Janssen Research & Development

Statistical Analysis Plan

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

The CANVAS-R Trial (CANagliflozin cardioVascular Assessment Study-Renal)

Protocol 28431754DIA4003; Phase 4**

JNJ-28431754 (canagliflozin)

**This is a Phase 4 postmarketing study required by the US Food & Drug Administration but may be considered a Phase 3 study in some countries in which canagliflozin has not been approved.

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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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SUMMARY OF AMENDMENT

Relative to the statistical analysis plan (SAP) dated 20 September 2016, the major amendments made in this version are summarized as follows.

Applicable Section(s)	Description of Change(s)
2.2	The On-Study analysis set was added for MACE and replaced the ITT analysis set for several adverse events of interest. The upper bound of the data period for the On-Treatment analysis set was clarified as last dose plus 2 days for laboratory parameters except ACR.
4.1.3	Additional subgroups were added for the analysis of ACR progression.
4.1.4.2 (4.4.1.2)	To be consistent with the protocol, confirmed progression (regression) is now changed to confirmed progression (regression) plus the unconfirmed progression (regression) from the last ACR measures.
4.1.4.3	Updated the multiple analysis section
4.2.1	Consistent with the analytic approach described in the Cardiovascular Endpoint adjudication charter, it is clarified that undetermined death is considered as CV death.
4.2.2.1	Additional subgroups were added for the analysis of secondary efficacy endpoints.
4.4.1	Clarified that any adjudicated non-CV death event where the adjudication committee assigned a renal proximate cause is considered a renal death.
4.4.2.1.3	Mixed model of repeated measure (MMRM) will include baseline and visit interaction.
5.1.2	Added examination of MACE data in the first 60 and 90 days on the top of the first 30 days analysis.
5.2.2.9	Added a section on the analysis of adjudicated pancreatitis.
Appendix 8	Additional lab analytes were included in the Pre-defined Limit of Change (PDLC) criteria.

ABBREVIATIONS

ACR	albumin creatinine ratio
AE	adverse event
AFT	accelerated failure time model
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BL	baseline
BMI	body mass index
CI	confidence interval
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
EAC	Endpoint Adjudication Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GTED	Global Trial End Date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MH	medical history
MI	myocardial infarction
PDLC	Pre-defined Limit of Change
PT	preferred term
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium- glucose cotransporter 2
SI	standard international
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
ULN	upper limit of normal
UTI	urinary tract infection

1. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA).

Following market authorization, the sponsor is required to demonstrate that the upper bound of the 2-sided 95% confidence interval (CI) of the cardiovascular (CV) risk ratio of test drug to comparator be less than 1.3 in accord with FDA Guidance on assessing CV safety of AHAs.[1] As a result of the discussions with FDA, 28431754DIA4003 (CANVAS-R) was initiated in January 2014. The design and the subject characteristics of CANVAS-R are purposefully similar to 28431754DIA3008 (CANVAS), an ongoing CV outcome study initiated in December 2009.

This SAP stipulates definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety specific for CANVAS-R based on the latest amendment INT-5 (September 2016) of the protocol.

