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Revision History

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Version 0.2	13-Sep-2017	Fang Zhu	Update per comments
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Version 1.0	21-Dec-2017	Fang Zhu	Update per comments on TLF shells
Version 1.1	27-Feb-2018	Fang Zhu	Update per FDA request: 1. Further clarification was made for use of last available ABPM in the primary analysis of ABPM; 2. Additional non-parametric sensitivity analysis (Wilcoxon rank test) was added per FDA suggestion.
Version 2.0	07-Dec-2018	Fang Zhu	1. Wilcoxon rank test was updated per FDA suggestion. 2. Additional exploratory analyses on ABPM for subgroup of patients taking appropriate doses of three or more types of antihypertensive therapies at baseline of study 603A. 3. Additional exploratory analyses on ABPM during treatment withdrawal period (ie, from Week 12 to Week 24 in study 603B) by response status of patients prior to withdrawal. 4. Other clinical relevant exploratory analyses were added, such as heart rate change, HbA1c change for diabetes subjects, etc. 6. Minor cosmetic, typographic error corrections.

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

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INC Research	
Lead Biostatistician Fang Zhu Sr. Biostatistician	07-Dec-2018 **Date** (dd-Mmm-yyyy)
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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ABPM	Ambulatory blood pressure monitoring
AE	Adverse Event
ALB	Albumin
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CEC	Cardiovascular Endpoint Committee
CI	Confidence Interval
Cl	Chloride
CRF	Case Report Form
dL	Deciliter
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ET	Early Termination
eGFR	Estimating Glomerular Filtration Rate
GMI	Genital Mycotic Infection
HbA1c	Hemoglobin A1c
Hct	Hematocrit
HDL-C	High Density Lipoprotein Cholesterol
Hgb	Hemoglobin

Abbreviation	Description
ICH	International Conference on Harmonization
ITT	Intention-to-Treat
IWRS	Interactive Web Response System
LDL-C	Low Density Lipoprotein Cholesterol
MACE	Major Adverse Cardiovascular Event
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hematocrit
MCV	Mean Cell Volume
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Myocardial Infarction
Min	Minimum
mL	Milliliter
NA	Not Applicable
Na	Sodium
PP	Per Protocol
PR	Time from the beginning of the P wave to the beginning of the QRS complex in electrocardiogram
PT	Preferred Term
QRS	Graphical deflections corresponding to ventricular depolarization in a typical electrocardiogram
QTc	Time between the start of the Q wave and the end of the T wave in the ECG, corrected for heart rate
RBC	Red Blood Cell
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

Abbreviation	Description
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TLF	Table, Listing And Figure
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 that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. Population pharmacokinetic assessments obtained for the study will be integrated with other studies, and will not be independently analyzed. A separate analysis plan details the integrated analysis methods.

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 the MediData RAVE platform.

INC Research will perform the statistical analyses and is 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 the MediData RAVE platform. An SAE case consists of the information reported in the SAE forms, subject characteristics documented in the case report forms, and additional source data such as hospital discharge summaries. Each SAE case is recorded in a validated ARGUS database which is managed by Covance. Any discrepancies in critical data fields of each SAE will be reconciled between the AUGUS and THR-1442-C-603 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 the ARGUS database and are not included in this report.

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

2.2. TIMINGS OF ANALYSES

An interim non-binding futility analysis is planned when 50% of the randomized subjects (i.e., 300) have completed 12 weeks of double blind treatment in study 603A.

The final analysis of safety and efficacy is planned after all subjects complete the planned 36 weeks of blinded study treatment or terminate early from the studies.

3. STUDY OBJECTIVES

3.1. STUDY 603A

In study 603A, the effectiveness of bexagliflozin tablets, 20 mg, will be assessed in a study population randomized 1:1 to receive either active agent or placebo.

3.1.1. Primary Objective

The primary endpoint will be the change from baseline (Day 1) to week 12 of the average ambulatory systolic blood pressure (SBP) of the bexagliflozin group compared to the placebo group.

3.1.2. Secondary Objectives

Secondary objectives based on mean ambulatory SBP:

- The proportion of subjects who achieve a reduction of mean ambulatory SBP of 10 mm Hg or greater;
- The proportion of subjects who achieve a mean ambulatory SBP of 135 mm Hg or less at week 12;
- The maximum and minimum treatment effect (trough-to-peak ratio) by Ambulatory blood pressure monitoring (ABPM) SBP at week 12.

Secondary objectives based on seated office SBP:

- The placebo-adjusted change from baseline to week 12 in seated office SBP;
- The proportion of subjects who achieve a mean seated office SBP of 140 mm Hg or less at week 12.

Secondary objectives based on mean ambulatory diastolic blood pressure (DBP):

- The placebo-adjusted change in mean ambulatory DBP from baseline to week 12;
- The proportion of subjects who achieve a mean ambulatory DBP of 87 mm Hg or less at week 12;
- The proportion of subjects who achieve a reduction of mean ambulatory DBP of 4 mm Hg or greater at week 12.

Secondary endpoints based on seated office DBP

- The placebo-adjusted change from baseline to week 12 in seated office DBP;
- The proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12.

3.2. STUDY 603B

In study 603B, the effectiveness of bexagliflozin tablets, 20 mg, will be assessed by measurement of the loss of the treatment effect following randomized withdrawal. All study entrants will first be dosed with bexagliflozin tablets, 20 mg, for 12 weeks. At week 12 the participants will undergo a 1:1 randomization to bexagliflozin tablets, 20 mg, or placebo.

3.2.1. Primary Objective

The primary endpoint will be the change from week 12 to week 24 of the mean ambulatory SBP of the bexagliflozin group compared to the placebo group.

3.2.2. Secondary Objectives of Study 603B

The secondary objectives of study 603B are based on assessments of effects on mean ambulatory and seated office systolic and diastolic blood pressures from week 12 to week 24. These will include:

- The placebo-adjusted change from week 12 to week 24 in seated office SBP;
- The placebo-adjusted change from week 12 to week 24 in ambulatory DBP;
- The placebo-adjusted change from week 12 to week 24 in seated office DBP;

Study 603B will also include a population pharmacokinetic assessment between weeks 6 and 12, when all participants will be receiving bexagliflozin tablets, 20 mg.

Population pharmacokinetic assessments obtained for the study will be integrated with other studies, and will not be independently analyzed. A separate analysis plan details the integrated analysis methods

3.3. INTEGRATIVE OBJECTIVES OF STUDY 603A AND 603B

- To assess consistent effects on mean ambulatory SBP/DBP after 12 weeks of bexagliflozin treatment, as well as longer treatment periods, i.e., 24 weeks or 36 weeks of bexagliflozin treatment.
- The seated office systolic and diastolic blood pressure will be collected at more frequent intervals than for ambulatory monitoring, and the changes over time will be evaluated to provide a composite profile of treatment effect as a function of time.

3.4. SAFETY OBJECTIVES

The integrated safety objectives will assess the hazard ratio for adverse events associated with bexagliflozin exposure compared to placebo in all segments of both

studies in which a placebo-exposed cohort is present. The safety objectives of the study are:

- To determine the frequency and severity of treatment emergent adverse events
- To determine the frequency and severity of treatment emergent adverse events of special interest
- To record and evaluate concomitant medication use
- To evaluate any potentially adverse changes in laboratory test values
- To assess changes in cardiac rhythm through 12-lead ECG
- To evaluate vital signs
- To assess general health detected by physical examination

3.5. BRIEF DESCRIPTION

THR-1442-C-603 is an integrated assessment of the potential utility of bexagliflozin tablets, 20 mg, for the treatment of essential hypertension. It is composed of two studies, 603A and 603B, measuring effects in a common population.

3.5.1. Study 603A

Study 603A is a double blind, placebo controlled multi-center study. Approximately 680 male and female adult subjects with an office sitting blood pressure ≥ 140 mm Hg and < 180 mm Hg, and who are taking no more than 4 anti-hypertensive medications will be enrolled in study 603A. The overall population should be selected to contain > 10% of subjects with a baseline ABPM >160 mm Hg and < 30% of subjects with type 2 diabetes mellitus.

Subjects who meet the eligibility criteria at the screening visit (visit 1) will start a 2 week run-in period. At the end of the run-in period, subjects who have not been disqualified will be eligible for participation. At the investigative site the subjects will take the last dose of run-in drug, will be fitted with an ABPM device and will start a 24-h ABPM to establish the baseline ABPM SBP and DBP. On the following day, qualified subjects who have completed the 24-h ABPM with a mean 24-h SBP ≥ 135 mm Hg will be randomly assigned to receive bexagliflozin tablets, 20 mg or placebo, using an interactive web response system (IWRS). If < 64 BP readings are recorded, the ABPM must be repeated within 2 days. Prior to randomization, subjects who cannot successfully complete the ABPM within two attempts will be considered screen failures.

