Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy

Protocol 28431754DNE3001; Phase 3

JNJ-28431754 (canagliflozin)

Amendment 2

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
AHA	antihyperglycemic agent
ARB	angiotensin-receptor blockers
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CM	concomitant medication
CV	cardiovascular
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
GCP	Good Clinical Practice
GTED	global trial end date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
IEAC	Independent Endpoint Adjudication Committee
IWRS	Interactive Web Response System
LDL-C	low-density lipoprotein cholesterol
MH	medical history
MedDRA	Medical Dictionary for Regulatory Activities
ITT	intent-to-treat
MACE	major adverse cardiovascular event
MI	myocardial infarction
PDLC	pre-defined limit of change
QD	once daily
ROW	Rest of the World
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
SI	standard units
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
UACR	urinary albumin/creatinine ratio
ULN	upper limit of normal
VS	vital sign
WHODRUG	World Health Organization Drug Utilization Research Group

Amendment 1 (September 11, 2017)

The major changes in this amendment include the clarification of alpha spending in the interim and the final analysis, the decrease of the number of primary composite events required for the interim analysis from 420 to 405, and re-ordering of the secondary endpoints as well as the addition of 2 new endpoints (MACE and hospitalized congestive heart failure) in the list of secondary endpoints.

Amendment 2 (June 1, 2018)

The reason for this amendment is to update the alpha level used for testing the secondary efficacy endpoints and include other minor clarifications of the analyses.

1. INTRODUCTION

This statistical analysis plan (SAP) contains the definitions of analysis sets, derived variables, and statistical methods for the final analyses of efficacy and safety data from the canagliflozin study 28431754DNE3001. An interim analysis will be conducted when the mean duration of follow-up is at least 2 years and the events within the primary composite have been adjudicated as endpoints in approximately 405 subjects. Details regarding the interim analysis will be provided in a separate SAP.

1.1. Trial Objectives

Primary Objective

In subjects with type 2 diabetes mellitus (T2DM), Stage 2 or 3 chronic kidney disease (CKD) and macroalbuminuria who are receiving standard of care, to assess the efficacy of canagliflozin relative to placebo in reducing:

- the composite endpoint of end-stage kidney disease (ESKD), doubling of serum creatinine, and renal or cardiovascular (CV) death.

Secondary Objectives

In subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria who are receiving standard of care, to assess the efficacy of canagliflozin relative to placebo in reducing:

- the composite endpoint of CV death and hospitalized congestive heart failure
- the composite endpoint of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (ie, 3-point major adverse cardiac event [MACE])
- hospitalized congestive heart failure
- the renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- CV death
- all-cause death
- the CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina

Exploratory Objectives

In subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria who are receiving standard of care, to assess efficacy of canagliflozin relative to placebo in reducing:

- the composite endpoint of ESKD, renal or CV death

- individual components of the renal and cardiovascular composite endpoints (ESKD, doubling of serum creatinine, renal death, CV death, fatal or non-fatal MI, fatal or non-fatal stroke, hospitalized congestive heart failure, hospitalized unstable angina)

and to assess the impact of canagliflozin relative to placebo on:

- changes in estimated glomerular filtration rate (eGFR) over time
- changes in urinary albumin-to-creatinine ratio (UACR) over time

Safety Objective

To assess the overall safety and tolerability of canagliflozin.

1.2. Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter study that will include a total of approximately 4,200 subjects. The study will have a pretreatment phase, consisting of a prescreening, screening (up to 8 weeks), and 2-week single-blind placebo run-in phase. Subjects will be prescreened on the basis of eGFR and UACR. Only subjects with an eGFR of ≥30 to <90 mL/min/1.73m^2 and a UACR of level >300 mg/g to ≤5,000 mg/g (as confirmed by a local laboratory within the 3 months prior to screening) will be eligible for screening by the central laboratory.

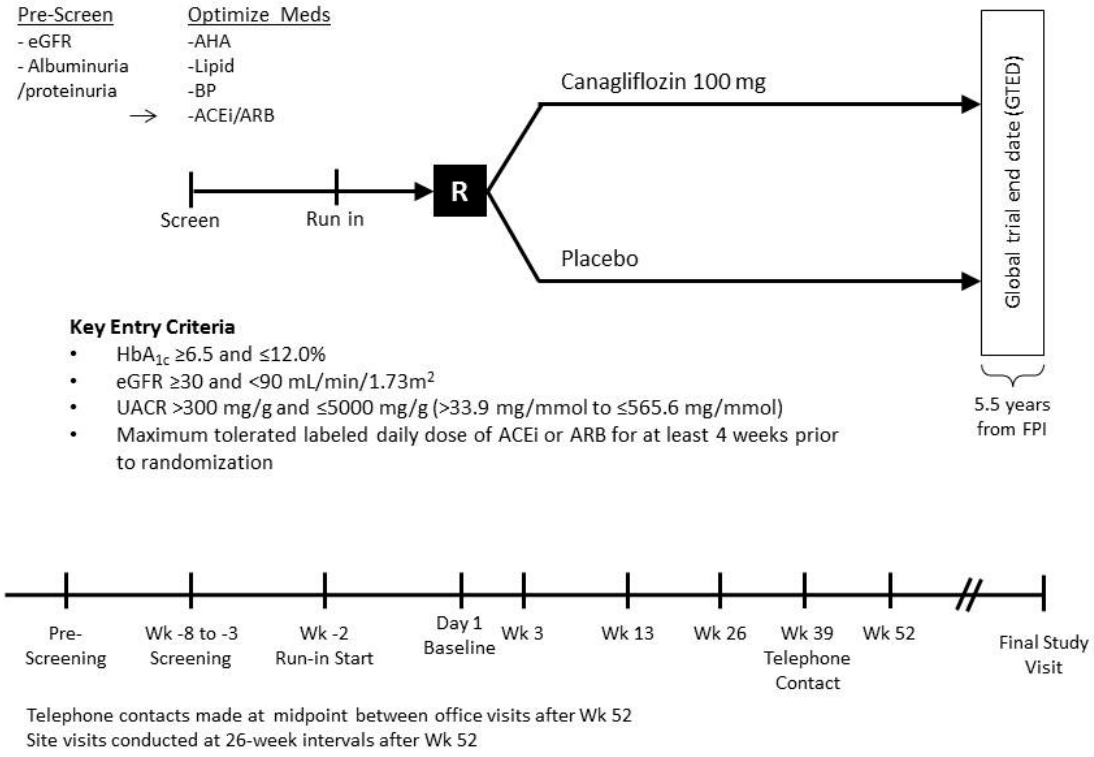
Subjects must be on a maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for a period of at least 4 weeks prior to randomization. To reach this requirement, the screening phase may be extended (up to 8 weeks). In addition, other anti-hypertensive, lipid-lowering and antihyperglycemic therapies should also be dose stable prior to randomization.

Subjects who meet all entry criteria will enter the single-blind placebo run-in phase at Week -2. During this phase, subjects will be instructed to take one capsule daily in order to assess their compliance with study intervention. Subjects who are compliant during the single-blind placebo run-in period (subjects must have ≥80% compliance by pill count) will be randomly assigned in a 1:1 ratio to canagliflozin or matching placebo group and will enter the double-blind treatment phase at the randomization visit (Day 1). Subjects randomized to canagliflozin will receive 100 mg canagliflozin, to be taken once daily (QD). After randomization, subjects will return to the clinic at Week 3, Week 13, Week 26, and every 26 weeks thereafter for laboratory assessments, concomitant medication review, adverse event collection and determination of clinical endpoints. At Week 39 and at the midpoint between office visits after Week 52, telephone contact will be made to check the subject status, including discussing study diary entries (ie, collection of self-monitoring of blood glucose (SMBG) and possible hypoglycemic event information), concomitant medication use, adverse events, and determining clinical endpoints (ie, all local laboratory data related to serum creatinine and eGFR). All subjects treated

by the investigator will be managed to reach their glycemic, blood pressure and lipid goals according to established local and regional guidelines, with medical therapies used according to approved local labels. A post-treatment follow-up contact will take place following the treatment phase. Subjects who discontinue study medication prematurely should continue to attend all subsequent study visits and be followed to the global trial end date (GTED). This event-driven study is estimated to have a total duration of approximately 5 to 5.5 years.

A Diagram of the study design is provided below:

Figure 1:



ACEi = angiotensin-converting enzyme inhibitor; UACR = urinary albumin-to-creatinine ratio; AHA = antihyperglycemic agent; ARB = angiotensin receptor blocker; BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; R = randomization; T2DM= type 2 diabetes mellitus; Wk=week.

1.3. Statistical Hypothesis for Trial Objectives

Canagliflozin reduces the risk of the composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death, relative to placebo, in subjects with T2DM, Stage 2 or 3 CKD and

macroalbuminuria, who are receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

1.4. Sample Size Justification

This is an event driven study. A total of approximately 4,200 subjects will be randomized to either canagliflozin 100 mg or matching placebo in a 1:1 ratio. The study aims to observe the occurrence of the primary efficacy events in 844 unique randomized subjects, on or before the GTED, to have 90% power to detect a 20% relative risk reduction (RRR, defined as one minus hazard ratio) accounting for the effect of treatment discontinuation on the primary endpoint at a 5%, 2-sided significance level.

The above sample size is estimated based on the following additional assumptions:

- Event rate for the composite endpoint in the placebo arm: 6.5% per year
- Premature discontinuation rate of study drug: 6% per year
- Overall lost-to-follow-up: 1%
- Duration of enrollment period: 27 months
- Duration of study (from first subject randomized to last end of study visit): estimated to be 60 months

This is an event driven trial and in order to ensure the number of events are obtained, the study duration and follow-up may be modified, if necessary, based on the observed event rate.

1.5. Randomization, Blinding, and Stratification

Upon successful completion of screening, eligible subjects will enter a 2-week run-in period, during which they will receive single-blind placebo capsules (one capsule to be taken once daily before the first meal of the day) to assess compliance with study intervention.

Subjects who are compliant during the single-blind placebo run-in period will be randomly assigned in a 1:1 ratio to canagliflozin 100 mg or matching placebo to be taken once daily, before the first meal of the day. All study intervention after randomization will be provided in a double-blind manner.

Eligible subjects will be stratified according to their screening eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73m^2), and will be randomized within the strata.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who receive at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For safety analysis (eg, adverse events [AEs]) and summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized. The treatment groups in this SAP will be referred to as canagliflozin and placebo.

2.2. Analysis Sets

Analysis sets consist of 2 components: 1) analysis population (Section 2.1), which specifies the subjects included in an analysis; 2) data period, defining the time window during which data will be included in the analysis.

Table 1: Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date (see Section 2.3.1) up to the GTED[a]
On-Study	Treated subjects	Day 1 to the last trial contact date (see Section 2.3.1) up to GTED[a]
On-Treatment	Treated subjects	Day 1 to the last dose date (see Section 2.3.1) plus X[b] days or the last trial contact date, whichever is earlier.

[a] For each subject, data collected up to the final visit will be used for analysis. If the final visit can't be arranged, the reported data such as public search of mortality will be bounded by the GTED.

[b] X is 2 days for laboratory and vital sign measurements, and 30 days for adverse events (AEs), CV, renal, and mortality endpoints.

