

Janssen Research & Development, LLC*

Clinical Protocol

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

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

Protocol 28431754DIA4003; Phase 4
AMENDMENT INT-5**

JNJ-28431754 (canagliflozin)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; or Janssen_Research & Development, LLC. The term “sponsor” is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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

Status: Approved
Date: 1 September 2016
Prepared by: Janssen Research & Development, LLC
EDMS No & Version: EDMS-ERI-65832346, 8.0
EudraCT No.: 2013-003050-25

GCP Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you that is indicated as *privileged* or *confidential*.

TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF ATTACHMENTS	4
LIST OF IN-TEXT FIGURES	4
PROTOCOL AMENDMENTS	5
SYNOPSIS	10
TIME AND EVENTS SCHEDULE: PRETREATMENT AND DOUBLE-BLIND TREATMENT	15
ABBREVIATIONS	20
1. INTRODUCTION	21
1.1. Background	22
1.1.1. Nonclinical Studies	22
1.1.2. Clinical Studies	23
1.2. Overall Rationale and Goals for the Study	28
2. OBJECTIVES AND HYPOTHESES	32
2.1. Objectives	32
2.2. Hypotheses	33
2.2.1. Primary Hypothesis	33
2.2.2. Secondary Hypotheses	33
3. OVERVIEW OF STUDY DESIGN	33
3.1. Study Design	34
3.2. Study Design Rationale	38
4. STUDY POPULATION	39
4.1. General Considerations	39
4.2. Inclusion Criteria	39
4.3. Exclusion Criteria	41
4.4. Prohibitions and Restrictions	43
4.5. Rescreening	43
5. TREATMENT ALLOCATION	43
6. DOSAGE AND ADMINISTRATION	44
6.1. Study Drugs	44
6.2. Concomitant Antihyperglycemic and Other Therapies	45
6.2.1. Management of Glycemic Control and CV Risk Factors	45
7. TREATMENT COMPLIANCE	46
8. PRESTUDY AND CONCOMITANT THERAPY	47
9. STUDY EVALUATIONS	47
9.1. Study Procedures	47
9.1.1. Overview	47
9.1.2. Pretreatment Phase	49
9.1.3. Double-Blind Treatment Phase	49
9.1.4. Post-Treatment Follow-up for Participants who Withdraw from Randomized Treatment Early	50
9.1.5. Post-Treatment Follow-up for Participants that Complete Randomized Treatment as Initially Scheduled	50

9.1.6.	Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits.....	51
9.2.	Reporting/Adjudication of MACE and Other Events for Adjudication	51
9.3.	Study Management: Committees.....	52
9.3.1.	Academic Research Organization	52
9.3.2.	Steering Committee	52
9.3.3.	Medical Safety Review Committee.....	52
9.3.4.	Independent Data Monitoring Committee.....	52
9.3.5.	Endpoint Adjudication Committee	52
9.4.	Safety Evaluations	53
9.5.	Measures of Efficacy/Efficacy Endpoints	55
10.	SUBJECT COMPLETION, PREMATURE DISCONTINUATION OF TREATMENT, LOSS TO FOLLOW-UP AND WITHDRAWAL OF CONSENT	56
10.1.	Subject Completion	56
10.2.	Premature Discontinuation of Study Medication	56
10.3.	Reinstitution of Treatment for Subjects Who Have Prematurely Discontinued Double-Blind Study Drug to Active Status	57
10.4.	Lost to Follow-up.....	57
10.5.	Circumstances for Reduced Follow-up	57
10.6.	Withdrawal of Consent	58
11.	STATISTICAL METHODS.....	58
11.1.	Analysis Sets.....	58
11.2.	Sample Size Determination	58
11.3.	Efficacy Analyses	59
11.3.1.	Primary Efficacy Analysis	59
11.3.2.	Secondary Efficacy Analyses	59
11.3.3.	Exploratory Efficacy Analyses	60
11.3.4.	Multiplicity Adjustment	60
11.4.	Safety Analyses	61
12.	ADVERSE EVENT REPORTING	62
12.1.	Definitions	64
12.1.1.	Adverse Event Definitions and Classifications	64
12.1.2.	Attribution Definitions.....	65
12.1.3.	Severity Criteria	65
12.2.	Procedures.....	66
12.2.1.	All Adverse Events.....	66
12.2.2.	Serious Adverse Events	68
12.2.3.	Pregnancy.....	68
12.3.	Contacting Sponsor Regarding Safety.....	69
13.	PRODUCT QUALITY COMPLAINT HANDLING.....	69
13.1.	Procedures.....	69
13.2.	Contacting Sponsor Regarding Product Quality	69
14.	STUDY DRUG INFORMATION.....	69
14.1.	Physical Description of Study Drug(s)	69
14.2.	Packaging	69
14.3.	Labeling.....	70
14.4.	Preparation, Handling, and Storage.....	70
14.5.	Drug Accountability	70
15.	STUDY-SPECIFIC MATERIALS.....	70
16.	ETHICAL ASPECTS	71
16.1.	Study-Specific Design Considerations.....	71
16.2.	Regulatory Ethics Compliance.....	72
16.2.1.	Investigator Responsibilities	72

16.2.2.	Independent Ethics Committee or Institutional Review Board (IEC/IRB).....	73
16.2.3.	Informed Consent	74
16.2.4.	Privacy of Personal Data	75
16.2.5.	Country Selection	75
17.	ADMINISTRATIVE REQUIREMENTS	76
17.1.	Protocol Amendments.....	76
17.2.	Regulatory Documentation	76
17.2.1.	Regulatory Approval/Notification	76
17.2.2.	Required Prestudy Documentation.....	76
17.3.	Subject Identification, Enrollment, and Screening Logs	77
17.4.	Source Documentation.....	77
17.5.	Case Report Form Completion	78
17.6.	Data Quality Assurance/Quality Control	78
17.7.	Record Retention	79
17.8.	Monitoring	79
17.9.	Study Completion/Termination.....	80
17.9.1.	Study Completion	80
17.9.2.	Study Termination.....	80
17.10.	On-Site Audits	80
17.11.	Use of Information and Publication	81
	REFERENCES.....	83
	INVESTIGATOR AGREEMENT	86
LIST OF ATTACHMENTS		
Attachment 1:	Clinical Laboratory Tests	85
LIST OF IN-TEXT FIGURES		
FIGURES		
Figure 1:	Mean Change in eGFR Over Time (DIA3009)	29
Figure 2:	Mean Change in eGFR Over Time (DIA3004)	30
Figure 3:	Hypotheses Regarding the Effect of ACEI and ARBs on the Progression of Diabetic Nephropathy	31
Figure 4:	Study Design Outline	35
Figure 5:	Follow-up of Randomized Subjects with Respect to the GTED	36

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	27 September 2013
INT-1	16 October 2013
INT-2	20 December 2013
INT-3	17 September 2015
INT-4	05May 2016
INT-5	01 September 2016

Amendments are listed beginning with the most recent amendment.

Amendment INT-5 (01 September 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason to amend the study protocol is to add secondary cardiovascular objectives and exploratory renal objectives.

Applicable Section(s)	Description of Change(s)
Rationale: Added secondary cardiovascular objectives to assess cardioprotective effects of canagliflozin and added exploratory renal objectives.	
Synopsis Section 2. Objectives and Hypotheses, Section 11.3.2. Secondary Efficacy Analyses Section 11.3.3. Exploratory Efficacy Analyses Section 11.3.4. Multiplicity Adjustment Section 11.4. Safety Analyses	Added secondary cardiovascular objectives of the composite endpoint of cardiovascular death or hospitalization for heart failure, and cardiovascular death. Added exploratory renal composite endpoints. Under ‘Multiplicity Adjustment’, removed statements about CV meta-analysis being pre-specified in the SAP for this study, and that the CV meta-analysis SAP will be pre-specified in a separate document, since these statements are not necessary and unrelated to the multiplicity adjustment.
Rationale: Added checkmark for foot care guidance that was erroneously omitted.	
Time and Events Schedule; footnote “h”	Added checkmark for foot care discussion/assessment and provision of foot care guidance during phone/email contact midway between 26-week visits until last on-treatment visit.
Rationale: Added rationale for expanded secondary CV objectives.	
Section 1.2: Overall rationale and goals for the study	Added rationale for expanded CV secondary objectives and exploratory renal objectives, including a brief summary of EMPA-REG OUTCOME data with empagliflozin.

Amendment INT-4 (05 May 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason to amend the study protocol is to include new safety information and guidance regarding subject management surrounding the event of lower extremity amputations.

Applicable Section(s)	Description of Change(s)
Rationale: Include guidance regarding subject management surrounding the event of lower extremity amputations.	
Time and Events Schedule footnote “f”; footnote “n” Section 12.2.1. All Adverse Events	Added foot examination to be consistent with standard diabetes treatment guidelines. Added guidance regarding foot care and reducing risk of amputation.
Rationale: To address a request from a Health Authority	
Time and Events Schedule (posttreatment)	Added collection of AHAs after study drug discontinuation
Rationale: To address a request from a Health Authority.	
Section 9.4. Safety Evaluations	Events with characteristics of DKA will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA.
Rationale: Include new safety information and guidance regarding subject management surrounding the event of lower extremity amputations.	
Section 1.1.2. Clinical Studies; Section 6.1. Study Drug;	Added amputation data from IDMC. Added statement that study drug should be interrupted for subjects who develop conditions that are associated with or leading to amputation.
Time and Events Schedule footnote “f” Section 3.1. Study Design; Section 9.4. Safety Evaluations Section 12. Adverse Event Reporting Section 12.2.1. All Adverse Events Section 16.1. Study- Specific Design Considerations	An additional AE of special interest was added, "amputations".
Rationale: Minor errors were noted.	
Throughout the protocol.	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-3 (17 September 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: In response to Agence Nationale de Securite de Medicament et des Produits de Sante (ANSM)- France IB addendum 2 - Canagliflozin - where a request to amend the study protocol to include diabetic ketoacidosis (DKA) safety information and handling of subjects surrounding this event.

Applicable Section(s)	Description of Change(s)
Rationale: To provide clarification of the urinary albumin/creatinine ratio (ACR) analysis and expand analysis scope for ACR to cover all the post-baseline data.	
Synopsis: Efficacy Outcome/Evaluation Criteria Primary Outcomes Secondary Outcomes Primary Efficacy Analysis Secondary Efficacy Analyses Section 2.1 Secondary Objectives Section 11.3.2 Efficacy Analysis	Additional wording and more detailed descriptions added
Rationale: To expand analysis scope for post-treatment eGFR to cover all the post-treatment data	
Synopsis: Secondary Objective Secondary Outcomes Secondary Efficacy Analyses Section 2.1 Secondary Objectives Section 11.3.2 Efficacy Analysis	Additional wording and more detailed descriptions added
Rationale: To remove a previously introduced error in the footnotes	
Time & Events Schedule Footnote “k”	Footnote was removed from the double-blind treatment period.
Rationale: Balanitis was added as an AE of interest and DKA as an AE of special interest to obtain and collect safety information surrounding these events.	
Time & Events Schedule Footnote “l”; Section 3.1 Study Design; Section 9.4 Safety Evaluations; Section 12 Adverse Event Reporting; Section 12.2.1 All Adverse Events; Section 16.1 Study-Specific Design Considerations	An AE of interest “male genital infections (balanitis, phimosis, events leading to circumcision)” and AE of special interest “Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page” were added; the statement “If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.” was added.
Rationale: To provide the most up to date data results of safety findings.	
Section 1.1.2. Clinical Studies	Additional paragraph added stating additional AE results as of 11, May 2015.

Applicable Section(s)	Description of Change(s)
Rationale: To provide clarification on study drug interruption	
Section 6.1 Study Drugs	Additional wording added to last paragraph to clarify study drug interruption requirements.
Rationale: To include an experience of a serious confirmed adverse event of diabetic DKA to the list of reasons for premature discontinuation of study drug.	
Section 10.2 Premature Discontinuation of Study Medication	The sentence “The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA” was added.
Rationale: To preserve the original randomization, the analysis set for primary analysis of all efficacy endpoints is intent-to-treat (ITT) and secondary is modified intent-to-treat (mITT/On-treatment) if applicable.	
Synopsis: Analysis Set	ITT set is added and analysis sets for primary and secondary efficacy analysis are clarified.
Section 11.1 Analysis Set	
Rationale: To provide guidance on the monitoring and management of DKA.	
Section 12.2.1 All Adverse Events	A paragraph was added: “Study research staff should make study subjects aware of potential signs and symptoms of diabetic ketoacidosis such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to diabetic ketoacidosis (even if the subject’s blood glucose levels are less than 250 mg/dL [13.9 mmol/L]), testing for urine or blood ketones should be considered.”
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical or formatting changes were made.
Amendment INT-2 (20 December 2013)	
This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.	
The overall reason for the amendment: The overall reason for the amendment is to add a baseline (Day 1) urinalysis measurement to provide baseline health status information and safety data.	
Applicable Section(s)	Description of Change(s)
Rationale: A baseline (Day 1) urinalysis measurement was added to provide baseline health status information and safety data.	
Time & Events Schedule	A spot urine collection at the clinic was added at Day 1. (Footnote “g” was also modified to add this procedure.)
Rationale: An inconsistency between a footnote and the text was noted.	
Time & Events Schedule footnote “h”	The timeframe to return a first morning void specimen to the site (if not provided on the day of the visit) was corrected to 7 days (previously 30 days).