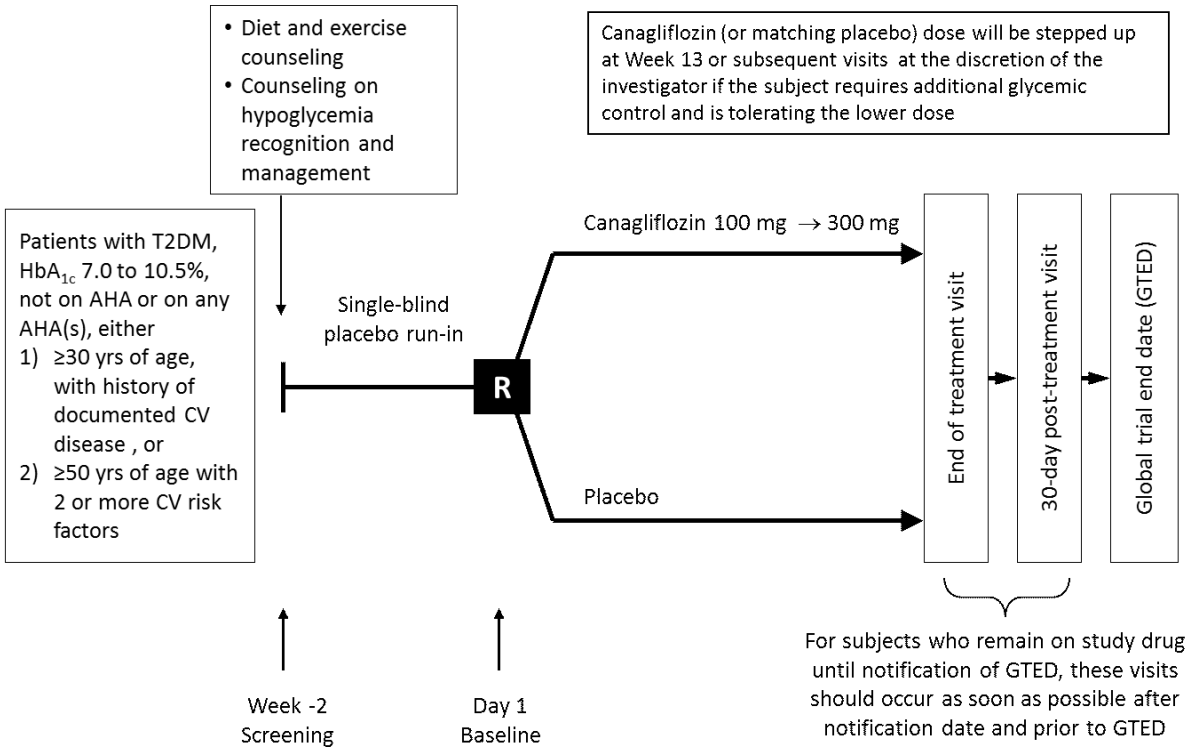
1.1. Trial Design

The CANVAS-R study enrolled the first subject in January 2014. The study recruited 5,812 subjects who met all inclusion criteria and none of the exclusion criteria. Subjects were randomly assigned to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). The randomization was balanced by using permutated blocks with no stratification factor. After 13 weeks, the dose of canagliflozin (or matching placebo) may be up titrated from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE are accumulated between both studies (estimated to occur between January 2017 and April 2017). The announcement of the GTED will mark the anticipated date on which one of these requirements for ending the study will occur.

Following announcement of the projected GTED, for subjects who remain on double-blind study drug, sites will be required to schedule the End of Treatment (EOT) and the 30-day off-drug follow-up visits as per the Time and Events schedule in the protocol; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (ie, schedule the last follow-up visit) or vital status check as soon as possible after announcement of the GTED. All visits (including the 30-day off-drug follow-up visit) will need to be completed prior to the GTED. A single Steering Committee (SC) and an Independent Data Monitoring Committee (IDMC) have been commissioned for this and the CANVAS study. The SC oversees the study conduct, and the IDMC regularly (and on an ad hoc basis) reviews safety data.

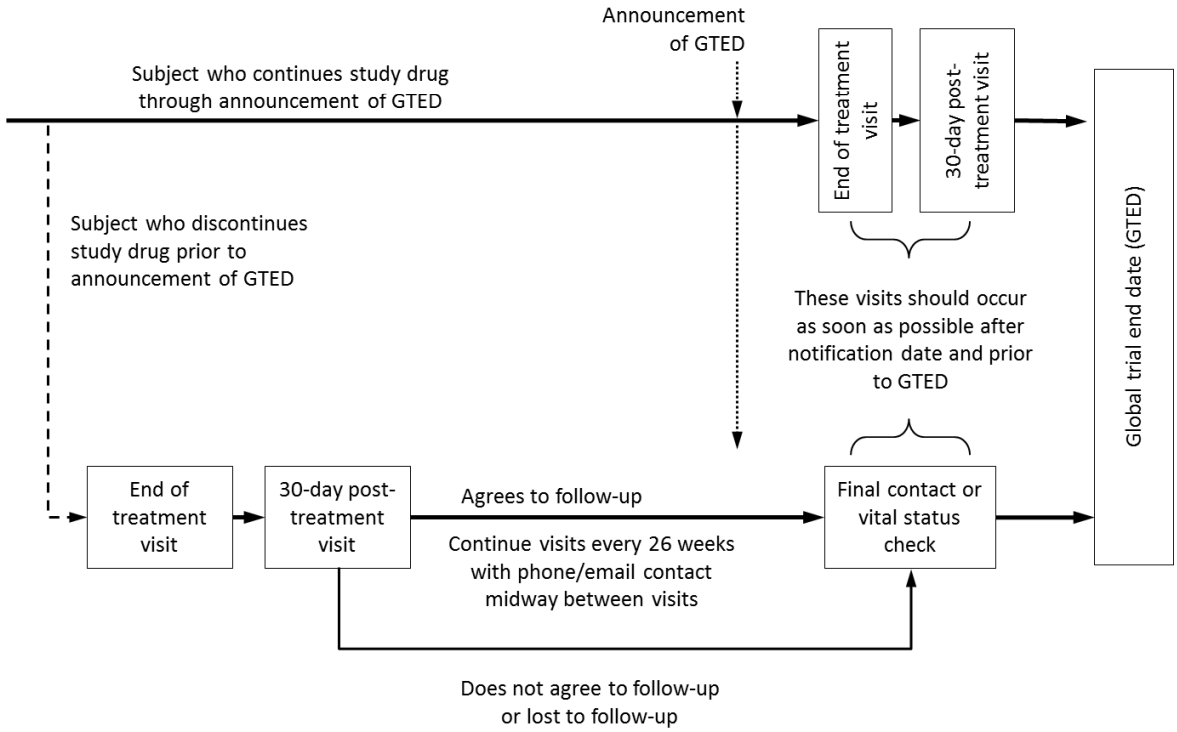
Figure 1 shows an overview of the study design and Figure 2 shows the scheduled follow-up of randomized subjects prior to the GTED.

Figure 1: Diagram of Study Design



AHA=antihyperglycemic agent; CV=cardiovascular; HbA_{1c}=hemoglobin A_{1c}; GTED=global trial end date; R=randomization; T2DM=type 2 diabetes mellitus

Figure 2: Follow-up of Randomized Subjects with Respect to the GTED



Note: Following the announcement of the GTED, investigators are not expected to continue collecting data for purposes of the clinical trial after the 30-day post-treatment contact.

In this study, duplicate urinary samples will be collected from 2 consecutive days (first morning void urine samples from the visit day and the day prior to the visit). The scheduled albumin creatinine ratio (ACR) measurements will be made on Day 1 (baseline), Week 26, Week 52, Week 78, Week 104, Week 156 and the last on-drug visit.

1.2. Randomization

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared by an external vendor based on the specification tested by the sponsor before the study. The randomization was balanced by using randomly permuted blocks; the randomization did not incorporate any stratification factors.

1.3. Trial Objectives

1.3.1. Primary Objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

1.3.2. Secondary Objectives

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes.