2.3. Time-to-Event Data

2.3.1. Subject-Level Trial Milestone Dates

Trial reference start date (Day 1): the first dose date for each subject.

First dose date: the date on which the first dose of study intervention is taken by the subject. If missing or incomplete, the first dose date will be imputed as the randomization date.

Last dose date: the date on which the last dose of study intervention is taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing,

impute the date as the date of the scheduled visit after the last visit when the study intervention was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study intervention discontinuation regardless of any temporary drug interruption.

Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:

- The date of last visit (scheduled or unscheduled visit; office or phone visit), or
- The latest known date of an adverse event (AE) or the study endpoint event status, concomitant medication (CM), vital sign measures (VS) or lab results (LB) as reported on their respective electronic case report from (eCRF) page, or
- The date of alternate contact made (eg, family members, relatives, friends, health care providers) confirming patient was alive at the time of GTED announcement.

For subjects who die during the study or are lost to follow-up, or withdraw consent before announcement of GTED, the last trial contact date will be defined as the date of death or lost to follow-up, or withdrawal of consent. In addition, for subjects who are lost to follow-up, or withdraw consent, where permissible, the available subsequent survival information from a locator agent or public record search will be used to determine the last contact date.

Serum Creatinine Event dates: A doubling of serum creatinine event is defined to occur when a serum creatinine measurement obtained at a post-baseline protocol visit is greater than or equal to twice the baseline average serum creatinine (ie, average value derived from the Day 1 value and the value immediately preceding the Day 1 determination, if both values are available; in addition, the screening value will be used as baseline if all other pre-treatment values are missing). Doubling is confirmed by repeat central laboratory measure after 30 days and preferably within 60 days after the index event and adjudicated as an endpoint event by a blinded Independent Endpoint Adjudication Committee (IEAC). Similarly, an endpoint of ESKD is defined to occur when an eGFR is < 15 ml/min/1.73m^2 based on a serum creatinine obtained at a post-baseline protocol visit, confirmed by repeat central laboratory measure after 30 days and preferably within 60 days after the index event and adjudicated as an endpoint event by the IEAC. In both cases, the date of the event will be defined as the date of the blood draw for the initial serum creatinine measurement (either by local or central laboratory) triggering the event and subsequent adjudication (see Section 5.1.2). If the confirmatory value for doubling of serum creatinine or eGFR < 15 ml/min/1.73m^2 is not available, the endpoint confirmation will be based on the IEAC determination of the event.

2.3.2. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (see Table 1) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of their last trial contact day or end of the respective data period, if not otherwise specified.

2.4. Visit Windows

The Time and Events Schedule of the protocol indicates the visit timing and procedures (eg, laboratory, vital signs, and other key safety variables) for each visit; however, the timing of a subject's actual visit may not be exactly as per the protocol indicated target day / visit window. Consequently, for by-visit or over-time summaries, depending on the time period(s) involved in the summaries, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining visit windows.

The reference start day is study Day 1 which is the first dose day for subjects who took at least one dose of study medication or the randomization day for subjects who were randomized but did not take any study medication.

Baseline will be defined as the pre-dosing measurement closest to or including Day 1 (prior to dose administration). If the pre-dosing measure on Day 1 is missing, the missing value will be imputed by the latest available measurement prior to Day 1. For serum creatinine, the average of the last two pre-dose measurements will be used as baseline.

If a subject has 2 or more actual visits in one analysis visit window, the visit closest to the target day will be used as the study visit for that analysis visit window. However, results from all visits will be included in the safety analyses (eg, pre-defined limits of change analysis) to ensure that all on-treatment results are included. If 2 study visits are the same number of days from the target day within the same visit window, the later visit will be considered the study visit for that target day. Even though all visits will be allocated an analysis visit window, only planned protocol visits for each variable will be presented in the by-visit analyses.

Note the algorithms for calculating visit windows are the same for all the data periods (see Table 1). Table 2 summarizes the analysis visit windows for laboratory, vital signs, physical examination, and other key safety variables.

Table 2: Time Intervals for Analysis Visit Windows

Scheduled In-Clinic Visit Time	Time Interval (Day)[a]	Target Time Point (Day)[a]
Baseline	≤1[b]	1
Week 3	1[c]-56	22
Week 13	57-137	92
Week 26	138-229	183

Week 39	230-320	274
Week 52	321-456	365
Week 78	457-638	547
Week 104	639-821	730
Week 130	822-1003	912
Week 156	1004-1186	1095
Week 182	1187-1368	1277
Week 208	1369-1551	1460
Week 234	1552-1733	1642
Week 260	1734-1916	1825
Week 286	1917-2098	2007
Week 312 [d]	2099-2281	2190
Week 338 [d]	≥2282	2373

[a] Relative to the day of the first dose of double-blind medication.
[b] Up to the first dose of double-blind medication.
[c] Immediately following the first dose of double-blind medication. For variables without time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.
[d] In case the duration of the study goes longer based on the observed event rate.

3. INTERIM ANALYSIS

An interim analysis will be conducted when the mean duration of follow-up is at least 2 years and primary efficacy events have been adjudicated as endpoints in approximately 405 subjects. An Independent Data Monitoring Committee (IDMC) will review results of the planned interim analysis and make a recommendation whether the study should be continued as planned, modified, or terminated prematurely due to efficacy, futility or safety reasons.

The analysis method for the primary efficacy endpoint described in Section 5.2 will be used for the interim analysis. The alpha spent in the interim analysis for the testing of the primary composite endpoint is 0.01 (two-sided) which is determined by the alpha spending function taking the form of $\alpha\tau^{\varphi}$ with τ as the information fraction and $\varphi = 2.19$.

The decision rules that trigger the IDMC to consider the recommendation of early study termination will be based on assessment of the primary composite endpoint as well as a "hard" composite endpoint of end-stage kidney disease (ESKD), renal death, and CV death, as specified below:

- Stop the study for efficacy, if the p-value (two-sided) of the primary composite endpoint comparison is <0.01, and the p-value (two-sided) of the composite endpoint of ESKD, renal death, and CV death comparison is <0.025 in favor of canagliflozin. (Note: both composite endpoints must meet their respective efficacy standards for the study to be prematurely terminated for efficacy)
- Stop the study for futility, if the conditional power (based on the assumption that the hazard ratio in the remaining study is 0.80) for achieving the primary composite endpoint at the completion of study is <10% and that the overall benefit profile taking into account both efficacy and safety would be unlikely to be positive at the final analysis of study completion.
- Otherwise continue the study.

If the IDMC recommends early study termination due to efficacy, the sponsor will consider announcing the global trial end date (GTED) and final clinical visits will be scheduled. The test of the primary and the secondary endpoints will be based on the data accrued through the last trial contact date up to the GTED (see Table 1).

4. SUBJECT INFORMATION

4.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group and overall (both treatments pooled together) for the ITT analysis sets. Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for continuous variables such as age, body weight, and BMI at baseline.

The number and percentage of subjects in the categories of the following variables at baseline will also be summarized by randomized treatment group:

- Age group: <55, 55 to <65, 65 to <75, ≥75 years old
- Sex: Male, Female
- Race: White, Black or African American, Asian, Others
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported
- Baseline BMI category: <30, and ≥30 kg/m^2
- Region: North America, Central/South America, Europe, Rest of the World [ROW].

4.1.1. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for the ITT analysis sets including baseline HbA_{1c}, duration of diabetes (in years), baseline eGFR, baseline UACR, baseline SBP/DBP, and baseline status of nicotine use.

The number and percentage of subjects will be summarized by treatment group and overall for the following:

- Baseline HbA_{1c} categories: <7%, ≥7% to <8%, ≥8%
- Baseline eGFR categories: <45, ≥45 to <60, ≥60 mL/min/1.73m^2
- Baseline UACR categories: ≤1000, >1000 mg/g

The number and percentage of subjects with the complications of diabetes (any and by specific complication) at baseline will be summarized by treatment group and overall. The categories of the complications of diabetes include diabetic retinopathy, autonomic neuropathy, peripheral diabetic neuropathy, other diabetic neuropathy.

In addition to providing results by specific complication, the number and percentage of subjects with at least 2 diabetic complications and all 3 diabetic complications (retinopathy, neuropathy, or nephropathy) will be summarized by treatment group and overall.

The number and percentage of subjects with history of medical conditions by system organ class and preferred term (based upon the general MH eCRF) will be summarized by treatment group and overall. In addition, the following pre-treatment conditions will also be summarized by treatment group and overall.

- Cardiovascular disorders
- Fractures
- Surgeries/Procedures

4.2. Disposition Information

Subject disposition will be summarized by treatment group and overall using the following:

- Screen failure
- Subjects who are randomized (ITT analysis set)
- Subjects who are treated
- Subjects who prematurely discontinued study medication prior to the announcement of the GTED

- Subjects who completed the study (ie, defined as having been followed until a time point between the announcement of the GTED and the GTED, or if the subject had died prior to the GTED)
- Subjects without final vital status

Incidences of premature discontinuation from the double-blinded study intervention and the proportion of time on treatment relative to the follow-up period will be provided by treatment group. Time to premature discontinuation from the double-blinded study intervention will be summarized by treatment group using the Kaplan-Meier method.

Listings will be provided for subjects whose predominant treatment differs from their randomized treatment and for subjects who temporarily took the wrong study medication.

4.3. Extent of Exposure and Follow-Up

Treatment duration is defined as the amount of elapsed time between the first and the last day that study medication was taken (inclusive). It will be calculated (in days) in terms of the difference in relative study days between the last and first dose of study medication, plus one day.

Follow-up time is defined as the number of days from Day 1 to the last trial contact day (inclusive) for each subject.

Descriptive statistics (N, mean, standard deviation, median, and range) will be presented by treatment group for treatment duration and follow-up.

4.4. Prior and Concomitant Medications

Prestudy (ie, medications taken before initiation of double-blind study medication) and concomitant medications (ie, medications taken after initiation of double-blind study medication that were either started prior or after initiation of double-blind study medication) including AHAs, ACE inhibitors and ARBs, and all other medications are collected.

All prestudy and concomitant medications are coded using World Health Organization Drug Utilization Research Group (WHODRUG) and Anatomical Therapeutic Chemical (ATC) codes.

Prestudy and concomitant medications will be summarized by the number of subjects taking pre-specified categories of medications by treatment group and overall.

The proportion of subjects on ARBs and ACEs, anti-thrombotics (including aspirin) and statins (ie, HMG-CoA reductase inhibitors) at baseline will be summarized by treatment groups based on pre-specified categories (Attachment 1). The proportion of subjects on a maximum labeled dose of ARBs and ACEs for diabetic nephropathy or hypertension at baseline, and the reasons for subjects not on a maximum labeled dose will be summarized. In addition, non-study drug SGLT2 inhibitor use during the follow-up period will be summarized by treatment group.

4.5. Patient Management of Cardiovascular Risk Factors

The proportion of subjects with HbA_{1c} <7% and < 8%, SBP < 140 mm Hg, LDL-C < 100 mg/dL, and the proportion of subjects on statins and on anti-thrombotics (including aspirin) will be summarized by treatment group at Week 52, Week 104, Week 156, Week 208 and Week 260. In addition, longitudinal plots of the mean changes from baseline to the end of study in HbA_{1c} and SBP will be presented.