Applicable Section(s)	Description of Change(s)
	Rationale: A baseline (Day 1) urinalysis measurement was added to provide baseline health status information and safety data.
	Rationale: New canagliflozin protocols have added additional bone mineral density data.
Section 1.1.2. Clinical Studies	Further clarification of the bone mineral density data in the 28431754DIA3010 study at Week 104 was made to ensure consistency in the description with other canagliflozin protocols.
	Rationale: An update to Attachment 1 was needed to align with updates in the Time & Events schedule for urinalysis.
Attachment 1: Clinical Laboratory Tests	Baseline (Day 1) urinalysis was added.
Amendment INT-1 (16 October 2013)	
This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.	
The overall reason for the amendment: The overall reason for the amendment is to ensure consistency with the standard protocol template text in the sections listed below.	
Applicable Section(s)	Description of Change(s)
Section 12.2.3, Pregnancy	Was removed: <i>“If a subject’s partner becomes pregnant any time between the start of study drug and 30 days after the last dose, the subject must inform the investigator as soon as possible.”</i>
Section 14.5, Drug Accountability	<i>“Study drug returned...”</i> was replaced with <i>“All study drug...”</i> Was added: <i>“Returned study drug must not be dispensed again, even to the same subject.”</i>
Section 16.2.2, Independent Ethics Committee or Institutional Review Board (IEC/IRB)	Was added throughout the section: <i>“...excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct...”</i>
Section 17.3, Subject Identification, Enrollment, and Screening Logs	<i>“...by initials and assigned number only...”</i> was replaced with <i>“...by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.”</i>
	Rationale: Minor errors were noted
Throughout the protocol	Minor grammatical or formatting changes were made.

SYNOPSIS

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

EUDRACT number: 2013-003050-25

PREAMBLE

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM).

In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy.

OBJECTIVES AND HYPOTHESES

Primary objective

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

Secondary objectives

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

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

Exploratory objectives

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

- Regression of albuminuria. Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary albumin creatinine ratio (ACR) value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of regression described above, a repeat ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. If the last value meets the definition of regression and no repeat ACR collection can be made, the subject will also be deemed to have regressed. Analyses using single ACR, as well as duplicate ACR assays will be performed.
- Change in estimated glomerular filtration rate (eGFR) from baseline to the last off-treatment value
- Urinary albumin/creatinine ratio (ACR)
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-treatment measures of eGFR made from the first on-treatment measurement to the final on-treatment measurement
- Changes in HbA_{1c}

- Utilization of AHA therapy
- The composite endpoint of 40% reduction in eGFR, renal death, or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, renal death, or requirement for renal replacement therapy
- The composite endpoint of 40% reduction in eGFR, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of doubling of serum creatinine, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of 40% reduction in eGFR, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy

Safety objective

Cardiovascular safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS; 28431754DIA3008; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus; NCT01032629) in a pre-specified meta-analysis of CV safety outcomes.

Hypotheses

Primary hypothesis

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

Secondary hypotheses

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

- Reduces the composite endpoint of death from CV causes or hospitalization for heart failure
- Reduces death from CV causes

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study's last subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of follow-up or when 688 major adverse cardiovascular events (MACE) events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R (DIA4003) studies (estimated to occur between January 2017 and April 2017). The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

STUDY POPULATION

Men or women with T2DM who have inadequate glycemic control ($HbA_{1c} \geq 7.0$ and $\leq 10.5\%$) with either a history of a prior CV event or 2 or more risk factors for a CV event are eligible. Subjects can be included whether they are drug naïve to antihyperglycemic agents, using monotherapy, or using combination antihyperglycemic therapy for the control of blood glucose levels.

DOSAGE AND ADMINISTRATION

Study Drugs

Upon successful completion of screening, all potentially eligible individuals will enter a 2-week run-in period, during which they will receive single-blind placebo capsules (one capsule to be taken once-daily) to assess compliance.

Individuals that meet inclusion/exclusion criteria and that are compliant during run-in will be randomly assigned in a 1:1 ratio to canagliflozin or matching placebo to be taken once daily, before the first meal of the day. Canagliflozin will be provided at the dose of 100 mg/day through Week 13 and then increased at the discretion of the investigator at Week 13 or a subsequent visit to the dose of 300 mg/day, if the subject requires additional glycemic control and is tolerating the 100 mg dose (see Section 3.1). All study drug after randomization will be provided in a double-blind manner.

EFFICACY OUTCOME DEFINITIONS/EVALUATION CRITERIA

Primary outcomes

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

The primary outcome is progression of albuminuria (as defined above). If the ACR at a visit meets the definition of progression described above, a repeat ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. If the last value meets the definition of progression and no repeat ACR collection can be made, the subject will also be deemed to have progressed. Analyses using single ACR, as well as duplicate ACR assays will be performed. Detail about the primary and sensitivity analysis approaches will be specified in the SAP.

ACR assessments will be based upon values obtained from first morning void urines analyzed by the central laboratory. In this study, duplicate urine specimens will be collected for all ACR measurements.

Secondary outcomes

The secondary outcomes are:

- Composite endpoint of death from CV causes or hospitalization for heart failure
- Death from CV causes

Safety outcomes

The data from this study will be combined with the data from another large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of CV safety outcomes to satisfy the US FDA Post Marketing Requirements.

STATISTICAL METHODS

Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects who are randomized via the Interactive Web Response System (IWRS). The assessment of the primary and most of the secondary objectives will be based upon this analysis set.

The modified intent-to-treat (mITT) or On-Treatment analysis set includes all subjects who are randomly assigned to a treatment group and receive at least one dose of double-blind study. It will be used in the analyses assessing on-treatment effects, e.g. time slope of on-treatment eGFR.

Sample Size Determination

Based on the interim data from the CANVAS study, where ACR was measured periodically at scheduled visits, it is projected that the annual progression rate for the CANVAS-R study will be approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month accrual period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it is estimated that 693 events of ACR progression will be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression is 90.5%, with type I error rate of 0.05 (two-sided).

Primary efficacy analysis

In this study, duplicate urine specimens will be collected for all ACR measurements. At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analysis unless otherwise specified.

Subjects will be classified as having normoalbuminuria (urinary ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥ 3.5 mg/mmol [≥ 30 mg/g] and ≤ 35 mg/mmol [≤ 300 mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]).

The primary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of albuminuria progression relative to placebo.

The time from first study drug administration to first visit date observing progression (i.e., not using the visit date of the repeat sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The model will include treatment and baseline albuminuria status as covariates. The hazard ratio between canagliflozin and placebo will be provided, including its 95% confidence interval. The observation period for this time-to-event analysis will include all available measurements from first study drug administration to the visit date of the last ACR measurement. Subjects with no progression will be censored at the visit date of the last albuminuria measurement.

As a sensitivity analysis, the actual onset time of progression of albuminuria can be determined to be within an interval from a sequence of examination times (ie, data are interval censored). As a supportive analysis, the accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring. The dependent variable in AFT model is the logarithm of time to progression of albuminuria. The model will include treatment group and baseline albuminuria status as covariates. We can use speed of progression to interpret AFT model. For any time (t), the probability of a subject on placebo progression-free beyond time t is the probability of a subject on canagliflozin progression-free beyond t/α , where α is the acceleration factor which can be estimated from the model. Additional sensitivity analyses will be specified in the study Statistical Analysis Plan (SAP).

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

Secondary efficacy analyses

The secondary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of the following CV events relative to placebo.

- Composite of CV death or hospitalization for heart failure
- CV death

The analysis of these CV endpoints will be based on the time to first occurrence of the events using the ITT analysis set. The hazard ratio of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factor.

Exploratory efficacy analyses

Regression of albuminuria will be analyzed in a similar fashion as the analysis for progression of albuminuria.

For change in eGFR from baseline to the off-treatment measurement, an analysis of covariance (ANCOVA) model will be used with treatment as a fixed effect and adjusting for the baseline eGFR value. The treatment difference in the least-squares means and their 2-sided 95% CI will be estimated.

Since the distribution of ACR is highly skewed, the log-transformed ACR values for all the post-baseline and scheduled visits will be modeled using a linear mixed effect model. The model will include treatment group and logarithm of baseline ACR value, visit, and treatment-by-visit interaction as fixed effects. The percentage treatment difference can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1.

For on-treatment eGFR measurements, a linear mixed effects model will be fitted to eGFR as a dependent variable, including treatment, baseline eGFR value, time (as a continuous variable), and treatment time interaction as fixed effects and including subject effect as a random intercept and time as a random slope. The parameter of interest is the coefficient for treatment and time interaction term, which measures the slope difference between canagliflozin and placebo.

The effect of canagliflozin relative to placebo on changes in HbA_{1c} over time will be evaluated using a linear mixed effects model. The use of AHA therapy over time will also be summarized by treatment group.

Safety analyses

The CV safety data from this study will be evaluated in conjunction with the data from the CANVAS study according to a pre-specified meta-analysis plan.

Multiplicity adjustment

A closed testing procedure will be implemented to control the overall type I error at 5% for primary (progression of albuminuria) and secondary endpoints (composite of CV death or hospitalization for heart failure, and death). There are no interim analyses planned.

TIME AND EVENTS SCHEDULE: PRETREATMENT AND DOUBLE-BLIND TREATMENT

Procedures and Evaluations	Pre-treatment		Double-blind treatment								
	Screening ^a	Baseline	Week -2	Day 1	Phone/email contact at Week 6	Week 13	Week 26	Phone/email contact at Week 39	Week 52 and every 26 weeks thereafter unless otherwise indicated	Phone/email contact midway between 26-week visits until last on-treatment visit	Last on-treatment visit (or after early discontinuation of treatment) ^b
Pretreatment/Administrative											
Informed consent ^c	X										
Diet, exercise, SMBG counseling	X										
Inclusion/exclusion criteria	X	X									
Medical history and demographics	X										
Prestudy therapy (drug classes of interest) ^e	X	X									
Dispense single-blind placebo	X										
Randomize		X									
Study Drug											
Administer/dispense double-blind study drug ^m		X				X	X		X		
Increase dose if subject requires additional glycemic control (see Section 3.1)						X	X		X		
Procedures											
Vital signs, weight, foot examination ^f	X	X				X	X		X	(ask about foot problems and provide foot care guidance)	X
Serum chemistry panel ^g	X	X				X	X		X		X
Hematology ^g		X							Week 52, 104 and 156		X
Fasting serum lipid profile ^g		X					X		Week 52, 104 and 156		X
HbA _{1c}	X	X				X	X		X		X
Duplicate first morning void urines for urine albumin/creatinine (provide collection containers at previous visit) ^{g, h}		X					X		Weeks 52, 78, 104 and 156		X
Urinalysis ^g		X									

Procedures and Evaluations	Pre-treatment		Double-blind treatment						
	Screening ^a	Baseline	Phone/email contact at Week 6	Week 13	Week 26	Phone/email contact at Week 39	Week 52 and thereafter unless otherwise indicated	Phone/email contact midway between 26-week visits until last on-treatment visit	Last on-treatment visit (or after early discontinuation of treatment) ^b
Time point	Week -2	Day 1							
Urine pregnancy test ¹		X							
Dispense glucose testing supplies (optional per country/region)		X		X	X		X		
Ongoing Review									
Concomitant therapy (drug classes of interest) ^j			X	X	X	X	X	X	X
Serious adverse events, and AEs causing discontinuation; vital status; AEs of interest ¹		X	X	X	X	X	X	X	X
CV events		X	X	X	X	X	X	X	X

For footnotes, see below

TIME AND EVENTS SCHEDULE: POSTTREATMENT

Posttreatment

Procedures and Evaluations		Posttreatment Follow-up		
		All Subjects	Subjects Who Withdraw Prior to End of Study	Subjects Who Withdraw Prior to End of Study
Time point		Final visit 30 days after last on-treatment visit (or after early discontinuation of treatment; preferably 30 days after last dose of study drug) ^e	Visit every 26 weeks after last dose until notification of global trial end date (GTED) ^b	Phone/email contact midway between 26 week visits until notification of the GTED ^{b,n}
Procedures				
Vital signs, weight, foot examination ^f			X	X (ask about foot problems and provide foot care guidance)
Serum chemistry panel ^g		X		
Hematology ^g				
Fasting serum lipid profile ^g				
HbA _{1c}				
Duplicate first morning void urines for urine albumin/creatinine (provide collection containers at previous visit) ^{g,i,h}				
Urine pregnancy test ⁱ				
Dispense glucose testing supplies (optional per country/region)				
Ongoing Review				
Concomitant AHA therapy ^j				X
Serious adverse events, and AEs causing discontinuation; vital status ^k ; AEs of interest ^l		X	X	X
CV events		X	X	X