A six week visit to the investigational site will allow seated office measures of systolic and diastolic BP to be recorded. At week 12 (end of study), the subject will visit the investigational site, consume the final tablet, and be fitted for ABPM.

An interim non-binding futility analysis is planned when 50% of the randomized subjects (i.e., 300) have completed study 603A.

3.5.2. Study 603B

Upon returning to the investigational site to return the ambulatory monitor at the conclusion of study 603A, subjects will begin participation in study 603B. They will receive a 12-week supply of bexagliflozin tablets, 20 mg.

At week 6 subjects will return to the investigational site for measurement of seated systolic and diastolic blood pressures. At week 12, subjects will visit the investigational site to consume the final tablet and to be fitted with an ambulatory monitor to record their baseline mean ambulatory blood pressure.

The following day, subjects will be randomized 1:1 to receive a 12-week supply of bexagliflozin tablets, 20 mg or bexagliflozin tablets, placebo.

An assessment of bexagliflozin population pharmacokinetics will also be conducted to include approximately 200 subjects. Samples will be taken between weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

3.6. SUBJECT SELECTION

The study population for the integrated program will include approximately 680 subjects with essential hypertension. Eligible subjects who consent to participate in the study will be enrolled in clinical investigational sites in the United States. Study subjects will be informed of the purpose of the program, the potential risks of participation in both studies, and will be requested to consent to the procedures and blood collection on a single consent form.

Plasma samples will be collected for population PK analysis in study 603B. Study subjects will be informed of the purpose of the PK study and requested to consent to the additional procedures and blood collection.

3.6.1. Inclusion Criteria

Refer to protocol section 4.2 for inclusion criteria.

3.6.2. Exclusion Criteria

Refer to protocol section 4.3 for exclusion criteria.

3.7. DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint of study 603A is the change from baseline (Day 1) to week 12 in the 24-hour average SBP of the bexagliflozin group compared to the placebo group using superiority testing at an overall two-sided 0.05 level of significance.

The primary efficacy endpoint of study 603B is the change from week 12 to week 24 in the 24-hour average SBP in the bexagliflozin group compared to the placebo group using superiority testing at an overall two-sided 0.05 level of significance.

Although the patient population was anticipated to be nearly identical between the two studies, they were to be carried out as independent investigations with respect to their individual primary and secondary endpoints. The assumptions used to estimate the sample size for the primary endpoint of study 603A were:

1. The magnitude of the decrease from baseline (Day 1) to week 12 of the 24 h mean SBP in the bexagliflozin treatment arm will exceed that found in the placebo arm by 5 mm Hg;

2. The standard deviation of the change from baseline to week 12 will be 15 mm Hg for both the active and placebo groups;

3. The two-sided significance level is 0.05.

The assumptions to estimate the sample size required for the primary endpoint of study 603B were:

1. Bexagliflozin will remain effective for at least 24 weeks. The 24-hour average ABPM SBP will not change between Week 12 and Week 24.

2. Subjects who are randomized to receive placebo will show an increase in ABPM SBP of 4 mm Hg between Week 12 and Week 24.

3. The standard deviation of the change is 15 mm Hg for both the active and placebo groups.

4. The two-sided significance level is 0.05.

A sample size of 254 per arm is required for the measurement to have 85% power to attain significance for the second primary endpoint. It is estimated that 75% of subjects will have completed the 36 weeks of study treatment since the first randomization. Thus a total sample size of 680 subjects is planned for the first randomization. It is estimated that approximately 8% will drop out for the first 12 weeks. A sample size of 626 subjects at the end of the first 12 weeks will provide >95% power for the first primary endpoint.

An interim non-binding futility analysis when half (i.e., 300) of subjects have completed the first 12 weeks of the treatment period will be conducted. Using an interpolated spending function of Type II error, i.e., with 0.5 proportion of Type II error being spent at the interim look, the study may stop for futility when the test statistic (Z score) is less than 0.656 (or p-value > 0.512). The overall power for the first primary endpoint remains >95% with this interim look. The futility boundary of this study is non-binding, meaning that the Type I error is properly controlled even if the study is continued after the futility boundary is crossed at the interim analysis.

3.8. TREATMENT ASSIGNMENT & BLINDING

3.8.1. Treatment Assignment

The study will be conducted in multiple investigative sites and will involve variable numbers of subjects at each site. Enrollment will be on a competitive basis, but each site will be capped at 68 randomized subjects. Activation of investigational sites will be centrally controlled by IWRS.

Subjects who meet the eligibility criteria required at the screening visit (visit 1) must be registered in the IWRS in order to be assigned a subject number and a bottle of run-in drug. During the study treatment periods, a new bottle will be assigned to the subject every 12 weeks by the IWRS at visits 3, 6, and 9. There are two randomization procedures planned in this study, at visit 3 and visit 9.

Subjects who complete the run-in period and meet the ABPM SBP ≥ 135 mm Hg criterion at visit 3 will be randomized to receive a bottle of bexagliflozin, 20 mg or placebo. Subjects will be assigned to each group in a 1:1 ratio. Randomization will be stratified according to diabetes status (history of type 2 diabetes or not), baseline ABPM SBP (≥ 160 mm Hg or not), unmedicated or not, and renal function (eGFR ≥ 60 or not). The investigator or designated staff will log into the IWRS to receive the randomization code and assigned kit number for bexagliflozin tablets, 20 mg or placebo.

At visit 6 after a subject has completed the ABPM successfully, a second bottle of study drug will be assigned to the subject by IWRS. All subjects will receive active treatment for the following 12 weeks. Subjects who experience persistent hypertension during the first 12 weeks of treatment may complete visits 5 and 6 prior to week 12.

At visit 9 after a subject has completed the 24 h ABPM successfully, the subject will be randomly assigned to receive either bexagliflozin or placebo. A new randomization number and a new bottle of double blind study drug will be assigned and dispensed to the subject. Assignment to the active or control arm will be balanced to approximately equalize the representation in each arm of the following groups:

- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 20 mm Hg reduction in mean SBP between cumulative weeks 1 and 24;
- Subjects not requiring rescue medication prior to week 24 and exhibiting a > 5 mm Hg and ≤ 20 mm Hg reduction in mean SBP between cumulative weeks 1 and 24;
- Subjects not requiring rescue medication prior to week 24 and exhibiting a ≤ 5 mm Hg reduction in mean SBP between cumulative weeks 1 and 24;
- Subjects requiring rescue medication prior to week 24.

If the mean SBP is missing at cumulative week 24, the subject will be withdrawn.

Subject randomization will be deactivated for all sites when the planned number of subjects is met and a minimum of 10% of the subjects have an average 24 h ABPM SBP ≥160 and <180 mm Hg at visit 3. However, if a potential subject has started the run-in period at that time and wishes to continue to participate, the subject will be allowed to continue and, if eligible, to be randomized.

3.8.2. Blinding

Both studies will have double-blind treatment phases. The sponsor study management team, investigators, study coordinators, pharmacists, study subjects and cardiovascular endpoint committee (CEC) will be blinded to the study medications. Protocol section 5.5 provides the general rule to maintain blinding of the individual treatment assignment.

There are periodical data safety monitoring reports and meetings planned for THR-1442-603. A designated unblinded statistician who is not involved with the study operation will hold the treatment codes and prepare reports to facilitate these activities. A separate data and safety monitoring board statistical analysis plan contains details for the types of analyses required and procedures to preserve blinding to treatment assignment.

A planned interim futility analysis was conducted by the unblinded statistician and an independent Data Monitoring Committee (DMC) after 50% of the randomized subjects received at least 12 weeks of treatment to evaluate the effectiveness of bexagliflozin. All study subjects were to continue to receive the investigational products during the data cleaning and analysis time. The unblinded statistician was responsible for preparation of the interim analysis report. The same procedures specified in the safety monitoring board statistical analysis plan were followed to preserve blinding and handle accidental unblinding.

3.9. ADMINISTRATION OF STUDY MEDICATION

The study subject will take one tablet per day of the following investigational products in addition to background medications such as treatments for diabetes, hyperlipidemia, or hypertension:

- Run-in period: placebo run-in medication
- Study 603A: bexagliflozin tablets, 20 mg or placebo
- Study 603B week 1 to week 12: bexagliflozin tablets, 20 mg only
- Study 603B week 13 to week 24: bexagliflozin tablets, 20 mg or placebo

The integrated dosing schedule is illustrated in Figure 1.