1.3.3. Exploratory Objectives

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria;
- Change in estimated glomerular filtration rate (eGFR) from baseline to the last off-drug value;
- Urinary albumin/creatinine ratio (ACR);
- The composite of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- The composite of doubling of serum creatinine (SCr), renal death or requirement for renal replacement therapy;
- The composite of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;

- The composite of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- The composite of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- The composite of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements (ie, off-drug values will not be included) of eGFR made from the first on-drug measurement to the final on-drug measurement;
- Changes in $HbA_{1c;}$
- Utilization of AHA therapy.

1.4. Statistical Hypotheses

The hypotheses in CANVAS-R are to support superiority claims of canagliflozin relative to placebo in reducing the following events:

- Progression of albuminuria;
- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes.

For each endpoint, the following statistical hypothesis on the hazard ratio (HR) of canagliflozin over placebo will be tested:

H_0: The hazard ratio ≥ 1.0, versus H_1: The hazard ratio < 1.0

Canagliflozin will be claimed to be superior in the reduction of the target events as compared to placebo if the upper bound of 95% CIs of the hazard ratio is less than 1.0.

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 received 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 referred in this SAP will be all 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 2.3.2) up to the GTED
On-Study	Treated subjects	Day 1 to the last trial contact date (see Section 2.3.2) up to GTED
On-Treatment	Treated subjects	Day 1 to the last dose date (see Section 2.3.2) plus X[a] days or the last trial contact date, whichever is earlier.

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

2.3. Data Handling

2.3.1. 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 the last trial contact day or end of the respective data period, if not otherwise specified.

2.3.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). 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 double-blind study drug was 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 subsequent to the last visit when the study drug 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, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug 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, vital sign measurements or laboratory results as reported on their respective electronic case report form (eCRF), or
  - The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the subject's survival status at the time of the GTED.

– For subjects who die during the study, the last trial contact date will be defined as the date of death.

2.3.3. 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.

Baseline will be defined as the pre-dose measurement closest to or including Day 1 (prior to dose administration). If the pre-dose measurement 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 2 pre-dose measurement 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 assure that all 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 included in the by-visit summaries or repeated measure analyses.

Note that 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, and other key safety variables.

Table 2: Time Intervals for Analysis (in clinic) Visit Windows

Scheduled Visit Time (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Baseline	≤1[b]	1
Week 13	1[c] –137	92
Week 26	138–229	183
Week 52	230–456	365
Week 78	457–638	547
Week 104	639–820	729
Week 130	821–1002	911
Week 156	1003–1184	1093
Week 182	1185–1366	1275
Week 208	1367–1548	1457

[a] Relative to the day of the first dose of double-blind study drug.
[b] Up to the first dose of double-blind study drug.
[c] Immediately following the first dose of double-blind study drug. For variables with no time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group. Descriptive statistics (N, mean, standard deviation [SD], median, and range) will be provided by treatment group for the baseline age and baseline body weight.

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

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for the following baseline continuous variables: duration of diabetes (in years), baseline eGFR, baseline ACR, systolic blood pressure (SBP), weight, body mass index (BMI), HbA_{1c}, LDL-C, HDL-C, triglycerides, total cholesterol and LDL-C/HDL-C.

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

- Baseline BMI categories (<30, ≥30 kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of T2DM ≥ 10 years: Yes/No;
- Baseline systolic blood pressure categories (≤140, >140 mmHg);
- Baseline LDL-C categories (≤70, >70 mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 $mL/min/1.73m^2$);
- Baseline albuminuria category:
  - Normoalbuminuria (0 ≤ ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR >300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR > 3000 mg/g).
- History of hypertension: Yes/No ;
- History of CV disease: Yes/No;

- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or automatic neuropathy] and nephropathy)
- History of fracture: Yes/No;

The number and percentage of subjects with a history of medical conditions by system organ class and preferred term (based upon the general medical history eCRF) will be summarized by treatment group and overall.

3.3. Disposition Information

Disposition will be summarized for all randomized subjects by treatment group using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who completed the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject had died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (eg, lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. The distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

Listings will be provided for subjects whose predominant treatment differs from their randomized treatment.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, SD, median, and range) for total exposure or follow-up time will be presented by treatment group.

The number of subjects with duration in each of the following categories (<13 weeks, 13 to <26 weeks, 26 to <52 weeks, 52 to <104 weeks, 104 to <156 weeks, ≥156 weeks) will also be presented by treatment group as well as overall.

3.5. Prior and Concomitant Medications

Concomitant medications of interest is collected on the eCRF at baseline and at each on-drug visit. The number of subjects receiving medication in pre-specified categories, such as insulin, sulphonylurea, metformin, statin, anti-thrombotic, diuretic (loop, and non-loop), renin angiotensin aldosterone system (RAAS) inhibitor, will be presented by treatment group at baseline and during on-drug period. In addition, SGLT2 inhibitor use during the off-drug follow-up period will be summarized by treatment group.

4. EFFICACY

The analysis will be performed based on the ITT analysis set, if not otherwise specified.

All statistical tests, except those for the primary and secondary efficacy endpoints, will be considered nominal and reported with a 2-sided 95% confidence level.

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

4.1. Primary Efficacy Endpoint

Subjects without baseline and/or post-baseline ACR measurements will be excluded from the primary efficacy analysis. Furthermore, subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis.

4.1.1. Definition

The primary efficacy endpoint is the time to the first occurrence of progression of albuminuria.

Urinary albumin creatinine ratio (ACR) is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR of >300 mg/g]).[2]

Progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.[3]

If the ACR at a visit meets the definition of progression as described, a confirmatory ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. In cases where a confirmatory sample is not collected within 1 to 2 months, the next available set of ACR measurements can be used for confirmation.