5. EFFICACY

The primary analysis and major secondary analyses will be performed based on the ITT analysis set.

5.1.1. Level of Significance

Unless otherwise specified, all statistical tests except those for the primary efficacy endpoint and major secondary efficacy endpoints, will be interpreted at a 2-sided significance level of 5% and all confidence intervals at a 2-sided confidence level of 95%.

At the interim analysis, the primary efficacy endpoint will be tested with alpha of 0.01 as determined by the alpha spending function taking form of $\alpha\tau^{\varphi}$ with τ as the information fraction and $\varphi = 2.19$.

If the IDMC recommends early study termination due to efficacy, the sponsor will consider announcing the global trial end date (GTED) and final clinical visits will be scheduled. The test of the primary composite endpoint will be based on the data accrued through the final clinic visit where the significance level will be determined by the alpha spending function (Lan et al, 2003 [1]).

If the IDMC does not recommend early study termination, the study will be continued until the target of 844 events have accrued. The primary composite endpoint will be tested with alpha of 0.045 in the final analysis.

Testing of the secondary efficacy endpoints will be based on the data accrued through the final clinic visit (regardless if the study stops after the interim analysis or proceeds to the planned completion of 844 primary composite events) using a two-sided alpha of 0.038. The overall type I error rate will be controlled at the 5% level across the primary and major secondary endpoints using a closed testing procedure, which is detailed in Section 5.5.

5.1.2. Data Handling Rules

Unless otherwise stated, all efficacy analyses will be based on the events and the dates identified by the IEAC. The onset of events of doubling of serum creatinine will be confirmed by a central laboratory value after 30 days and preferably within 60 days after the initial doubling. The date of the first documented doubling of serum creatinine will be considered as the onset date of the

event, with the confirmatory value reported by the central laboratory captured as serum creatinine value for the event.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint is the composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death.

Definitions for each component of the primary composite endpoint are:

- ESKD: Initiation of maintenance dialysis for at least 30 days, or renal transplantation, or a eGFR of <15 mL/min/1.73m^2 (by CKD-EPI formula; sustained and confirmed by repeat central laboratory measure after at least 30 days and preferable within 60 days)
- Doubling of serum creatinine: from the baseline determination (sustained and confirmed by repeat central laboratory measure after at least 30 days and preferable within 60 days)
- Renal death: death in patients who have reached ESKD, die without initiating renal replacement therapy, and no other cause of death is determined via adjudication.
- CV death: includes death due to MI, stroke, heart failure, sudden cardiac death, death during a CV procedure or as a result of procedure-related complications, or death due to other CV causes. For analytic purposes, undetermined causes of death will be considered CV deaths. In determining whether a death event is CV in nature, the endpoint adjudication committee will take into consideration both the proximate and underlying causes.

For subjects who have ESKD and doubling of serum creatinine determined to have occurred on the same date by the IEAC, the ESKD will be counted as the component for the primary composite endpoint.

5.2.2. Analysis Methods

Based on the time from study Day 1 to the first occurrence of the primary efficacy endpoint, the objective of the primary efficacy analysis is to establish that canagliflozin is superior to placebo, in the reduction of the rate of occurrence of the primary efficacy composite endpoint, in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

The hypothesis of the superiority on the primary efficacy endpoint for the comparison of canagliflozin versus placebo will be analyzed using a stratified Cox proportional hazard model including treatment, with stratification of the baseline hazard by screening eGFR (<45, ≥45 to <60, ≥60 mL/min/1.73m^2). The primary analysis will be based on the ITT analysis set from study

Day 1 up to the GTED. If the study is not stopped prematurely for efficacy based on the interim analysis, the superiority will be evaluated at the final analysis using a 2-sided test with α=0.045.

Estimates of the RRR (defined as one minus the hazard ratio), the hazard ratio and corresponding 95% CIs will be provided.

5.2.2.1. Supportive Efficacy Analyses

The cumulative incidence of the primary efficacy composite over time will be presented using Kaplan-Meier curves for each of the 2 treatment groups. Cumulative incidence curves will also be presented for each of the components of the primary composite (ESKD, doubling of serum creatinine, renal death, and CV death) in order to assess competing risks, depending on the event counts of the individual components.

In addition, ratios of cause-specific hazards between the treatment groups will be obtained for each component of the primary efficacy composite endpoint (ESKD, doubling of serum creatinine, renal death, or CV death), with stratification of the baseline hazard by screening eGFR group as in the analysis of the primary efficacy composite.

To assess the robustness of the primary efficacy analysis, sensitivity analysis of the primary efficacy endpoint using a log-rank test stratified by screening eGFR will also be performed. The log-rank test does not require the proportional hazards assumption as for Cox proportional hazard model.

Extensive efforts will be made to collect complete event and vital status data for all subjects randomized in this study. To illustrate the extent of missingness for the primary efficacy endpoint, the numbers of subjects with missing follow-up and the percentages of total missing follow-up time vs total number of subjects randomized and expected follow-up time will be summarized. Missing follow-up time for subjects who did not die will be calculated from last contact date to the announcement of GTED. For each subject, expected follow-up time will be calculated from study Day 1 to the earliest date of announcement of GTED or first occurrence of the primary efficacy endpoint.

An On-Treatment analysis (which includes composite endpoints with an onset after the initiation of double-blind study medication and before the last study medication date + 30 days) will also be performed to assess the consistency of the primary efficacy analysis. This will use a similar analysis model to the primary analysis.

5.2.2.1. Assessment of Model Assumption in the Primary Efficacy Analysis

The proportional hazards assumption for the primary efficacy analysis model will be assessed graphically using Log (-log) plots and/or plots of Schoenfeld residuals. In addition, a linear non-proportionality test will be performed. If evidence of deviations from the proportional hazards assumption is detected, additional Cox regression analyses with time-dependent hazard

ratios for the treatment effect may be explored to better understand the degree and nature of the treatment effect differences over time.

5.3. Subgroup Analyses for the Primary Endpoint

The homogeneity of treatment effects on the occurrence of the primary efficacy endpoint across subgroups (if a total number of events is greater than 10 for both treatment groups and at least 1 event in both groups) will be examined (at a 2-sided significance level of 0.10) via a test for the treatment by subgroup interaction by adding this term and the subgroup as covariates (viewed as class variables) to the primary efficacy analysis model. Factors exhibiting interactions with $p < 0.10$ will be identified as exhibiting a possible treatment effect heterogeneity, recognizing that one or more p-values under 0.10 may be expected to be observed by chance when multiple subgroup factors are examined.

If a significant interaction is observed, the results will be examined to determine whether the interaction is qualitative. If the interaction is qualitative in nature, clinical explanations of the significant interaction will be explored.

Estimates and 2-sided 95% confidence intervals for the hazard ratio (canagliflozin/placebo) will be provided for each subgroup. The analyses will be based on the primary efficacy analysis model separated for each subgroup.

The subgroups are listed below:

- Sex: male or female
- Age group: <65, ≥65 years old
- Race group: White, Black or African American, Asian, Other
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported/Unknown
- Region: North America, Central/South America, Europe, and ROW
- Duration of diabetes at baseline <median or ≥ median years
- CV history at baseline: Yes, No
- Baseline BMI: <30 or ≥30 kg/m^2
- Baseline HbA_{1c} categories: <8%, ≥8%
- Baseline eGFR: <45, ≥45 to <60, ≥60 $mL/min/1.73m^2$
- Baseline UACR categories: ≤1000, >1000 mg/g
- Baseline SBP categories: ≤ the median, > the median

- History of amputation: Yes, No

5.4. Major Secondary Endpoints

5.4.1. Definition

Major secondary efficacy endpoints include:

- Composite endpoint of CV death and hospitalized congestive heart failure
- Composite endpoint of CV death, non-fatal MI, and non-fatal stroke (ie, 3-point MACE)
- Hospitalized congestive heart failure
- Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- CV death
- All-cause death
- CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina

5.4.2. Analysis Methods

If superiority of canagliflozin over placebo in reducing the risk of the primary efficacy endpoint is established, the hypothesis of superiority on major secondary efficacy endpoints of canagliflozin versus placebo will be subsequently tested in the following hierarchical order:

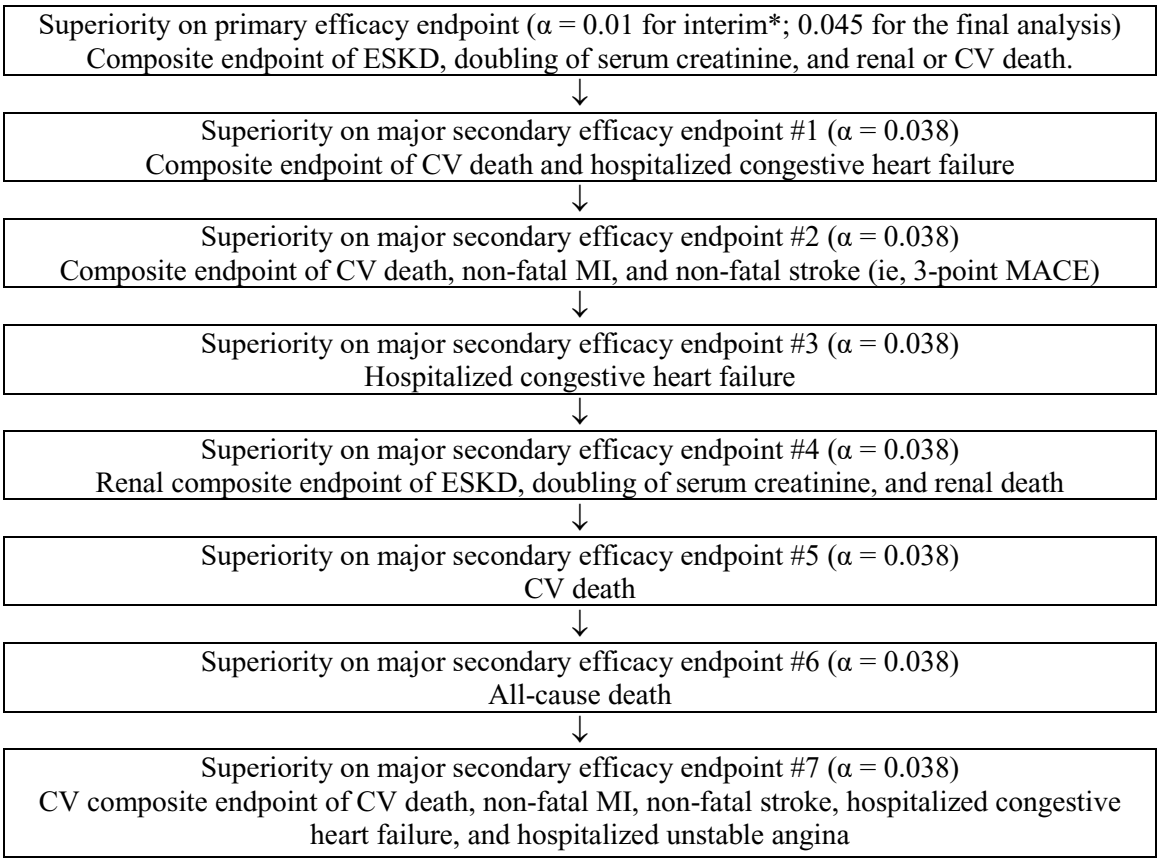
1. Composite endpoint of CV death and hospitalized congestive heart failure
2. Composite endpoint of CV death, non-fatal MI, and non-fatal stroke (ie, 3-point MACE)
3. Hospitalized congestive heart failure
4. Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
5. CV death
6. All-cause death
7. CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina

Time from study Day 1 to the first occurrence of a major secondary efficacy endpoint will be analyzed using the same approach as the primary analysis based on the data scope from study Day 1 to GTED in the ITT analysis set.