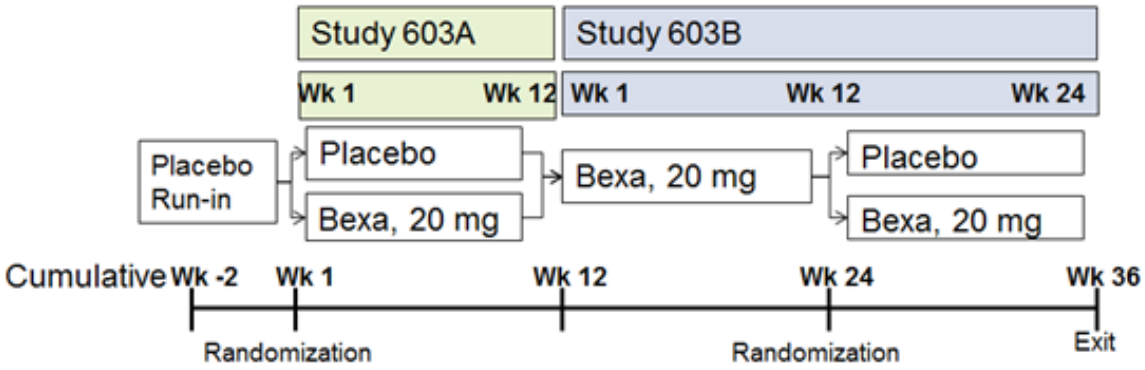

Figure 1 THR-1442-C-603 Study Design

3.10. 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 post-randomization visits. Visit 3 is the day of randomization and the basis for the visit window. A repeat ABPM shall be performed within 2 days if the 24h-ABPM is incomplete. Only the second set of ABPM data will be entered in the case report form on visits 2-3, 5-6, 8-9, and 10-11. The other specified procedures in the same assessment period do not need to be repeated. If the ABPM fails twice at visit 3 prior to randomization, the subject is considered a screen failed subject. If the ABPM cannot be completed successfully twice after randomization, the ABPM BP for that assessment period is considered missing.

Procedures listed for visit 10 and 11 will be completed if a subject is withdrawn from the study.

Table 1 Schedule of Events

	Screening/ Run-in		Study 603A			Study 603B					
Procedures			**Weeks 1 to 12**			**Weeks 1 to 12**			**Week 13 to 24**		
Cumulative study week			**1 -12**			**13-24**			**25-36**		
Visit Number	1	2	3	4	5	6	7	8	9	10	11
Time to first randomization	-13 or -12 d	-1d	0w +1d	6w	12w	12w +1d	18w	24w	24w +1d	36w	36w +1d
Informed Consent	x										
Medical History	x										
Inclusion/Exclusion Criteria	x	x	x								
Run-in drug dispensation	x										
Randomization			x						x		
Begin 24-h ABPM		x			x			x		x	
End 24-h ABPM			x			x			x		x
Double blind drug dispensation			x			x			x		
Whole blood sample	x	x			x			x		x	
Hematology	x	x			x			x		x	
HbA1c	x	x			x			x			
Serum sample										x	
Chemistry	x	x			x			x		x	
Lipids	x	x			x			x		x	
Urine sample											
Urinalysis	x	x			x			x		x	
Pregnancy test (WCBP)	x	x			x			x		x	
Population PK Sampling							x	x			
12-Lead ECG	x	x			x			x		x	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x
Abbreviated PE & weight	x				x			x		x	
Complete PE & weight		x									
Adverse Events Assessments		x		x	x		x	x		x	x
Concomitant Medication Assessments		x		x	x		x	x		x	x

4. ENDPOINTS

4.1. STUDY 603A

4.1.1. Primary Efficacy Endpoint

- Change from baseline (Day 1) to week 12 of the 24-hour mean SBP.

4.1.2. Secondary Efficacy Endpoints

- The proportion of subjects who achieve a reduction of mean ambulatory SBP of 10 mm Hg or greater;
- The proportion of subjects who achieve a mean ambulatory SBP of 135 mm Hg or less;
- The trough-to-peak ratio of ambulatory SBP at week 12;
- The placebo-adjusted change from baseline to week 12 in seated office SBP;
- The proportion of subjects who achieve a mean seated office SBP of 140 mm Hg or less at week 12;
- The placebo-adjusted change in mean ambulatory DBP from baseline to week 12;
- The proportion of subjects who achieve a mean ambulatory DBP of 87 mm Hg or less at week 12;
- The proportion of subjects who achieve a reduction of mean ambulatory DBP of 4 mm Hg or greater;
- The placebo-adjusted change from baseline to week 12 in seated office DBP;
- The proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12;

4.1.3. Exploratory Efficacy Endpoints

To further assess treatment effect in key subset populations as well as clinically relevant measurements associated with blood pressures, following exploratory efficacy endpoints will be analyzed.

- The placebo-adjusted change from baseline in the 24-hour mean ambulatory SBP at week 12 for subjects who had three or more types of antihypertensive therapies at baseline;
- The placebo-adjusted change from baseline in 24-hour mean pulse pressure at week 12;

- The placebo-adjusted change from baseline to week 12 in 24-hour mean ambulatory SBP (among dippers, and among non-dippers);
- The placebo-adjusted change from baseline to week 12 in 24-hour mean ambulatory heart rate (HR);
- The placebo-adjusted change from baseline to week 12 in body weight;
- The placebo-adjusted change from baseline to week 12 in HbA1c;
- The proportion of subjects requiring any rescue medication at week 12.

4.2. STUDY 603B

4.2.1. Primary Efficacy Endpoint

- Change from baseline week 12 (cumulative week 24) to week 24 (cumulative week 36) of the 24-hour mean SBP.

4.2.2. Secondary Efficacy Endpoints

- The placebo-adjusted change from week 12 to week 24 in seated office SBP;
- The placebo-adjusted change in mean ambulatory DBP from week 12 to week 24;
- The placebo-adjusted change from week 12 to week 24 in seated office DBP.

4.2.3. Exploratory Efficacy Endpoints

To further assess treatment withdrawal effect, following exploratory endpoints will be analyzed.

- The placebo-adjusted change from baseline week 12 to week 24 in 24-hour mean ambulatory SBP by baseline week 12 response status (rescued, >20 mm Hg, >5 and ≤20 mm Hg, ≤5 mm Hg, and >5 mm Hg);
- The proportion of subjects requiring any rescue medication at week 24.

4.3. INTEGRATED ANALYSES

Assessments for studies 603A and 603B will be combined to further assess the effectiveness of bexagliflozin after treatment of 12, 24, and 36 weeks.

There are four (4) separate treatment sequences after combining studies 603A and 603B (Table 2).

Table 2 Treatment Sequences for combined studies 603A and 603B

Sequence	Period 1	Period 2	Period 3
Seq 1 PBB	(603A) placebo	(603B) bexagliflozin	(603B) bexagliflozin
Seq 2 PBP	(603A) placebo	(603B) bexagliflozin	(603B) placebo
Seq 3 BBB	(603A) bexagliflozin	(603B) bexagliflozin	(603B) bexagliflozin
Seq 4 BBP	(603A) bexagliflozin	(603B) bexagliflozin	(603B) placebo

The following secondary endpoints will be assessed:

- Change in mean ambulatory SBP or DBP after 12 weeks treatment with bexagliflozin using week 12 assessments for Seq 3 or 4 (end of Period 1) and cumulative week 24 assessments for Seq 1 or 2 (end of Period 2);
- Change in mean ambulatory SBP or DBP after 24 weeks treatment with bexagliflozin using cumulative week 24 assessments for Seq 3 or 4 (end of Period 2) and cumulative week 36 assessment of Seq 1 (end of Period 3);
- Change in mean ambulatory SBP or DBP after 36 weeks treatment with bexagliflozin using cumulative week 36 assessments for Seq 3 (end of Period 3);
- Change in seated office SBP or DBP after 12 weeks treatment with bexagliflozin using week 12 assessments for Seq 3 or 4 (end of Period 1) and cumulative week 24 assessments of Seq 1 or 2 (end of Period 2);
- Change in seated office SBP or DBP after 24 weeks treatment with bexagliflozin using cumulative week 24 assessments for Seq 3 or 4 (end of Period 2) and cumulative week 36 assessments for Seq 1 (end of Period 3);
- Change in seated office SBP or DBP after 36 weeks treatment with bexagliflozin using cumulative week 36 assessments for Seq 3 (end of Period 3).
- Cumulative mean change from baseline in seated office SBP as a function of time (including all scheduled office visits) for subjects exposed to bexagliflozin
- Cumulative mean change from baseline in seated office DBP as a function of time (including all scheduled office visits) for subjects exposed to bexagliflozin

4.4. SAFETY ENDPOINTS

- Treatment emergent adverse events
- Treatment emergent adverse events of special interest
- Concomitant medication use

- Laboratory test
- Cardiac rhythm determined by 12-lead ECG
- Vital signs
- Physical examination

5. ANALYSIS SETS

5.1.1. Study 603A

The following analysis sets will be analyzed:

- Intention-to-Treat (ITT) Analysis Set: will include all subjects who are randomized to the study. All subjects will be analyzed according to the treatment to which they were randomized to receive.
- Safety Analysis Set: will include all subjects who are randomized to the study and have taken at least one dose of double blind investigational product. This analysis set will be used for study 603A safety analyses. All subjects will be analyzed according to the treatment they receive.