See footnotes on the following page

FOOTNOTES

- ^a Subjects will receive diet/exercise counseling at the screening visit, be counseled on hypoglycemia recognition and management, and be dispensed single-blind placebo capsules. During the 2-week run-in period between screening and randomization, the investigator should adjust/optimize the subject's antihyperglycemic agents and agents to reduce CV risk (eg, lipid-altering, and blood pressure-lowering medications) as necessary. Subjects who fail protocol-specified screening criteria for study entry may be rescreened (Section 4.5), at the discretion of the investigator.
- ^b Every subject who remains on study drug through the end of the double-blind treatment period will have a scheduled date for a last on-treatment visit as soon as possible after site notification of the projected global trial end date (GTED) expected to occur between January 2017 and April 2017. Early withdrawal (EW) evaluations will be performed when a subject stops the double-blind treatment prematurely prior to the site notification of the GTED. EW evaluations will be performed on the day study drug is discontinued or as soon as possible after stopping the study drug. For subjects who prematurely discontinue study drug prior to the announcement of GTED, sites will be required to make a final contact or vital status check after announcement of GTED. For subjects who prematurely discontinue double-blind study drug prior to the site notification of the GTED, the study's informed consent form will enable efforts to achieve follow-up of lost participants using all reasonable means to contact the subject, family members, the subject's physicians and medical records, and the use of locator agencies and checking public records, as allowed by local law. It is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study (ie between the notification of the GTED and the actual GTED), including using all reasonable means outlined above.
- ^c A study visit will be conducted for all subjects approximately 30 days (+/- 12 days) after the last dose of study drug. (note: this applies to subjects who prematurely discontinue study drug and also those who discontinue study drug after site notification of the projected GTED) This will require a clinic visit for collection of lab specimens. If a study visit is not immediately possible, follow-up information may be collected by telephone, via email or other electronic or non-electronic means, and a subsequent study visit should be attempted.
- ^d The informed consent form must be signed before any study procedure is performed.
- ^e Record as prestudy therapy the classes of medications taken from 30 days before screening.
- ^f Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart); the average of the 3 blood pressure readings will be recorded on eCRFs. Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section 12.2.1 for further detail).
- ^g Specific details about specimen collection, storage, and processing will be provided in operations manuals. Attachment 1 lists the laboratory studies to be performed. Urinalysis will be performed from a spot urine collection in the clinic on Day 1.
- ^h The subject will provide first morning void (FMV) urine specimens (collection of the first urine void after the individual awakes from sleep). At each visit, the subject will bring in 2 FMV specimens: one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects progression or regression of albuminuria from the baseline (eg, progression from normoalbuminuria to microalbuminuria or macroalbuminuria accompanied by a urinary ACR value increase of $\geq 30\%$ from baseline; or regression from macroalbuminuria to microalbuminuria or normoalbuminuria accompanied by a urinary ACR value decrease of $\geq 30\%$ from baseline), the investigator will be notified to have the subject bring 2 additional consecutive-morning FMV specimens to the clinic approximately 1 to 2 months later. If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collection on the day of the visit, the subject may bring first morning void specimens to the investigational site during the subsequent 7 days. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period.
- ⁱ Urine pregnancy testing will be performed locally for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. Additional pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. If positive, the subject is not eligible to enter the study or continue study drug. A urine pregnancy test will be performed as specified, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations; in such situations, the serum pregnancy test will be performed at the screening visit instead of the baseline visit, in order to determine the subject's pregnancy status prior to randomization.
- ^j Concomitant therapy includes all medications from drug classes of interest taken regularly after the initiation of double-blind study medication (Day 1); after study drug discontinuation, use of AHA therapies will be recorded at the final visit or contact.
- ^k This applies only to subjects who prematurely discontinue study drug any time prior to the site notification of the GTED. As noted above, it is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study, including using all reasonable means to contact the subject, family members, the subject's physicians and medical records, or other sources, as well as the use of locator agencies and checking public records, as allowed by local law.

- ^l Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications..
- ^m An unscheduled visit may be used for increasing or decreasing the dose of study drug, any time after Week 13.
- ⁿ At each telephone contact, investigators should ask subject about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

ABBREVIATIONS

ACR	urinary albumin/creatinine ratio
ADA	American Diabetes Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ARO	Academic Research Organization
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CV	cardiovascular
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FMV	first morning void
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GTED	global trial end date
HbA _{1c}	hemoglobin A _{1c}
HDL-C	high-density lipoprotein cholesterol
IB	Investigator Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MI	myocardial infarction
mITT	modified intent-to-treat
MSRC	Medical Safety Review Committee
NYHA	New York Heart Association
PG	plasma glucose
PQC	Product Quality Complaint
SAP	statistical analysis plan
SGLT1/SGLT2	sodium-glucose co-transporter 1/sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

1. INTRODUCTION

Over the past decades, the incidence of type 2 diabetes mellitus (T2DM) has been rapidly rising worldwide, driven primarily by an increasing incidence of obesity and sedentary lifestyles. Patients with T2DM can develop severe microvascular complications, related to persistently elevated glucose concentrations, including blindness, renal failure, or nerve damage, and have a higher incidence of atherosclerotic vascular disease with complications such as myocardial infarction (MI), stroke, and amputations due to vascular insufficiency. Improved glucose control reduces the incidence of microvascular complications in patients with both type 1 diabetes mellitus (T1DM) and T2DM. The impact of improved glycemic control on macrovascular events is less well established. Despite the availability of a range of therapeutic options, many patients with T2DM do not achieve or maintain glycemic control. Many of these treatments are associated with safety or tolerability issues, including hypoglycemia, edema, or gastrointestinal adverse experiences which can limit dose and hence therapeutic benefit. Further, some of the current antihyperglycemic agents (AHAs) are associated with weight gain, and only a few agents (eg, metformin and glucagon-like peptide-1 [GLP-1] analogues) lead to weight loss, an important advantage in a patient population that is often obese. Most patients with T2DM are initially managed with single-agent therapy, usually metformin. Over time, patients often require more intensive regimens, combinations of 2 or 3 agents, and eventually require insulin to maintain target glycemic control. Underlying this need for increasingly intensive treatment is a progressive loss of beta-cell mass and function, with consequent diminished insulin secretion. There remains a substantial unmet medical need for new medications to treat patients with T2DM that are well tolerated and efficacious, provide good durability, beneficially impact beta-cell function and insulin secretion, and are associated with weight loss.

In healthy individuals, glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules. The renal threshold for glucose (RT_G) is the glucose plasma concentration above which glucose reabsorption by the proximal renal tubules is incomplete and glucose is excreted into the urine. A typical RT_G level in healthy individuals is approximately 180 mg/dL (10 mmol/L) (Ganong 2005; Rave 2006; Seifter 2005). Glucose reabsorption in the renal tubules, determining the renal threshold is largely due to 2 key glucose transporters: sodium glucose co-transporter 2 (SGLT2) and sodium glucose co-transporter 1 (SGLT1). Sodium glucose co-transporter 2 is a high-capacity and low-affinity glucose transporter exclusively expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules. Sodium glucose co-transporter 2 is responsible for the majority of filtered glucose reabsorption from the lumen. Sodium-glucose co-transporter 1 expressed in the S3 segment, a low capacity and high-affinity transporter, is also involved in reabsorption of filtered glucose from the lumen (Wright 2001). Sodium-glucose co-transporter 1 is also highly expressed in the intestine and is responsible for intestinal glucose and galactose absorption.

Pharmacologic inhibition of SGLT2 is a novel mechanism to decrease renal glucose reabsorption, as it lowers RT_G and leads to an increase in urinary glucose excretion (UGE), thereby directly lowering plasma glucose in individuals with elevated glucose concentrations. Canagliflozin is an orally active inhibitor of SGLT2. This agent has much higher potency for SGLT2 relative to SGLT1; at the plasma drug concentrations achieved with the doses in this

study, canagliflozin would be expected to provide significant systemic inhibition of SGLT2 and not of SGLT1. In addition to lowering plasma glucose concentrations, the increased renal glucose excretion with SGLT2 inhibition also translates to a loss of calories, leading to a net negative energy balance and the potential for weight loss as well as an osmotic diuretic effect, which can lead to reductions in blood pressure and osmotic diuresis- and volume depletion-related adverse events.

A Phase 3 development program including 9 controlled studies was conducted providing evidence for the effectiveness of canagliflozin both as monotherapy and in combination with approved, commonly prescribed AHA therapies in T2DM. These 9 studies spanned a range of clinical uses (as monotherapy or as combination therapy) to treat T2DM. Three of the Phase 3 studies evaluated canagliflozin in special populations, including older adults with T2DM, subjects with T2DM who had moderate renal impairment, and subjects with T2DM who had or were at high risk for cardiovascular (CV) disease. Results of the extensive Phase 3 clinical development program, involving approximately 10,285 subjects with T2DM and including nearly 6,650 subjects treated with 100 mg or 300 mg doses of canagliflozin, indicate that canagliflozin has the potential to be a useful addition to currently available antihyperglycemic agents. Across all of the studies, clinically meaningful reductions in hemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) were seen. Statistically significant (relative to placebo) reductions in body weight (predominantly fat mass) were also achieved with canagliflozin 100 mg and 300 mg across the spectrum of T2DM patients evaluated in the Phase 3 program. Canagliflozin also showed benefit in improving other clinical endpoints associated with diabetic comorbidities, including systolic and diastolic blood pressure (SBP and DBP), and lipid parameters (high-density lipoprotein cholesterol [HDL-C], and triglyceride). Improvements in beta-cell function, presumably through an indirect effect, such as reductions in glucotoxicity and insulin secretory demand, were also seen with canagliflozin treatment.

In March 2013, canagliflozin was approved for marketing by the United States Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and the progression of diabetic nephropathy.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For more detailed and current information regarding the preclinical characterization of canagliflozin pharmacokinetics (PK) (ie, absorption, distribution, metabolism and excretion) and toxicology, and clinical study results, refer to the current version of the Investigator's Brochure for canagliflozin ([IB JNJ-28431754](#)).

1.1.1. Nonclinical Studies

For a complete review of the findings and discussions regarding implications for human risk, please refer to the current version of the canagliflozin IB.

1.1.2. Clinical Studies

Overview

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in patients with T2DM. The program consists of 52 completed or ongoing clinical studies, including data from 10,285 subjects as of late 2012 (who received at least 1 dose of double-blind study drug) in 9 Phase 3 studies, 1,210 subjects in 3 Phase 2 studies, and 1,300 subjects in 40 Phase 1 studies.

Pharmacokinetics

Canagliflozin exhibits similar PK in healthy subjects and subjects with T2DM. The mean absolute oral bioavailability of canagliflozin was 65% following single-dose administration of the canagliflozin 300 mg tablet in healthy subjects. In healthy subjects (25 to 1,600 mg once-daily [QD]) and subjects with T2DM (50 mg to 300 mg QD and 300 mg twice-daily [BID]), after oral administration of single and multiple doses, mean canagliflozin $AUC_{0-\infty}$ increased in an approximately dose-proportional manner whereas mean maximum plasma concentration (C_{max}) increased in an approximately dose-proportional manner up to 1,200 mg. Following oral administration of canagliflozin, the median time to reach maximum plasma concentration (t_{max}) was approximately 1 to 2 hours. The mean terminal plasma elimination half-life ($t_{1/2}$) of canagliflozin was 10 and 13 hours with canagliflozin doses of 100 and 300 mg, respectively. The t_{max} was independent of dose. After repeated dosing with 50 to 300 mg canagliflozin, steady state was reached by 4 to 5 days. Minimal accumulation of canagliflozin was observed at steady-state across 50, 100, and 300 mg doses with mean accumulation ratios ranging from 1.3 to 1.4 in subjects with T2DM. Bioavailability of canagliflozin was not affected after co-administration of canagliflozin 300 mg with food in healthy subjects indicating that the canagliflozin tablet formulation may be taken without regard to meals.

O-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans. In human plasma, two non-pharmacologically active O-glucuronide conjugates of unchanged drug, M5 (formed by UGT2B4) and M7 (formed by UGT1A9), were present. Co-administration with rifampin, a nonselective inducer of several UGT enzymes, decreased canagliflozin area under the curve (AUC) by 51%, which may decrease efficacy. There was an increase in the AUC and C_{max} of digoxin when co-administered with canagliflozin 300 mg. Subjects taking concomitant digoxin should be monitored appropriately. The C_{max} of canagliflozin was not meaningfully altered by renal impairment.

Based on in vitro data and the clinical drug-drug interaction studies conducted to date, the potential for clinically significant CYP450 based PK interactions appears to be low.

