs. ≥ 8.5%), background anti-diabetic treatment status (metformin-only or metformin-and-OHA), eGFR at screening, and eGFR at screening categories (≥ 90 or < 90 and ≥ 60 mL/min/1.73 m^2). Stratification factors from IWRS will be summarized. 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 at screening visit collected on CRF will be used.

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

7.4. MEDICAL HISTORY

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

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 Enhanced B2 format. 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. 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 stop date prior to or on first dose date for the double-blind treatment period will be considered a 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 taken in any time during the study treatment period. In the case of completely missing stop date, medication will be assumed to be concomitant.

All medication should be recorded in the concomitant medication log. Any medication given to treat hyperglycemia and continued for more than 2 weeks during the efficacy evaluation period of 60 weeks is considered a rescue therapy. Increase total daily dose of metformin, the background hypoglycemic therapy, during the treatment period is not allowed. However, if the dose of metformin is intensified during the double-blind treatment period for more than 2 weeks before the week 60 assessment, or study treatment stops if subject dropped out before week 60, it is also considered as rescue medication. All medications given to treat hyperglycemia will be recorded as concomitant medications 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 flagged in the same listing.

8. EFFICACY

Efficacy data include HbA_{1c}, FPG, body weight, SBP, and hypoglycemia event.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy hypothesis is that bexagliflozin is non-inferior to glimepiride in reducing HbA_{1c} after 60 weeks of treatment. For all analysis of primary efficacy endpoint, all post-baseline values up to week 60 will be used. All visits, including visits after 60 weeks, will be summarized.

8.1.1. Primary Efficacy Analysis

Let $\mu_{bexagliflozon}$ and $\mu_{Glimepiride}$ represent the mean changes from baseline in HbA_{1c} at Week 60 for bexagliflozin and comparator groups, respectively. The following hypotheses will be tested:

H_0: $\mu_{bexagliflozon} - \mu_{Glimepirider} > \delta$ versus

H_1: $\mu_{bexagliflozon} - \mu_{Glimepirider} \leq \delta$

Non-inferiority margin δ is chosen to be 0.35% using clinical judgment, with reference to relevant regulatory guidance, and justified by published glimepiride efficacy study (Charpentier et al. 2001).

This hypothesis will be tested based on ITT analysis set. Missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputations techniques; HbA_{1c} values collected after the start of rescue medication will not be excluded. A pattern-mixture model will be used to explore the impact of the missing data. Imputation will be conducted within each treatment arm and subgroup (treatment completer vs. treatment terminated early) under the assumption that non-adherent subjects with missing data will follow the same trajectory of non-adherent subjects with values observed. All efforts will be made to retain subjects in the study. If treatment is discontinued, subjects are encouraged to remain in the study and complete all scheduled visits, including final follow-up visit. However, with all efforts, insufficient values may be available for reliable imputation. This analysis will be performed only if ≥3% (approximately 6) of subjects in each treatment arm completed scheduled week 60 visit after treatment is stopped. This number is chosen to allow sufficient data to establish a regression model for imputation. For this analysis, the following three-step approach outlined below will be used:

1. Non-monotone (intermediate visits) missing data will be imputed first using the Monte Carlo Markov Chain (MCMC) method under the MAR assumption in all

treatment arms (using the MCMC statement in PROC MI). Multiple chains option (CHAIN=MULTIPLE option in the MCMC statement of PROC MI) will be used. For the non-monotone imputation of the HbA_{1c} missing data, a multivariate normal model will be used including variables for the HbA_{1c} at baseline and all post-baseline visits within each treatment group. Five hundred imputed datasets will be generated.

2. After the non-monotone missing data have been imputed, the remaining monotone missing data will be imputed within each treatment arm and subgroup, defined by whether subject completed 60 week of study treatment, using regression approach. The predictors for the regression imputation model at any time point will be region, treatment background (metformin only or metformin and OHA), baseline eGRF (≥ 90 or < 90 ml/min/1.73 m2), and HbA_{1c} at all previous time points, including baseline. Imputations will be performed using a sequence of regression-based imputations (using PROC MI statement MONOTONE REG) at each post-baseline time point.