The primary efficacy analysis will be based on results of ACR measurements from a single visit whether confirmed or unconfirmed. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings. A sensitivity analysis (see Section 4.1.4.2) will be based on results of ACR measurements from a single visit that were confirmed at a subsequent visit.

4.1.2. Analysis Methods

At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analyses unless otherwise specified. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used in the geometric mean calculation.

As the primary analysis for the primary efficacy endpoint, the time from Day 1 to first visit date observing progression (ie, using the visit date of the original sample collection and not using the visit date of the confirmatory sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The response variable in the model is time to progression and the model will include treatment and baseline albuminuria status as the explanatory variables. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated. Canagliflozin will be considered superior to placebo in the reduction of progression if the p-value of the test of significance, ie, the Wald test from the Cox model specified above, is ≤ 0.05 in the context of multiplicity adjustment described in Section 4.3.

For ITT analysis, endpoint events that occur during the data period (see Table 1) will be considered as eligible events; otherwise subjects will be censored at the last ACR measurement up to GTED.

4.1.3. Subgroup Analyses

The homogeneity of treatment effect on the occurrence of the primary endpoint across subgroups will be examined (at a 2-sided significance level of 0.05) via a test for the treatment by subgroup interaction by adding this term and the subgroup as covariates (treated as class variables) to the primary efficacy analysis (Section 4.1.2) model. Subgroup analysis will be conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups. Factors exhibiting interactions at a significance level of $p < 0.05$ will be identified as suggesting treatment effect heterogeneity, recognizing the multiplicity in testing multiple subgroups such that one or more p-values < 0.05 may be expected to be observed by chance alone.

If a significant interaction is observed, the Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

The hazard ratio of canagliflozin (all canagliflozin group) compared to placebo and its 95% confidence interval will be estimated for each of the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;

- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline BMI categories (<30, ≥30 kg/m^2);
- Baseline composite blood pressure categories ([SBP<140or DBP<90 mmHg] vs. [SBP ≥ 140 and DBP ≥90 mmHg]);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥8%: Yes/No;
- Baseline albuminuria: Normoalbuminuria, Microalbuminuria;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- Baseline use of Renin angiotensin aldosterone system (RAAS) inhibitor: Yes/No.

4.1.4. Supportive Analyses

If not otherwise specified, the supportive analyses will use the same analysis set as in the primary efficacy analysis.

4.1.4.1. On-Treatment Analysis

For On-Treatment analysis, endpoint events that occur within the data period (see Table 1) will be eligible events; otherwise subjects will be censored at the earliest of the last ACR measurement date, last study drug dose date + 30 days, or GTED.

The Cox model for primary analysis (as described in Section 4.1.2) will be repeated using the On-Treatment analysis set.

4.1.4.2. Additional Supportive Analyses

Several Cox models analogous to the primary efficacy analysis model will also be performed for exploratory purposes:

- The first Cox proportional hazards model involves the use of confirmed progression, plus the unconfirmed progression from the last ACR values;
- Secondly, there will be an analysis that only excludes subjects with baseline nephrotic range macroalbuminuria (ie, ACR > 3000 mg/g). This analysis will evaluate time to first occurrence of ≥1 step progression in the following categories (ie, baseline normoalbuminuria, baseline microalbuminuria, baseline non-nephrotic range macroalbuminuria).

Additionally, the actual onset time of progression of albuminuria can be determined to occur within an interval from a sequence of examination times (ie, data are interval censored). The accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring excluding subjects with baseline macroalbuminuria.[4] The dependent variable in the AFT model is the logarithm of time to progression of albuminuria,

expressed as time intervals. The model will include treatment group and baseline albuminuria status as the explanatory variables.

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

4.1.4.3. Assessment of Missing Data

The potential impact of missing data in the interpretation of the primary efficacy analysis will be explored. The primary efficacy endpoint, progression of albuminuria was derived from urinary albumin/creatinine ratio (ACR) laboratory measurements which were generally collected biannually while subjects were on treatment (ie on treatment period) up to the global trial end date (GTED). For subjects who discontinue from treatment early before the development of progression of albuminuria, unobserved data of post-baseline ACR measurements at each scheduled visit up to the GTED will be considered missing and will be imputed. The multiple imputation procedure will apply to ACR data and the time to ACR progession data will then be generated based on the imputed data at the schedule visits.

Data for model development

Due to the staggered enrollment of the study, for those randomized at a later stage of the enrollment period, pseudo visits up to the max possible visit week prior to GTED, i.e. week 130, will be created according to the protocol schedule. In addition, multiple data points at each visit, e.g. confirmatory samples, will be aggregated using geometric mean according to the variability of ACR data. There is small proportion of subjects (less than 2.5%) with unscheduled visits which will be combined with the closest scheduled visit using the same approach.

Imputation model

Assuming that after treatment discontinuation, subjects discontinued from the canagliflozin arm will exhibit a response similar to subjects in the placebo arm, the imputation model will be fit using the non-missing data in the placebo group and adjusted for covariates that may be related to the missing data mechanism and the risk of progression based on clinical judgment. The potential covariates include:

- Baseline ACR (continuous);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline blood pressure (SBP<140, DBP<90 mmHg): Yes/No;
- Baseline HbA_{1c} ≥8%: Yes/No;
- Age group: <65, ≥65 years old;
- Race: White, Other;
- Sex: Male, Female;

In case of convergence issues, the covariates will be removed from the model in the descending order of the list (ie, starting from the bottom of the list).

