Janssen Research & Development

Statistical Analysis Plan

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus

The CANVAS Trial (CANagliflozin cardioVascular Assessment Study)

Protocol 28431754DIA3008; Phase 3

JNJ-28431754 (canagliflozin)

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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)
1.3.3 4.4	Removed 'Change in eGFR from baseline to the last off-drug value' from objectives and exploratory efficacy endpoints.
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	Consistent with the analytic approach described in the Cardiovascular Endpoint adjudication charter, it is clarified that undetermined death is considered as CV death.
4.1.3	Additional subgroups were added for the analysis of MACE.
4.1.4.3.1	Added an analysis of MACE in the first 30, 60 and 90 days.
4.1.4.3.3	Updated the multiple imputation analysis section
4.2	Added analysis based on MMRM for continuous secondary efficacy endpoints.
4.4	Clarified that any adjudicated non-CV death event where the adjudication committee assigned a renal proximate cause is considered a renal death.
5.2.2.10	Added a section on the analysis of adjudicated pancreatitis.
Appendix 1.3	Additional lab analytes were included in the Pre-defined Limit of Change (PDLC) criteria.

ABBREVIATIONS

ACR	albumin creatinine ratio
AE	adverse event
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BL	baseline
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
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
FPG	fasting plasma glucose
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
MI	myocardial infarction
PDLC	pre-defined limit of change
PT	preferred term
QTcF	QTc using the Fridericia
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 co-transporter 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
VTE	venous thromboembolic events

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). To meet the FDA guidance on assessing cardiovascular (CV) safety of AHAs, the sponsor initiated the CV outcomes study 28431754DIA3008 (CANVAS) in December, 2009 intended to supply data to support the CV safety of canagliflozin and to also evaluate whether canagliflozin reduces CV risk.

As part of the marketing authorization application, the sponsor performed an integrated analysis of CV events from the Phase 2 and Phase 3 canagliflozin program using data from 9,632 subjects, which included interim data harvested on 31 January 2012 from the ongoing CANVAS study of 4,330 subjects at high risk for CV disease. Subsequently, in response to a request arising during review of the canagliflozin Marketing Authorization Application by the Committee for Medicinal Products for Human Use (CHMP), the sponsor conducted a second integrated CV analysis of the Phase 2 and Phase 3 studies, which included interim data from CANVAS harvested on 19 November 2012. Data on major adverse cardiovascular events (MACE) and mortality outcomes beyond 19 November 2012 have remained blinded to the sponsor.

The primary endpoint of CANVAS was to evaluate whether there was a risk reduction in MACE associated with canagliflozin treatment. Due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated. Accordingly, the study itself is underpowered for the primary hypothesis of the reduction in CV risk as measured by the hazard ratio (HR) for MACE.

As a result of the discussions with FDA, the sponsor proposed to conduct a second CANVAS-like study (referenced as CANVAS-R) with approximately 5,700 randomized subjects. As such, the CANVAS and CANVAS-R trials are purposefully similar in design and in subject characteristics. Data from these studies are to be harvested for an integrated analysis to meet the FDA post-approval CV safety requirement and if safety is demonstrated, to assess whether canagliflozin reduces all-cause mortality no later than June 2017 with study reports submitted to FDA by September 2017.

This statistical analysis plan (SAP) stipulates definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety specific for CANVAS based on the latest amendment INT-8 (5 May 2016) of the protocol. Additional CV and renal outcome endpoints are added in this SAP for exploratory analysis. Since the Clinical Study Reports of the 18-week substudies were submitted in the NDA of canagliflozin and the 52-week interim results were published, the analyses in these sub studies will not be addressed in this plan.

1.1. Trial Design

The CANVAS study enrolled the first subject in December 2009. The original design called for the study to be conducted in 2 cohorts (an initial cohort of 4,500 subjects enrolled prior to regulatory submissions followed by a subsequent cohort of 14,000 subjects to be enrolled post approval).

However, due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated.