3. Imputed data in each of the multiple imputed datasets will be analyzed using a mixed model repeated measures (MMRM) approach. The MMRM model will include region, terms for treatment background (metformin only or metformin and OHA), baseline eGRF (≥ 90 or < 90 ml/min/1.73 m2), treatment, visit, treatment-by-visit interaction, and the baseline HbA_{1c} value, as a fixed effect covariate. The analysis will evaluate the mean change from baseline in HbA_{1c} over the 60-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. HbA_{1c} values obtained after the start of rescue medication will not be excluded from the analysis. The treatment and treatment by visit interaction terms allow for comparisons of the treatment groups at each visit, and over week 12 to week 60. Least squares (LS) mean treatment differences between the bexagliflozin group and the placebo group at week 60 will be estimated from the model The LS mean results from all imputed datasets will be combined using the Rubin's combination rule (PROC MIANALYZE).

If no sufficient week 60 values from treatment discontinued subjects are available for imputation, MMRM analysis as in step 3 will be performed using all available data.

Sample SAS code will be provided in Appendix.

In non-inferiority analysis, a CI is calculated to estimate the range of values in which the treatment difference is likely to lie. This CI is used to provide the basis for drawing the study's conclusions. In this specific test, if the 95% CI lies below the specified non-inferiority margin 0.35%, the results would lead to a conclusion of non-inferiority of

bexagliflozin treatment to glimepiride treatment. Lower HbA_{1c} value indicates improvement on subject diabetes condition. Larger decrease would indicate better treatment effect of bexagliflozin compared to glimepiride. Hence, superiority of bexagliflozin group over glimepiride group at week 60 in HbA_{1c} change from baseline will be declared if the upper bound of 95% CI is less than 0.

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, regardless of having sufficient week 24 values from treatment discontinued subjects are available for imputation or not, MMRM analysis will be performed using all available data. The primary efficacy endpoint will also be analyzed with all observed available data using MMRM method for the PP analysis set.

8.1.2. Sensitivity Analyses

Randomized subjects who withdraw consent to participate in the study will not be replaced. The early withdrawal rate is estimated to be 18%. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct.

To investigate the possible implications of missing values in efficacy assessments, the number, timing, pattern, and reason for the missing value will be summarized. The reason for withdrawal will be reviewed. If there are missing values for the primary analysis described in section 8.1.1, only available data will be analyzed and data obtained after rescue will not be excluded.

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

To evaluate the impact from missing data and rescue medication, the following sensitivity analyses will be conducted:

1) Tipping point analysis will be conducted. Data after rescue medication will be considered as missing. The following steps will be implemented:
   a. Create monotone missing data as step a in the primary analysis in section 8.1.1 with 100 imputed datasets;
   b. Regression approach under MAR will be used to generate complete datasets. The predictors for the regression imputation model at any time point will be region,

treatment background (metformin only or metformin and OHA), baseline eGRF (≥ 90 or < 90 ml/min/1.73 m2), treatment, and HbA_{1c} at all previous time points, including baseline. The first imputed values will be penalized or rewarded based on the treatment subject received:

- Subjects in the bexagliflozin group: missing value will be analyzed assuming the treatment effect is worsened by δ_1 (where δ_1 = 0.1 to 0.5, in step of 0.1) compared to the subjects who have no missing value in the reduction of HbA_{1c} value;
- Subjects in the glimepiride group: missing value will be analyzed assuming the treatment effect is better by δ_2 (where δ_2 = 0.1 to 0.5, in step of 0.1) compared to the subjects who have no missing value in the reduction of HbA_{1c} value;

The penalty or reward will not be applied to the values from later time points as these values are penalized or rewarded through regression on previous time points.

c. Imputed datasets will be analyzed and results combined as step 3 in section 8.1.1.