5.1.2. Study 603B

- ITT Analysis Set: will include all subjects who are randomized at week 12. All subjects will be analyzed according to the treatment to which they were randomized to receive.
- Safety Analysis Set: will include all subjects who have taken at least one dose of investigational product.
- Safety Analysis Set for withdrawal period: will include all subjects who are randomized at week 12 and have taken at least one dose of double blind investigational product. All subjects will be analyzed according to the treatment they receive.

5.1.3. Integrated Analyses

- Integrated ITT Analysis Set: will include all subjects who are randomized to bexagliflozin in 603A, or entered study 603B run-in period. The set will include all subjects to whom a study kit is dispensed in 603B run-in period, and subjects who are randomized to bexagliflozin in 603A.
- Integrated Safety Analysis Set: will include all subjects who are treated with at least one dose of bexagliflozin in either study. This will include subjects in the 603B safety analysis set and subjects who received at least one dose of bexagliflozin during 603A.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

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

Tables, listings and figures (TLFs) will be produced in accordance with the principles outlined by the ICH E3 guidelines. For most summary statistics, data will be analyzed by the following treatment groups: Bexagliflozin 20 mg; Placebo. For 603B, unless otherwise specified, data will be analyzed by treatment in the 603B withdrawal period. Treatment in 603B withdrawal period will be further split by treatment sequence (as shown in Table 2). For integrated analyses, unless otherwise specified, summaries will be by total of all patients in the analysis set.

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

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

Only scheduled visits will be included in by visit summaries. All visit assessment data will be included in shift tables and will appear in the subject listings.

No data imputation will be applied for missing values in safety analysis. Efficacy data imputation method will be described in Section 8.

6.2. KEY DEFINITIONS

6.2.1. Baseline Values

Unless otherwise specified, baseline is defined as:

- For study 603A endpoints, baseline is defined as the last non-missing measurement prior to the first dose of double-blind study medication in 603A.
- For study 603B endpoints, baseline is defined as the last non-missing measurement prior to the first dose of double-blind study medication in 603B.
- For integrated endpoints by weeks from first exposure to bexagliflozin, baseline is defined as the last non-missing measurement prior to the first exposure of bexagliflozin. Considering the 4 sequences in Table 2, baseline for Seq 3 or 4 is the

last non-missing measurement prior to first dose of bexagliflozin in 603A. Baseline for Seq 1 or 2 is defined as the last non-missing measurement prior to the first dose of bexagliflozin in 603B run-in period. This applies to all integrated efficacy endpoints or the safety summaries by weeks of bexagliflozin treatment.

6.2.2. First Dose Date

In general, the first dose date for 603A will be the date that the first dose of study drug is administered after the first randomization. The first dose date for 603B will be the date that the first dose of study drug is administered after the second randomization. The first dose date for integrated analysis will be the date that the first dose of bexagliflozin is administered.

6.2.3. Last Dose Date

The date of the last dose will be recorded in CRF at Day -1, cumulative weeks 12, 24, and 36. The last dose date for 603A will be the date recorded at week 12 and 603B will be the one recorded at 603B week 24. The date of the last dose in integrated analyses will be the latest last dose dates for any bexagliflozin kit dispensed.

6.2.4. Study Day

Study Day is the number of days starting from the first administration of double-blind study drug in each study, 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.

6.2.5. Duration

Duration of treatment for each period will be determined as Duration = date of the last dose in the specific period minus date of the first dose date in the specific period plus 1.

6.2.6. The 24-hr Mean ABPM

The 24-hour mean ABPM is computed following the steps below:

- The mean for each clock hour on each day are computed as the average of all readings within the hour on that day, e.g. Day 1 hour 9 is the average of all values on Day 1 09:00 – 09:59. The measures on different days from same clock hour are considered as separate values.
- The 24-hour mean will be computed as the average all available hourly mean.

6.3. MISSING DATA

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

6.4. ANALYSIS VISIT WINDOWS

No analysis visit windows will be used. For by visit safety analysis, the early termination (ET) visit will be included in the derivation of the end of the study visit. For efficacy analysis, unscheduled or ET visit will be used if the scheduled visit is missing, described in Section 8. Nominal visits will be used for scheduled visit. In case if there are multiple assessments for a visit, the later one will be used.

6.5. POOLING OF CENTERS

Analysis will not be pooled by center.

6.6. TERMINOLOGY USED IN SAP

In general, terms below will be used:

- "Weeks" refer to study week, unless cumulative week is specified;
- Analysis for 603B refers to after randomization in 603B. The bexagliflozin dosing period before randomization is referred to as the "603B run-in period".

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition data will be presented in list form. Separate disposition tables will present the number and percentage of subjects who complete each of the salient study milestones. The disposition table for study 603A will be presented by treatment in 603A and overall. Those milestones will be: signing of the informed consent, screen pass prior to 603A run-in, screen pass after 603A run-in, randomization to 603A, completion of 603A, entered into 603B run-in. Table for 603B will be presented first by treatment sequence, then by treatment in 603B, and lastly, overall. Milestones will be: completion of the 603B run-in, randomization to 603B, and completion of 603B. In addition, the number and percentage of subjects who require rescue medication will be listed for each overall treatment period, either 603A (Period 1), 603B run-in (Period 2), or 603B (Period 3).

The reasons for early withdrawal will be summarized.

Assignment to the analysis sets (safety, ITT) at study 603A, study 603B will be summarized.

7.2. SUBJECT ELIGIBILITY AND PROTOCOL DEVIATIONS

All subjects, including screen failure subjects before and after run-in, who do not meet the Inclusion/exclusion criteria, will be listed. A table will display the number of subjects who fail at screening or 603A run-in (non-randomized subjects) with a summary of the reasons for screen fail prior to randomization.

The number and percent of subjects who had any major deviation will be tabulated along with disposition tables for the ITT Analysis Set.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be descriptively summarized for all ITT analysis sets by treatment group for studies 603A, 603B, and integrated ITT analysis set. Key variables will include: age, gender, race, ethnicity, baseline vital signs (includes office pulse, SBP, DBP in sitting, supine, and standing positions, 24-hour mean ambulatory SBP and 24-hour mean ambulatory DBP), ECG measures (to include RR interval, PR interval, QRS duration, and QT interval), renal function (to include eGFR), body weight, BMI, initial randomization stratification factors (to include diabetic status [history of type 2 diabetes or not], baseline ABPM SBP [≥ 160 mm Hg or not], and renal function [eGFR ≥ 60 mL/min/1.73 m^2 or not]), and background antihypertensive medications (4 most common medication types determined by ATC class 4 and all other

antihypertensive medications). Separate demographic and baseline characteristics tables will be prepared for each study. 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. Subject age will be calculated in the clinical database as the age at date of informed consent in 603A. Summaries for integrated analyses will be presented by bexagliflozin 20 mg in 603A, placebo in 603A and entered 603B, and all subjects in integrated ITT analysis set. Subjects randomized to the placebo arm in 603A and did not enter 603B will also be summarized in a separate group.

7.4. MEDICAL HISTORY

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

Medical and surgical history will be summarized for the safety analysis set by system organ class (SOC), and MedDRA preferred term (PT) for each study. Subject data will be listed. Medical history for 603B will be summarized by treatment received during withdrawal period.

Subject diabetic, renal, and cardiovascular disease histories will be summarized for all categorical variables by frequency and percentage for both studies in the safety analysis set. Cardiovascular disease histories for 603B will be summarized by treatment received during the withdrawal period, then further split by treatment sequence. Diabetic and renal disease histories for 603B will be summarized by treatment received during 603 withdrawal period.

7.5. MEDICATION

All medication will be coded using the World Health Organization Drug Dictionary (WHO-DD) version March 2016 or above. 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 for each study, by 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.

7.5.1. Prior Medication

Any medication with a stop date prior to the first dose date for study 603A will be considered a prior medication.