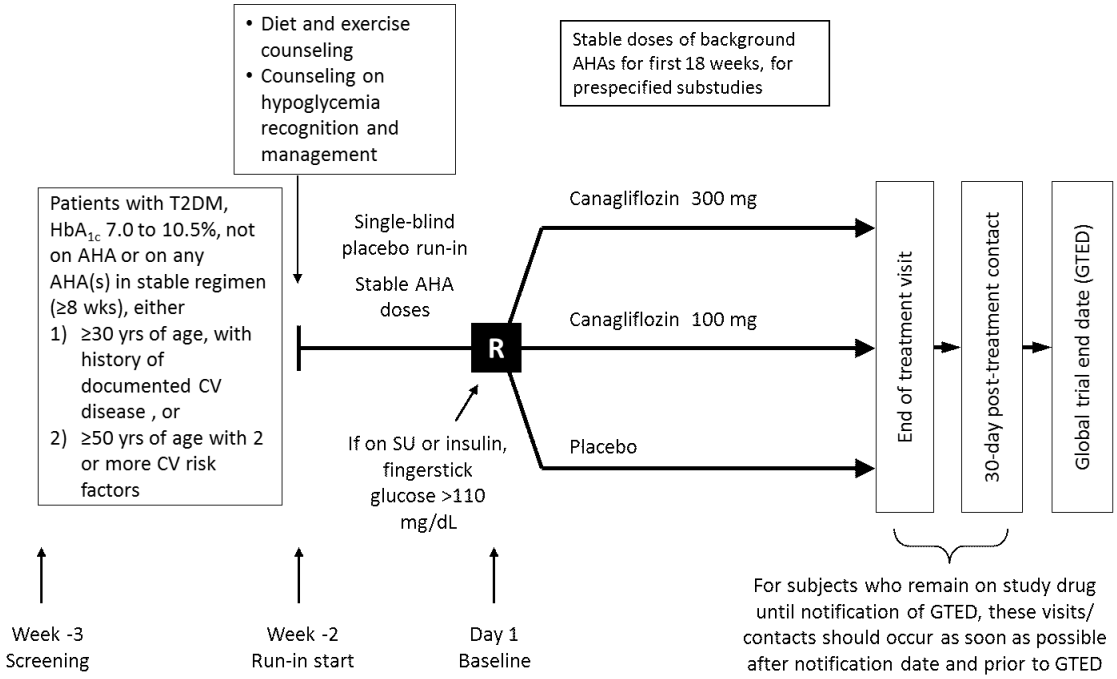
The study enrolled 4,330 subjects who met all inclusion criteria and none of the exclusion criteria. Subjects were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio. The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events are accumulated between both studies (estimated to occur between January 2017 and April 2017). The announcement of the Global Trial End Date (GTED) will mark the anticipated date on which one of these requirements for ending the study will occur.

Following announcement of the projected GTED and for subjects remaining on double-blind study drug, sites will schedule the End of Treatment (EOT) and the 30-day off-drug follow-up contact as per the Time and Events schedule in the protocol; for subjects that have prematurely discontinued study drug prior to the announcement of the projected GTED, sites will be required to make a final contact or vital status check as soon as possible after the announcement of the GTED.

A single Steering Committee (SC) and an Independent Data Monitoring Committee (IDMC) are commissioned for this and the CANVAS-R study. The SC oversees the study conduct, and the IDMC regularly (and on an ad hoc basis) reviews safety data.

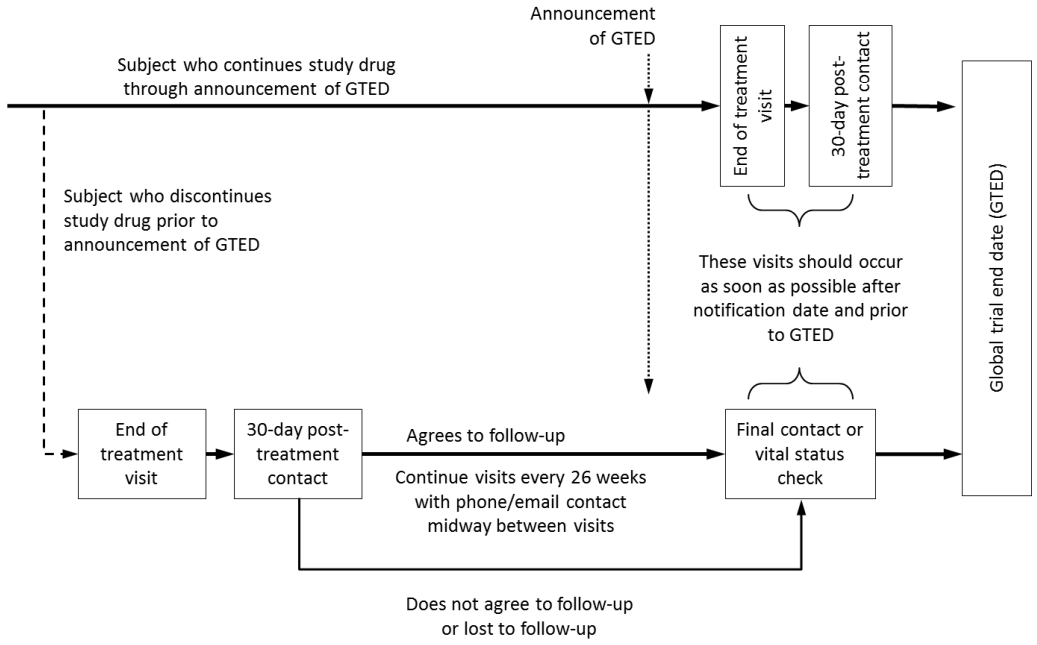
Figure 1 shows an overview of the study design and Figure 2 shows the scheduled follow-up of randomized subjects prior to the GTED.