5.5. Multiplicity Adjustment

A closed testing procedure will be implemented to control the family-wise type I error rate at 5% for primary and secondary endpoints. The hypothesis of superiority on primary and major secondary efficacy endpoints of canagliflozin versus placebo will be tested in the following hierarchical order. If an individual test during any step is not statistically significant, later tests will not be declared to be statistically significant.

Figure 2: Hypothesis Testing Sequence



* If IDMC recommends early study termination due to efficacy, the primary composite endpoint will be tested after final study visit for the last subject completed the study, with the significance level determined by the accrued events and the alpha spending function.

5.6. Other Efficacy Analyses

5.6.1. Definition of Exploratory Efficacy Endpoints

In addition to the primary and major secondary endpoints previously described, the following endpoints and measurements will also be analyzed:

1. Composite endpoint events of ESKD (defined as a sustained eGFR of <15 mL/min/1.73m^2 or initiation of dialysis with maintenance for at least 30 days, or renal transplantation) and CV death or renal death
2. Individual components of the renal and cardiovascular composite endpoints (ESKD, doubling of serum creatinine, renal death, CV death, fatal or non-fatal MI, fatal or non-fatal stroke, hospitalized congestive heart failure, hospitalized unstable angina)
3. Changes in estimated glomerular filtration rate (eGFR) over time
4. Changes in urinary albumin-to-creatinine ratio (UACR) over time

5.6.2. Definition of Other Efficacy Endpoints

1. Composite endpoint events of ESKD (defined as a sustained eGFR of <15 mL/min/1.73m^2 or initiation of dialysis with maintenance for at least 30 days, or renal transplantation) and renal death
2. Composite endpoint events of ESKD (defined as a sustained eGFR <15 mL/min/1.73m^2 with symptoms of uremia or a sustained eGFR of <8 mL/min/1.73m^2 or initiation of dialysis with maintenance for at least 30 days, or renal transplantation) and CV death or renal death
3. Composite endpoint events of ESKD (defined as a sustained eGFR <15 mL/min/1.73m^2 with symptoms of uremia or a sustained eGFR of <8 mL/min/1.73m^2 or initiation of dialysis with maintenance for at least 30 days, or renal transplantation) and renal death

5.6.3. Analysis Methods for Other Efficacy Analyses

Composite endpoint events (described in Section 5.6.1)

The time from study Day 1 to the first occurrence of composite endpoint events in each of the aforementioned composites will be analyzed by a method similar to that used for the primary efficacy analysis based on the data scope from study Day 1 to GTED in the ITT analysis set.

eGFR change over time

The on-treatment eGFRs include all central laboratory eGFR measurements from study Day 1 up to the last dose plus 2 days. The change from baseline in eGFR will be analyzed using a restricted maximum likelihood (REML) repeated measures approach. The analysis will be based on observed data and will include the fixed, categorical effects of treatment, stratification factor, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline eGFR and baseline-by-visit interaction. An unstructured covariance will be used to model the within-patient errors. The adjusted mean changes in eGFR from baseline will be plotted over time by treatment group to depict the pattern of change in mean eGFR over time. Linear contrasts will be constructed to estimate the treatment effect on the mean change in eGFR to

6 months (early effect), the mean change in eGFR from 6 months to 4 years (late effect), and the mean change in eGFR from baseline to 4 years (overall effect).

If the changes in mean eGFR in the above analysis exhibit a linear trajectory after 6 months, a multi-slope mixed effects linear spline model will be fitted with separate slopes from baseline to month 3, from month 3 to month 6, and from month 6 to the GTED. This model will be constructed with fixed effects for the screening eGFR randomization strata and with random intercepts and slopes to account for variation in progression rates over time. Likelihood based comparisons of goodness of fit will be used to determine if the model should be expanded to include additional terms to account for auto-correlation in residual over time, differences in variance between the treatment and control groups, or other deviations from the random slope-intercept model. The mean slopes from baseline to month 3 and from baseline to month 6 will be compared between the treatment groups to estimate the immediate and longer term acute effects of canagliflozin vs. placebo. The long-term slopes after month 6 will be used to estimate the effect of canagliflozin on the "chronic" slope after 6 months. The estimated mean change in eGFR from baseline to 4 years will also be compared under the 3 slope model to estimate the overall effect of canagliflozin on the mean change in eGFR.

A similar analysis based on all central laboratory eGFR measurements from study Day 1 up to the end of study will be conducted using the similar model.

If the distribution of eGFR value is positively skewed, log transformation of eGFR values may be considered prior to the modeling.

UACR change over time

On-treatment central laboratory UACR will be analyzed using the similar model for eGFR. Log transformation of UACR values will be made prior to the modeling, since the distribution of UACR value is highly skewed.

A similar analysis for UACR measurements from study Day 1 up to the end of study will be performed using the similar model.

6. SAFETY

Treatment-emergent safety analyses and summaries will be based on the On-Treatment analysis set (Section 2.2). All safety analyses and summaries will utilize this approach unless otherwise specified.

There will be no imputation of missing values for clinical laboratory test results and vital sign measurements in the safety analyses, and there will be no hypothesis testing for results from safety analyses.

The study objective regarding safety and tolerability will be assessed based upon a review of the incidence of all adverse events, as well as laboratory results, and other safety and tolerability measurements.

6.1. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Therefore, the preferred terms presented in Attachment 2 may be modified to reflect such updates. A treatment-emergent AE (TEAE) is defined as an adverse event with an onset after the initiation of double-blind study medication and before the last study medication date + 30 days (ie, the On-Treatment analysis set). AEs with a start date prior to initiation of double-blind study medication which are subsequently reported to have either an increase in intensity or change in attribution in relationship to study medication (ie, no attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs.

In addition to treatment-emergent AE analyses for selected AEs with an onset after the initiation of study medication and regardless of time off the study medication will also be performed.

6.1.1. General Adverse Events

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Any AEs
- Serious AEs
- Deaths
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

SAEs and AEs leading to discontinuation of study medication (by system organ class and preferred term) will be summarized by treatment group using the On-Treatment analysis set. AEs by system organ class (ie, number and percent of subjects with one or more AEs within a system organ class) will similarly be summarized by treatment group.

The overall incidence (ie, number and percent of subjects with one or more AE in each category) of AEs, AEs leading to discontinuation, drug-related AEs, drug-related AEs leading to discontinuation of study medication, serious AEs, serious AEs leading to discontinuation, serious drug-related AEs, serious drug-related AEs leading to discontinuation of study medication and deaths, will be summarized by treatment group.

For each AE, the percentage of subjects who experienced at least one occurrence of the given event will be provided by preferred term, grouped by system organ class (SOC), and presented by treatment group. In addition, the incidence of AEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by severity (by each designation, and pooling mild or moderate), by the relationship to study medication, by the action taken regarding the study medication, as well as by the outcome. The relationship to study medication will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator), as well as by individual designation.

Listings will also be generated for deaths, SAEs, and discontinuations due to AEs.

As a screening tool, the 95% CIs for the percentage difference between canagliflozin and placebo will be provided for the AEs which are reported in at least four or more subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT)[2]. No multiplicity adjustment will be applied. The exclusion of "0" in the 95% CI around the difference in incidence for a particular AE does not necessarily imply that the higher incidence is related to drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. Adverse events for which there is an imbalance in incidence with 0% in placebo and 0.5% or higher in canagliflozin will be further evaluated.

Adverse events that are identified by the above screening procedure will be subject to further evaluation. The additional assessment may include some or all of the following:

1. Investigator assessed relationship of AE to study intervention, investigator assessed intensity of AE
2. Time to AE relative to start of double-blind study medication, duration of AE, action taken on study intervention/occurrence of AEs leading to discontinuation
3. Other relevant safety information such as observations in other canagliflozin trials, observations in trials of other members of the SGLT2 inhibitor class, biological plausibility of the AE as related to SGLT2 inhibition or to canagliflozin.

6.2. Adverse Events of Interest

In order to support the additional assessment of particular categories of adverse events, such as fractures and volume depletion, medical queries of selected preferred terms have been created. A blinded review prior to database lock will be performed to ensure that no reported term suggestive of the AE of interest is omitted. The list of preferred terms that are to be combined for the assessment of each of the pre-specified adverse events (eg, malignancies, severe hypersensitivity reactions [eg, angioedema, anaphylaxis, Stevens-Johnson syndrome], photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney

injury, venous thromboembolic events, diabetic ketoacidosis [DKA], pancreatitis, fractures, and amputation) are provided in Attachment 2. The primary analysis of DKA, pancreatitis, and fracture will be based on adjudication results. Selected adverse events (eg, DKA, amputation, malignancy, and fracture) will be performed in both On-Treatment and On-Study analysis sets.

The incidences and descriptive statistics of the additional information collected for each AE of interest will be summarized by treatment group. Additionally, the percentage of subjects with each AE of interest will be summarized by severity and relationship to study intervention. Treatment differences in incidence rates and corresponding 95% CI will be provided.

The Kaplan-Meier plots for the time to first occurrence by treatment group will also be generated for certain AEs such as adjudicated fractures and amputation AEs. The time to first occurrence of the AE will be defined as the number of days between the study Day 1 and the onset day of the first occurrence. Subjects without the AE will be censored at the last dose date plus 30 days or the last trial contact date as defined in Section 2.2, whichever is earlier.

6.3. Modified Rankin Scores for Stroke

The ordinal categories of modified Rankin scores for the events of stroke will be summarized by treatment group based on investigator's assessment. The modified Rankin score will be grouped to the ordered categories: 0−2 = nondisabling, 3−5 =disabling, 6 =death. For adjudicated stroke cases, the change of the score before and after the event will be calculated and used to assess the severity of the event.

6.4. Hypoglycemia

All hypoglycemic episodes are to be reported on an eCRF page specific for hypoglycemia. If the hypoglycemia episode is considered to be an AE/SAE in the opinion of the investigator, the episode is also to be recorded on the AE/SAE eCRF page. Hypoglycemia as AEs/SAEs will be presented in the tabulation of AEs described above. All additional analyses of hypoglycemia episodes will be based on results collected using the hypoglycemia eCRF. Reconciliation will be conducted to ensure that all hypoglycemia episodes reported as AEs are also recorded on the hypoglycemia eCRF form; however, hypoglycemia episodes reported on the hypoglycemia eCRF do not have to be reported as an AE (deferred to the investigator's determination). Analyses discussed below are based upon episodes reported through the hypoglycemia eCRF.