Pharmacodynamics

In subjects with T2DM following single and multiple oral doses (30 to 600 mg QD and 300 mg BID), canagliflozin treatment dose dependently increased UGE_{0-24h} , with mean UGE_{0-24h} of approximately 100 g/day typically observed with doses of 100 mg/day or higher.

In subjects with T2DM, canagliflozin treatment with 100 mg and 300 mg once daily lowered RT_G to approximately 70 to 90 mg/dL (3.9 to 5.0 mmol/L), respectively. Because RT_G remains above PG levels associated with hypoglycemia and because very little UGE occurs whenever plasma glucose (PG) is below the RT_G, canagliflozin, itself, is not expected to pose a risk for hypoglycemia.

Efficacy

In the Phase 3 studies, canagliflozin has been assessed as monotherapy, as add-on therapy with metformin, sulphonylurea (SU), metformin and SU, metformin and a peroxisome proliferator-activated receptor (PPAR γ) agonist (pioglitazone), and as add-on therapy with insulin (with or without other AHAs). The Phase 3 program also includes studies in special populations of patients with T2DM: subjects with renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 50 mL/min/1.73 m²); subjects with or at high risk for CV complications; and older subjects. The latter 2 studies also included subjects on incretin-based therapies, including DPP-4 inhibitors and GLP-1 agonists.

Glycemic Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing HbA_{1c} in a broad range of subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin or to SU agents), in triple oral AHA combinations (add-on to metformin plus an SU agent or metformin plus pioglitazone), in combination with insulin (alone or in combination with other agents), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). In the monotherapy study, HbA_{1c} reductions of -0.91% and -1.16% relative to placebo for canagliflozin 100 mg and 300 mg, respectively, were observed. In the studies examining specific add-on combination uses, the efficacy of canagliflozin in lowering HbA_{1c}, relative to placebo, was generally consistent ranging from -0.62% to -0.74% with the 100 mg dose and from -0.73% to -0.92% with the 300 mg dose. Across all studies, the 300 mg dose consistently provided greater HbA_{1c} lowering relative to the 100 mg dose; since reduction in diabetic microvascular complications is continuous with improvements in glycemic control, the additional glucose-lowering efficacy with the 300 mg dose is considered likely to be clinically relevant (UKPDS 1998, DCCT 1993).

Results of subgroup analyses performed in a pooled population of the placebo-controlled Phase 3 studies found no important differences when comparing the effect of canagliflozin in change from baseline in HbA_{1c} based on baseline demographic characteristics (age, sex, race, ethnicity), body mass index (BMI), or geographic region. Greater reductions in HbA_{1c} relative to placebo were observed with canagliflozin among subjects with higher baseline HbA_{1c} and higher eGFR values compared with subjects with lower baseline values. In subjects with moderate renal impairment (ie, baseline eGFR's between 30 to 60 mL/min/1.73m²), the mean, placebo-subtracted reduction in HbA_{1c} was 0.38% and 0.47% on canagliflozin 100 mg and 300 mg respectively. A total of 24% and 32% of subjects achieved a target HbA_{1c} $< 7\%$ at the end

of treatment on canagliflozin 100 mg and 300 mg respectively compared to 17% of subjects on placebo.

With regard to other glycemic endpoints, canagliflozin provided improvements in FPG as well as in the PPG excursion. Canagliflozin also provided improvements in beta-cell function and a reduction in beta cell stress as reflected by a decrease in the proinsulin/C-peptide ratio. The improvement in beta-cell function and reduction in beta-cell stress is consistent with the sustained effect of canagliflozin on both HbA_{1c} and FPG observed in the 52-week studies.

Weight and Blood Pressure Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo. Weight loss with canagliflozin appeared dose-related (with -1.4% to -2.7% reductions with 100 mg and -1.8% to -3.7% reductions with 300 mg, relative to placebo). Results of specialized body composition investigations using dual energy X-ray absorptiometry (DXA) in 2 of the Phase 3 studies showed that the body weight reduction with canagliflozin was attributable to a greater decrease in body fat mass relative to lean body mass.

Reductions in SBP were observed with canagliflozin in Phase 3 studies (ranging from -2.2 to -5.7 mm Hg of SBP with canagliflozin 100 mg dose, and -1.6 to -7.9 mm Hg with the 300 mg dose, relative to placebo, in placebo-controlled 26-week studies), and were generally statistically significantly greater for both doses relative to placebo, and also greater relative to comparator agents (glimepiride and sitagliptin).

Safety

For a complete review of the adverse drug reactions (ADRs) and laboratory findings associated with canagliflozin, please refer to the current version of the canagliflozin Investigator's Brochure ([IB JNJ-28431754](#)).

The safety and tolerability profile that emerges from the development program for canagliflozin shows a medication that is overall well tolerated. The incidence of discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific ADRs, described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

Adverse drug reactions associated with canagliflozin include genital mycotic infections, urinary tract infections (UTIs), adverse events related to osmotic diuresis, and adverse events related to reduced intravascular volume, as well as constipation, and a low incidence of rash or urticaria.

In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals and in those with a past history of genital mycotic infections, generally did not lead to discontinuation from the study. Circumcision was performed in 17/3569 (0.5%) and 3/1924 (0.2%) of men treated with canagliflozin and control, respectively.

In women, genital mycotic infections (including candidal vulvovaginitis) occurred more commonly in women with a prior history of genital mycotic infections and did not generally lead to discontinuation. A modest increase in the incidence of adverse events of UTI (mostly lower tract infections) was observed with canagliflozin relative to control, without an increase in serious adverse events of UTI.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension. Risk factors for volume-related adverse events on canagliflozin treatment were ≥ 75 years of age, eGFR of 30 to 60 ml/min/1.73m² and use of loop diuretics. These adverse events were generally considered as mild or moderate in intensity, and infrequently led to discontinuation. No increase in serious adverse events related to reduced intravascular volume were seen with canagliflozin treatment. The reduction in intravascular volume also led to reversible reductions in eGFR that generally attenuated with continued treatment.

Based on the observations from the 2-year rat carcinogenicity study (findings of renal tubular cell cancers, Leydig cell tumors [LCTs], and pheochromocytomas), an extensive preclinical toxicology program was conducted that demonstrated that these tumors related to effects of canagliflozin in rats, not seen in humans (including rises in luteinizing hormone [LH] associated with LCT, and carbohydrate malabsorption leading to associated metabolic effects, including marked hypercalciuria, inducing renal tubular tumors and pheochromocytomas). In the clinical program, there were no reports of LCT or pheochromocytoma and no imbalance in the low incidence across groups of renal cell cancers.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed; mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using DXA in a dedicated Phase 3 study (a study conducted in older subjects [ages ≥ 55 and ≤ 80 years] with T2DM) and a cross-program assessment of fracture incidence. Bone mineral density (BMD) was examined at 4 sites: at the lumbar spine, total hip, distal radius, and femoral neck. Minimal changes in BMD from baseline to Week 104 were seen in the lumbar spine (a cancellous bone region), femoral neck (a mixed cancellous and cortical bone region), and distal forearm. A decrease in BMD from baseline to Week 104 in the total hip, a site comprised of mixed cortical and cancellous bone (like the femoral neck), was observed for both canagliflozin treatment groups (-0.9% and -1.2% in the canagliflozin 100 mg and 300 mg groups, respectively, placebo adjusted). In a pool of 8 clinical trials with a longer mean duration of exposure, the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1,000 patient-years of exposure to comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Increases in low-density lipoprotein-cholesterol (LDL-C) were observed with canagliflozin: in a pooled analysis of placebo-controlled 26-week studies, increases in LDL-C relative to placebo were 4.4 mg/dL (0.11 mmol/L) and 8.2 mg/dL (0.21 mmol/L) at the 100 mg and 300 mg doses, respectively. Relative increases in Apo B, non-HDL-C, and LDL particle number were approximately half as large as the rise in LDL-C. The changes in the CV risk profile with canagliflozin include reductions in SBP and increases in LDL-C, both established CV risk factors, and validated as surrogate endpoints. Improvements in other endpoints associated with CV risk, but not established as surrogate endpoints for CV benefit, such as body weight, glycemic control, HDL-C, and TG were also observed with canagliflozin. The cross-program CV meta-analysis (including results from the dedicated CV safety study) observed a hazard ratio of 0.91 for a pre-specified composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina (95% CI: 0.68, 1.22), showing no signal for an increase in the CV risk.

As of 11 May 2015, in the T2DM clinical development program, incidence rates of unblinded serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5337), 0.0763 (0.11%, 6/5350), and 0.0238 (0.03%, 2/6909) per 100 subject-years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator, respectively. Of the 12 subjects with serious adverse events of DKA, ketoacidosis, metabolic acidosis, or acidosis (all of whom were hospitalized), 6 subjects on canagliflozin (3 on canagliflozin 100 mg and 3 on canagliflozin 300 mg), and none on comparator were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or tested positive for GAD65 antibodies after being diagnosed with a serious DKA-related event. Eight of the 10 subjects on canagliflozin were receiving insulin therapy. The blood glucose values around the time of admission in 9 of 10 subjects on canagliflozin ranged from 347 to 571 mg/dL (9.3 to 31.7 mmol/L). The remaining subject had blood glucose values ranging from 148 to 320 mg/dL (8.2 to 17.8 mmol/L). Diabetic ketoacidosis has also been reported during post-marketing surveillance and has occurred in patients with blood glucose values less than 250 mg/dL (13.9 mmol/L). As a result, diabetic ketoacidosis is considered a rare adverse drug reaction.

During a routine review of unblinded interim data from the ongoing CANVAS study (DIA3008), the Independent Data Monitoring Committee observed a non-dose-dependent increase in the incidence of non-traumatic, lower-extremity amputations (mostly of the toes) in the canagliflozin 100 mg and 300 mg groups compared with placebo. With a mean duration of follow-up in CANVAS of approximately 4.5 years, the annualized incidence of lower-extremity amputation was 0.73, 0.54, and 0.30 events per 100 patient-years in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. Overall, treatment with canagliflozin was associated with an approximately 2-fold increase in amputation event rates (relative risk [RR] 2.15; 95% CI: 1.3- 3.5). The CANVAS/CANVAS-R IDMC, which has access to unblinded CV outcomes data, notified the sponsor that “after consideration of all outcomes, the IDMC feels the study should continue.” Infections were the events most commonly associated with amputations, and most amputations were of the toe. The factors associated with the greatest risk for amputations include prior amputation, peripheral vascular disease, and neuropathy.

1.2. Overall Rationale and Goals for the Study

Patients with T2DM have an increased risk of both microvascular and macrovascular complications which lead to morbidity and mortality. A key issue in patients with T2DM is the potential for hyperglycemia to lead to progressive damage to the kidney. Early on, this damage is reflected by microalbuminuria that may progress to macroalbuminuria and eventually loss of renal function. Hyperglycemia, possibly through production of advanced glycation end products (Diabetes Control and Complications Trial [DCCT]; [Brownlee 2001](#)) and systemic hypertension (DCCT) are known to be risk factors for the onset and progression of diabetic nephropathy. By virtue of its improvement in glycemic control, which has been shown to reduce albuminuria progression in prior studies ([ADVANCE 2008](#); [DCCT 1993](#); [UKPDS 1998](#)), and effects to reduce blood pressure, canagliflozin may slow the progression of diabetic nephropathy.

Hyperglycemia increases glucose levels delivered to the proximal tubule, which is reabsorbed, predominantly via an SGLT-2-dependent mechanism ([Vallon 1999](#)). Increased proximal tubule resorption of glucose results in increases in the proximal tubule reabsorption of sodium and reduces the delivery of sodium to the distal tubule. Decreases in sodium levels in the distal tubule reduce macula densa-dependent tubuloglomerular feedback, which results in afferent glomerular arteriole vasodilation and increases in glomerular pressure ([Vallon 1999](#)). Increases in glomerular pressure are believed to be an important factor in the onset and progression of diabetic nephropathy ([Anderson 1986](#); [American Diabetes Association \[ADA\] 2004](#)). ACEI and ARB decrease glomerular pressure by stimulating efferent glomerular arteriole vasodilation and reduce albuminuria and the progression of diabetic nephropathy (IDNT, [Lewis 2001](#), and RENAAL, [de Zeeuw 2004](#)).

In preclinical diabetic rodent models, SGLT2 inhibition increases tubuloglomerular feedback and reduces single nephron glomerular filtration rates, consistent with an increase in tubuloglomerular feedback leading to a decrease in glomerular pressure ([Vallon 2011](#)). In a Phase 1 study in subjects with T1DM who exhibited glomerular hyperfiltration (eGFR 172 ml/min/1.73 m²), an 8-week treatment with empagliflozin, a selective SGLT2 inhibitor, significantly reduced glomerular hyperfiltration (eGFR 139 ml/min/1.73 m²) ([Cherney 2013 ADA poster](#)). The reduction in hyperfiltration was associated with increases in renal vascular resistance and reductions in renal blood flow, both consistent with an increase in afferent glomerular arteriole tone. Thus, in preclinical and clinical models, SGLT2 inhibition reduces glomerular pressure, a factor known to be associated with the onset and progression of diabetic nephropathy.