For each combination of (δ1, δ2), 100 imputed datasets will be obtained. These 25 combinations will be separately analyzed to explore under which condition where the null hypothesis can no longer having evidence to be rejected.

2) Additionally, the impact of the data after the start of rescue medication will be evaluated. HbA_{1c} values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be performed. Same statistics provided for the primary analysis will be presented.

8.1.3. Subgroups

Descriptive and MMRM model comparison using all available data for the primary endpoint will be repeated by subgroups. The nominal p-value will be presented without adjustment to the multiple comparisons. They are not used for inferential purpose. The subgroups include:

- Age (< 65 years or ≥ 65 years)
- Gender (male or female)
- Race (white or Caucasian; black or African-American; other)
- Baseline HbA_{1c} (< 8.5% or ≥ 8. 5%)
- Treatment background (metformin-only or metformin-and-OHA)
- Baseline eGFR (≥ 90 or < 90 mL/min/1.73m^2)

- Region

8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

The secondary endpoints will only be tested when the non-inferiority of the primary efficacy assessment is established at one-sided significance level of 0.025. To control the overall type I error of 0.05, the secondary efficacy objectives will be tested at one-sided 0.025 significance level following the sequence below:

- Superiority test of the change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2 at week 60.
- Superiority test of the change in SBP in subjects with baseline SBP ≥ 140 mmHg from baseline at week 60.
- Superiority test of the difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks

Analysis for secondary endpoints will be based on ITT analysis set and repeated for PP analysis set. For body weight and SBP, all post-baseline values up to week 60 will be used for model analysis. All values will be summarized.

8.2.1. Change in body weight in subjects with baseline body mass index (BMI) ≥ 25 kg/m^2 at week 60

This will be tested if the non-inferiority of HbA_{1c} and the previous secondary efficacy endpoints are significant. Data after rescue medication will not be excluded. The comparison of change in body weight between randomized treatments at week 60 will be carried out using the similar MMRM model as section 8.1.1 using all available data. The model will include terms for region, treatment, baseline HbA_{1c} as continuous variable, treatment background (metformin-only or metformin-and-OHA), and baseline eGFR (≥ 90 or < 90 mL/min/1.73 m^2) as fixed effects and the corresponding baseline weight value as covariate. Treatment comparison p-values and difference at week 60 will be estimated from the model, with the two-sided 95 % CIs of the treatment difference also presented. If the superiority of HbA_{1c} is not established, the nominal p-value will not be used for inferential purposes. Summary table will be presented and figures will be displayed for ITT population.

8.2.2. Change in SBP in subjects with baseline SBP ≥ 140 mmHg from baseline at week 60

This will be tested if the change from baseline body weight is significantly different between bexagliflozin and glimepiride groups based on ITT analysis set for subjects with a BMI ≥ 25 kg/m^2. Change from baseline in SBP at week 60 will be analyzed in a similar manner as change in body weight, Section 8.2.1, based on ITT analysis set for all

subjects. Baseline SBP will be used in place of baseline weight. Summary table will be presented and figures will be displayed for ITT population.

8.2.3. Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia event over 96 weeks

This will be formally tested if the previous secondary efficacy endpoints are significant. Events after the start of rescue medication will be counted. Descriptive statistics of frequency and percentage will be provided. Logistic regression model will be used, with region, treatment, baseline HbA_{1c}, treatment background (metformin-only or metformin-and-OHA), and baseline eGFR (≥ 90 or < 90 mL/min/1.73 m^2) as fixed effects. Odd ratio estimates, 95% two-sided confidence intervals and p-values for the treatment difference will be provided. Summary table will be presented and figures will be displayed for ITT population.