Figure 1: Diagram of Study Design



AHA=antihyperglycemic agent; CV=cardiovascular; HbA_{1c}=hemoglobin A_{1c}; GTED=global trial end date; R=randomization; SU=sulfonylurea; 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.

1.2. Randomization

Subjects were stratified into one of 6 predefined strata based on AHA use at the run-in visit through to the randomization visit. The investigators were instructed to hold AHA use constant through Week 18 and to adjust the subject's AHA regimen after Week 18 so as to achieve target glycemic control throughout the remainder of the study.

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared by the sponsor before the study. The randomization was balanced by using randomly permuted blocks and was stratified based on the use of specific concomitant AHA medications at baseline.

1.3. Trial Objectives

1.3.1. Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- To assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the HR for a composite endpoint (MACE including CV death, nonfatal MI, or nonfatal stroke);
- To assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care.

1.3.2. Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at the end of the treatment period on:

- Fasting measures of beta-cell function (HOMA-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at sites that elected to participate, including only subjects who did not receive insulin at randomization);
- The proportion of subjects with progression of albuminuria (progression defined as the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria);
- Urinary albumin/creatinine ratio (ACR);
- Change from baseline in estimated glomerular filtration rate (eGFR);
- Change from baseline in HbA_{1c} and fasting plasma glucose (FPG);
- Change in body weight;
- Change in blood pressure (systolic and diastolic);
- Change in fasting plasma lipids (triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C).

1.3.3. Exploratory Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

- Hospitalization for heart failure;
- The composite of hospitalization for heart failure or CV death;
- 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;

- Progression of albuminuria (defined as 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;
- Regression of albuminuria (regression defined as 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 an ACR value decrease of greater than or equal to 30% from baseline;
- 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.

1.4. Statistical Hypotheses

The following hypotheses are specified in the study protocol, however they are considered to be exploratory in the canagliflozin CV outcome consisting of CANVAS and CANVAS-R. The hypotheses in this trial are not included as part of the testing sequence of the program. Accordingly, any p-value reported will be considered as nominal and 95% confidence intervals (CIs) for the treatment effect will be presented for descriptive purposes.

In subjects with T2DM with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care:

- Reduces CV risk (as measured by the HR for MACE including CV death, nonfatal MI, and nonfatal stroke);
- Improves beta-cell function (change from baseline in HOMA-B) at the end of the treatment period;
- Reduces progression of albuminuria (ie, proportion of subjects with a ≥1-step progression of albuminuria measured by the urine ACR) at the end of the treatment period.

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 analyses (eg, adverse events [AEs]) and the 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.

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.

Safety data collection in CANVAS was streamlined after protocol amendment INT-6 (effective starting on 07 January 2014) such that AEs were only collected if they were serious or leading to study drug discontinuation, with the exception of selected AEs of interest. For the purpose of summarizing safety data *prior* to amendment INT-6, the On-Treatment Pre-INT6 analysis set was created as described below.

Table 1: Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date (refer to Section 2.3.2) up to the GTED
On-Study	Treated subjects	Day 1 to the last trial contact date (see Section 2.3.1) up to GTED
On-Treatment	Treated subjects	Day 1 to the last dose date (refer to Section 2.3.2) plus X[a] days or the last trial contact date, whichever is earlier
On-Treatment Pre-INT6	Treated subjects	Day 1 to the last dose date plus X[a] days or the last trial contact date, whichever is earlier, up to 07 January 2014

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

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 (refer to 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 date 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 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.

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 (refer to 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 6	1[c] – 64	43
Week 12	65 – 99	85
Week 18	100 – 155	127
Week 26	156 – 197	183
Week 39	198 – 288	274
Week 52	289 – 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
Week 234	1549 – 1730	1639
Week 260	1731 – 1912	1821
Week 286	1913 – 2094	2003
Week 312	2095 – 2276	2185
Week 338	2277 – 2458	2367
Week 364	2459 – 2640	2549
Week 390	2641 – 2822	2731

[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 (each canagliflozin dose and all canagliflozin group, as well as placebo). Descriptive statistics (N, mean, standard deviation, median, and range) will be provided by treatment group for 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), eGFR, 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 categories:
  - 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 autonomic 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 complete 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 has 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 (<3 week, 3 to <13 week, 13 to <26 weeks, 26 to <52 weeks, 52 to <78 weeks, 78 to <104 weeks, 104 to <130 weeks, 130 to <156 weeks, 156 to <182 weeks, 182 to <208 weeks, 208 to <234 weeks, 234 to <260 weeks, 260 to <286 weeks, 286 to <312 weeks, 312 to <338 weeks, and ≥338 weeks) will also be presented by treatment group as well as overall.

3.5. Prior and Concomitant Medications

Concomitant medication usage is collected on the eCRF at baseline, and during the on-drug period. The number of subjects receiving medication in pre-specified categories will be presented by treatment group at baseline and on-drug period. In addition, SGLT2 inhibitor use during the off-drug follow-up period will also be summarized by treatment group.