No summary for prior medication will be presented. Prior and concomitant medications will be presented together in a single listing. The listing will be ordered by subject number, and medication start/end dates. Prior medication for study 603A will be flagged separately.

7.5.2. Concomitant Medication

A concomitant medication is any medication that the subject has been taking prior to the first dose of double blind study medication and that the subject is expected to continue to take for some portion of the study treatment period, as well as any medication other than the investigational product that the subject takes during the course of the study treatment period. Concomitant medication for 603B will be summarized by treatment received during the withdrawal period.

A rescue medication is defined as a dose increase of an existing blood pressure medication or initiation of a new blood pressure medication for the purpose of lowering blood pressure. Medications prescribed for other indications are not considered rescue medication. Replacing a blood pressure lowering medication with another medication of the same class within the recommended dose will not be considered a rescue medication. Rescue medication will be summarized for 603A, 603B run-in period, 603B, and integrated. For period-specific summaries of 603A and 603B, rescue medication will be summarized for the period during which the medication started or the dose increased. For integrated summaries, any rescue medication started or dose increased during bexagliflozin treatment will be included.

Concomitant medications will be presented in summary tables for

1) 603A, based on the 603A safety analysis set;
2) 603B, based on the safety analysis set for withdrawal period;
3) Integrated, based on the integrated safety analysis set.

Medication is considered to be concomitant to 603A, the 603B run-in period, or 603B, if it satisfies the conditions below:

- The start date is before the last dose of the study medication for that period;
- The end date is after the first dose of the study medication for that period or the medication is ongoing.

For integrated summaries, medication is considered to be concomitant to bexagliflozin if it satisfies the condition below:

- The start date is before the last dose of bexagliflozin;
- The end date is after the first dose of bexagliflozin or the medication is ongoing.

In the case of completely missing stop date, medication will be assumed to be concomitant to all treatment periods.

8. EFFICACY

Changes from baseline for efficacy data will be calculated as the post-treatment value minus the corresponding defined baseline (see Section 6.2.1). Descriptive summaries will be presented for observed and change values by treatment and visit. Assessment of proportion data will be presented by frequency and proportion by treatment and visit.

8.1. STUDY 603A

For all analyses at Week 12, LOCF will be used for subjects who lack Week 12 assessments or who require intensification of anti-hypertensive therapy. Only post-baseline values before rescue medication will be carried forward.

8.1.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the change from baseline to week 12 of the 24-hour mean ambulatory SBP in the bexagliflozin group compared to the change in the placebo group, testing for superiority at a two-sided 0.05 level of significance. A valid ABPM reading will require:

- ≥ 64 BP total readings; and
- ≥ 51 BP daytime readings or ≥ 13 BP nighttime readings.

Only valid ABPM will be used for analysis.

8.1.1.1. Primary Efficacy Analysis

Let $\mu_{Bexagliflozon,\ 12}$ and $\mu_{PBO,\ 12}$ represent the mean changes from baseline in 24-hour ambulatory SBP at Week 12 for bexagliflozin and placebo arm, respectively. The following hypotheses will be tested:

$$H_0: \mu_{Bexagliflozon,\ 12} = \mu_{PBO,\ 12} \text{ versus } H_1: \mu_{Bexagliflozon,\ 12} \neq \mu_{PBO,\ 12}$$

To test this hypothesis, an analysis of covariance (ANCOVA) will be applied to analyze the mean change in 24-hour average ABPM SBP. The ANCOVA model will include terms for diabetes status (history of type 2 diabetes mellitus [T2DM] or not), renal function (eGFR at screening as continuous variable), pre-treatment status (presently medicated for hypertension or not), randomized treatment, and the baseline 24-hour mean SBP as fixed effect covariates. Change from baseline will be the dependent variable. Analysis will be conducted on ITT analysis set. The last ABPM SBP post baseline will be used for the analysis.

Descriptive statistics (n, mean, Q1, median, Q3, SD, minimum, and maximum) will be reported by treatment group, along with the least squares means, differences between LS means, a 2-sided 95% confidence interval (CI) for each difference, p-value from the model effects.

8.1.1.2. Sensitivity Analysis

Sensitivity analyses will be conducted to examine the robustness of the inference:

- If subject receives rescue medication and has an ABPM value after rescue medication, this value will be analyzed as an outcome. In study 603A, a subject who requires rescue medication will attempt to complete an ABPM before initiating rescue medication. A subject will be terminated if rescue medication starts within the first 6 weeks, or will start study 603B (after the first 6 weeks). No post-rescue medication value is expected and as a result, analysis of post-rescue data will not be conducted. This sensitivity analysis will only be conducted if >5 subjects have post rescue medication values.
- Subjects without scheduled Week 12 assessment (i.e., post baseline ABPM for subjects who did not complete 12 weeks treatment) will be excluded from the analysis.
- A tipping point analysis will be conducted for subjects without Week 12 assessments. The following steps will be taken:
    - If subject has withdrawn from the study or has initiated rescue medication, the value will be considered as missing.
    - A regression model will be used to impute the missing change value using SAS PROC MI procedure. Covariate will include baseline 24-hr mean SBP, diabetes status (history of T2DM or not), renal function (eGFR at screening), pre-treatment status (presently medicated for hypertension or not) and randomized treatment. One hundred datasets will be imputed.
    - If subjects with missing values are in the placebo treatment arm, the imputed value will be used in the analysis.
    - If the subject is in the bexagliflozin treatment arm, a series of δ mm Hg will be added to the imputed values. The δ value will range from 0.5 to 5, with step size of 0.5.
    - The same ANCOVA analysis from Section 8.1.1.1 will be conducted for each imputed dataset and δ. The results will be combined using PROC MIANALYZE in SAS.
- Wilcoxon rank sum test will be conducted including all post baseline ABPM SBP values. For a subject who has no post baseline assessment, the worst outcome within the treatment group (i.e., change from baseline = the maximum increase from baseline in the same treatment group) will be considered.

8.1.1.3. Subgroup Analysis

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

- Age (< 65 years or ≥ 65 years);
- Gender (male or female);
- Race (White or Caucasian; Black or African-American; Asian; Other). If the number of Asian subjects is less than 5 in any treatment group, they will be included with Other; subjects identifying with more than one racial group will also be treated as Other;
- Diabetes status (history of T2DM or not);
- Renal function (eGFR at screening ≥ 60 or not);
- Pre-treatment status (presently medicated for hypertension or not);
- Types of anti-hypertension medication used;
- Baseline 24-hour mean SBP status (SBP≤160 mm Hg or SBP>160 mm Hg);

Same summary and ANCOVA model will be presented as in section 8.1.1.1 for each level of the subgroup.

In addition, univariate and multivariate exploratory analyses will be conducted to assess potential baseline and diagnosis effect in controlling of hypertension. For univariate analysis, ANOVA with each subgroup factor, treatment, and interaction between subgroup factor and treatment will be performed. Statistically significant subgroup factors, judging by the type 3 test of the factor (P-value < 0.1), will be further explored in multivariate analyses. ANOVA with these subgroup factors and treatment will be implemented.

8.1.2. Secondary Efficacy Endpoints and Analyses

The secondary efficacy endpoints include mean ambulatory and seated office SBP, mean ambulatory and seated office DBP. Secondary efficacy endpoints will be accessed without multiplicity adjustment. Analyses will be primarily based on ITT analysis set.

8.1.2.1. The proportion of subjects who achieve a reduction of mean ambulatory SBP of 10 mm Hg or greater

Subjects who achieve a reduction of mean ambulatory SBP of ≥ 10 mm Hg will be summarized using frequency and percentage by treatment arm. Logistic regression will be used to analyze the treatment effect. The model will include diabetes status (history of T2DM or not), renal function (eGFR at screening as continuous variable), pre-treatment status (presently medicated for hypertension or not), baseline mean

ambulatory SBP value and randomized treatment. The LS Mean responding proportion and 95% CI will be estimated within each treatment group from a logistic regression model. A p-value for comparison by treatment group will also be provided. Two different outcomes will be explored:

- Responder will be defined using the last-post baseline value. If a subject received rescue medication, the value prior to the initiation of rescue medication will be used (primary analysis);
- Subjects with no post baseline assessments prior to early withdrawal from the study or initiation of the rescue medication will be considered as non-responders (sensitivity analysis).

8.1.2.2. The proportion of subjects who achieve ambulatory SBP of 135 mm Hg or less

The summary and analyses will be provided as in section 8.1.2.1.

8.1.2.3. The placebo-adjusted change from baseline to week 12 in seated office SBP

A summary and ANCOVA model will be presented as in section 8.1.1.1. The model will use baseline seated office SBP in place of baseline mean ambulatory SBP.