In the clinical program, clinically-important, favorable changes were observed with canagliflozin compared to placebo in the progression of albuminuria. In a post hoc analysis performed in CANVAS ([28431754DIA3008](#); A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus), after approximately 20 months of mean follow-up, 253/1390 (18.2%) of placebo-treated subjects showed albuminuria progression (defined by albuminuria status change and 30% increase in albumin/creatinine ratio (ACR) from baseline) relative to baseline versus 221/1406 (15.7%) with canagliflozin 100 mg, 191/1397 (13.7%) with

canagliflozin 300 mg, and 412/2803 (14.7%) with canagliflozin overall. In a pooled analysis of subjects with moderate renal impairment (defined as a baseline eGFR of ≥ 30 mL/min/1.73 m² and ≤ 60 mL/min/1.73 m²) that included subjects from the CANVAS study and other studies in the Phase 3 program, the observed mean change from baseline in the albumin/creatinine ratio was 28 mg/g, -22 mg/g, and -41 mg/g for placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The corresponding observed median changes from baseline in the 3 groups respectively were 1.2 mg/g, -0.6 mg/g, and -0.7 mg/g.

In the Phase 3 program, treatment with canagliflozin was associated with a dose-dependent, reversible reduction in eGFR that was maximal at the first post baseline visit and was either stable or attenuated with continued treatment. The time course of eGFR changes over a 104-week, active comparator study and over a 52-week week study in subjects with moderate renal impairment are shown in [Figure 1](#) and [Figure 2](#) below.

Figure 1: Mean Change in eGFR Over Time (DIA3009)

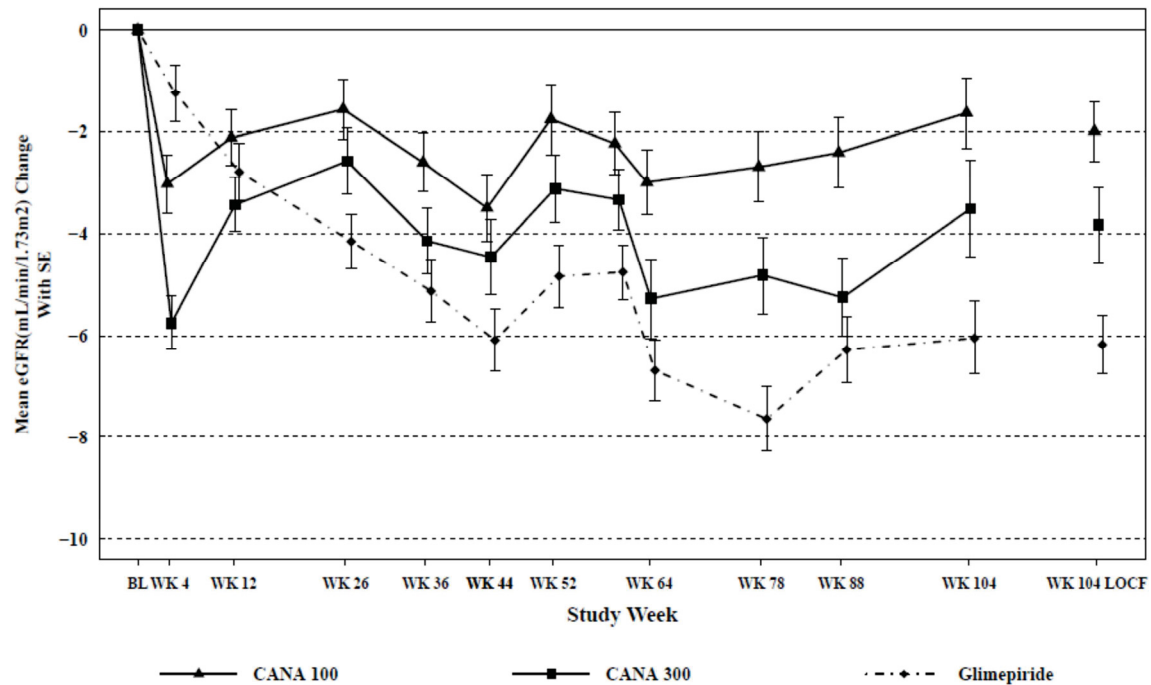
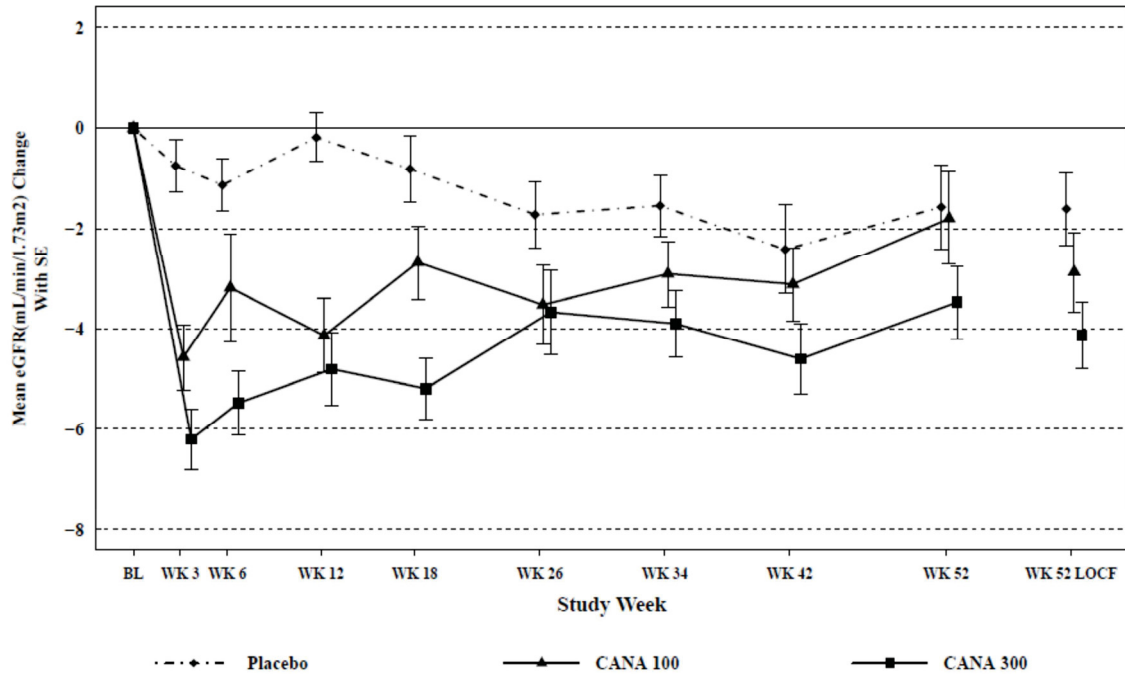
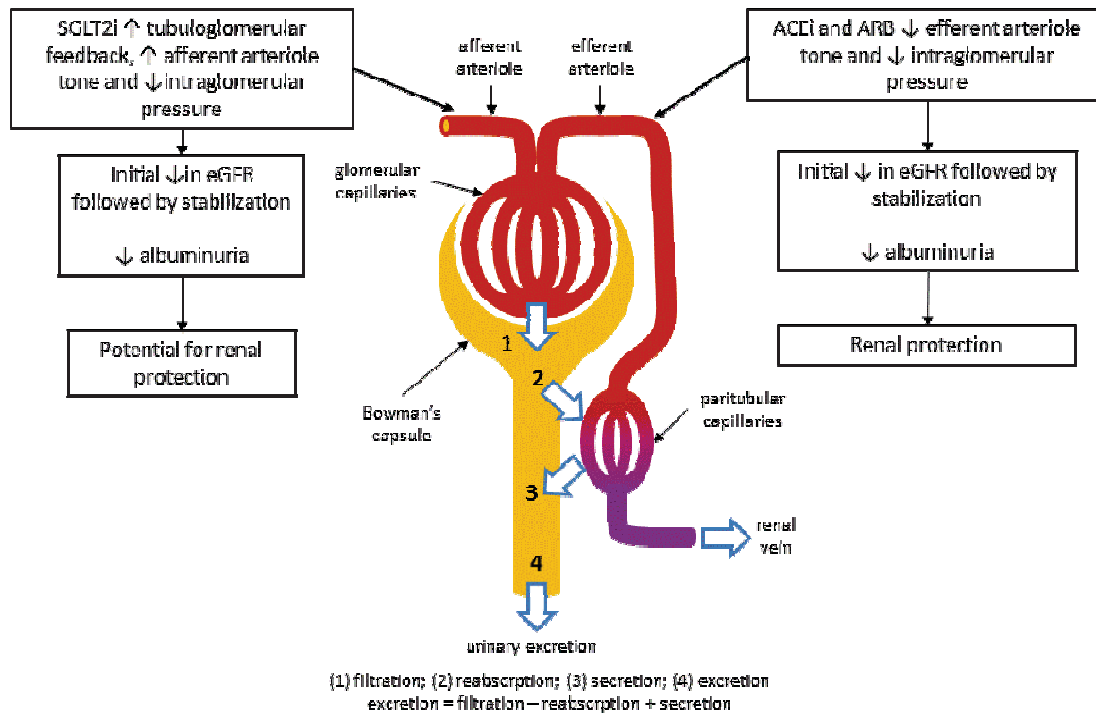


Figure 2: Mean Change in eGFR Over Time (DIA3004)

Based on these data, it is hypothesized that SGLT2 inhibition with canagliflozin will reduce glomerular pressure by increasing afferent glomerular arteriole tone, which will lead to a hemodynamically mediated decrease in glomerular pressure, as reflected by an acute, mild decrease in GFR. The reduction in glomerular pressure is hypothesized to mediate the reduction in albuminuria seen with canagliflozin treatment and to potentially lead to a reduction in progression of diabetic nephropathy. A schematic of these hypotheses and the effect of ACEI and ARBs on the progression of diabetic nephropathy is shown in [Figure 3](#), below.

Figure 3: Hypotheses Regarding the Effect of ACEI and ARBs on the Progression of Diabetic Nephropathy



The present study is intended to determine if treatment of subjects with T2DM with canagliflozin reduces the progression of albuminuria, a biomarker for renal injury and for progression of diabetic nephropathy. The study will also explore the effects of canagliflozin on the regression of albuminuria, and changes in eGFR.

Data from this study will also be used for a pre-specified meta-analysis with data from CANVAS for the assessment of CV safety, examining a composite endpoint of the major adverse cardiovascular events (MACE) of cardiovascular death, nonfatal MI, and nonfatal stroke. The details of the meta-analysis are described in a separate statistical analysis plan (SAP).

Results of a CV outcomes trial with another SGLT2 inhibitor were recently reported. EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled CV outcome trial to examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV outcomes in patients with T2DM and established CV disease, ie, EMPA-REG was a secondary prevention study (Zinman 2015). This study had a median observation time of 3.1 years and was conducted in 7,020 subjects. In this study, empagliflozin, compared to placebo, was associated with a reduction in the MACE primary outcome (CV death, nonfatal MI, and nonfatal stroke; hazard ratio 0.86 [0.74, 0.99], $p=0.04$), but the key secondary outcome of MACE-Plus (CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina; hazard ratio 0.89 [0.78, 1.01], $p=0.08$) did not achieve statistical significance. The effect on the primary MACE outcome was numerically smaller than the effects on the secondary endpoints of CV death (hazard ratio 0.62 [0.49, 0.77], $p<0.001$), and the composite endpoint of CV death and hospitalization for heart failure (hazard ratio 0.66 [0.55, 0.79], $p<0.001$). The reductions in CV

death and hospitalization for heart failure with empagliflozin treatment were apparent within 3 months after randomization. No statistical differences were seen relative to placebo on non-fatal MI and non-fatal stroke. In order to assess whether these effects are specific to the SGLT2 inhibitor class, the composite event of death from CV causes or hospitalization for heart failure and the event of death from CV causes are being added as secondary endpoints to CANVAS-R.

Post-hoc analysis of data from EMPA-REG OUTCOME also demonstrated a benefit on renal endpoints, particularly on the composite endpoint of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal cause. These and other renal events are being added as exploratory endpoints to CANVAS-R.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objective

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

Secondary Objectives

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

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

Exploratory objective

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

- Regression of albuminuria
- Change in eGFR from baseline to the last off-treatment value.
- Urinary ACR
- Change in eGFR determined from a between group comparison of the eGFR slopes using all on-treatment measures of eGFR made from the first on-treatment measurement to the final on-treatment measurement
- Changes in HbA_{1c}
- Utilization of AHA therapy
- The composite endpoint of 40% reduction in eGFR, renal death or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, renal death, or requirement for renal replacement therapy

- The composite endpoint of 40% reduction in eGFR, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of doubling of serum creatinine, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of 40% reduction in eGFR, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy

Safety Objective

Cardiovascular safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes.