Due to the highly skewed data of ACR, both baseline and post baseline ACR in the imputation model will be log transformed.

Imputation Procedures

There are about 3% of subjects with intermittent missing in post-baseline ACR data. Those missing data will be imputed with data estimated from all observed data using the Markov Chain Monte Carlo procedure such that the missing data pattern is monotonic.

The post-treatment ACR data increased gradually over time from the end-of-treatment data. Therefore, a "copy control" strategy will be applied and the imputation model will be fit sequentially at each visit using non-missing data in the placebo arm and any preceding visits (O'Kelly and Ratitch 2014, Section 7.4.2)[5]. The estimates of the model parameters are then used to parameterize a Bayesian posterior distribution. At each imputation, missing data in both active and placebo arms will be replaced with predicted values randomly drawn from the distribution. The imputed data will also be applied to the models of subsequent visits. For example, the imputation model at week 26 will be fit using baseline and covariate data (see Section of Imputation Model) and week 26 data of the placebo arm. The ACR data that are missing at week 26 in both active and treatment arms will be imputed in the same way. Similarly, the imputation model for week 52 will utilize observed data of control arm at week 52 and all the preceding data points, whether imputed or observed.

For subjects with missing data, the imputed data up to the earlier of death date or GTED will be combined with observed data. For subjects completing the treatment or developing progression, only data imputed for intermittent missing will be added back to the observed data.

Re-construction of time to progression data

The time to progression will be re-defined based on the imputed dataset where subjects with imputed or observed ACR that met the progression criteria will be considered having events at the corresponding visit. Subjects remaining event-free will be censored at the last scheduled visit before death date or GTED, whichever is earlier.

Analysis summary

The imputed data will be re-analyzed using the same Cox model for the primary analysis (see Section 4.1.2). The imputation process will be repeated 1000 times and the multiple versions of analysis results will be combined into single inferential summary using Rubin's rule.

4.2. Secondary Efficacy Endpoints

4.2.1. Definition

There are 2 secondary efficacy endpoints specified in this study:

- The composite endpoint of death from CV causes[a] or hospitalization for heart failure;
- Death from CV causes (CV Death).

Analyses will be using adjudicated events and adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) will be done in a blinded fashion.

4.2.2. Analysis Methods

The analyses will be using the ITT analysis set.

4.2.2.1. The Composite of CV Death or Hospitalization for Heart Failure

The analysis will be based on time to the first occurrence of the composite event using ITT analysis set. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log rank test for the treatment effect will also be reported.

The subgroup analysis will be conducted using the same approaches described in Section 4.1.3 and the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline BMI categories (<30, ≥30 kg/m^2);
- Baseline composite blood pressure categories ([SBP <140 or DBP <90 mmHg] vs. [SBP ≥140 and DBP ≥90 mmHg]);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;

[a] Undetermined death is considered CV death.

- History of amputation: Yes/No;
- Baseline use of statin;
- Baseline use of anti-thrombotics;
- Baseline use of RAAS inhibitor;
- Baseline use of Beta blocker;
- Baseline use of insulin;
- Baseline use of diuretics.

4.2.2.2. CV Death

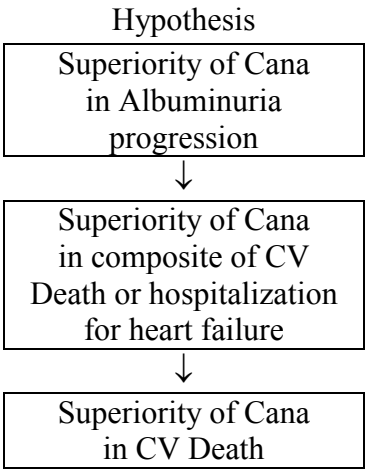
The analysis will be based on time to the first occurrence of CV death using ITT analysis set. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log rank test for the treatment effect will also be reported.

Subgroup analyses will be performed using the same subgroups and the analysis methods described in Section 4.2.2.1.

4.3. Multiplicity Adjustment

Per the SAP of the integrated summary of CANVAS and CANVAS-R studies, only one alpha family is proposed for the testing of the multiple hypotheses based on the integrated data and the CANVAS-R data. The Type I error for these tests will be strictly controlled via a gatekeeping procedure. If the MACE and the mortality endpoints in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to the CANVAS-R for testing of the primary and the secondary hypotheses of the study. Tests for CANVAS-R hypotheses will proceed sequentially conditional on the statistical significance of the hypothesis tests in the integrated summary at the 5% significant level.

Figure 3: Hypothesis Testing Sequence



4.4. Exploratory Efficacy Endpoints

4.4.1. Definition

The following exploratory endpoints will be analyzed:

- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death[a] or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Regression of albuminuria;

  Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the ACR value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of potential regression described above, a confirmatory ACR collection approximately 1 to 2 months later

[a] Non-CV death with a renal proximate cause is considered as renal death.

(or sooner under unusual circumstances, eg, subject is stopping study drug), should be done. In cases where a confirmatory sample is not collected within 1 to 2 months, the next available set of ACR measurements can be used for confirmation.

- Change in urinary ACR over time;
- Change in eGFR from baseline to the last off-drug measurement;
- Estimated eGFR slopes using all on-drug measurements;
- Changes in HbA_{1c}.
- AHA utilization

4.4.2. Analysis Methods

4.4.2.1. Renal Endpoints

4.4.2.1.1. Composite Endpoints

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of serum creatinine, identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

The time to the first occurrence of each of the renal composite endpoints (see Section 4.4.1) will be analyzed in the ITT analysis set using a Cox proportional hazards model with treatment and baseline eGFR (< 60, ≥ 60 mL/min/1.73m^2) as the explanatory variables. The hazard ratio of canagliflozin compared to placebo and its 95% confidence interval will be estimated from the model.