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

Additionally, the number and percentage of subjects taking the following concomitant medications at baseline will be summarized by treatment group and overall:

- Baseline insulin use: Yes/No;
- Baseline sulphonylurea use: Yes/No;
- Baseline metformin use: Yes/No;
- Baseline statin use: Yes/No;
- Baseline anti-thrombotic use: Yes/No;
- Baseline diuretic use: Yes/No;
  - Baseline loop diuretic use: Yes/No;
  - Baseline non-loop diuretic use: Yes/No;
- Baseline renin angiotensin aldosterone system (RAAS) inhibitor use: Yes/No.

4. EFFICACY

The primary analysis will be performed based on the ITT analysis set and secondary efficacy endpoints will be based on the On-treatment analysis set, if not otherwise specified.

As noted in Section 1, there will be no formal statistical hypothesis testing and therefore all statistical tests will be considered nominal and reported using a 2-sided 95% confidence level.

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

A tabulation of all the key analyses planned for the CV endpoints and the mortality endpoint is presented in Appendix 1.1.

4.1. Primary Efficacy Endpoint

4.1.1. Definition

The primary efficacy endpoint is the time to MACE (ie, composite of CV death[a], non-fatal MI[b], and non-fatal stroke), which is calculated as the time from Day 1 to the first occurrence of MACE. Adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) will be done in a blinded fashion.

4.1.2. Analysis Methods

The primary analysis will be based on the ITT analysis set for adjudicated MACE. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and

[a] Undetermined death is considered CV death.

[b] Silent MIs are excluded from the analysis.

its 95% CI will be estimated using a stratified Cox proportional hazards model with a term for treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

The percentage of subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported. The cumulative event rate over time will be presented using a Kaplan-Meier plot by treatment (all canagliflozin group and placebo as well as each canagliflozin dose and placebo).

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 $p \leq 0.05$ 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 HR of canagliflozin (all canagliflozin group) compared to placebo and its 95% CI 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;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- 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.

4.1.4. 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-Study Analysis

The stratified Cox proportional hazards model (as described in Section 4.1.2) will be repeated using the On-Study analysis set, in which data of treated subjects from Day 1 to the last trial contact date up to the GTED are used.

The percentage of treated subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported.

4.1.4.2. On-Treatment Analysis

The primary analysis (as described in Section 4.1.2) will be repeated using the On-Treatment analysis set, in which data from Day 1 to 30 days after the last dose of the study drug are used.

4.1.4.3. Additional Supportive Analyses

4.1.4.3.1. MACE in the First 30, 60 and 90 Days

In addition to the Kaplan-Meier plot described in Section 4.1.2, frequency counts (n and %) of subjects experiencing the first occurrence of MACE within the first 30 days, 60 days and 90 days will be provided in the ITT analysis set.

4.1.4.3.2. Hazard Ratio Estimation for Individual MACE Components

A separate analysis will be performed for each individual MACE component (CV death, nonfatal MI, or nonfatal stroke) in both the ITT analysis set and the On-Treatment analysis set. Additionally, analyses of fatal/non-fatal MI as well as fatal/non-fatal stroke will be performed. For subjects who experience more than one MACE component, all events will be counted in the analysis for the relevant component (eg, if a subject has both non-fatal MI and non-fatal stroke, the subject will be counted as having each event). The percentage of subjects who experience each MACE component and the corresponding incidence rate per 1,000 patient-years will be summarized by treatment. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards model with a term for treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

4.1.4.3.3. Assessment of Missing Data

The impact of missing data in the interpretation of the primary efficacy analysis will be explored. For subjects who are lost to follow-up or withdrew consent before the development of a MACE in the ITT analysis set, data collected between the last trial contact date and the GTED will be considered missing.

The proportion of data missing, defined as the ratio of the duration of missing follow-up (eg, days between last contact date + 1 day and the GTED) and the duration of intended follow-up (eg, days between randomization date and the GTED) will be summarized.

Multiple Imputation

The estimate of interest is the hazard ratio to develop MACE among all randomized subjects regardless of adherence to study medication over the period between randomization and the global trial end date (GTED). For subjects who are lost to follow up or withdrew consent before the development of a MACE, data between the last trial contact date and the GTED will be considered missing.

The subjects who discontinued from study medication prematurely prior to the announcement of the GTED can have a different hazard from those who stay on treatment throughout the trial, and their corresponding drop-out could be considered informative. This subpopulation is defined to be the subjects who

- discontinued from study medication prior to the announcement of the GTED, and
- for whom death is not the reason for the discontinuation of study medication.