A subject will be counted as having a documented hypoglycemia episode when there is either a biochemically confirmed hypoglycemic episode (ie, concurrent fingerstick glucose or plasma glucose ≤70 mg/dL (3.9 mmol/L), and/or a severe hypoglycemic episode, as reported on the hypoglycemia eCRF, as follows:

- Biochemically documented hypoglycemia episode: a hypoglycemia episode with a concurrent reported glucose value of ≤70 mg/dL (3.9 mmol/L), regardless of whether the

episode is associated with symptoms (symptomatic hypoglycemia) or not (asymptomatic hypoglycemia)

- Severe hypoglycemia episode: a hypoglycemia episode that has the answer "Yes" recorded for any of the following 3 questions on the hypoglycemia eCRF: "Did the subject require assistance for this episode?", "Did the subject lose consciousness during the episode?", or "Did the subject have a seizure during the episode?"

Only treatment-emergent hypoglycemia episodes (defined the same way as treatment-emergent AEs in Section 6.1) reported on the eCRF for hypoglycemia will be summarized.

The percentage of subjects with documented hypoglycemia episodes (ie, biochemically documented and/or severe) and subjects with biochemically documented, and with severe hypoglycemia episodes separately, will be summarized by treatment group. For subjects with biochemically documented hypoglycemia episodes, the percentage of subjects will be summarized for each of the following glucose levels (≤70 mg/dL [3.9 mmol/L], <56 mg/dL [3.1 mmol/L], and <36 mg/dL [2.0 mmol/L], "Low" results will be included in all three categories) by treatment group. For subjects with severe hypoglycemia episodes, the percentage of subjects by each answer of the 3 questions for severe hypoglycemia on the eCRF will be summarized by treatment group. Event rate by person-year (total number of episodes/total exposure) will be calculated by treatment group separately for documented and for severe hypoglycemia.

Subjects who had 0, 1, 2, or ≥3 documented episodes and subjects who had 0, 1, 2, or ≥3 severe hypoglycemic episodes will be summarized by treatment group.

In addition, the incidence of all episodes of hypoglycemia reported on the eCRF for hypoglycemia will be provided (this includes events without concurrent fingerstick glucose reported and events with fingerstick glucose >70 mg/dL [3.9 mmol/L]) by treatment group.

6.5. Clinical Laboratory Tests

Laboratory data will be summarized for each type of laboratory test listed in Attachment 3. Normal reference ranges for each test will be provided. Descriptive statistics (N, mean, standard deviation, median, and range, as well as the 95% CI for the change from baseline) will be reported for each laboratory analyte at baseline and at each scheduled time point for absolute value and for change and percent change from baseline. Descriptive statistics will be presented for the On-Treatment analysis set (ie, based on measurements on study medication, including up to a maximum of 2 days after the last dose of study medication) as well as for the On-Study analysis set (ie, all measurements regardless of the time of the last dose of double-blind study intervention). Summaries based on both standard units (SI) and conventional units will be provided.

The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria will be summarized for these laboratory analytes. The 95% CI for the percentage difference between canagliflozin and placebo will be provided for each PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided. The criteria for PDLC values are listed in Attachment 4.

6.6. Vital Signs

Descriptive statistics (N, mean, standard deviation, median, and range, as well as the 95% CI for the change from baseline) will be reported for systolic and diastolic blood pressure (SBP and DBP), and pulse at each scheduled time point for absolute value and for change from baseline. Descriptive statistics will be presented for the On-Treatment analysis set (ie, based on measurements on study medication, including up to a maximum of 2 days after the last dose of study medication) as well as On-Study analysis set (ie, all measurements regardless of the time of the last dose). The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the PDLC criteria listed in Attachment 4. For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. The 95% CI for the percentage difference between canagliflozin and placebo will be provided for each PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided.

REFERENCES

1. Lan K. K. G., Lachin, J M, and Bautista, O. (2003), Over-ruling a group sequential boundary - a stopping rule versus a guideline. Statistics in Medicine 22, 3347–3355.

2. Brenda J, Crowe, H etc. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clin Trials 2009 6: 430-440

ATTACHMENT 1

Prestudy and Concomitant Medications Classified by ATC Code and/or Other Conditions

Note: The ATC code might be changed based on the latest version at the time of database lock

Medication	ATC code and/or Other Conditions
Anti-Hyperglycemic Agents (AHA)	ATC Code starts with 'A10' (Drugs used in diabetes)
Insulin	ATC Code starts with 'A10A' (Insulins and analogues)
Biguanides	ATC Codes start with 'A10BA' (Biguanides); and/or appropriate 'A10BD' (combinations of oral blood glucose lowering drugs)
Sulfonamides	ATC Codes start with 'A10BB' (sulfonamides, urea derivatives), 'A10BC' (sulfonamides [heterocyclic]); and/or appropriate 'A10BD' (combinations of oral blood glucose lowering drugs)
Alpha glucosidase Inhibitors	ATC Code starts with 'A10BF' (alpha glucosidase inhibitors)
Thiazolidinediones (PPARγ)	ATC Codes start with 'A10BG' (Thiazolidinediones); and/or appropriate 'A10BD' (combinations of oral blood glucose lowering drugs) and/or 'A10BX' (other blood glucose lowering drugs, excluding insulins)
Dipeptidyl peptidase 4 (DDP-4) Inhibitors	ATC Codes start with 'A10BH' (Dipeptidyl peptidase 4 [DPP-4]); and/or appropriate 'A10BD' (combinations of oral blood glucose lowering drugs)
GLP 1	ATC Codes start with 'A10BJ' (other blood glucose lowering drugs, excluding insulins)
Glinides	ATC Codes start with appropriate 'A10BD' (combinations of oral blood glucose lowering drugs) and/or 'A10BX' (other blood glucose lowering drugs, excluding insulins)
SGLT2i	ATC Code starts with 'A10BK' (with ingredient of 'dapagliflozin', 'canagliflozin', 'empagliflozin', 'dapagliflozin propanediol monohydrate', or 'ertugliflozin') or ATC Code start with appropriate 'A10BD' (with ingredient of 'canagliflozin, metformin hydrochloride', 'empagliflozin,

Medication	ATC code and/or Other Conditions
	linagliptin')
Other Anti-Hyperglycemic Agents	ATC Code starts with 'A10BX' (other blood glucose lowering drugs, excluding insulins)
Lipid-Altering Medications	ATC Codes start with 'C10' • Lipid modifying agents, plain ATC Codes start with 'C10A' • Lipid modifying agents, combinations ATC Codes start with 'C10B'
Antihypertensives	Angiotensin-Converting Enzyme Inhibitors (ACEi): ATC Codes start with 'C09A' (ACE inhibitors, plain), and/or 'C09B' (ACE inhibitors, combinations) with one of the following combination ingredients containing ACE inhibitors. Angiotensin-Receptor Blockers (ARB): ATC Codes start with 'C09C' (Angiotensin II antagonists); and/or 'C09D' (Angiotensin II antagonists, combinations) with one of the following combination ingredients containing an angiotensin II antagonist.

1. DIURETICS

Diuretics (loop) or diuretics (non-loop):

1.1. Diuretics [loop]

ATC Codes start with 'C03C' (High-ceiling diuretics), and/or 'C02LA' (Rauwolfia alkaloids and diuretics in combination) with one of the following combination ingredients:

Dihydralazine Sulfate,Furosemide,Reserpine
Dihydralazine Sulfate,Furosemide,Reserpine,Triamterene
Furosemide,Reserpine

and/or 'C03EB' (High-ceiling diuretics and potassium-sparing agents) with one of the following combination ingredients:

Amiloride Hydrochloride,Bumetanide
Amiloride Hydrochloride,Furosemide
Amiloride,Furosemide
Furosemide Xantinol,Triamterene
Furosemide,Spironolactone
Furosemide,Triamterene
Furosemide Sodium,Potassium Canrenoate

and/or 'C09BA' (ACE inhibitors and diuretics) with one of the following combination ingredients:

Furosemide,Ramipril
Piretanide,Ramipril

1.2. Diuretics [non-loop]

ATC Codes start with 'C03A' (Low-ceiling diuretics, thiazides), 'C03B' (Low-ceiling diuretics, excluding thiazides), 'C03D' (Potassium-sparing agents), and/or 'C02LA' (Rauwolfia alkaloids and diuretics in combination) with one of the following combination ingredients:

Adonis Vernalis Extract,Benzthiazide,Convallaria Majalis Extract,Drimia Maritima Extract,Oleandrin,Potassium Aspartate,Rauwolfia Serpentina
Ajmaline,Benzylhydrochlorthiazide,Potassium Chloride,Raupine,Rescinnamine,Reserpine Hydrochloride,Yohimbine
Ajmaline,Benzylhydrochlorthiazide,Potassium Chloride,Raupine,Rescinnamine,Yohimbine
Ajmaline,Corynanthine,Hydrochlorothiazide,Raupine,Rescinnamine,Reserpine Hydrochloride
Altizide,Potassium Canrenoate,Rescinnamine
Bemetizide,Potassium Chloride,Pyridoxine Hydrochloride,Reserpine,Retinol,Thiamine Mononitrate,Tocopheryl Acetate
Bendroflumethiazide,Methiomeprazine,Reserpine
Bendroflumethiazide,Potassium Chloride,Rauwolfia Serpentina
Bendroflumethiazide,Potassium Chloride,Reserpine
Bendroflumethiazide,Rauwolfia Serpentina
Bendroflumethiazide,Reserpine
Benziodarone,Hydroflumethiazide,Potassium Chloride,Reserpine
Benzthiazide,Methoserpidine
Benzthiazide,Reserpine
Benzylhydrochlorthiazide,Carbazochrome,Reserpine
Benzylhydrochlorthiazide,Diisopropylamine Dichloroacetate,Rescinnamine
Butizide,Carbocromen,Potassium Chloride,Raubasine,Rescinnamine,Reserpine
Butizide,Potassium Chloride,Raubasine,Rescinnamine,Reserpine
Butizide,Reserpine,Spironolactone
Chlorothiazide,Dihydralazine Tartrate,Rauwolfia Serpentina
Chlorothiazide,Rescinnamine
Chlorothiazide,Reserpine
Chlortalidone,Dihydralazine Hydrochloride,Oxazepam,Potassium Gluconate,Protoveratrines A And B,Reserpine,Rutoside,Xantinol Nicotinate
Chlortalidone,Dihydroergocristine,Magnesium Sulfate Heptahydrate,Methylergometrini Tartras,Reserpine,Thiourea
Chlortalidone,Reserpine
Chlortalidone,Reserpine,Spironolactone
Clofenamide,Reserpine
Clofenamide,Reserpine,Rutoside