8.2.4. Sensitivity analysis

For all secondary analysis of body weight and SBP, missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputations techniques; Values collected after the start of rescue medication will be considered missing. Imputation steps include:

a. Create monotone missing data as step a of section 8.1.1 with 100 imputed datasets;

b. Regression approach under MAR will be used to generate complete datasets. The predictors for the regression imputation model at any time point will be region, treatment background (metformin only or metformin and OHA), baseline eGRF (≥ 90 or < 90 ml/min/1.73 m2), treatment, and values at all previous time points, including baseline. Values at each visit will be imputed sequentially. The first imputed values for subjects in bexagliflozin arm will be penalized by the mean improvement at week 60 on that endpoint (i.e. the mean change from baseline at week 60). Imputed values for subjects in glimepiride will not be penalized. Imputed values after the first missing value will be penalized through regression on first penalized value.

c. Imputed datasets will be analyzed and results combined as in step c in section 8.1.1.

For the sensitivity analyses of proportion of subjects with hypoglycemia event, to account for subject discontinuation, incidence rate will be analyzed using negative binomial regression model. Data collected after the start of rescue medication will be considered as missing. The number of severe or documented symptomatic

hypoglycemia events will be used as outcome. Model will include region, treatment background (metformin only or metformin and OHA), baseline eGRF (≥ 90 or < 90 ml/min/1.73 m2), treatment, and baseline HbA_{1c} as fixed effect and the logarithm of the duration from first dose of double-blind treatment to date of week 96 visit as offset. If subject discontinued before week 96 visit, the date of discontinuation will be used. If subject used rescue medication, the last date before rescue medication will be used. The adjusted mean incidence over 96 weeks, 95% CI for each treatment arm, the risk ratio, 95% CI, and p-value will be presented.

8.3. EXPLORATORY EFFICACY ENDPOINTS AND ANALYSES

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

8.3.1. Changes from baseline in HbA_{1c}, body weight, SBP, and in FPG over time

The schedule of HbA_{1c}, FPG, body weight, and SBP/DBP can be found in Table 1. The absolute value and change from baseline in HbA_{1c}, FPG, body weight and SBP/DBP during the double-blind treatment period will be summarized by descriptive statistics at each visit. Change from baseline in HbA_{1c} will be analyzed as part of primary efficacy analysis. The change from baseline in body weight for subjects with baseline BMI ≥ 25 kg/m^2, SBP for subject with baseline SBP ≥ 140 mmHg, SBP for all subjects, and FPG will be analyzed using the MMRM ANCOVA model from primary analysis as a template (Section 8.1.1). The fixed effect for change from baseline in body weight and SBP will include region, baseline HbA_{1c} as continuous variable, treatment background (metformin-only or metformin-and-OHA), and baseline eGFR (≥ 90 or < 90 mL/min/1.73 m^2), treatment, visit, and treatment-by-visit. The change from baseline in FPG will include region, treatment background (metformin-only or metformin-and-OHA), and baseline eGFR (≥ 90 or < 90 mL/min/1.73 m^2), treatment, visit, and treatment-by-visit. The appropriate baseline values will be used as covariate. LS means for each treatment and the difference between treatments will be estimated at each visit and across all post-baseline visits. The corresponding p-values will also be presented.

8.3.2. Proportions of subjects with HbA_{1c} of < 7% and the proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over time

Summary on the proportion of subjects achieving HbA_{1c} < 7% at each visit and the proportion of subjects with documented hypoglycemia event during each 12-week visit interval will be presented over time. They will be analyzed using generalized estimating equation (GEE) logistic regression. The fixed effect will include region, treatment background (metformin-only or metformin-and-OHA), baseline eGFR (≥ 90 or

< 90 mL/min/1.73 m^2) and baseline HbA_{1c}, treatment, visit, and treatment-by-visit. An unstructured correlation structure will be used (or autoregressive(1) if the model with the unstructured structure does not converge). The LS mean proportion for each treatment will be estimated at each post-baseline visit and across all post-baseline visits. The odds ratios of bexagliflozin group over the glimepiride 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.