8.1.2.4. The proportion of subjects who achieve a mean seated office SBP of 140 mm Hg or less at week 12

A summary and analysis will be presented as in section 8.1.2.1. The model will use baseline seated office SBP in place of baseline mean ambulatory SBP.

8.1.2.5. The placebo-adjusted change from baseline to week 12 in mean ambulatory DBP

A summary and ANCOVA model will be presented as in section 8.1.1.1. The model will use baseline mean ambulatory DBP in place of baseline mean ambulatory SBP.

8.1.2.6. The proportion of subjects who achieve a mean ambulatory DBP of 87 mm Hg or less at week 12

A summary and analysis will be presented as in section 8.1.2.1. The model will use baseline mean ambulatory DBP in place of baseline mean ambulatory SBP.

8.1.2.7. The proportion of subjects who achieve a mean ambulatory DBP of 4 mm Hg or greater

A summary and analysis will be presented as in section 8.1.2.1. The model will use baseline mean ambulatory DBP in place of baseline mean ambulatory SBP.

8.1.2.8. The placebo-adjusted change from baseline to week 12 in seated office DBP

A summary and ANCOVA model will be presented as in section 8.1.1.1. The model will use baseline seated office DBP in place of baseline mean ambulatory SBP.

8.1.2.9. The proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12

A summary and logistic model will be presented as in section 8.1.2.1. The model will use baseline seated office DBP in place of baseline mean ambulatory SBP.

8.1.2.10. The trough-to-peak ratio of ABPM SBP at week 12

Trough/Peak ratio will be calculated based on the four valid measurements centered on approximate T_{max} (4 h post-dose, i.e. 2 measurements on or before 4 h and 2 measurements after 4 h) and the four valid measurements immediately preceding the removal of the monitor and prior to administering a tablet. The ratio will be summarized by treatment arm at week 12. The first 24-hour hourly change from baseline since dose administration will be summarized by treatment group and time (i.e., 0h post-dose, 2h post-dose, …, and 23h post-dose). Hour 0 will be the hour when dosing is occurred. All measures at 0h post-dose are measures within the same clock hour, but after dosing.

8.1.3. Exploratory Endpoints and Analyses

The exploratory efficacy endpoints include change from baseline in 24-hours mean ambulatory SBP, DBP, heart rate, pulse pressure, body weight, HbA1c, and subjects requiring rescue medication. Analyses will be primarily based on ITT analysis set.

8.1.3.1. The placebo-adjusted change from baseline to week 12 in 24-hour mean ABPM SBP among subjects taking appropriate doses of three or more types of antihypertensive therapies at baseline

A summary and ANCOVA model will be presented as in section 8.1.1.1 using only subjects taking ≥ 3 types of antihypertensive therapies at baseline.

8.1.3.2. The placebo-adjusted 24-hour mean pulse pressure at week 12

The pulse pressure will be calculated as the difference between ambulatory SBP and ambulatory DBP. The 24-hour mean pulse pressure will be calculated as the mean of all hourly ambulatory pulse per day per clock hour. A summary and ANCOVA model will be presented as in section 8.1.1.1. The model will include baseline pulse pressure in place of baseline mean ambulatory SBP.

8.1.3.3. The placebo-adjusted change from baseline to week 12 in 24-hour ambulatory SBP among dippers and non-dippers

Dippers and non-dippers are defined as:
Dippers: nocturnal mean SBP ≤ 90% of diurnal mean SBP;
Non-dippers: nocturnal mean SBP >90% of diurnal mean SBP.
The nocturnal time interval is between 12:00 AM – 8:00 AM and diurnal time interval is between 11:00 AM – 7:00 PM. The nocturnal time mean is computed as the mean of 8 (or fewer, if failures occur) hourly mean SBP values in the nocturnal range and the diurnal time mean SBP is computed as the mean of 8 (or fewer) hourly mean SBP in the diurnal range of times.

Summaries and ANCOVA models will be presented as in section 8.1.1.1 for dippers and non-dippers, respectively.

8.1.3.4. The placebo-adjusted change from baseline in 24-hour ambulatory HR at week 12

A summary and ANCOVA model will be presented as in section 8.1.1.1. In addition, baseline 24-hour ambulatory HR will also be included as covariate.

8.1.3.5. The placebo-adjusted change from baseline in body weight at week 12

A summary and ANCOVA model will be presented as in section 8.1.1.1. The model will include baseline weight in place of baseline mean ambulatory SBP. Baseline 24-hour ambulatory SBP will also be included as covariate.

8.1.3.6. The placebo-adjusted change from baseline in HbA1c at week 12

A summary and ANCOVA model will be presented as in section 8.1.1.1. The model will include baseline HbA1c in place of baseline mean ambulatory SBP. Baseline 24-hour ambulatory SBP will also be included as covariate.

8.1.3.7. The proportion of subjects requiring any rescue medication at week 12

The summary and analyses will be provided as in section 8.1.2.1 primary analysis.

8.2. STUDY 603B

For all efficacy analyses in study 603B the baseline will be defined as the last non-missing measurement prior to the first dose of double-blind study medication in 603B. Change is defined as the observed value minus baseline value. Similar to study 603A, the values from early termination visits, or values before the initiation of rescue medication in 603B will be used.

8.2.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the change from baseline (at week 12) to week 24 of the 24-hour mean ambulatory SBP in the bexagliflozin group compared to the change in the placebo group, testing for superiority at a two-sided 0.05 level of significance.

8.2.1.1. Primary Efficacy Analysis

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

$$H_0: \mu_{Bexagliflozon,\ 24} = \mu_{PBO,\ 24} \text{ versus } H_1: \mu_{Bexagliflozon,\ 24} \neq \mu_{PBO,\ 24}$$

To test this hypothesis, an ANCOVA will be applied to analyze the mean change in 24-hour average ABPM SBP. The ANCOVA model will be used to adjust for the treatment group stratification by rescue medication/response as assessed by ABPM SBP at baseline (Week 12) (i.e., require rescue medication, not require rescue medication: SBP change≤5 mmHg, >5 to ≤20 mmHg, >20 mmHg), baseline ABPM SBP value, and randomized treatment for study 603B as fixed effects.

Similar descriptive analysis as in Section 8.1.1.1 will be provided.

In addition, the interaction of the response stratification class (response ≤ 5 mm Hg, 5 < response ≤ 20 mm Hg, and response > 20 mm Hg, requiring rescue medication prior to week 24) and randomized treatment for study 603B will be added to the model. P-value for the type 3 test will be presented to check the significance of the interaction terms at 0.10 significant level. LS means, standard errors, and 95% CI for each combination of stratification class and treatment will be estimated from the model.

8.2.1.2. Sensitivity Analysis

- If subject has received rescue medication and has an ABPM value after rescue medication, this value will be analyzed as an outcome. Per protocol, if subject requires rescue medication, ABPM will be taken before starting rescue medication. In such case, ABPM is not normally measured again after rescue medication. This sensitivity analysis will only be conducted if >5 subjects have post rescue medication values.
- Subjects without scheduled Week 24 assessments will be excluded from the analysis.
- A tipping point analysis will be conducted if there are subjects missing Week 24 assessment. Steps below will be followed:
    - If subject used rescue medication or discontinued during withdrawal period, value will be considered as missing.
    - A regression model will be used to impute the missing change value using SAS PROC MI procedure. Covariate will include baseline 24-hr mean SBP, the treatment group stratification by response as assessed by ABPM SBP at baseline (Week 12), and randomized treatment for study 603B. One hundred datasets will be imputed.
    - If subjects with missing value are in the placebo treatment arm, the imputed values will be used.
    - If the subject is in the bexagliflozin treatment arm, a series of δ will be added to the imputed values. The δ value will range from 0.5 to 5, with step size equals 0.5.
    - Same ANCOVA analysis from Section 8.2.1.1 will be conducted for each imputed dataset and δ. Results will be combined using PROC MIANALYZE in SAS.
- Wilcoxon rank sum test will be conducted including all Week 24 ABPM SBP values. If subject requires rescue medication, ABPM before starting rescue medication will be used; for a subject who has no post baseline assessment, the worst outcome within the treatment group (i.e., change from baseline = the maximum increase from baseline in the same treatment group) will be considered.

8.2.2. Secondary Efficacy Endpoint(s) and Analyses

The secondary efficacy endpoints include mean seated office SBP, and mean ambulatory and seated office DBP. No adjustment for multiple comparisons will be applied.

8.2.2.1. The placebo-adjusted change from week 12 to week 24 in seated office SBP

A summary and analyses will be provided as in section 8.2.1.1. The model will include baseline seated office SBP in place of baseline mean ambulatory SBP.