Clopamide,Dihydroergocristine Mesilate,Reserpine
Clopamide,Dihydroergocristine,Reserpine
Clopamide,Dihydroergotoxine Mesilate
Clopamide,Reserpine
Cyclopenthiazide,Potassium Chloride,Reserpine
Cyclothiazide,Diprophylline,Methoserpidine
Cyclothiazide,Reserpine
Deserpidine,Hydrochlorothiazide
Deserpidine,Methyclothiazide
Dihydralazine Sulfate,Hydrochlorothiazide,Potassium Chloride,Reserpine
Dihydralazine Sulfate,Hydrochlorothiazide,Reserpine
Dihydralazine,Hydrochlorothiazide,Potassium Chloride,Reserpine
Dihydralazine,Hydrochlorothiazide,Reserpine
Dihydroergotamine Mesilate,Hydrochlorothiazide,Reserpine
Ethiazide,Potassium Chloride,Rauwolfia Serpentina
Flumethiazide,Potassium Chloride,Rauwolfia Serpentina
Guanethidine Sulfate,Hydrochlorothiazide,Methyldopa,Reserpine
Hydralazine Hydrochloride,Hydrochlorothiazide,Reserpine
Hydrochlorothiazide,Mecamylamine Hydrochloride,Neostigmine Metilsulfate,Rescinnamine
Hydrochlorothiazide,Methoserpidine
Hydrochlorothiazide,Methyldopa,Reserpine,Triamterene
Hydrochlorothiazide,Nicergoline,Reserpine
Hydrochlorothiazide,Pentosan Polysulfate,Rauwolfia Serpentina Extract,Trichlormethiazide,Xantinol Nicotinate
Hydrochlorothiazide,Potassium Chloride,Rauwolfia Serpentina,Rescinnamine,Reserpine,Retinol Palmitate,Tocopheryl Acetate
Hydrochlorothiazide,Potassium Chloride,Reserpine
Hydrochlorothiazide,Reserpine
Hydrochlorothiazide,Reserpine,Secbutabarbital
Hydrochlorothiazide,Reserpine,Triamterene
Hydroflumethiazide,Reserpine
Inositol Nicotinate,Mefruside,Rescinnamine
Inositol Nicotinate,Mefruside,Reserpine
Mefruside,Methyldopa,Reserpine
Mefruside,Reserpine
Methyclothiazide,Reserpine
Polythiazide,Reserpine
Quinethazone,Reserpine
Reserpine,Trichlormethiazide
Reserpine,Xipamide

and/or ‘C02LB’ (Methyldopa and diuretics in combination) with one of the following combination ingredients:

Amiloride Hydrochloride,Hydrochlorothiazide,Methyldopa
Amiloride,Hydrochlorothiazide,Methyldopa

Benzthiazide,Methyldopa
Butizide,Methyldopa
Chlorothiazide,Methyldopa
Hydrochlorothiazide,Methyldopa
Mefruside,Methyldopa

and/or 'C02LC' (Imidazoline receptor agonists in combination with diuretics) with one of the following combination ingredients:

Bencyclane Fumarate,Clonidine Hydrochloride,Hydrochlorothiazide
Bendroflumethiazide,Clonidine
Chlortalidone,Clonidine
Chlortalidone,Clonidine Hydrochloride
Chrysanthemum Spp.,Clonidine Hydrochloride,Concha Margaritifera,Hydrochlorothiazide,Rutoside
Clonidine Hydrochloride,Cyclothiazide
Clonidine Hydrochloride,Hydrochlorothiazide,Triamterene

and/or 'C02LF' (Guanidine derivatives and diuretics) with one of the following combination ingredients:

Polythiazide,Prazosin Hydrochloride
Bemetizide,Guabenxan
Cyclopenthiazide,Guanethidine Sulfate
Cyclopenthiazide,Guanethidine Sulfate,Potassium Chloride
Guanethidine Sulfate,Hydrochlorothiazide
Guanoxan Sulfate,Polythiazide

and/or 'C02LG' (Hydrazinophthalazine derivatives and diuretics) with one of the following combination ingredients:

Dihydralazine Tartrate,Hydrochlorothiazide,Mebutamate,Potassium Chloride
Hydralazine Hydrochloride,Hydrochlorothiazide

and/or 'C02LK' (Alkaloids, excluding rauwolfia, in combination with diuretics) with one of the following ingredients:

Cryptenamine Tannates,Methyclothiazide

and/or 'C02LL' (MAO inhibitors and diuretics) with one of the following combination ingredients:

Methyclothiazide,Pargyline Hydrochloride

and/or 'C02LX' (Other antihypertensives and diuretics) with one of the following combination ingredients:

Bemetizide,Bupranolol Hydrochloride,Dihydralazine Sulfate,Triamterene

and/or 'C03EA' (Low-ceiling diuretics and potassium-sparing agents) with one of the following combination ingredients:

Altizide,Spironolactone
Amiloride Hydrochloride,Bendroflumethiazide
Amiloride Hydrochloride,Chlortalidone
Amiloride Hydrochloride,Cyclopenthiazide
Amiloride Hydrochloride,Hydrochlorothiazide
Amiloride,Amiloride Hydrochloride,Methyclothiazide
Amiloride,Hydrochlorothiazide
Bemetizide,Hesperidin Complex,Thiamine Mononitrate,Triamterene
Bemetizide,Triamterene
Bendroflumethiazide,Spironolactone
Benzthiazide,Triamterene
Butizide,Potassium Canrenoate
Butizide,Spironolactone
Chlortalidone,Spironolactone
Chlortalidone,Triamterene
Clofenamide,Triamterene
Cyclothiazide,Triamterene
Epitizide,Triamterene
Hydrochlorothiazide,Spironolactone
Hydrochlorothiazide,Triamterene
Hydrochlorothiazide,Triamterene,Verapamil Hydrochloride
Hydroflumethiazide,Spironolactone
Mebutizide,Triamterene
Methyclothiazide,Triamterene
Metolazone,Triamterene
Triamterene,Trichlormethiazide
Triamterene,Xipamide

and/or 'C03EB' (High-ceiling diuretics and potassium-sparing agents) with one of the following combination ingredients:

Amiloride Hydrochloride,Bumetanide
Amiloride Hydrochloride,Furosemide
Amiloride,Furosemide
Furosemide Xantinol,Triamterene
Furosemide,Spironolactone
Furosemide,Triamterene

and/or 'C03XA' (Vasopressin antagonists) with one of the following ingredients or combination ingredients:

Conivaptan
Conivaptan Hydrochloride
Satavaptan
Tolvaptan

and/or 'C09BA' (ACE inhibitors and diuretics) with one of the following combination ingredients:

Benazepril Hydrochloride,Hydrochlorothiazide
Benazepril,Hydrochlorothiazide
Captopril,Hydrochlorothiazide
Cilazapril,Hydrochlorothiazide
Delapril Hydrochloride,Indapamide
Delapril,Indapamide
Enalapril Maleate,Hydrochlorothiazide
Enalapril,Hydrochlorothiazide
Fosinopril Sodium,Hydrochlorothiazide
Fosinopril,Hydrochlorothiazide
Hydrochlorothiazide,Imidapril Hydrochloride
Hydrochlorothiazide,Lisinopril
Hydrochlorothiazide,Lisinopril Dihydrate
Hydrochlorothiazide,Moexipril Hydrochloride
Hydrochlorothiazide,Quinapril
Hydrochlorothiazide,Quinapril Hydrochloride
Hydrochlorothiazide,Ramipril
Indapamide,Perindopril
Indapamide,Perindopril Erbumine

and/or 'C09BB' (ACE inhibitors and calcium channel blockers) with one of the following combination ingredients:

Trandolapril,Verapamil Hydrochloride

and/or 'C09DA' (Angiotensin II antagonists and diuretics) with one of the following combination ingredients:

Trandolapril,Verapamil Hydrochloride
Candesartan Cilexetil,Hydrochlorothiazide
Candesartan,Hydrochlorothiazide
Eprosartan Mesilate,Hydrochlorothiazide
Hydrochlorothiazide,Irbesartan
Hydrochlorothiazide,Losartan
Hydrochlorothiazide,Losartan Potassium
Hydrochlorothiazide,Olmesartan
Hydrochlorothiazide,Olmesartan Medoxomil
Hydrochlorothiazide,Telmisartan
Hydrochlorothiazide,Valsartan

and/or 'C09DX' (Angiotensin II antagonists, other combinations) with one of the following combination ingredients:

Amlodipine Besilate,Hydrochlorothiazide,Valsartan

and/or ‘C09XA’ (Renin-inhibitors) with one of the following combination ingredients:

Aliskiren Fumarate,Hydrochlorothiazide
Aliskiren,Hydrochlorothiazide

ATTACHMENT 2

Medical History and AEs of Interest Defined by MedDRA Preferred Term

1. MEDICAL HISTORY

1.1. Hypertension

- Essential hypertension
- Hypertension
- Hypertensive angiopathy
- Hypertensive cardiomyopathy
- Hypertensive crisis
- Hypertensive heart disease
- Retinopathy hypertensive

1.2. Dyslipidemia

- Blood cholesterol
- Blood cholesterol increased
- Blood triglycerides increased
- Dyslipidaemia
- Hypercholesterolaemia
- Hyperlipidaemia
- Hypertriglyceridaemia
- Xanthelasma

1.3. Fractures

- Acetabulum fracture
- Hip fracture
- Ankle fracture
- Humerus fracture
- Avulsion fracture
- Ilium fracture
- Bone fragmentation
- Impacted fracture
- Cervical vertebral fracture
- Chance fracture
- Clavicle fracture
- Jaw fracture
- Comminuted fracture
- Limb crushing injury
- Complicated fracture
- Lumbar vertebral fracture
- Lower limb fracture
- Compression fracture
- Forearm fracture
- Radius fracture
- Fracture
- Rib fracture
- Fracture debridement
- Scapula fracture
- Fracture delayed union
- Skull fracture
- Fracture displacement
- Skull fractured base
- Fracture malunion
- Spinal compression fracture
- Fracture nonunion
- Sternal fracture
- Fracture reduction
- Stress fracture
- Fractured coccyx
- Thoracic vertebral fracture

- Multiple fractures
- Elevation skull fracture
- Open fracture
- Epiphyseal fracture
- Osteoporotic fracture
- Facial bones fracture
- Patella fracture
- Femoral neck fracture
- Pathological fracture
- Femur fracture
- Pelvic fracture
- Fibula fracture
- Pubis fracture
- Foot fracture
- Periprosthetic fracture
- Atypical femur fracture
- Closed fracture manipulation
- Costal cartilage fracture
- Craniofacial fracture
- External fixation of fracture
- Fracture pain
- Fracture treatment
- Internal fixation of fracture
- Limb fracture
- Loss of anatomical alignment after fracture reduction
- Open reduction of fracture
- Open reduction of spinal fracture
- Osteochondral fracture
- Sacroiliac fracture
- Spinal fusion fracture
- Fractured ischium
- Tibia fracture
- Fractured sacrum
- Torus fracture
- Fractured maxilla elevation
- Traumatic fracture
- Fractured skull depressed
- Ulna fracture
- Fractured zygomatic arch elevation
- Upper limb fracture
- Greenstick fracture
- Wrist fracture
- Hand fracture
- Spinal fracture
- Atypical fracture