4.4.2.1.2. Regression of Albuminuria

Regression of albuminuria will be analyzed in a similar fashion in modeling and censoring rule as the analysis for progression of albuminuria. The analysis will be using the ITT analysis set based on ACR measurements from a single visit whether confirmed or unconfirmed. Subjects with normal albuminuria at baseline will be excluded. The hazard ratio of canagliflozin compared to placebo and its 95% confidence interval will be estimated from the model. Additionally, analyses based on confirmed regression plus unconfirmed regression from the last ACR values will be performed in a similar fashion using ITT analysis set.

4.4.2.1.3. Urinary ACR

Post-baseline ACR will be analyzed using mixed effect model repeat measurement (MMRM) and the ITT analysis set.

Since the distribution of ACR is highly skewed, the log transformed ACR values of all the post-baseline and scheduled visits will be modeled, using a linear mixed effects model. The linear mixed effects model will be fit to the logarithm of ACR as a dependent variable, including treatment, logarithm of baseline ACR value, visit, treatment by visit interaction, and logarithm of baseline ACR value by visit interaction as fixed effects. The percentage of treatment difference,

ie, treatment difference in mean ACR relative to placebo, can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1. The ratio of mean ACR in treatment compared to placebo and its 95% CI will be presented. An unstructured covariance will be used to model the within subject errors.

4.4.2.1.4. Change in eGFR

For change in eGFR from baseline to the last off-drug measurement will be analyzed in the ITT analysis set using an analysis of covariance (ANCOVA) model with treatment and the baseline eGFR value as covariates. The treatment difference of canagliflozin compared to placebo in the least-squares means and associated 95% CI will be estimated from the model.

4.4.2.1.5. eGFR Slope

The time slope of eGFR will be analyzed in the On-Treatment analysis set using a linear mixed effects model with eGFR as a dependent variable and treatment, baseline eGFR value, time (as a continuous variable), and treatment by time interaction as fixed effects and intercept and time as random effects. The parameter of interest is the coefficient for treatment by time interaction term, which measures the slope difference between canagliflozin and placebo over time.

4.4.2.2. Changes in HbA_{1c}

Change in HbA_{1c} from baseline will be analyzed using MMRM and the ITT analysis set. The effect of canagliflozin relative to placebo on the changes in HbA_{1c} from baseline over time will be assessed using MMRM. The analysis will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within subject errors.

4.4.2.3. AHA Utilization

Summary of AHA utilization is described under Section 3.5.

5. SAFETY

The safety analysis will be mainly based on the On-Treatment analysis set unless otherwise specified.

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

5.1. Adjudicated MACE Events

The MACE is the composite of CV outcomes including CV death, non-fatal MI[a], or non-fatal stroke. Adjudication of these outcomes by the EAC has been done in a blinded fashion.

[a] Silent MIs are excluded from the analysis.

5.1.1. Analysis Methods

The analysis will be based on the time to first occurrence of MACE using the ITT analysis set. The HR of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable, and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. P-value of stratified log rank test for treatment effect will also be reported for the primary analysis.

5.1.2. Supplementary Analysis

A prior post-hoc analysis performed by the FDA of the MACE-plus events occurring during the first 30 days post-randomization in CANVAS showed an imbalance in favor of placebo. In the PMR, FDA requested that the pattern of MACE events occurring in the first 30 days post randomization in CANVAS-R be explored. Additional examination of the MACE events in the first 60 and 90 days using the ITT analysis set will be made.

An excess of volume depletion AEs in the canagliflozin groups could provide a possible biologic basis for an imbalance in MACE events between canagliflozin and control. In the CANVAS study, the Kaplan-Meier (KM) time-to-event analysis comparing canagliflozin and placebo showed that the greatest separation in the curves for volume depletion AEs occurred during the first 90 days post-randomization.

To assess the potential association between MACE events and volume depletion AEs and fulfill the PMR request, hazard ratio will be estimated using the same stratified Cox model as in the main analysis (see Section 5.1.1) for events occurring within the first 30 days, and within the first 90 days post-randomization. In addition, Kaplan-Meier plots including data within first 30 days and first 90 days will be presented.

Additionally, time to the first occurrence of each component of MACE as well as fatal/non-fatal MI and fatal/non-fatal stroke will be analyzied using the same Cox model described in Section 5.1.1.

5.2. 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.

A treatment-emergent AE (TEAE) is defined as an AE with an onset after the initiation of double-blind study drug and before the last study medication date plus 30 days. AEs with a start date prior to initiation of double-blind study drug which are subsequently reported to have either an increase in intensity or change in attribution in relationship to study drug (ie, attribution to possible, probably, very likely) after the initiation of double-blind study drug will also be considered as TEAEs.

5.2.1. Adverse Event Collection

The AE collection in CANVAS-R is streamlined to include serious adverse events (SAEs), AEs that lead to study drug discontinuation, and all AEs (serious and non-serious) for selected AEs of interest (Table 3, Section B).

For selected AEs of interest, additional data will be collected on supplementary CRF pages mainly for the purposes of narrative description of certain events. Table 3 lists the AEs of interest.

Table 3: Adverse Events of Interest

Section A: For the AEs listed below, only serious AEs or AEs that led to drug discontinuation were collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B: The AEs listed below were collected regardless of whether they were serious and/or led to study drug discontinuation for the study: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic Ketoacidosis

The AEs listed above will be identified using a MedDRA preferred term list (Appendix 1.3).