8.2.2.2. The placebo-adjusted change from week 12 to week 24 in mean ambulatory DBP from week 12 to week 24

A summary and analyses will be provided as in section 8.2.1.1. The model will include baseline mean ambulatory DBP in place of baseline mean ambulatory SBP.

8.2.2.3. The placebo-adjusted change from week 12 to week 24 in seated office DBP

A summary and analyses will be provided as in section 8.2.1.1. The model will include baseline seated office DBP in place of baseline mean ambulatory SBP.

8.2.3. Exploratory Endpoints and Analyses

8.2.3.1. The proportion of subjects requiring any rescue medication at week 24

Subjects who require any rescue medication will be summarized using frequency and percentage by treatment arm. Logistic regression will be used to analyze the treatment effect. The model will include the rescue medication/response as assessed by ABPM SBP at baseline (Week 12) (i.e., require rescue medication, not require rescue medication: SBP change ≤ 5 mmHg, > 5 - ≤ 20 mmHg, > 20 mmHg), baseline ABPM SBP value, and randomized treatment for study 603B as fixed effects. LS Mean responding proportion and 95% CI will be estimated within each treatment group from the logistic regression model. P-value for comparison of treatment group will also be provided.

8.2.3.2. The placebo-adjusted change from week 12 to week 24 in 24-hour ABPM SBP by response status

The effect of withdrawal will be studied for each subgroup of subjects separated by their response status at baseline week 12 (i.e., require rescue medication, not require rescue medication: SBP change ≤ 5 mmHg, > 5 - ≤ 20 mmHg, > 20 mmHg, and >5 mmHg). A summary and analyses will be provided as in section 8.2.1.1 for subjects in each group. Baseline ABPM SBP value will be used as covariate and the randomized treatment will be included as the fix effects in the model.

8.3. INTEGRATED ANALYSES

Assessments for studies 603A and 603B will be combined to further assess the effectiveness of bexagliflozin after treatment for 12, 24, and 36 weeks. The sequence numbers in this section refer to the numbers in Table 2. All analyses will be based on the integrated ITT analysis set.

8.3.1. Change in mean ambulatory SBP or DBP after 12, 24, and 36 weeks of treatment of bexagliflozin

Summary statistics will be provided for actual value at baseline, and actual value and change from baseline after 12, 24, and 36 weeks treatment with bexagliflozin. The 95% CI based on normal distribution will also be presented for the change value. For subjects who require rescue medication, the ABPM taken prior to rescue medication (as was used for the primary analyses for studies 603A and 603B) for the time point will be used.

The proportion of subjects who achieve defined goals will be summarized after 12, 24, and 36 weeks treatment with bexagliflozin using frequency, percentage and 95% binomial confidence interval. These goals will include:

- A reduction of mean ambulatory SBP of 10 mm Hg or greater;
- A reduction of mean ambulatory DBP of 4 mm Hg or greater.

8.3.2. Change in seated office SBP or DBP after 12, 24, and 36 weeks treatment of bexagliflozin

Summary statistics as in section 8.3.1 will be provided for seated office SBP or DBP. The proportion of subjects who achieve defined goals will be summarized after 12, 24, and 36 weeks treatment with bexagliflozin using frequency, percentage and 95% binomial confidence interval. These goals will include:

- The proportion of subjects who achieve a mean seated office SBP of 140 mm Hg or less at week 12.
- The proportion of subjects who achieve a mean seated office DBP of 90 mm Hg or less at week 12.

8.3.3. Cumulative mean change from baseline in seated office SBP and DBP as a function of time (including all scheduled office visits) for subjects exposed to bexagliflozin

Summary tables will be presented for seated office SBP and DBP by treatment sequence for all subjects in 603B ITT population. Table will include baseline, actual value and change from baseline at cumulative weeks 6, 12, 18, 24, and 36. Baseline is defined as the last non-missing value before the first dose of bexagliflozin in 603A. A by-sequence plot of change from baseline will include mean and standard error.

9. SAFETY

All analyses described in this section will be performed separately for each study and integrated analysis. The analysis set used for safety analyses will be the safety analysis

set for 603A, safety analysis set for withdrawal period for 603B, safety analysis set for 603B run-in period, and integrated safety analysis set for integrated analysis. Safety data include AEs; physical examination results; vital signs, including blood pressures; ECG results; and clinical laboratory results, including serum chemistry, hematology, serum lipids, and urinalysis.

9.1. EXTENT OF EXPOSURE

Study drug exposure will include:

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

Treatment duration (in weeks) is calculated as (the date of the last dose of study drug - the date of the first dose of study drug + 1) / 7 and rounded to 1 decimal place. Total dose consumed will be calculated as number of tablets dispensed on the first day after randomization – number of tablets returned on the last day of the period. If any of the bottles dispensed are not returned, it will not be possible to compute the total dose consumed. In this case, the number of tablets consumed will be considered as missing.

Exposure will be summarized for study 603A, 603B, and integrated.

Summary statistics for treatment duration (in weeks) and total dose consumed, as well as a frequency summary of treatment duration categories (e.g., < 1, 1 - < 3 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. Treatment compliance will be summarized by treatment for 603A and 603B.

Compliance in studies 603A, 603B, and integrated will be calculated as follows:

- Percent compliance = (number of tablets consumed / number of tablets that should have been taken) x 100.
- Number of tablets consumed is computed as in Section 9.1.
- Number of tablets should have taken = number of exposure days.
- Number of exposure days = last dose date – first dose date + 1.

If any of the bottles dispensed are not returned, the number of tablets consumed and compliance will be considered as missing. Compliance will be summarized for each period by actual treatment for safety analysis set. A separate table for overall compliance will be presented without treatment arms. 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 after a subject is enrolled in the study to the last scheduled contact. Any 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, will be included in the analysis.

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

A treatment-emergent adverse event (TEAE) is defined as an AE that begins (or an existing condition that worsens) after the first administration of double-blind study medication in study 603A). TEAE will be summarized separately for periods: study 603A and study 603B after randomization, dependent upon in which period the event started. TEAE summary for all periods combined will include all bexagliflozin TEAEs started on or after the first dose of bexagliflozin and before the last dose of bexagliflozin.

Drug-related AEs will be considered those to be possibly, probably and definitely related to bexagliflozin administration based on the investigator's assessment.

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

9.3.1. Derived Data

AE onset day is calculated as (date of AE start – date of first double-blind dose of each study + 1).

9.3.2. Data Summarization

The AE summaries will include:

- An overall summary of the number and percentage of subjects reporting any TEAEs, serious TEAEs, treatment-related TEAEs, serious treatment-related TEAE, any TEAEs leading to treatment discontinuation, any TEAEs leading to subject withdrawal 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 withdrawal, overall and by SOC and PT
- Common TEAEs. Common TEAEs are as TEAEs that occur in > 5% of the subjects in either of the treatment groups.

Except for common TEAEs, each data summary will be presented for the 603A period, for the 603B period after randomization, and for the integrated bexagliflozin treatment periods. Common TEAEs will be presented for the integrated bexagliflozin treatment period. Tables for the 603A will be summarized by treatment received in 603A and overall. The summary table for the 603B period after randomization will contain 2 layers: 1) 603B treatment, and 2) split 603B treatment by 603A treatment groups. Tables for integrated bexagliflozin treatment periods will present number and percentage of subjects with event, and exposure adjusted AE rate (i.e. rate per 100 patient years of bexagliflozin). Events will be summarized according to the actual treatment when the event starts. The denominator for percentage calculations will be the total number of subjects who receive at least one dose of the specified treatment. All subjects should have received at least one dose of bexagliflozin unless they were withdrawn from study 603A.

All AE summary tables will be prepared by actual treatment arm for the safety analysis set. For summary tables, subjects having more than 1 event with the same PT in the period will be counted once for that term. Subjects having more than 1 event with the same SOC in the period 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) in the period will be counted; similarly, for tabulations by relationship, only a subject's most related event within a category in the period will be counted. The denominator for percentages will be the number of subjects in the safety analysis set for the given treatment group.

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

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

Additional information will be collected in the event diabetic ketoacidosis (DKA) is

suspected or observed. These data will be listed.

9.3.3. AEs of Special Interest

AEs of special interest include, but are not limited to, diuretic effects, urinary tract infections (UTI), genital mycotic infections (GMI), hypoglycemia, hepatotoxicity, major adverse cardiovascular events (MACE), diabetic ketoacidosis (DKA), hypotension episodes, malignancies, fractures, renal failure events, hypersensitivity reactions, rash, pyelonephritis or urosepsis, and events may be associated with SGLT2 inhibition, including amputations, , and Fournier's gangrene. These AEs of special interest, except for MACE, 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. MACE and hypoglycemia events by severity will be summarized separately. All AEs of special interest will be presented for 603A, 603B run-in, 603B post-randomization, and all periods combined in the same format as in Section 9.3.2.