2.2. Hypotheses

2.2.1. Primary Hypothesis

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

2.2.2. Secondary Hypotheses

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

- Reduces the composite endpoint of death from CV causes or hospitalization for heart failure
- Reduces death from CV causes

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study's last subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events are accumulated between the CANVAS and CANVAS-R (DIA4003) studies (estimated to occur between January 2017 and April 2017). The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

3.1. Study Design

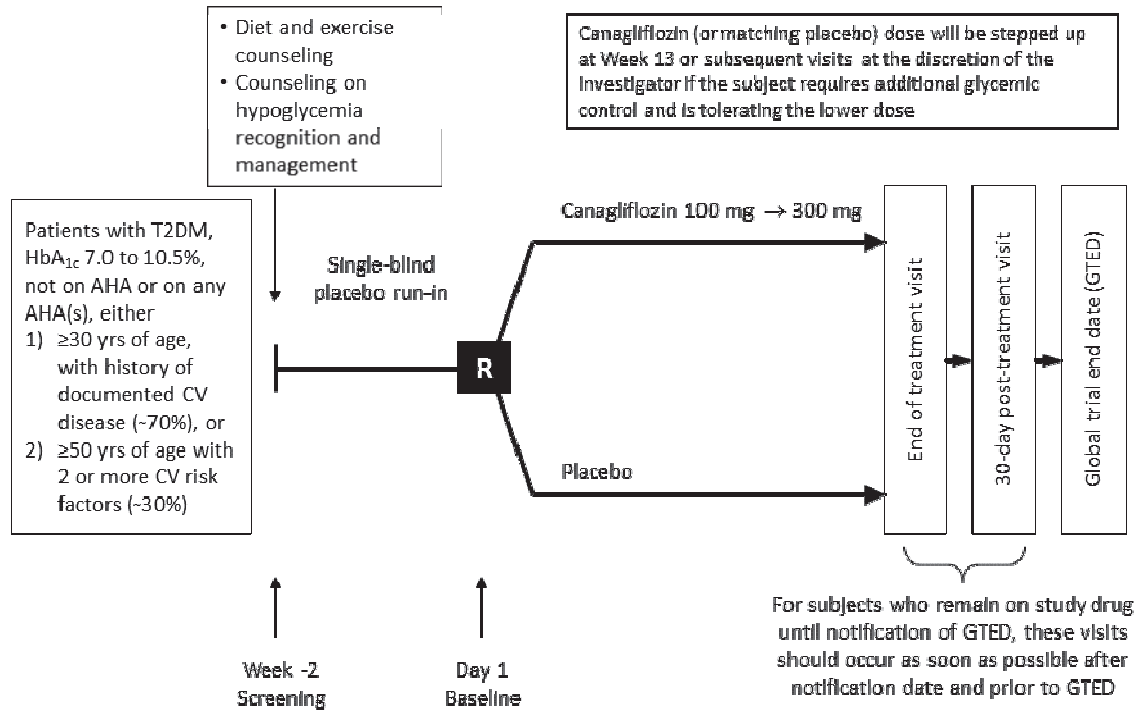
The following section provides an overview of subject management including screening, run-in, and double-blind treatment.

Screening Period

Subjects will undergo a screening visit for a preliminary determination of eligibility. Men or women with T2DM who are known to have inadequate glycemic control ($HbA_{1c} \geq 7.0$ and $\leq 10.5\%$), not on an AHA, or on an AHA (oral or injectable [eg, insulin or GLP-1 analogue] in monotherapy or combination therapy, and who have known CV events or who have 2 or more risk factors for CV events are eligible (refer to Section 4.2, Inclusion Criteria).

At this visit, potentially-eligible subjects will enter a 2-week single-blind placebo run-in period. All subjects should receive diet/exercise counseling at the screening visit, be counseled on hypoglycemia recognition and management, and be dispensed single-blind placebo capsules. During this period, the investigator should also adjust/optimize the subject's medications to reduce CV risk (eg, anti-hyperglycemic, lipid-altering or blood pressure-lowering medications) as necessary. If in the investigator's opinion additional time is required for adjustment/optimization of these medications, the 2-week period between screening and randomization may be extended by having the subject continue single-blind placebo up to 2 additional weeks. Subjects should be counseled to perform fasting self-monitored blood glucose (SMBG) determinations, according to standard guidelines. This counseling, as well as the counseling regarding diet/exercise and hypoglycemia recognition/management, should begin with a focus during the screening phase and be reinforced as needed throughout the study.

An overview of the study design is illustrated in [Figure 4](#).

Figure 4: Study Design Outline

AHA=antihyperglycemic agent; CV=cardiovascular; R = randomization; SU=sulfonylurea; T2DM= type 2 diabetes mellitus

Double-Blind Treatment Phase

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, will be randomly allocated to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). A total of 5,700 subjects will be randomized. After 13 weeks, the dose of canagliflozin (or matching placebo) may be increased from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The dose should be increased if the subject requires additional glycemic control (eg, $\geq 50\%$ of the subject's glucose determinations from the fasting SMBG [finger stick] readings [a minimum of 3 readings recommended] are >110 mg/dL [6 mmol/L] during the 2 weeks preceding the clinic visit or telephone contact) and the subject had no events of hypoglycemia or volume depletion in the preceding 2-week interval that in the opinion of the investigator would preclude dose titration. After increasing the dose to 300 mg, the dose should remain at 300 mg; however, if necessary, in the investigator's judgment, the dose may be decreased to 100 mg at any time point (eg, due to an adverse event of reduced intravascular volume). In addition, if there is need for additional glycemic control, the investigator should adjust the subject's AHA regimen as, per standard diabetes care guidelines, individualized as considered appropriate by the investigator. Adjustments in the AHA regimen should be carefully implemented throughout the study to minimize the risk of hypoglycemia. The investigator should optimize agents to reduce CV risk (eg, antihyperglycemic, lipid-altering and blood pressure-lowering medications) as required during the course of the trial to assure appropriate control consistent with standard care guidelines.

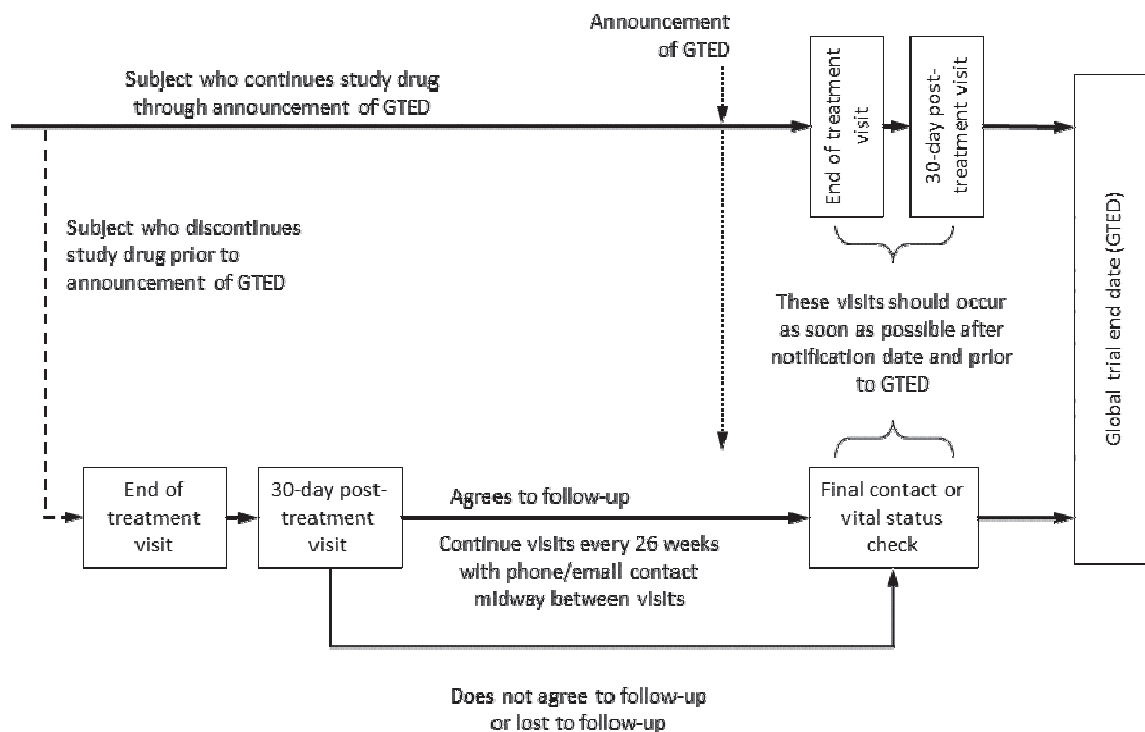
Study Duration

Subjects are expected to be followed for a maximum of about 3.5 years with the last visit for the last subject targeted to occur when all subjects have approximately 78 weeks of follow-up or when 688 MACE events are accumulated between the CANVAS and CANVAS-R (DIA4003) studies. All sites will be notified of the projected global trial end date (GTED) (projected to occur between January 2017 and April 2017). Immediately after the projected GTED notification is sent, for subjects who remain on double-blind study drug, sites will be required to schedule the last on treatment visits and the 30-day off drug follow-up visits as per the Time and Events schedule; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

All visits (including the 30-day off drug follow-up visit) will need to be completed prior to the GTED.

Figure 5 shows the intended follow-up of randomized subjects with respect to the GTED.

Figure 5: Follow-up of Randomized Subjects with Respect to the GTED



Collection of data about Cardiovascular Safety Outcomes

Investigators will be required to report any cardiovascular (CV) event that they consider could possibly be a nonfatal MI or nonfatal stroke (refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication), as well as all deaths. Additional information and documentation will be requested from investigators for all such

events to support a detailed assessment of these outcomes by an Endpoint Adjudication Committee.

Collection of Information After Early Discontinuation of Randomized Treatment

It is the intent that subjects who discontinue treatment with the study drug will continue in the study according to the visit schedule described in the Post-treatment Time & Events Schedule. After early discontinuation of randomized treatment, subjects will continue to be followed up for specific data collection, including any MACE events, vital signs, serious adverse events, and adverse events of interest.

Participants who prematurely discontinue study drug will require an immediate follow-up assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) as well as a follow-up assessment approximately 30 days (± 12 days) after last dose after which they should then continue to be followed for the full originally scheduled follow-up period through to study completion. If for some reason the subject is unable to be seen shortly after discontinuing study drug, the end of treatment visit may be omitted, but the 30-day off-drug follow-up visit should be performed. The follow-up regimen for these individuals will require 26-week visits interspersed with phone/email contact exactly as for those individuals that continue with randomized therapy (refer to Section 9.1.4, End-of-Treatment/Early Withdrawal, and Section 9.1.5, Posttreatment Phase [Follow-Up] for collection of information on CV events and other assessments). Safety Evaluations and Adverse Events of Interest

Safety evaluations will include the monitoring of serious adverse events, adverse events resulting in discontinuation, adverse events of interest, clinical laboratory tests, vital sign measurements, and measurement of body weight. For adverse events of interest, investigators will be asked to provide additional information, on separate electronic case report forms (eCRFs), so as to support more detailed analyses. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and

therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications. Investigators may also be asked to provide additional information on other adverse events, based upon review by the Medical Safety Review Committee (MSRC) or the study Independent Data Monitoring Committee (IDMC) (Section 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

Section 9.3, Study Management: Committees, provides details regarding the committees commissioned to provide oversight for the management of this study.

3.2. Study Design Rationale

Overall Design, Blinding, Control, Study Phases/Periods, Treatment Groups

This study was based upon the design of CANVAS and developed both to address the primary renal hypothesis and to meet the post-marketing requirements for canagliflozin defined by the US FDA. Broadly, the pretreatment phase allows sufficient time for study-related procedures to be performed, for subject eligibility to be determined and for optimization of background therapy by the investigators. Randomization, placebo control, and blinding will be used to minimize bias in the assignment of subjects to treatment groups and throughout data collection, and to maximize the likelihood that the study precisely and reliably addresses the questions it is designed to answer.

Study Population

The study population includes a broad spectrum of subjects on a variety of different AHAs with a range of different levels of baseline glycemic control and background risks of vascular and renal disease. The ratio of subjects with a history of CV events versus a high risk of CV events will be approximately 70% to 30%, respectively. Conducting the trial in this population will ensure broad generalizability of the trial results upon study completion.

Dosage Selection, Route of Administration, Dose Interval, Treatment Period

Both the 100 mg and 300 mg doses of canagliflozin are being used in this study. These are the doses that have been filed with health agencies for approval based on the results of the clinical program, and have been approved for marketing in some countries.

Choice of Renal Efficacy Measures

The development and progression of renal disease in people with diabetes follows a clearly defined pathway starting with microalbuminuria, progressing to macroalbuminuria, then to reduced renal function (lower glomerular filtration rate), and finally to renal failure with the need for dialysis or transplantation. To assess the effects of canagliflozin on the progression of diabetic nephropathy, the proportion of subjects with categorical progression of albuminuria based upon the urinary albumin/creatinine ratio in the first morning void is the primary endpoint

and will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of microalbuminuria is urinary albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macroalbuminuria is urinary albumin/creatinine ratio greater than 300 mg/g.