2. LIST OF PREFERRED TERMS FOR SELECTED ADVERSE EVENTS OF INTEREST

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
Acidosis	Genital candidiasis	Acetabulum fracture
Acidosis aggravated	Genital infection	Ankle fracture
Acidosis diabetic	Genital infection female	Atypical femur fracture
Acidosis metabolic	Genital infection fungal	Atypical fracture
Acidosis NOS	Urogenital infection fungal	Avulsion fracture
Acute acidosis	Vaginal infection	Bone fragmentation
Anion gap acidosis	Vaginal inflammation	Cervical vertebral fracture
Blood ketone body	Vulvitis	Chance fracture
Blood ketone body increased	Vulvovaginal candidiasis	Clavicle fracture
		Closed fracture manipulation
		Costal cartilage fracture
Blood ketone body present	Vulvovaginal mycotic infection	
	Vulvovaginitis	
	Vulvovaginal inflammation	
Diabetes mellitus with ketoacidosis		Comminuted fracture
Diabetes with hyperosmolarity		Complicated fracture
Diabetes with ketoacidosis		Compression fracture
Diabetic acidosis		Craniofacial fracture
Diabetic hyperglycemic coma		Elevation skull fracture
Diabetic hyperosmolar coma		Epiphyseal fracture
Diabetic ketoacidosis		External fixation of fracture
Diabetic ketoacidotic hyperglycemic coma		Facial bones fracture
Diabetic metabolic decompensation		Femoral neck fracture
High anion gap metabolic acidosis		Femur fracture
Hyperglycemic seizure		Fibula fracture
Hyperglycaemic hyperosmolar nonketotic syndrome		
Hyperosmolar hyperglycemic state		Foot fracture
Hyperosmolar state		Forearm fracture
Ketoacidosis		Fracture
Ketonuria		Fracture debridement
Ketosis		Fracture delayed union
Metabolic acidosis		Fracture displacement
Metabolic acidosis exacerbated		Fracture malunion
Metabolic acidosis NOS exacerbated		Fracture nonunion
Metabolic acidosis not otherwise specified (NOS)		Fracture pain
Metabolic acidosis worsened		Fracture reduction
Type I diabetes mellitus with ketoacidosis		Fracture treatment
Type II diabetes mellitus with ketoacidosis		Fractured coccyx
		Fractured ischium
		Fractured maxilla elevation
		Fractured sacrum
		Fractured skull depressed
		Fractured zygomatic arch elevation

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
		Greenstick fracture
		Hand fracture
		Hip fracture
		Humerus fracture
		Ilium fracture
		Impacted fracture
		Internal fixation of fracture
		Jaw fracture
		Limb crushing injury
		Limb fracture
		Loss of anatomical alignment after fracture reduction
		Lower limb fracture
		Lumbar vertebral fracture
		Multiple fractures
		Open fracture
		Open reduction of fracture
		Open reduction of spinal fracture
		Osteochondral fracture
		Osteoporotic fracture
		Patella fracture
		Pathological fracture
		Pelvic fracture
		Periprosthetic fracture
		Pubis fracture
		Radius fracture
		Rib fracture
		Sacroiliac fracture
		Scapula fracture
		Skull fracture
		Skull fractured base
		Spinal compression fracture
		Spinal fracture
		Spinal fusion fracture
		Sternal fracture
		Stress fracture
		Thoracic vertebral fracture
		Tibia fracture
		Torus fracture
		Traumatic fracture
		Ulna fracture
		Upper limb fracture
		Wrist fracture

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Acute graft versus host disease in liver	Hypoglycaemia	Balanitis
Acute hepatic failure	Hypoglycaemic coma	Balanitis candida
Acute yellow liver atrophy	Hypoglycaemic seizure	Balanoposthitis
	Blood glucose decreased	
Allergic hepatitis		Balanoposthitis infective

Hepatic Injury	**Hypoglycaemia**	**Male Mycotic Genital Infections**
Ammonia increased		Erosive balanitis
Ascites		Gangrenous balanitis
Asterixis		Genital candidiasis
Autoimmune hepatitis		Genital infection
Bacterascites		Genital infection fungal
Biliary ascites		Genital infection male
Biliary cirrhosis		Penile infection
Biliary cirrhosis primary		Posthitis
Biliary fibrosis		
Bilirubin excretion disorder		
Biopsy liver abnormal		
Child-Pugh-Turcotte score increased		
Cholaemia		
Cholestasis		
Cholestatic liver injury		
Cholestatic pruritus		
Chronic graft versus host disease in liver		
Chronic hepatic failure		
Chronic hepatitis		
Coma hepatic		
Cryptogenic cirrhosis		
Diabetic hepatopathy		
Drug-induced liver injury		
Duodenal varices		
Focal nodular hyperplasia		
Gallbladder varices		
Gastric varices		
Gastric varices haemorrhage		
Graft versus host disease in liver		
Haemangioma of liver		
Haemorrhagic ascites		
Haemorrhagic hepatic cyst		
Hepatectomy		
Hepatic adenoma		
Hepatic atrophy		
Hepatic calcification		
Hepatic cirrhosis		
Hepatic cyst		
Hepatic cyst ruptured		
Hepatic encephalopathy		
Hepatic encephalopathy prophylaxis		
Hepatic failure		
Hepatic fibrosis		
Hepatic fibrosis marker abnormal		
Hepatic haemangioma rupture		
Hepatic hydrothorax		
Hepatic infiltration eosinophilic		
Hepatic lesion		
Hepatic necrosis		
Hepatic steatosis		
Hepatitis		
Hepatitis acute		
Hepatitis cholestatic		
Hepatitis chronic active		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Hepatitis chronic persistent		
Hepatitis fulminant		
Hepatitis toxic		
Hepatobiliary disease		
Hepatocellular foamy cell syndrome		
Hepatocellular injury		
Hepatopulmonary syndrome		
Hepatorenal failure		
Hepatorenal syndrome		
Hepatotoxicity		
Hyperbilirubinaemia		
Icterus index increased		
Intestinal varices		
Ischaemic hepatitis		
Jaundice		
Jaundice cholestatic		
Jaundice hepatocellular		
Liver and small intestine transplant		
Liver disorder		
Liver injury		
Lupoid hepatic cirrhosis		
Lupus hepatitis		
Mixed liver injury		
Nodular regenerative hyperplasia		
Non-alcoholic steatohepatitis		
Non-cirrhotic portal hypertension		
Ocular icterus		
Oedema due to hepatic disease		
Oesophageal varices haemorrhage		
Parenteral nutrition associated liver disease		
Peripancreatic varices		
Periportal oedema		
Portal hypertension		
Portal hypertensive enteropathy		
Portal hypertensive gastropathy		
Portal triaditis		
Portal vein cavernous transformation		
Portal vein dilatation		
Portopulmonary hypertension		
Radiation hepatitis		
Renal and liver transplant		
Retrograde portal vein flow		
Reye's syndrome		
Reynold's syndrome		
Splenic varices		
Splenic varices haemorrhage		
Subacute hepatic failure		
Varices oesophageal		
Varicose veins of abdominal wall		

Malignancy Renal Cell Cancer	**Malignancy Testicular**	**Osmotic Diuresis**
Bladder adenocarcinoma recurrent	Apocrine breast carcinoma	Phaeochromocytoma
Bladder adenocarcinoma stage 0	Breast angiosarcoma	Phaeochromocytoma crisis
Bladder adenocarcinoma stage I	Breast angiosarcoma metastatic	Phaeochromocytoma excision
Bladder adenocarcinoma stage II	Breast cancer	Phaeochromocytoma malignant
Bladder adenocarcinoma stage III	Breast cancer female	
Bladder adenocarcinoma stage IV	Breast cancer in situ	
Bladder adenocarcinoma stage unspecified	Breast cancer male	
Bladder cancer	Breast cancer metastatic	
Bladder cancer recurrent	Breast cancer recurrent	
Bladder cancer stage 0, with cancer in situ	Breast cancer stage I	
Bladder cancer stage 0, without cancer in situ	Breast cancer stage II	
Bladder cancer stage I, with cancer in situ	Breast cancer stage III	
Bladder cancer stage I, without cancer in situ	Breast cancer stage IV	
Bladder cancer stage II	Breast neoplasm	
Bladder cancer stage III	Breast sarcoma	
Bladder cancer stage IV	Breast sarcoma metastatic	
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	
Bladder squamous cell carcinoma stage I	HER-2 positive breast cancer	
Bladder squamous cell carcinoma stage II	Hormone refractory breast cancer	
Bladder squamous cell carcinoma stage III	Inflammatory carcinoma of breast recurrent	
Bladder squamous cell carcinoma stage IV	Inflammatory carcinoma of breast stage III	
Bladder squamous cell carcinoma stage unspecified	Inflammatory carcinoma of breast stage IV	
Bladder transitional cell carcinoma	Inflammatory carcinoma of the breast	
Bladder transitional cell carcinoma metastatic	Intraductal papillary breast neoplasm	
Bladder transitional cell carcinoma recurrent	Intraductal proliferative breast lesion	
Bladder transitional cell carcinoma stage 0	Invasive breast carcinoma	
Bladder transitional cell carcinoma stage I	Invasive ductal breast carcinoma	
Bladder transitional cell carcinoma stage II	Invasive lobular breast carcinoma	
Bladder transitional cell carcinoma stage III	Invasive papillary breast carcinoma	
Bladder transitional cell carcinoma stage IV	Lobular breast carcinoma in situ	
Metastases to bladder	Malignant nipple neoplasm	
Metastatic carcinoma of the bladder	Malignant nipple neoplasm female	
Transitional cell carcinoma	Malignant nipple neoplasm male	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
Neuroendocrine carcinoma of the bladder		
	Medullary carcinoma of breast	
	Metaplastic breast carcinoma	
	Metastases to breast	
	Mucinous breast carcinoma	
	Neuroendocrine breast tumour	
	Nipple neoplasm	
	Oestrogen receptor positive breast cancer	
	Paget's disease of nipple	
	Phyllodes tumour	
	Triple negative breast cancer	
	Tubular breast carcinoma	
Bladder adenocarcinoma recurrent	Apocrine breast carcinoma	Phaeochromocytoma
Bladder adenocarcinoma stage 0	Breast angiosarcoma	Phaeochromocytoma crisis
Bladder adenocarcinoma stage I	Breast angiosarcoma metastatic	Phaeochromocytoma excision
Bladder adenocarcinoma stage II	Breast cancer	Phaeochromocytoma malignant
Bladder adenocarcinoma stage III	Breast cancer female	
Bladder adenocarcinoma stage IV	Breast cancer in situ	
Bladder adenocarcinoma stage unspecified	Breast cancer male	
Bladder cancer	Breast cancer metastatic	
Bladder cancer recurrent	Breast cancer recurrent	
Bladder cancer stage 0, with cancer in situ	Breast cancer stage I	
Bladder cancer stage 0, without cancer in situ	Breast cancer stage II	
Bladder cancer stage I, with cancer in situ	Breast cancer stage III	
Bladder cancer stage I, without cancer in situ	Breast cancer stage IV	
Bladder cancer stage II	Breast neoplasm	
Bladder cancer stage III	Breast sarcoma	
Bladder cancer stage IV	Breast sarcoma metastatic	
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	
Bladder squamous cell carcinoma stage I	HER-2 positive breast cancer	
Bladder squamous cell carcinoma stage II	Hormone refractory breast cancer	
Bladder squamous cell carcinoma stage III	Inflammatory carcinoma of breast recurrent	
Bladder squamous cell carcinoma stage IV	Inflammatory carcinoma of breast stage III	
Bladder squamous cell carcinoma stage unspecified	Inflammatory carcinoma of breast stage IV	
Bladder transitional cell carcinoma	Inflammatory carcinoma of the breast	
Bladder transitional cell carcinoma metastatic	Intraductal papillary breast neoplasm	
Bladder transitional cell carcinoma recurrent	Intraductal proliferative breast lesion	
Bladder transitional cell carcinoma stage 0	Invasive breast carcinoma	
Bladder transitional cell carcinoma stage I	Invasive ductal breast carcinoma	
Bladder transitional cell carcinoma stage II	Invasive lobular breast carcinoma	
Bladder transitional cell carcinoma stage III	Invasive papillary breast carcinoma	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
Bladder transitional cell carcinoma stage IV	Lobular breast carcinoma in situ	
Metastases to bladder	Malignant nipple neoplasm	
Metastatic carcinoma of the bladder	Malignant nipple neoplasm female	
Transitional cell carcinoma	Malignant nipple neoplasm male	
Neuroendocrine carcinoma of the bladder		
	Medullary carcinoma of breast	
	Metaplastic breast carcinoma	
	Metastases to breast	
	Mucinous breast carcinoma	
	Neuroendocrine breast tumour	
	Nipple neoplasm	
	Oestrogen receptor positive breast cancer	
	Paget's disease of nipple	
	Phyllodes tumour	
	Triple negative breast cancer	
	Tubular breast carcinoma	
Clear cell renal cell carcinoma	Benign neoplasm of testis	Dry mouth
Clear cell sarcoma of the kidney	Leydig cell tumour of the testis	Dry throat
Denys-Drash syndrome	Sertoli cell testicular tumour	Micturition disorder
Hereditary leiomyomatosis renal cell carcinoma	Spermatocytic seminoma	Micturition urgency
Hereditary papillary renal carcinoma	Testicle adenoma	Nocturia
Metastatic renal cell carcinoma	Testicular cancer metastatic	Pollakiuria
Nephroblastoma	Testicular neoplasm	Polydipsia
Non-renal cell carcinoma of kidney	Testicular papilloma	Polyuria
Renal cancer	Testis cancer	Thirst
Renal cancer metastatic		Tongue dry
Renal cancer recurrent		Urine output increased
Renal cancer stage I		
Renal cancer stage II		
Renal cancer stage III		
Renal cancer stage IV		
Renal cell carcinoma		
Renal cell carcinoma recurrent		
Renal cell carcinoma stage I		
Renal cell carcinoma stage II		
Renal cell carcinoma stage III		
Renal cell carcinoma stage IV		
Rhabdoid tumour of the kidney		
Papillary renal cell carcinoma		