9. SAFETY

The Safety Analysis Set will be used for analyzing the safety parameters. Safety data include AEs; physical examination results; vital signs; 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, minimum, and maximum for continuous variables. All subjects who are randomized and receive at least one dose of double-blind study medication will be included in the safety analysis. All safety data will be presented in by-subject listings and included in the clinical trial report.

9.1. EXTENT OF EXPOSURE

Study drug exposure will include:

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

Treatment duration of tablets/capsules (in weeks) is calculated as (the date of the last dose of study drug – the date of the first dose of double-blind study drug + 1) / 7 and rounded to 1 decimal place. For glimepiride, this includes doses taken during up-titration period. The exposure will be summarized for bexagliflozin tablets, 20 mg or glimepiride, 2, 4, or 6 mg.

Total dose taken will be calculated as number of tablets/capsules dispensed – number of tablets/capsules, including all doses for glimepiride, returned. For unreturned bottles, if subject has completed the study, all study medications are considered as completely taken. If a subject withdrew early, and it is not the last kit dispensed, all medication will be considered as completely taken. If a subject withdrew early, and the last kit dispensed is not returned, the number taken is considered as what expected from date of dispense to the date of last dose date. Summary statistics for total dose taken will be provided by treatment group for the double-blind treatment period.

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

9.2. TREATMENT COMPLIANCE

Subjects will be provided with dosing instructions each time study medication is dispensed. Subjects will also be instructed to bring their medication with them to every visit. During the run-in period, subjects will be considered compliant in investigational product administration by missing no more than two doses 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 double-blind phase is calculated for as follows:

- Percent compliance = (number of tablets or capsules 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.

In case of the unreturned bottles:

- If subjects completed the study, all the unreturned bottles will be assumed to be completely consumed.
- If subjects discontinued, the unreturned bottles will be assumed to be completely consumed if a) unreturned bottles are not from the last visit, or b) if only one of the two bottles dispensed from week 60 or week 72 is not returned.
- If subjects discontinued and all bottles from the last visit are not returned (e.g. lost to follow-up), subjects will be assumed to consume the medication as expected:

  Number of tablets assumed taken=last dose date – date bottles dispensed +1;

Summary statistics for tablet or capsule compliance (%) will be provided by treatment group for the double-blind treatment period. The compliance will only be summarized for non-placebo tablets/capsule. 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 presented in the standard international order 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 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.
- Serious treatment-related TEAEs, overall and by SOC and PT.

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 at least possibly related to study treatment
- 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 UTI, pyelonephritis urosepsis, GMI, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, MACE, fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis, rash, and renal failure events. 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

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

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

- Type of cardiovascular related procedures –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 and chemistry will be performed at the following time points: at the screening visit (Week - 11), on baseline visit (Day -3 to -5), and at weeks 6, 24, 48, 60, 96, and 98. Urinalysis will be performed at the following time points: at the screening visit (Week - 11), on baseline visit (Day -3 to -5), and at weeks 6, 12, 24, 36, 48, 60, 72, 96 and 98. Serum lipids will be performed at the screening visit (Week - 11), on baseline visit (Day -3 to -5), and on weeks 24, 60, 96, and 98. Renal functional testing by UACR will be determined at the screening visit, on baseline visit and at Week 60. 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. 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.

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

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

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	• HbA_{1c}	
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), both visits of run-in (Week -2 and Day -3 to -5), and at weeks 2, 4, 6, 12, 24, 36, 48, and 60. 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 mapped visit using descriptive statistics (n, mean and median, standard deviation, minimum and maximum). BP summary will include supine, sitting, standing and orthostatic BP. Safety analysis set will be used for table summary.

9.6. ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) will be conducted at the screening visit (Day - 11), on baseline visit (Day -3 to -5), at weeks 24, 60, and 96. ECG parameters measured will be the RR interval, PR interval, QRS duration, QT interval, and QTcB. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities or arrhythmia.