9.3.3.1. AE of Special Interest Identified by PTs

The number and percentage of subjects experiencing TEAEs of special interest will be summarized for each treatment group by type of event. The incidence rate of AE of special interest per 100 patient years will also be summarized. Each category of events will be displayed in a separate listing.

9.3.3.2. Hypoglycemic Events

Hypoglycemic event categories include:

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

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

The number and percentage will be summarized for the integrated bexagliflozin treatment period:

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

9.3.3.3. Major Adverse Cardiovascular Events

Cardiovascular events considered to be potential MACE by the investigator will be submitted to an independent CEC for adjudication. The events of interest include cardiovascular mortality, MI, stroke, hospitalization for acute coronary syndromes, urgent revascularization procedures, and other possible serious cardiovascular events. The number, percentage and incidence rate per 100 patient years of adjudicated MACE will be summarized for each treatment group. Adjudicated MACE will be further summarized by PTs.

9.4. LABORATORY EVALUATIONS

Laboratory tests will include hematology panel, chemistry panel, serum lipids, and urinalysis testing. Hematology, HbA1c, chemistry, serum lipids, and urinalysis will be performed at the following time points: at the screening visit (Week - 12), on Day -1 visit, and at cumulative week 12, 24, and 36. A list of laboratory tests is included in Table 3.

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

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

Among those subjects who have screening triglycerides >350 and have both calculated and direct LDL values, only the direct LDL will be analyzed.

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.

All scheduled and unscheduled results will be considered in tables that assess maximum severity.

Observed values (in SI units) and change from baseline over time will be summarized for each scheduled visit and the end of the study visit. Laboratory data will be classified as low, normal, or high relative to the parameter's reference range. Laboratory abnormalities for each treatment will also be summarized with shift tables for selected parameters. All summary tables will be presented by treatment group and for each visit for study 603A and 603B. In addition, summaries based on assessments from both studies (603A and 603B) will also be presented by weeks of exposure of bexagliflozin (12 weeks, 24 weeks, and 36 weeks).

All continuous variables will be summarized by number of subjects [n], mean, SD, Q1, median, Q3, minimum and maximum and categorical variables will be summarized by frequency and percentage. For hematology, chemistry, and serum lipids, columns will be included for normal ranges and individual abnormal laboratory values will be flagged and clinical significance will be indicated. A listing for the microscopic examination will be provided for subjects who have a positive result from the urinalysis dipstick evaluation.

Table 3 List of Laboratory Tests

Hematology:
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Urinalysis:
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- pH
- Protein
- Specific gravity
- Urobilinogen

Pregnancy test:
Urine human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

Serum Chemistry:
- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- creatinine kinase (CK)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Bicarbonate (HCO_3)
- Chloride (Cl)
- Creatinine
- Glucose
- Magnesium (Mg)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- Total protein
- Triglycerides
- Uric acid

Glycemic control
- HbA1c

Population PK Sampling
- Bexagliflozin plasma level

9.5. VITAL SIGNS

Vital signs will be measured at the screening visit (Week -12), on Day -1, Day 1, cumulative week 6, 12, 12 + 1 Day, 18, 24, 24 + 1 Day, 36 and 36 + 1 Day. Measurements of vital signs will include measurement of supine and standing blood pressure (BP) measurements, and heart rate. Heart-rate in seated position will also be summarized. Orthostatic systolic and diastolic BP will be calculated as supine measurement – standing measurement. Summary tables will be provided by treatment group and visit for study 603A and 603B. An overall summary based on integrated data will be presented at 6, 12, 18, 24, and 36 weeks of bexagliflozin treatment.

Vital sign assessment on the clinical visit day is scheduled to be before the dosing of study medication. Study level baseline will be defined as the last non-missing measurement on or prior to the first dose of double-blind study medication. For integrated summary by weeks from first exposure of bexagliflozin, baseline is defined as the last non-missing measurement on or prior to the first exposure to bexagliflozin.

For BP, pulse rate, and respiration rate, observed values and change from baseline will be summarized using descriptive statistics (n, mean and median, standard deviation, Q1, and Q3, minimum and maximum) at each scheduled visit and the end of the study visit. For BP, supine, standing, and orthostatic BP will be summarized for safety analysis set.

9.6. ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) will be conducted at the screening visit (Week - 12), on Day -1, and at cumulative week 12, 24, and 36. ECG parameters measured will be the RR interval, PR interval, QRS duration, and QT interval. Each ECG should also be assessed by the investigator for signs of ischemia, clinically significant hypertrophy, and clinically significant T-wave abnormalities or arrhythmia.

For each abnormal ECG result, the investigator shall ascertain if the observation represents a clinically significant change from the screening ECG for that individual subject. This determination does not 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 for each study.

In addition, an integrated summary table will be presented for 12 weeks, 24 weeks, and 36 weeks of exposure to bexagliflozin.

9.7. PHYSICAL EXAMINATION

A complete physical examination will be conducted at the Day -1. 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 -12) and at cumulative week 12, 24, and 36. 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.

10. INTERIM ANALYSIS

An interim non-binding futility analysis when half (i.e., 300) patients have completed the first 12 weeks of the treatment period was conducted. Using an interpolated spending function of Type II error, i.e., with 0.5 proportion of Type II error being spent at the interim look, the study could have stopped for futility when the test statistics (Z score) was less than 0.656 (or p-value > 0.512). The overall power for the first primary endpoint was maintained at >95% with this interim look. The interim analysis was conducted by an independent group that was not part of the study management team. All study subjects were to continue to receive the investigational products during the data cleaning and analysis time. Results from the interim analysis were reviewed by an independent Data Monitoring Committee (DMC). The data extraction and transfer methods and measures for preservation of blinding/access to interim results followed the rules described in the DSMB SAP.

11. DATA AND SAFETY MONITORING BOARD

An independent data and safety monitoring board (DSMB) has been charged with reviewing descriptive summaries of accumulating safety, subject disposition and limited efficacy data every 6 months, or at a frequency recommended by the DSMB.

A designated statistician who is not involved with the study operation has been assigned to 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 for DSMB review will be prepared by an unblinded team. Personnel involved in the conduct of the study will not participate in the preparation of the data and will not receive the data, or participate in the unblinded portions of the DSMB meetings. Additional details can be found in the DSMB charter and DSMB SAP.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Wilcoxon rank sum tests were added to both primary endpoints as sensitivity analysis.

Protocol specified that if < 64 BP readings (51 day time and 13 night time BP readings) are recorded, ABPM is considered as invalid and is repeated. In SAP, the validity criteria has been relax to include more subjects (section 8.1.1.1).

Additional exploratory endpoints are added in sections 4.1.3 and 4.2.3.

Baselines for efficacy endpoints are defined as the last measurement prior to the first dose of double-blind study medication, not prior to randomization per protocol. Randomization date is only used if subject is not dosed.

Adverse events occurred during 603B run-in period will not be summarized separately as stated in the protocol, instead, adverse events occurred during bexagliflozin treatment period will be summarized based on integrated safety analysis set. Some tables are only prepared for integrated safety analysis set due to lack of event occurrences.

13. PROGRAMMING CONSIDERATIONS

The following conventions will hold for programming of outputs:

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

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

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

- Descriptive statistics will be displayed in the following order:

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

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

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

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

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

13.1. 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

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. 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.

13.2.2. Headers

- All output should have the following header at the top left of each page:
  Theracos Sub, LLC
  Protocol Number: THR-1442-C-603
- 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.

13.2.3. 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

13.2.4. 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).

13.2.5. Body of the Data Display

13.2.5.1. 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.

13.2.5.2. Table Conventions

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

Severity Rating	N
severe	0
moderate	8
mild	3

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

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

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

- P-values should be output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If the rounded percentage is 0.0, display as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an

observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for concomitant and rescue medications should be presented by treatment class with the highest occurrence in the total column in decreasing order. Tabular display of data for medical history and adverse event data should be presented by the SOC using descending order. Within the drug class and SOC, medical history (by preferred term), drugs (by ATC2 code), and adverse events (by preferred term) should be displayed in decreasing order in the total column. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

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

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

13.2.5.3. 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

13.2.5.4. 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.

13.2.6. 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').

14. 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. Details will be provided in a separate QC plan.

15. MOCK-UPS

Shells for tables, figures, and listings are provided in a separate document.