In diabetes, the onset of urinary albumin excretion is a strong signal for progression of diabetic nephropathy (ADA 2004), and is associated with an increase in CV events (de Zeeuw 2004). In the present study, duplicate first morning void urine collections on consecutive days, made by subjects at home (collection of the first urine void after the individual awakes from sleep), are being used. These collections have been shown to be more accurate than spot urine collections (Witte 2009) because they are less influenced by urinary albumin changes associated with physical activity. In addition to the progression and regression of albuminuria, changes in eGFR will be analyzed in this study, since it is the basic measurement of renal function and is used to assess progression of renal disease (ADA 2004).

4. STUDY POPULATION

4.1. General Considerations

The study will include subjects with a diagnosis of T2DM and a history or high risk of CV events; the ratio of subjects with a history of versus high risk of CV events will be approximately 70% to 30%, respectively. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

4.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria at Screening Visit

- Man or woman with a diagnosis of T2DM with HbA_{1c} level $\geq 7.0\%$ to $\leq 10.5\%$ at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
- History or high risk of CV events defined on the basis of either:
 - Age ≥ 30 years with documented symptomatic atherosclerotic CV events: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease.
 - Age ≥ 50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented

micro- or macroalbuminuria (see Section 3.2, Study Design Rationale, for definition) within one year of screening, or documented HDL-C of <1 mmol/L (<39 mg/dL) within one year of screening.

Note: An overall target ratio of approximately 70%:30% for CV history (first category):risk factors (second category) will be implemented (with a maximum of approximately 40% in the second category). This target is intended to be a global ratio and may vary by region. The proportion of subjects in these categories will be monitored centrally.

Note: the term “documented” in the above paragraphs refers to the required information being clearly noted in hospital/clinical records or in physician-referral documents, copies of which should be retained in the subject’s study files.

- Women must be:
 - postmenopausal, defined as
 - >45 years of age with amenorrhea for at least 18 months, or
 - >45 years of age with amenorrhea for at least 6 months and less than 18 months and a known serum follicle stimulating hormone (FSH) level >40 IU/L, or
 - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion), or otherwise be incapable of pregnancy, or
 - heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or
 - not heterosexually active.

Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.
- Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above, regardless of age) must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations (Note: a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations).
- Willing and able to adhere to the prohibitions and restrictions specified in this protocol
- Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

Inclusion Criterion for Randomization

- Subjects must have taken ≥80% of their single-blind placebo doses during the 2-weeks prior to randomization on Day 1 to be eligible for randomization.

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

- History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- History of one or more severe hypoglycemic episodes within 6 months before screening
Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- Ongoing, inadequately controlled thyroid disorder
Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.

Renal/Cardiovascular

- Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease ([The Criteria Committee of the New York Heart Association](#)).
- Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)

Gastrointestinal

- Known history of hepatitis B surface antigen or hepatitis C antibody positive (unless known to be associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease
- Any history of or planned bariatric surgery

Laboratory

- eGFR <30 mL/min/1.73m² at screening visit
- ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease

Other conditions

- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)
- History of human immunodeficiency virus (HIV) antibody positive
- Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia)
- Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments
- Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia)
- Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements

Medications/Therapies

- Current or prior use of an SGLT2 inhibitor.
- Prior or current participation in another canagliflozin study.
- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug[s])
- Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. **Note:** subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate
- Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline

General

- History of drug or alcohol abuse within 3 years before screening
- Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

Note: Investigators should assure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since screening. Before randomization, subjects whose status changes after screening, such that they now meet an exclusion criterion, should be excluded from participation.

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Prohibited medications include other SGLT2 inhibitors (including commercially available canagliflozin); subjects must not take any other investigational agents during the study (if a subject prematurely discontinues from the study medication but continues in the posttreatment follow-up phase, entering another investigational trial is discouraged but is not prohibited; however, entering another canagliflozin trial is prohibited)
- Strenuous exercise may affect urine protein excretion and other safety laboratory results; for this reason, strenuous exercise should be avoided within 72 hours before planned study visits
- Subjects should not collect first morning void urine specimens during acute illness with fever. The collection and respective visit should be postponed until the subject is recovered from the acute illness.

4.5. Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened if appropriate clinical management leads to study eligibility (eg, HbA_{1c} >10.5% that prompts adjustment of the subject's AHA regimen). Generally, a subject may only be rescreened once, but an additional rescreening may be allowed with concurrence of the sponsor's Medical Monitor.

Typically, rescreening will require that all screening parameters be repeated. However, with the concurrence of the sponsor's Medical Monitor, a non-qualifying laboratory test may be repeated one time, without completely rescreening the subject, in situations where there is a clinical reason to do so.

5. TREATMENT ALLOCATION

To ensure sufficient experience in subjects with a documented history of CV events – the highest risk group – approximately 70% of subjects (globally) are targeted to be in this group. The proportion of subjects in these categories will be monitored centrally.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks. Based on this randomization schedule, the study drug will be packaged and labeled. Medication numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to double-blind treatment.

At baseline (Day 1), the randomization number and medication numbers, the treatment code, which is linked to the randomization schedule, will be assigned after logging on to the interactive web response system (IWRS) designated by the sponsor. The requestor must use his/her own

user identification (ID) and personal identification number (PIN) when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and study drug kit for the subject. As subjects are randomly assigned to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IWRS is contacted for dispensing additional study drug. The randomization (or initial subject allocation) number at baseline will be the identifying number linking all subsequent kits to the individual subject.

The study drugs, whether canagliflozin or placebo, will be identical in appearance and will be packaged accordingly to maintain the blind. The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

The treatment blind should be broken to provide unblinded information to the site only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment through IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. The reason for unblinding is not captured through IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF) and in the source documents. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, in a sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

All randomization codes will be released after completion of the study. The translation of randomization codes into treatment and control groups will be disclosed only to those authorized.

Urine glucose measurements will not be performed on first morning void urine specimens, as an additional step to ensure the maintenance of the treatment blind. If a urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

6. DOSAGE AND ADMINISTRATION

6.1. Study Drugs

Two-week Single-Blind Placebo period following Screening

Upon completion of initial screening, all potentially eligible individuals will receive single-blind placebo capsules (one capsule to be administered once-daily) for 2-weeks to assess compliance.

Double-Blind Study Medication

On Day 1, subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: canagliflozin or matching placebo. Initially, canagliflozin will be provided at a dose of 100 mg daily, but at Week 13 (or any time thereafter) the dose of canagliflozin (or matching placebo) may be increased from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The dose of study drug should be increased if the subject requires additional glycemic control (for example, $\geq 50\%$ of the subject's glucose determinations from the fasting SMBG [finger stick] readings [a minimum of 3 readings recommended] are >110 mg/dL [6 mmol/L] during the 2 weeks preceding the clinic visit or telephone contact) and the subject had no events of hypoglycemia or volume depletion in the preceding 2-week interval that in the opinion of the investigator would preclude dose titration. After increasing the dose to 300 mg, the dose should remain at 300 mg; however, if necessary, in the investigator's judgment, the dose may be decreased to 100 mg at any time point (eg, due to an adverse event of reduced intravascular volume).

Subjects will be counseled to take their dose of canagliflozin or matching placebo, one capsule once daily, before the first meal of the day for the duration of the study or until early discontinuation. Subjects should take the first dose of study drug at the study center on Day 1.

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject does not take the study drug within 12 hours after the first meal of the day, the dose of study drug should be skipped for that day and the subject should be instructed to take the study drug on the following day before the first meal of the day.

Study drug may be interrupted (eg, for safety and/or tolerability reasons such as hospitalizations for major surgical procedure or serious medical illness). Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF. Study drug should be reinstated once the subject has recovered and the safety and/or tolerability concern is no longer present.

For subjects who develop conditions that are associated with or leading to amputation such as a lower extremity infection, skin ulcer, osteomyelitis, gangrene or critical limb ischemia, study drug should be interrupted until the condition has resolved in the opinion of the investigator. In the event of an amputation, restarting of dosing with canagliflozin should only be done after careful consideration of the individual risk:benefit and following discussion with the sponsor.

6.2. Concomitant Antihyperglycemic and Other Therapies

6.2.1. Management of Glycemic Control and CV Risk Factors

Screening Management

Subjects will receive diet/exercise counseling at entry into the screening period. During this visit, subjects should also be counseled to perform fasting self-monitored blood glucose (SMBG) determinations, according to standard guidelines.

Double-blind Treatment Phase Glycemic Management

The background AHA regimen may be adjusted at any time during the study to achieve glycemic goals, using standard guidelines, and as considered appropriate by the investigator for the individual subject. Adjustment to the AHA regimen should be carefully implemented so as to avoid events of hypoglycemia.

Adjustment of AHA therapy after randomization will be performed by the investigator. The preferred initial option for enhancing glucose control is to increase the dose of canagliflozin/placebo, so if possible, after Week 13 the investigator should increase the dose of canagliflozin/placebo from 100 mg to 300 mg (see Section 6.1). If increasing the dose of canagliflozin/placebo is not effective, there is no specific AHA treatment algorithm required for this study and the responsible clinician is free to adjust therapy as appropriate. Treatment may include reinforcement of lifestyle counseling, addition of or up-titration to maximum labeled doses of oral and/or injectable AHAs as locally applicable, **except the use of any other approved SGLT2 inhibitor**. Investigators should make all reasonable efforts to achieve and maintain the subject's individualized target glycemic control, and may add unscheduled visits, if clinically appropriate, to monitor glycemic control, and adjust the subject's regimen. Adjustments to the AHA regimen should be documented in the appropriate eCRF.

During the double-blind treatment period, investigators should counsel subjects to perform fasting SMBG determinations according to standard guidelines.

Therapeutic Management of CV Risk Factors

Before randomization and throughout the study, investigators will be expected to manage the subject's diet/exercise and other medication regimens so as to achieve goals for CV risk factors (eg, HbA_{1c}, lipid levels, blood pressure) based upon standard guidelines for the care of subjects with T2DM.

The 2-week period between screening and randomization provides investigators with the opportunity to adjust the subject's regimen as needed to optimize the subject's CV risk factors. If in the investigator's opinion additional time is required for adjustment/optimization of agents to reduce CV risk (eg, anti-hyperglycemia, lipid-altering or blood pressure-lowering medications) prior to randomization, the 2-week period pre-randomization may be extended by having the subject continue single-blind placebo up to 2 additional weeks. Additional amendments can also be made to background therapy at any time during the course of follow-up.

7. TREATMENT COMPLIANCE

The investigator or designated study research staff will maintain a log of all drug dispensed and returned (including a count of capsules dispensed and returned). Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with the study drug (based on capsule counts) should receive counseling on the importance of dosing compliance and should continue in the study.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study research staff will be

responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with making required clinic visits.

Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapy is defined as any therapy used before the first dose of double-blind study medication. Concomitant therapy is defined as any therapy used after the first dose of double-blind study drug.

Selected classes of prestudy therapies administered up to 30 days before screening and up to the time of the first dose of double-blind study drug will be documented. Likewise, selected classes of concomitant therapies taken after the first dose of double-blind study drug will be documented. Examples of the classes of interest may include AHAs such as sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, GLP-1 analogs, DPP-4 inhibitors, all forms of insulin, as well as non-AHAs such as renin angiotensin aldosterone system (RAAS) inhibitors, diuretics, beta-blockers, calcium channel blockers, statins, and anti-thrombotics. Checkboxes may be used on eCRFs to capture the required information on prestudy and concomitant agents. Details will be provided in the eCRF completion guidelines regarding the specific types of medications that fall in the categories of interest and what information will be collected.

Concomitant therapies will not be provided or reimbursed by the sponsor.

Disallowed Therapies

Other SGLT2 inhibitors (including canagliflozin) may not be used concurrently, and subjects should not take any other investigational agents during the study. If the use of another SGLT2 inhibitor or investigational agent is reported during the study, the subject's physician should be contacted, the other agent discontinued, and the subject should continue in the study.

The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

Visit Schedules and Visit Windows

Single-blind pre-randomization period - The recommended visit window for the initial single-blind placebo phase of the study is 2 weeks \pm 4 days. If in the investigator's opinion

additional screening time is required for adjustment/optimization of agents to reduce CV risk (eg, anti-hyperglycemia, lipid-altering, blood pressure-lowering or other medications), the screening period may be extended by having the subject continue single-blind placebo therapy for up to 2 additional weeks.

Post-randomization period - Subsequent scheduled in-clinic study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization) and Weeks 13, 26, and 52. After the first year, scheduled in-clinic study visits should occur at 26-week intervals with telephone contacts approximately midway between visits. For the Week 13 and Week 26 visits, the recommended visit window is ± 7 days. After Week 26, the recommended visit window is ± 14 days. Phone/email contacts will occur at approximately 26-week intervals in between the scheduled in-clinic visits. Similar windows are proposed for the phone/email contacts made between visits.