5.2.2. Analysis Methods

The study duration of CANVAS-R is long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting the AEs) derived from the study are not comparable to the incidences generated in the Phase 3 program. Therefore, the exposure-adjusted incidence rate will be reported in addition to the incidence. The rate is calculated as the total number of subjects with the AE divided by the On-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow

up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the AEs divided by the total follow-up time in subject-years.

For general AEs and selected AEs of interest that are not routinely collected in CANVAS-R (refer to Section A of Table 3), the main interest will be the serious AEs and the AEs leading to discontinuation of study medication.

5.2.2.1. General Adverse Events

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

- 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 by system organ class and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AE leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug 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).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs which are reported in at least 4 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).[6] The exclusion of "0" from the 95% CI for the between-group difference in incidence for a particular AE does not necessarily imply that the difference is due to drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. AEs identified by the above screening procedure will be presented and may be subject to further evaluation.

Listings will also be provided for deaths, SAEs, and AEs leading to study drug discontinuation.

For AEs of interest in Section A of Table 3, a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA preferred terms listed in Appendix 1.3.

5.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Treatment analysis set.

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

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- 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.

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified using the sponsor's pharmacovigilance database and summarized by treatment group.

5.2.2.3. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA Preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Study analysis set.

For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- 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.

The preferred terms associated with each selected malignancy type will be summarized by treatment.

A summary of all malignancy events as reported in the malignancy supplementary page will be reported by treatment and primary site. For breast, bladder, or renal cancers, the risk factors for each cancer type captured in the supplementary page will be summarized by treatment.

5.2.2.4. Photosensitivity

Photosensitivity AE will be identified using the MedDRA preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Treatment analysis set.

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

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- 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.

AEs by preferred term will be summarized by treatment group.

5.2.2.5. Venous Thromboembolic Events

Venous thromboembolic (VTE) events will be identified using the MedDRA preferred terms listed in Appendix 1.3.

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

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- 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.

AEs by preferred term will be summarized by treatment group.

5.2.2.6. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that

events were fractures and to determine fracture location (anatomic region) and type (low trauma or not). The main analyses of the adjudicated low trauma fracture AEs will be based on the On-Study analysis set.

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

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication.

A summary of adjudicated fracture stratified by anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

Adjudicated AEs associated with fall will be summarized by treatment group.

A Kaplan-Meier plot for the time to the first occurrence of adjudicated fracture event will be provided by treatment group. The hazard ratio between canagliflozin (all canagliflozin) compared to placebo and its 95% confidence interval will be estimated from a Cox proportion hazards model with treatment as the explanatory variable.

A summary of all adjudicated fractures by anatomic location will be provided. The hazard ratio and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fractures will be provided using the same analysis as the adjudicated low trauma fractures.

5.2.2.7. Amputation

The main analysis of lower extremity amputations as documented in the dedicated case report form page will be based on the On-Study analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be generated for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, trans-metatarsal, below knee, above knee) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to the first occurrence of event will be provided by treatment group.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 1.4:

- Infections and Infestations;
- Vascular disorders;
- Nervous System disorders;
- Skin and subcutaneous tissue disorders;
- Osteomyelitis.

The selected preferred terms in infections and infestation are further split into "Reversible Infection" and "Irreversible Infections". In addition, the preferred terms grouped under the MedDRA high level term of "skin and subcutaneous tissue ulcerations" are also of interest.

For each AE group listed above, the incidence of the respective preferred terms will be summarized by treatment group.

5.2.2.8. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 1.3. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent DKA Adjudication Committee. The main analysis of the DKA events will be based on adjudicated events of DKA in the On-Study analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included. For the adjudicated DKA events, a table will summarize the incidence and the follow-up-adjusted incidence rate.

A listing of all DKA and related events identified by the sponsor's medical monitoring team and the subset of these events that went for adjudication will be provided.

5.2.2.9. Pancreatitis

Pancreatitis and related AEs identified by the sponsor using the list of MedDRA terms pre-specified in the charter will be sent to the independent Pancreatitis Adjudication Committee. The main analysis of events will be based on adjudicated, confirmed events in the On-Treatment analysis set. Analysis based on events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be performed. The incidence rate and proportion of adjudicated pancreatitis events by severity will be summarized. The total number of subjects with an event not confirmed by the Pancreatitis Adjudication Committee will also be summarized.

5.3. Clinical Laboratory Tests

A list of clinical laboratory assessments made during the study is provided in Appendix 1.1. The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 1.2 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to placebo group 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. As described above, PDLC values will be presented based on measurements on study drug and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

5.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the PDLC criteria in Appendix 1.2. For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study medication.

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.

5.5. Electrocardiogram

Electrocardiogram was not be collected in this study.

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APPENDIX

Appendix 1.1: 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
- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol).
- HbA_{1c}
- Urinalysis (dipstick analysis; from spot urine collection in the clinic on Day 1; performed at central laboratory; microscopic analysis is not required). Urine glucose will not be measured by the central laboratory
  - specific gravity - ketones
  - pH - bilirubin/urobilinogen
  - protein - nitrite
  - blood - leukocyte esterase
- Central laboratory will report the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured. The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

  For creatinine in mg/dL:

  $$eGFR\ (mL/min/1.73\ m^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

For creatinine in µmol/L:

eGFR (mL/min/1.73m^2) = 175 x (serum creatinine x 0.0113) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.21 if black)

Appendix 1.2: Criteria for Pre-defined Limit of Change (PDLC) and Abnormal Values