The data used to model imputed outcomes for subjects with missing data will be those of the subpopulation including the retrieved drop-out data. The definition of the retrieved drop-out data is the follow up data between treatment discontinuation and the GTED. Subjects who developed MACE prior to the treatment discontinuation are included in the subpopulation and their time to MACE data will be used for the imputation modeling. With these subjects included, the model estimate of hazard should fully reflect the potential hazard of the subjects with missing outcome.

A Weibull parametric time to event model (the imputation model) will be fit using the observed time to MACE data from the subpopulation described above. The model will be stratified by study and prior cardiovascular disease (Yes/No), and adjust for treatment and the following covariates potentially correlated with missing mechanism and risk of MACE so that bias due to informative censoring in the estimation of hazard could be minimized and the precision could be optimized.

- Completion of follow up to GTED: Yes/No
- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Baseline use of Metformin: Yes/No;

- History of heart failure: Yes/No;
- Baseline SBP >140 mmHg: Yes/No;
- Baseline $HbA_{1c} \geq 8\%$: Yes/No;

In case the model does not converge, covariates will be removed from the model in the descending order as listed.

For subjects with missing data, follow up time post drop-out will be imputed with random values derived from the conditional distribution of the missing data, given the observed data and the parameters estimated from the imputation model with the pre-specified covariates. If the sum of the observed time and the simulated time is less than the expected follow-up time, ie, from randomization to the GTED, an event is imputed for the corresponding subject. Otherwise, the subjects will be censored at GTED.

The imputed events and follow-up times will be integrated with the observed data. The primary efficacy model will be reanalyzed with the imputed dataset. This process will be repeated 1,000 times. The multiple analysis results will be combined into a single inferential summary (ie, HR and 95% CI) using Rubin's rules.[1]

4.2. Secondary Efficacy Endpoints

4.2.1. Definition

The secondary efficacy endpoints are:

- Change from baseline to the end of treatment in HOMA-B;
- The proportion of subjects with progression of albuminuria at the end of treatment (ie, the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria);
- Change in proinsulin/insulin ratio;
- Change in urinary ACR;
- Change in eGFR;
- Change in HbA_{1c};
- Change in FPG;
- Percent change in body weight;
- Change in blood pressure (systolic and diastolic);
- Percent change in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C).

4.2.2. Analysis Methods

Unless otherwise specified, the analyses for the secondary efficacy endpoints will be using the On-Treatment analysis set. Only subjects with a baseline and at least 1 post-baseline measurement will be included in the analysis.

4.2.2.1. HOMA-B

The analyses for beta-cell function will be conducted in a subset of subjects at sites that elected to participate, including only subjects who are not receiving insulin at randomization. For subjects who initiated insulin during the study, all HOMA-B data after the initiation of insulin will be censored.

Changes in HOMA-B from baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the explanatory variable and baseline HOMA-B value as a covariate. The treatment difference in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

Change from baseline in HOMA-B over time will be analyzed using a mixed model for repeated measures (MMRM) based on restricted maximum likelihood (REML). The analysis will be based on observed data and 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-patient errors. The treatment comparison will be based on the least squares means and the 2-sided 95% CI will be estimated.

Descriptive statistics will be calculated for the change from baseline over time based on observed data.

4.2.2.2. Progression of Albuminuria

The proportion of subjects with progression of albuminuria at the end of treatment will be analyzed using the logistic model with treatment as the explanatory variable and baseline albuminuria status as a covariate. Subjects without baseline and/or post-baseline ACR measurements will be excluded from the analysis. Furthermore, subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis. Baseline ACR value is derived as the geometric mean of all predose ACR measurements. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used for analysis. The odds ratios and the 2-sided 95% CIs for the treatment comparisons will be derived from the model. Albuminuria will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1:[2] microalbuminuria is defined as ACR of 30 to 300 mg/g and macroalbuminuria is defined as an ACR greater than 300 mg/g.

Data obtained up to last dose plus 30 days will be included this analysis.

4.2.2.3. Additional Secondary Endpoints

The analyses for the additional secondary efficacy endpoints will be based on the On-Treatment analysis set. Only subjects with baseline and at least one post-baseline measurement will be included in the analysis.

Changes at the end of treatment from baseline in proinsulin/insulin ratio, eGFR, HbA_{1c}, FPG, blood pressure, percent change in body weight and fasting lipids (HDL-C, LDL-C, triglycerides, total cholesterol, and LDL-C/HDL-C) will be analyzed using an analysis of covariance (ANCOVA) model with treatment and the corresponding baseline value as covariates. The treatment difference in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

Given the skewed nature of the ACR, the analysis will be performed similarly as described above on the log scale. 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.

Only subjects with baseline and at least one post-baseline measurement will be included in the analysis. The analysis for proinsulin/insulin ratio will be conducted on subjects who are not receiving insulin at randomization. For subjects who are started on insulin during the study, all proinsulin/insulin data after initiation of insulin will be censored.