If a subject's ECG parameters cannot be determined due to pacemaker placement or atrial fibrillation, the ECG parameters will be considered missing. Any machine generated values such as 0 or 9999 will be excluded from the analyses.

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 weeks 60, and 98. 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 weeks 6, 24, 36, 48, 72, and 96 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. HEALTH RELATED QUALITY OF LIFE ASSESSMENT

Health related quality of life will be assessed by EQ-5D-3L. It will be performed on Day 1, Weeks 24, 60, and 96.

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a measure of health for clinical and economic appraisal. The questionnaire consists of 2 components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system is comprised of the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has 5 possible responses scored from 1 (unimpaired) to 5 (most impaired). The EQ VAS records the respondent's self-rated overall health on a vertical, visual analogue scale where the endpoints are labeled, "Best imaginable health state" and "Worst imaginable health state". Health states in the EQ-5D-3L can be converted into a single index value, where index values are presented in the country specific value sets to facilitate the calculation of quality-adjusted life years (QALYs). EQ-5D-3L value sets can be used to obtain the EQ-5D-3L index values based on the UK version. The index score in this version range from -0.594 to 1 with higher score indicating better quality of life. To compute the value of any health state, first of all a value of 1 is assigned for the 11111 status (without health problems in any dimension). If the status is different to 11111, the constant value is subtracted (see below table). Later, if at least one moderate problem (value of 2 reported in the database) is reported in any of the dimensions, the correspondent dimension value is subtracted. The same procedure is followed when there is at least one extreme problem (value of 3 reported in the database), but multiplying by 2 the appropriate constant value. Finally, if at least one extreme problem is reported then the N3 value is subtracted.

Parameter	Coefficient (UK)
Constant	-0.081
Mobility=2	-0.069
Mobility=3	-0.314
Self care=2	-0.104
Self care=3	-0.214
Usual activities=2	-0.036
Usual activities=3	-0.094
Pain/discomfort=2	-0.123
Pain/discomfort=3	-0.386
Anxiety/Depr.=2	-0.071
Anxiety/Depr.=3	-0.236
N3	-0.269

Descriptive statistics will be presented for each item of the questionnaire, the EQ-5D-3L index score and VAS for ITT analysis. Both actual values and changes from baseline will be summarized by treatment group for each visit. In addition, the treatment effect for change from baseline in index score and VAS will be assessed using the MMRM model in Section 8.1.1 as template. The model will include treatment, visit, treatment-by-visit interaction and randomization stratification factors, including baseline HbA_{1c}, as the fixed effects terms and the baseline EQ-5D-3L index score (or VAS) as covariate. All analysis will be based on ITT analysis set.

11. INTERIM ANALYSES

No interim analyses are planned.

12. DATA AND SAFETY MONITORING BOARD

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

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

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

In all analysis models, continuous HbA_{1c} at baseline is used as fixed affect, in place of randomization stratification factor of HbA_{1c} group at baseline. In all models, eGFR at baseline category is used as fixed effect, in place of randomization stratification factor of eGFR at screening.

Primary analysis of the primary endpoint was MMRM using available data in the protocol. In SAP, a “retrieved dropout” analysis is used for handling missing data is used as primary analysis if data allows. Retrieve dropouts are subjects who discontinued treatment but still had their efficacy measurements at the planned visit. Sensitivity analysis of LOCF is planned in the protocol, but removed in SAP since LOCF does not add more information on sensitivity in addition to tipping point analysis.

14. REFERENCE LIST

https://www.economicsnetwork.ac.uk/health/EQ_5D_index_calculator.xls; Szende, Oppe, Devlin (ed.): EQ-5D Value Sets: Inventory, comparative review, and user guide.

Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in Type 2 diabetic patients. *Diabetic Medicine* 2001, 18, 828-834

15. PROGRAMMING CONSIDERATIONS

The following conventions will hold for programming of outputs:

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

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

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

- Descriptive statistics will be displayed in the following order:

n
Mean
Standard deviation (SD)
Q1
Median
Q3
Minimum (Min)
Maximum (Max)

- 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 < or > (e.g., "< 10", "> 10", "≥ 10", or "≤ 10") the numeric portion of the result will be used (e.g. < 10, ≤ 10, > 10, and ≥ 10 become 10) for summary; the actual recorded results, (e.g. "< 10" or "> 10") will appear in listings.

15.1. GENERAL CONSIDERATIONS

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

15.2. TABLE, LISTING, AND FIGURE FORMAT

15.2.1. General

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

15.2.2. Headers

- All output should have the following header at the top left of each page:
  Theracos Sub, LLC
  Protocol Number: THR-1442-C-480
- Draft or Final in top right corner.
- All output should have Page n of N at the top of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

15.2.3. Display Titles

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

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

15.2.4. Column Headers

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

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

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

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

15.2.5.2. Table Conventions

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

Severity Rating	N
severe	0
moderate	8
mild	3

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

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, 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
Std Dev	X.XX
Q1	XXX.X
Median	XXX.X
Q3	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If the rounded percentage is 0.0, display as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be

displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for concomitant and rescue medications should be presented by treatment class with the highest occurrence in the total column in decreasing order. Tabular display of data for medical history and adverse event data should be presented by the SOC using internationally agreed order. Within the drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order in the total column. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

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

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

15.2.5.3. Listing Conventions

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

15.2.5.4. Figure Conventions

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

15.2.6. Footnotes

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

16. QUALITY CONTROL

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

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

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Listing 16.2.5.1.1	Study Drug Accountability – Bexagliflozin (Safety Analysis Set)
Listing 16.2.5.1.2	Study Drug Accountability and Up-Titration – Glimpepiride (Safety Analysis Set)
Listing 16.2.5.2	Study Drug Exposure and Compliance (Safety Analysis Set)
Listing 16.2.6.1	Glycemic Control Tests: HbA1c (%) (ITT Analysis Set)
Listing 16.2.6.2	Glycemic Control Tests: Fasting Plasma Glucose (mmol/L) (ITT Analysis Set)
Listing 16.2.6.3	Hypoglycemia Events (ITT Analysis Set)
Listing 16.2.6.4	Weight (kg) (ITT Analysis Set)
Listing 16.2.7.1	Adverse Events (Safety Analysis Set)
Listing 16.2.7.2.1	Adverse Events of Interest (Safety Analysis Set)

Number	Title
Listing 16.2.7.2.2	Major Adverse Cardiovascular Events (Safety Analysis Set))
Listing 16.2.7.2.3	Revascularization and Amputations (Safety Analysis Set)
Listing 16.2.7.3.1	DKA Symptoms Assessment (Safety Analysis Set)
Listing 16.2.7.3.2	Suspected DKA Assessment (Safety Analysis Set)
Listing 16.2.7.3.3	Suspected DKA Clinic/Hospital Report (Safety Analysis Set)
Listing 16.2.7.3.4	Suspected DKA Outpatient Clinic (Safety Analysis Set)
Listing 16.2.7.3.5	Suspected DKA Hospitalization (Safety Analysis Set)
Listing 16.2.8.1	Urine Pregnancy Test (Safety Analysis Set)
Listing 16.2.9.1	12-Lead Electrocardiogram (Safety Analysis Set)
Listing 16.2.9.2	Physical Examination (Safety Analysis Set)
Listing 16.2.10	EQ-5D-3L Scores (ITT Analysis Set)

20. MOCK-UPS

Attachment 1: Planned Table Shells

Attachment 2: Planned Listing Shells

Attachment 3: Planned Figure Shells

21. APPENDICES

Attachment 4: Appendix.