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
Albumin	Composite: <LLN and >25% decrease from BL
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
Creatinine Kinase	Absolute Value: >1000U/L
eGFR	Composite: < 80 and decrease>30% from BL
	Change: decrease>50% from BL
Magnesium	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Phosphorus	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
Uric Acid	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

Appendix 1.3: List of Preferred Terms for Selected AEs 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
Blood ketone body present	Vulvovaginal mycotic infection	Closed fracture manipulation
Diabetes mellitus with ketoacidosis	Vulvovaginitis	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
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
		Greenstick fracture
		Hand fracture
		Hip fracture
		Humerus fracture
		Ilium fracture
		Impacted fracture
		Internal fixation of fracture
		Jaw fracture
		Limb crushing injury
		Limb fracture

Diabetic ketoacidosis	Female Mycotic Genital Infections	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
Allergic hepatitis		Balanoposthitis infective
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		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
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 encelalopathy		
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		
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		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
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 Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
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	

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
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	
	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	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
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		

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
	Photodermatosis
	Photokeratitis
	Photoonycholysis
	Photosensitivity reaction
	Polymorphic light eruption
	Solar dermatitis
	Solar urticaria
	Sunburn
	Vaccination site photosensitivity

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
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	
	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	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	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	
	Throat tightness	
	Tongue exfoliation	
	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
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 vein 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

UTI	Venous Thromboembolic events	Volume Depletion
Ureteritis	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		

Appendix 1.4: Adverse Events with Potential Amputation Association

List of selected preferred terms included within the system organ classes of infections and infestations, vascular disorders, nervous system disorders, and skin and subcutaneous tissue disorders

Infections and Infestations	Vascular Disorders	Nervous System Disorders	Skin and Subcutaneous Tissue Disorders	High Level Term (HLT) Skin and subcutaneous tissue ulcerations	
Infected skin ulcer	Arteriosclerosis	Paraesthesia	Diabetic ulcer	Penile ulceration	Medical device site erosion
Skin infection	Peripheral arterial occlusive disease	Hypoaesthesia	Neuropathic ulcer	Implant site ulcer	Ulcerated haemangioma
Staphylococcal skin infection	Peripheral vascular disorder	Diabetic neuropathy	Fungating wound	Cytomegalovirus mucocutaneous ulcer	Incision site erosion
Gangrene	Peripheral artery stenosis	Neuropathy peripheral	Diabetic foot	Skin ulcer	Incision site ulcer
Osteomyelitis	Peripheral ischaemia	Areflexia	Diabetic neuropathic ulcer	Eyelid erosion	Vaccination site ulcer
Diabetic gangrene	Arterial stenosis	Hyporeflexia	Skin erosion	Implant site erosion	Fungating wound
Localised infection	Diabetic vascular disorder	Polyneuropathy		Diabetic foot infection	Ecthyma
Wound abscess	Femoral artery occlusion	Autonomic neuropathy		Application site erosion	Perineal ulceration
Wound infection	Thrombosis	Neuropathy peripheral		Infusion site erosion	Tropical ulcer
Subcutaneous abscess	Poor peripheral circulation	Burning sensation		Mycobacterium ulcerans infection	Injection site erosion
Abscess limb	Microangiopathy	Diabetic autonomic neuropathy		Infusion site ulcer	Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
Staphylococcal osteomyelitis	Peripheral coldness	Peripheral sensory neuropathy		Neuropathic ulcer	Scleroderma associated digital ulcer
Diabetic foot infection	Diabetic microangiopathy	Peripheral sensorimotor neuropathy		Skin ulcer haemorrhage	Vulval ulceration
Staphylococcal skin infection	Arterial occlusive disease	Sensory disturbance		Burn infection	Mucocutaneous ulceration
Soft tissue infection	Arterial thrombosis	Diabetic neuropathic ulcer		Diabetic foot	Injection site ulcer
Bone abscess	Peripheral artery thrombosis			Diabetic ulcer	Pyoderma gangrenosum
Osteitis	Arterial occlusive disease			Catheter site erosion	Scrotal ulcer
Cellulitis	Angiopathy			Pyostomatitis vegetans	Application site ulcer
Wound [a]	Intermittent claudication			Catheter site ulcer	Genital ulceration
Dry gangrene	Arterial disorder			Medical device site ulcer	Infected skin ulcer
Post-operative wound infection	Impaired healing [a]			Administration site ulcer	Diabetic neuropathic ulcer
Post-operative wound complication [a]				Instillation site erosion	Varicose ulceration
Wound dehiscence				Breast ulceration	Vaginal ulceration
Burn infection				Instillation site ulcer	Vulvovaginal ulceration
Extremity necrosis				Administration site erosion	Auditory meatus external erosion
				Vasculitic ulcer	Skin erosion
				Vaccination site erosion	

[a] Although these PTs belong in the SOC of Injury, Poisoning and Procedural Complications or in the SOC of General Disorders and Administration Site Conditions, these terms were retained for the search strategy because of their relevance

List of preferred terms classified as reversible infections, irreversible infections and osteomyelitis

Reversible Infections	Irreversible Infections	Osteomyelitis
Abscess limb	Diabetic gangrene	Bone abscess
Burn infection	Dry gangrene	Osteitis
Cellulitis	Extremity necrosis	Osteomyelitis
Diabetic foot infection	Gangrene	Staphylococcal osteomyelitis
Infected skin ulcer	**Osteomyelitis**	
Localised infection	Bone abscess	
Skin infection	Osteitis	
Soft tissue infection	Osteomyelitis	
Staphylococcal skin infection	Staphylococcal osteomyelitis	
Subcutaneous abscess		
Wound		
Wound abscess		
Wound dehiscence		
Wound infection		