Given the skewed nature of the distribution of the percent change in triglycerides, this additional secondary endpoint will be analyzed using nonparametric methods as outlined below. A Wilcoxon rank sum test will be performed. The Hodges-Lehman estimator for the difference in the medians and the distribution-free 95% CIs based on the Wilcoxon rank sum test[3] will also be presented.

The change in these additional secondary endpoints from baseline over time will be explored using an MMRM model similar to the one used to analyze the change in HOMA-B (Section 4.2.2.1).

4.3. Multiplicity Adjustment

Per the SAP for the integrated summary, only one alpha is proposed for the testing of the multiple hypotheses based on the integrated data and the data from CANVAS-R alone. The Type I error for these tests will be strictly controlled via a gatekeeping procedure. No alpha is preserved for evaluating hypotheses in CANVAS and all tests will be considered nominal with 2-sided 95% CIs provided for descriptive purposes.

4.4. Exploratory Efficacy Endpoints

4.4.1. Definition

The following exploratory endpoints will be analyzed:

- Time to the first occurrence of hospitalization for heart failure;

- Time to the first occurrence of the composite endpoint of hospitalization for heart failure or CV death;
- Time to all-cause mortality;
- 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;
- Time to first progression of albuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline;
- Time to first regression of albuminuria, accompanied by an ACR value decrease of greater than or equal to 30% from baseline;
- Change in eGFR from baseline to the last off-drug measurement;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements of eGFR made from the first on-drug measurement to the final on-drug measurement.

4.4.2. Analysis Methods

4.4.2.1. CV Endpoints

The analyses of hospitalization for heart failure and the composite of hospitalization for heart failure or CV death will be based on both the ITT analysis set and the On-Treatment analysis set. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) 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 the history of CV disease (secondary and primary prevention) as the stratification factor.

4.4.2.2. All-Cause Mortality

All-cause mortality will be analyzed in both the ITT analysis set and the On-Treatment analysis set using a stratified Cox proportional hazards model with treatment as the explanatory variable and

[a] Adjudicated non-CV death with a renal proximate cause is considered as renal death

history of CV disease (secondary and primary prevention) as a stratification factor. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3. Renal Endpoints

4.4.2.3.1. 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 (refer to Section 4.4.1) will be analyzed in the ITT analysis set using a Cox proportional hazards model with treatment and baseline eGFR ($< 60, \geq 60$ mL/min/1.73m^2) as explanatory variables. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.2. Progression of Albuminuria

For the purpose of an exploratory analysis, progression of albuminuria will be assessed as in Section 4.2.2.2 with the additional condition that it must be accompanied by an increase in ACR value greater than or equal to 30% from baseline. The time to the first occurrence of the event will be analyzed in the ITT analysis set using a Cox proportional hazards regression model with treatment and baseline albuminuria status as the explanatory variables, excluding subjects with baseline macroalbuminuria. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.3. Regression of Albuminuria

Regression of albuminuria is defined as at least a one stage improvement of albuminuria, accompanied by an ACR value decrease of greater than or equal to 30% from baseline. The time to the first occurrence of the event will be analyzed in the ITT analysis set, using a Cox proportional hazards regression model with treatment and baseline albuminuria status as the explanatory variables, excluding subjects with baseline normal albuminuria. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.4. 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), treatment by time interaction as fixed effects, and intercept and time as random effects. The parameter of interest is the coefficient for the treatment-by-time interaction term, which measures the slope difference between canagliflozin and placebo over time. Data will be censored at the date of last study medication plus 2 days.

5. SAFETY

Unless otherwise specified, 2 sets of summaries of AEs will be provided. The first set will be based on the data collected up to 07 January 2014 when INT-6 was first approved. The second set of summaries will focus on the serious AEs and AEs leading to study drug discontinuation throughout the entire study periods.

All other safety analyses and summaries (laboratory tests and vital signs) will be based on data collected throughout the entire study period using either the On-Treatment analysis set or the On-Treatment Pre-INT-6 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 and there will be no hypothesis testing for results from safety analyses.

The treatment groups will be canagliflozin 100 mg, canagliflozin 300 mg, all canagliflozin, and placebo.

5.1. Adjudicated MACE Events

Please refer to Section 4.1 for the primary efficacy analysis of adjudicated MACE events.

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

5.2.1. Adverse Event Collection

As one of the initial studies in the Phase 3 program, CANVAS was designed to collect detailed information on AEs. Upon the approval of canagliflozin in the United States, the safety profile of canagliflozin had been well established. The AE collection was then streamlined following the approval of INT-6 to include only:

- Serious adverse events (SAEs);
- Adverse events that resulted in study drug discontinuation;
- All AEs (serious and non-serious) for AEs of interest (refer to Table 3 below).

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

Table 3: Adverse Events of Interest

Section A. All AEs (serious and non-serious) listed below were collected in CANVAS through INT-6. After INT-6, only the AEs that were serious or that led to study 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 entire 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 (DKA)

The AEs listed above will be identified using a MedDRA preferred term list (Appendix 1.4).