Phimosis	**Photosensitivity**
Acquired phimosis	Actinic elastosis
Phimosis	Actinic prurigo
	Administration site photosensitivity reaction
	Application site photosensitivity reaction
	Chronic actinic dermatitis
	Hartnup disease
	Implant site photosensitivity
	Infusion site photosensitivity reaction
	Injection site photosensitivity reaction
	Juvenile spring eruption
	Medical device site photosensitivity reaction
	Photodermatosis
	Photokeratitis
	Photoonycholysis
	Photosensitivity reaction
	Polymorphic light eruption
	Solar dermatitis
	Solar urticaria
	Sunburn
	Vaccination site photosensitivity reaction

Renal Related	**Severe Hypersensitivity/Cutaneous AEs**	**Upper UTI**
Acute kidney injury	Acute generalised exanthematous pustulosis	Bacterial pyelonephritis
Acute phosphate nephropathy	Allergic oedema	Emphysematous pyelonephritis
Acute prerenal failure	Anaphylactic reaction	Kidney infection
Anuria	Anaphylactic shock	Perinephric abscess
Azotaemia	Anaphylactic transfusion reaction	Pyelocystitis
Blood creatinine increased	Anaphylactoid reaction	Pyelonephritis
Blood urea increased	Anaphylactoid shock	Pyelonephritis acute
Continuous haemodiafiltration	Angioedema	Pyelonephritis chronic
Dialysis	Circulatory collapse	Pyelonephritis fungal
Glomerular filtration rate decreased	Circumoral oedema	Pyelonephritis mycoplasmal
Haemodialysis	Conjunctival oedema	Pyelonephritis viral
Haemofiltration	Corneal exfoliation	Pyonephrosis
Hypercreatininaemia	Corneal oedema	Renal abscess
Neonatal anuria	Cutaneous vasculitis	Renal cyst infection
Nephritis	Dermatitis bullous	Urosepsis
		Pyelitis
Nephropathy toxic	Dermatitis exfoliative	
Oliguria	Dermatitis exfoliative generalised	
Peritoneal dialysis	Drug eruption	
Prerenal failure	Drug hypersensitivity	
Renal failure	Drug reaction with eosinophilia and systemic symptoms	
Renal failure acute	Epidermal necrosis	
Renal failure neonatal	Epiglottic oedema	
Renal impairment	Erythema multiforme	
Renal impairment neonatal	Exfoliative rash	
	Eye oedema	
	Eye swelling	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	Eyelid oedema	
	Face oedema	
	First use syndrome	
	Fixed drug eruption	
	Gingival oedema	
	Gingival swelling	
	Gleich's syndrome	
	Hereditary angioedema	
	Hypersensitivity vasculitis	
	Idiopathic angioedema	
	Idiopathic urticaria	
	Kounis syndrome	
	Laryngeal dyspnoea	
	Laryngeal oedema	
	Laryngospasm	
	Laryngotracheal oedema	
	Limbal swelling	
	Lip exfoliation	
	Lip oedema	
	Lip swelling	
	Mucocutaneous ulceration	
	Mucosa vesicle	
	Mucosal erosion	
	Mucosal exfoliation	
	Mucosal necrosis	
	Mucosal ulceration	
	Nikolsky's sign	
	Oculomucocutaneous syndrome	
	Oculorespiratory syndrome	
	Oedema mouth	
	Oedema mucosal	
	Oral mucosal blistering	
	Oral mucosal exfoliation	
	Orbital oedema	
	Oropharyngeal blistering	
	Oropharyngeal swelling	
	Palatal oedema	
	Penile exfoliation	
	Periorbital oedema	
	Pharyngeal oedema	
	Scleral oedema	
	Shock	
	Shock symptom	
	Skin exfoliation	
	Skin necrosis	
	Small bowel angioedema	
	Stevens-Johnson syndrome	
	Stridor	
	Swelling face	
	Swollen tongue	
	Symmetrical drug-related intertriginous and flexural exanthema	
	Throat tightness	
	Tongue exfoliation	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	Tongue oedema	
	Toxic epidermal necrolysis	
	Type I hypersensitivity	
	Urticaria	
	Urticaria cholinergic	
	Urticaria chronic	
	Urticaria papular	
	Urticarial vasculitis	
	Vaginal exfoliation	

UTI	Venous Thromboembolic events	Volume Depletion
Bacterial ureteritis		
Bacterial urethritis		
Bladder candidiasis	Deep vein thrombosis	Blood pressure decreased
Cystitis	Deep vein thrombosis postoperative	Blood pressure orthostatic decreased
Cystitis bacterial	Embolism venous	Dehydration
Cystitis escherichia	Iliac vein occlusion	Diastolic hypotension
Cystitis gonococcal	Inferior vena cava syndrome	Dizziness postural
Cystitis haemorrhagic	Inferior vena caval occlusion	Hypotension
Cystitis interstitial	Jugular vein occlusion	Hypovolaemia
Cystitis klebsiella	Mesenteric venous occlusion	Hypovolaemic shock
Cystitis pseudomonal	Obstructive shock	Orthostatic hypotension
Emphysematous cystitis	Portosplenomesenteric venous thrombosis	Orthostatic intolerance
Escherichia urinary tract infection	Post procedural pulmonary embolism	Postural orthostatic tachycardia syndrome
Fungal cystitis	Postpartum venous thrombosis	Presyncope
Funguria	Pulmonary embolism	Shock
Genitourinary tract infection	Pulmonary infarction	Shock symptom
Streptococcal urinary tract infection	Pulmonary microemboli	Syncope
Ureter abscess	Pulmonary oil microembolism	Urine output decreased
Ureteritis		
Urethritis		
Urethritis noninfective	Pulmonary thrombosis	
Uretheritis	Renal vein embolism	
Urethral abscess	Renal vein occlusion	
Urethral carbuncle	Subclavian vein thrombosis	
Urethral stricture post infection	Vascular occlusion	
Urinary bladder abscess	Venous thrombosis	
Urinary tract abscess	Venous thrombosis in pregnancy	
Urinary tract infection	Venous thrombosis limb	
Urinary tract infection bacterial	Visceral venous thrombosis	
Urinary tract infection enterococcal		
Urinary tract infection fungal		
Urinary tract infection pseudomonal		
Urinary tract infection staphylococcal		

ATTACHMENT 3

CLINICAL LABORATORY TESTS

The clinical laboratory tests include following panels and assessments:

- Hematology panel
  - hemoglobin
  - platelet count
  - hematocrit
  - red blood cell (RBC) count
  - white blood cell (WBC) count with differential
- Serum chemistry panel
  - Sodium
  - potassium
  - chloride
  - bicarbonate
  - BUN
  - creatinine
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - gamma-glutamyltransferase (GGT)
  - total bilirubin
  - alkaline phosphatase
  - creatine phosphokinase (CPK)
  - lactic acid dehydrogenase (LDH)
  - uric acid
  - calcium
  - phosphate
  - albumin
  - total protein
  - magnesium
- Urinalysis
- Lipid panel
  - Triglycerides
  - Total cholesterol
  - HDL cholesterol
  - LDL cholesterol
  - LDL/HDL ratio
- Plasma glucose
- Hemoglobin A_{1c}
- **Estimated Glomerular Filtration Rate (eGFR)**

The estimated glomerular filtration rate (eGFR) will be reported according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at study visits when serum creatinine is measured by the central laboratory.

ATTACHMENT 4

CRITERIA FOR PRE-DEFINED LIMIT OF CHANGE (PDLC) AND ABNORMAL VALUES

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Bilirubin	Composite: >ULN and > 25% increase from BL
	Absolute Value: >2XULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcium	Composite: >ULN and > 10 % increase from BL
eGFR from creatinine adjusted for BSA	eGFR < 80 mL/min/1.73m2 and decrease > 30% from BL
	eGFR decrease > 50% from BL
Magnesium	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Phosphate	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
	Absolute Value: ≥ 6.5 mEq/L
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase>5 mEq/L or more from BL
Albumin	Composite: <LLN and >25% decrease from BL
Urate	Composite: <LLN and >25% decrease from BL
HEMATOLOGY	
Hemoglobin	Change: ≥ 2 g/dl decrease from BL
	Change: ≥ 2 g/dL increase from BL
Platelets	Composite: <LLN and decrease >25% from BL
	Composite: >ULN and increase >25% from BL
White Blood Count	Composite: < LLN and >25% decrease from BL
	Composite: > ULN and >50 % increase from BL
VITAL SIGNS	
Pulse	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥100 beats per minute
Systolic Blood Pressure	Composite: ≥ 20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥ 20 mm Hg increase from BL and ≥ 160 mm Hg
Diastolic Blood Pressure	Composite: ≥ 15 mm Hg decrease from BL and ≤ 50 mm Hg
	Composite: ≥ 15 mm Hg increase from BL and ≥ 100 mm Hg