5.2.2. Analysis Methods

The study duration of CANVAS is long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting an AE) reported from this study are not comparable to the incidences generated in the Phase 3 program. Therefore, the exposure-adjusted incidence rate will also be reported in addition to the incidence. The exposure-adjusted incidence 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 related AE divided by the follow-up time in subject-years.

For general AEs and selected AEs of interest that are not routinely collected (refer to Section A of Table 3) after implementation of INT-6, the focus of the summary will be the serious AEs and the AEs leading to discontinuation of study medication.

5.2.2.1. General Adverse Events

Prior to the Approval of INT-6

On-Treatment Pre-INT6 analysis set will be used for the summary of general AEs prior to the approval of INT-6 unless otherwise specified.

The overall incidence and the exposure-adjusted incidence rate of AEs, AEs leading to discontinuation, drug-related AEs, drug-related AEs leading to discontinuation, SAEs, SAEs leading to discontinuation, serious drug-related AEs, serious drug-related AEs leading to discontinuation, and deaths will be summarized by treatment group.

AEs by System Organ Class (SOC) 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 SOC, and presented by treatment group. In addition, the incidence of severe AEs and drug-related AEs (possibly related, probably related and very likely related, as reported by the investigator) will be summarized by preferred term, grouped by SOC, and presented by treatment group). The incidence of AEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the action taken regarding the study medication, as well as by the outcome.

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 subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT).[4] 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 the 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 subject to further evaluation.

Through the Entire Study

Serious AEs and the AEs leading to discontinuation collected throughout the entire study will be analyzed based on On-Treatment analysis set unless otherwise specified.

An overview summary table with the incidence and the exposure-adjusted incidence will be generated 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 SOC and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AEs 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 (regardless of seriousness) which are reported in at least 4 or more subjects in any treatment group. Only the AEs identified by the above screening procedure will be presented and 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 (with the exception of hypoglycemia, see Section 5.2.2.3), 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 1.4.

5.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will be based on On-Treatment analysis set only.

Using 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 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 based on blinded medical review of the clinical database prior to the database lock and summarized by treatment group.

Based on the additional information collected on the designated supplemental eCRF page in CANVAS, the following additional study-specific analyses will be performed:

- The incidence of male subjects with any genital mycotic infections will be summarized by treatment group and by circumcision status.
- Descriptive statistics (N, mean, SD, median, and range) will be calculated by treatment group for the duration (days) and severity (grouped as mild or moderate vs. severe) of all infections. If a subject experienced multiple events, all durations will be included in the summary.
- Descriptive statistics (N, mean, SD, median, and range) will be calculated by treatment group for the number of days from start of the AE treatment to the resolution of the symptoms.

5.2.2.3. Hypoglycemia

Hypoglycemia episodes were collected by a specific, dedicated eCRF for all hypoglycemia up to INT-6. Hypoglycemia episodes reported on the supplemental eCRF up to 07 January 2014 will be analyzed based on On-Treatment Pre-INT6 analysis set. For hypoglycemia reported on the general AE page throughout the study period, focus will be the serious events or the events leading to study drug discontinuation.

Prior to the Approval of INT-6

A subject will be counted as having a documented hypoglycemia episode when there is either a biochemically documented 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 the assistance of others to treat?", "Did the subject lose consciousness during the episode?", or "Did the subject have a seizure during the episode?"

Only treatment emergent hypoglycemia episodes, reported on the eCRF for hypoglycemia, will be summarized. Treatment emergent is defined the same way as TEAEs (defined in Section 5.2).

The percentages 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 3 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. The

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 summarized (this includes events without concurrent fingerstick glucose reported and events with fingerstick glucose > 70 mg/dL [3.9 mmol/L]) by treatment group.

Through the Entire Study

Using the On-Treatment analysis set, an overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs;
- 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 preferred term will be summarized by treatment group.

5.2.2.4. 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 1.4 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.

5.2.2.5. Photosensitivity

Photosensitivity AE will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will use 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.

5.2.2.6. Venous Thromboembolic Events

Venous thromboembolic (VTE) events will be identified using the list of MedDRA terms in Appendix 1.4. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC for confirmation. The analyses will use the On-Treatment analysis set of adjudicated VTEs. Additionally, a similar analysis of investigator reported VTE events will also be provided.

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.

The incidence of VTEs identified by the MedDRA preferred terms listed in Appendix 1.4 will also be summarized by preferred term. A summary table of all VTEs (regardless of adjudication) will also be provided by preferred term.

5.2.2.7. 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, to determine fracture location (anatomic region) and type (low trauma or not). The main analysis will be based on the adjudicated low trauma fractures in 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.

A Kaplan-Meier plot for the time to the first occurrence of adjudicated fracture event will be provided by treatment group. The HR and the 95% CI will be derived from a Cox proportion hazards model with a term for treatment as an explanatory variable. The HR will be estimated in subgroups based on sex, baseline age (<65 and ≥65 years), duration of T2DM (<10 and ≥10 years), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and prior fracture history (yes or no).

A summary of all adjudicated fractures by anatomic location will be provided. The HR 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 low trauma fracture.

5.2.2.8. Amputation

The main analysis of lower extremity amputations as documented in the dedicated eCRF 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:

- 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. The association of amputation with treatment and the baseline risk factors listed in Table 4 will be assessed via logistic regression modeling. The relationship between amputation and some post-treatment factors such as volume depletion will also be explored.

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 1.5:

- 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. Stratified by treatment, the odds ratio of amputation and each AE group listed above will be estimated.

Table 4: Baseline Factors Included in the Logistic Regression Analysis

Baseline Categorical Factors	

• Gender
• Cardiovascular disease history
• Peripheral vascular disease history [a]
• Amputation history
• Neuropathy history
• Retinopathy history
• Nephropathy history
• Any diuretic use
• Loop diuretic use
• Non-loop diuretic use
	• Smoking
	• Use of insulin
	• Baseline Systolic Blood Pressure
	  ○ > 120 vs ≤120 mmHg
	  ○ > 140 vs ≤140 mmHg
	• Baseline eGFR (ml/min/1.73m^2)
	  ○ < 60 vs ≥60
	  ○ < 45 vs ≥45
	• Diabetes duration (< 10 vs ≥10 yrs.)
	• Baseline HbA_{1c} (> 8 vs ≤8%)

Baseline Continuous Factors	
• Age (yrs.) • Diabetes duration (yrs.) • Systolic blood pressure (mmHg)	• eGFR (mL/min/1.73m^2) • HbA_{1c} (%) • Hemoglobin (g/L)

[a] Excludes amputation history

5.2.2.9. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 1.4. 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 events identified by the sponsor's medical monitoring team and the subset of the events that went for adjudication will be provided.

5.2.2.10. 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 1.2. The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 1.3 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to the placebo group will be provided for each PDLC criterion which has 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 listed in Appendix 1.3. 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 drug.

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

The decision was made to stop collecting ECG measurements after Week 52 since INT-6. The analyses will use all the ECG data available up to the approval of INT-6. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc using the Fridericia (QTcF) correction methods. The QTcF corrected interval values are based on the following formula:[5]

- *Fridericia*: QTcF (msec) = QT(msec) * (HR(bpm)/60)1/3.

The PDLC criteria for defining an ECG abnormality for PR interval, QRS interval, QTcF values, and changes from baseline within each category are listed in Appendix 1.3. The number and the percentage of subjects in each category will be summarized by treatment group up to 2 days after the last dose of study drug.

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5. Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. *Acta Medica Scandinavica.* 1920; 53:469 – 486.

APPENDIX

Appendix 1.1: List of Key Analyses of CV and Mortality Endpoints

Analysis Set	Endpoint	Section
Primary Efficacy Assessment of MACE		
ITT	MACE	4.1.2
On-Study	MACE	4.1.4.1
On-Treatment	MACE	4.1.4.2
ITT	MACE components	4.1
On-Treatment	MACE components	4.1
ITT	Subgroup analysis of MACE	4.1.3
Exploratory Assessment of Additional CV Endpoints		
ITT	Hospitalization for heart failure	4.4.2.1
On-Treatment	Hospitalization for heart failure	4.4.2.1
ITT	Composite of hospitalization for heart failure or CV Death	4.4.2.1
On-Treatment	Composite of hospitalization for heart failure or CV Death	4.4.2.1
ITT	All-cause Mortality	4.4.2.2
On-Treatment	All-cause Mortality	4.4.2.2

Appendix 1.2: 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:

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

Appendix 1.3: Pre-defined Limit of Change (PDLC) Criteria

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: >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
ECG PARAMETERS	
QTcF	
	Change: >30-60 ms
	Change: >60 ms
	Absolute Value: > 450-480 ms
	Absolute Value: > 480-500 ms
	Absolute Value: >500 ms
PR Interval	Absolute Value: ≥ 200 ms
QRS Interval	Absolute Value: ≤ 50 ms
	Absolute Value: ≥ 120 ms

Appendix 1.4: 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		
Cholestatic pruritus		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
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		
Jaundice hepatocellular		
Liver and small intestine transplant		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
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	
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
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	
	Oculomucocutaneous syndrome	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	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
Ureteritis	Pulmonary thrombosis	
Uretheritis	Renal vein embolism	

UTI	Venous Thromboembolic events	Volume Depletion
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 1.5: Adverse Events with Potential Amputation Association

List of selected preferred terms included within the SOCs 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		
Localised infection		
Skin infection		
Soft tissue infection		
Staphylococcal skin infection		
Subcutaneous abscess		
Wound		
Wound abscess		
Wound dehiscence		
Wound infection		