In the event that it is impossible for a subject to make a scheduled clinic visit, telephone contacts may be conducted at the time of the missed visit, but a clinic visit should be scheduled as soon as possible thereafter. If a telephone contact or study visit is not possible, follow-up information may be collected via email or any other appropriate means. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as close as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit.

For subjects who complete double-blind study drug through the time of site notification of the projected GTED, it will be important for sites to schedule the last on-treatment visit as soon as possible after the notification date and the 30-day off drug visit prior to the GTED.

For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

Pregnancy Testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to the Time and Events Schedule that follows the Synopsis for further details regarding urine pregnancy testing).

9.1.2. Pretreatment Phase

Screening Visit (Week -2)

Potential subjects will be seen at a screening visit, approximately 2 weeks before scheduled randomization, at which informed consent will be obtained and an initial assessment of eligibility will be performed.

At the screening visit, a focused medical history and initial screening assessment of inclusion/exclusion criteria will be performed and samples for required laboratory tests will be collected. Laboratory specimens will be obtained as described in the Time and Events Schedule. An operations manual will be provided to describe collection, processing, and shipping procedures for the duration of the study.

At this visit, subjects who appear to meet enrollment criteria may then be dispensed single-blind placebo capsules and enter the 2-week single-blind placebo run-in period. An assessment of the subjects' adherence to protocol procedures during this period will be made at the end of the period, before randomization, and will provide investigators with an opportunity to assess subjects' compliance with taking the single-blind study drug (by counting capsules).

Subjects who do not meet all inclusion criteria or meet a study exclusion criterion should be excluded from the study.

The screening visit and the 2-week run-in period provide investigators with the opportunity to evaluate and optimize management of CV risk factors prior to randomization as required (refer to Section 6.2.1, Management of Glycemic Control and CV Risk Factors) and to provide subjects with counseling regarding diet and exercise consistent with applicable local guidelines.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Potential participants who return for the Day 1 (baseline) visit, who have taken $\geq 80\%$ of the scheduled single-blind placebo capsules during the period between screening and randomization, and who meet the enrollment criteria will be randomly assigned to once-daily treatment with canagliflozin or matching placebo. Subjects will continue treatment until the study completes or the subject is prematurely withdrawn from double-blind study medication (refer to Section 10.2, Withdrawal From the Study, for reasons for withdrawal).

At the randomization visit, in some countries or regions (at the option of local sponsor representatives), subjects will be given a glucose meter and materials for SMBG measurements and instructed on the performance of SMBG.

Visits Following Randomization

Subjects will be seen in the clinic at visits as described in Section 9.1.1, Overview, and in the Time and Events Schedule. Procedures and clinical laboratory assessments for each visit or contact are outlined in the Time and Events Schedule.

Subjects who experience nonfatal CV events (ie, nonfatal MI, nonfatal stroke) during the double-blind treatment phase will continue in the study, continuing to receive double-blind study drug and complete all assessments at all scheduled visits, as appropriate.

On designated visits (see the Time and Events Schedule that follows the Synopsis), subjects will bring to the clinic duplicate first morning void urine specimens (collection of the first urine void after the individual awakes from sleep), one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects a stage change from an earlier measurement (eg, progression from normoalbuminuria to microalbuminuria, or regression from macroalbuminuria to microalbuminuria), the subject will be contacted to bring 2 additional consecutive-morning first morning void urine specimens to the clinic approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is discontinuing study drug). If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collections on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Collection containers and directions will be provided to subjects at prior visits. The site staff should call subjects a few days prior to visits to remind them to make the consecutive urine collections and bring them to the clinic.

9.1.4. Post-Treatment Follow-up for Participants who Withdraw from Randomized Treatment Early

Early withdrawal from randomized treatment will require the immediate collection of key data as soon as possible after stopping the study drug as well as an off-drug clinic visit approximately 30 days (+/-12 days) after discontinuation. The Time and Events Schedule that follows the Synopsis describes the evaluation required. It is important to note that subjects who discontinue randomized treatment early will be required, wherever possible, to continue with scheduled visits. While the data collection required for participants who discontinue randomized treatment early will be somewhat modified, comprehensive follow-up, as described in the Time and Events Schedule will be essential for every randomized subject.

For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

9.1.5. Post-Treatment Follow-up for Participants that Complete Randomized Treatment as Initially Scheduled

Subjects who complete double-blind study drug through the time of notification of the projected GTED will have a final on-treatment visit as soon as possible followed by a 30-day off-drug visit to occur no later than the GTED. At this visit, a blood specimen for laboratory measurement will be collected as well as assessments of any serious adverse event, CV event, or adverse events of interest.

9.1.6. Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits

Subjects who are no longer able to continue to attend clinic visits for scheduled follow-up must have an alternate follow-up plan put in place. The options for this follow-up include:

- Less frequent clinic visits (eg, annual or to coincide with other care)
- Telephone, e-mail, letter, social media, fax, or other contact with the subject
- Telephone, e-mail, letter, social media, fax, or other contact with relatives of the subject
- Telephone, e-mail, letter, social media, fax, or other contact the subject's physicians (family or specialist)
- Review of any available medical records

These alternate follow-up methods should be planned to coincide with the visit times outlined in Time and Events schedule. Wherever possible follow-up should be made at least once each year and in very rare cases where this cannot be achieved arrangements must be made to follow-up with the participant at the scheduled completion of the study. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

If all means of follow-up fail, at a minimum, the site must attempt to collect vital status data, as noted in Section 10.5, Circumstances for Reduced Follow-up, by consulting family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law.

In the rare instance that a site closes for operational, financial or other reasons and subjects are unable to be contacted regarding site closure, data from that site will be transferred to another site for a check of public records and/or vital status (at a minimum).

9.2. Reporting/Adjudication of MACE and Other Events for Adjudication

Investigators will be counseled to report any event that they assess as potentially being a MACE (CV death, nonfatal MI, nonfatal stroke). In addition, all deaths (to determine cause of death), as well as events of hospitalized heart failure, will be submitted for adjudication.

Investigators must provide a specific package of information to be submitted for adjudication evaluation that will be provided in a procedural manual. An independent Endpoint Adjudication Committee will assess these events according to the committee's charter. The Endpoint Adjudication Committee will classify the events while blinded to treatment assignment.

Note that events assessed by the investigator as nonfatal MI or nonfatal stroke (ie, nonfatal MACE) are not immediately subject to expedited serious adverse experiences reporting requirements (refer to Section 12, Adverse Event Reporting). If the event is adjudicated by the Endpoint Adjudication Committee as not meeting the nonfatal MACE definition, then the event will then be subject to expedited serious adverse experiences reporting requirements, (with

reporting timelines starting at the time of notification of this by the Endpoint Adjudication Committee).

9.3. Study Management: Committees

9.3.1. Academic Research Organization

An Academic Research Organization (ARO) will provide scientific and academic oversight of the study. The ARO will also have a role in site management and monitoring for a portion of the sites.

9.3.2. Steering Committee

The Steering Committee responsible for monitoring the CANVAS study will also be responsible for monitoring the current study, CANVAS-R. This Steering Committee, made up of external scientific experts, will provide scientific advice regarding the study design, conduct, and data collection. The Steering Committee is responsible for providing input on study design, academic leadership to study sites, reviewing study progress, and reviewing study results before publication. Details of the composition, roles, and responsibilities of the Steering Committee are documented in its charter.

9.3.3. Medical Safety Review Committee

An MSRC will be established to ensure that the safety of subjects participating in the study is not compromised. The MSRC will include, but will not be limited to, at least one medical expert and at least one statistician. The MSRC will include members from the sponsor organization and may also involve ARO representatives. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to the IDMC.

Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.4. Independent Data Monitoring Committee

The IDMC responsible for monitoring the CANVAS study to periodically review accumulating unblinded safety information during the study will also be responsible for monitoring the current study, CANVAS-R. Details of the composition, roles, and responsibilities are documented in its charter.

The IDMC will have responsibility for review of serious adverse events, events resulting in study drug discontinuation, CV events, and adverse events of interest for this study as well as across the broader canagliflozin clinical trials program.

9.3.5. Endpoint Adjudication Committee

The independent Endpoint Adjudication Committee (EAC) responsible for adjudicating CV events in the CANVAS study will also be responsible for adjudicating CV events in the current study, CANVAS-R. The EAC is composed of external specialists, blinded to treatment assignment. The operations, processes, and endpoint definitions to be employed by the committee are defined in its charter.

9.4. Safety Evaluations

Safety and tolerability will be evaluated on the basis of the overall incidence of serious adverse events, adverse events that lead to study drug discontinuation, adverse events of interest, the incidence of MACE events (overall and within the first 30 days of study drug treatment), vital signs (pulse, blood pressure), and body weight. Adverse events that do not meet the definitions above will not be collected.

The safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes to meet regulatory requirements set at the time marketing authorization for canagliflozin was granted. The CV meta-analysis will be described in a separate document with a specific statistical analysis plan.

Serious Adverse Events and Adverse Events Leading to Discontinuation

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study, beginning from when informed consent is provided. Information about all adverse events (serious or not) should be recorded in source documents (eg, progress notes) according to good clinical practice, and retained at the investigative sites. Only serious adverse events, nonserious adverse events that result in study drug discontinuation, and adverse events of interest will be recorded on eCRFs.

For purposes of reporting serious adverse events for this study, nonfatal MI and nonfatal stroke events (ie, nonfatal MACE) will not immediately be subject to expedited serious adverse event reporting requirements. Refer to Section 12, Adverse Event Reporting, for details regarding the handling of MACE.

Collection of Additional Information for Adverse Events of Interest

Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours

of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Investigators will be asked to provide additional information so as to support more detailed analyses. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Section 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee).

Events with characteristics of DKA will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA. Other categories of events (eg, renal) may undergo adjudication as necessary based on regulatory agency requests or to supplement data analyses.

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time treatment is discontinued (either prematurely or at completion of the study) will be followed by the investigator until resolution or until a clinically stable outcome is reached, or until further follow-up is no longer considered by the investigator to provide clinically meaningful information. (see Sections 9.1.4, 9.1.5, and 12.2.2 for additional details regarding follow-up).

Clinical Safety Laboratory Tests

Subjects will be monitored with safety laboratory measurements as described in [Attachment 1](#).

The investigator must review the laboratory reports, document this review, and record any serious adverse changes occurring during the study in the adverse event section of the eCRF.

Vital Signs (pulse, blood pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. Blood pressure will be assessed manually with a mercury sphygmomanometer, or an automated blood pressure monitor; if neither of these is available, a high-quality aneroid sphygmomanometer will be acceptable. Calibration of the blood pressure measuring device is not required for this trial, but if the institution has a calibration policy, compliance with this policy is expected. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart, as specified in the Time and Events Schedule; the average of the 3 readings will be recorded in the eCRFs.

For each subject, a consistent arm should be used for blood pressure measurements across the course of the study. If possible, if blood pressure is measured manually, it should be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Body Weight

Body weight will be measured using a consistent scale at each visit. Scale calibration is not required for this trial, but if the institution has a scale calibration policy, compliance with this policy is expected. As far as possible, subjects should be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes (note: if disrobing for weighing is logistically impossible, the subject should be dressed as lightly as possible, with consistency from visit to visit); subjects will be asked to urinate before being weighed.

Urine Pregnancy Testing

Urine pregnancy testing will be performed on all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. A urine pregnancy test will be performed at the baseline visit unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations (if a serum pregnancy test is required, it will be performed at the screening visit). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test).

9.5. Measures of Efficacy/Efficacy Endpoints

The categorical efficacy endpoint of the proportion of subjects with progression of albuminuria (defined as ≥ 1 step increase in category of albuminuria [ie, none to micro- or macro, or micro- to macroalbuminuria]) will be assessed from urine collections according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007). The definition of microalbuminuria is urinary albumin/creatinine ratio of 30 to 300 mg/g and the definition of macroalbuminuria is urinary albumin/creatinine ratio greater than 300 mg/g.

On designated visits, subjects will bring to the clinic duplicate first morning void urine specimens (collection of the first urine void after the individual awakes from sleep), one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects progression or regression of albuminuria from the baseline (eg, progression from normoalbuminuria to microalbuminuria or macroalbuminuria accompanied by a urinary ACR value increase of $\geq 30\%$ from baseline; or regression from macroalbuminuria to microalbuminuria or normoalbuminuria accompanied by a urinary ACR value decrease of $\geq 30\%$ from baseline), the subject will be contacted to bring 2 additional consecutive-morning first morning void urine specimens to the clinic approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is discontinuing study drug). If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collections on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Collection containers and directions will be provided to subjects at prior visits. The site staff should call subjects a few

days prior to visits to remind them to make the consecutive urine collections and bring them to the clinic.

10. SUBJECT COMPLETION, PREMATURE DISCONTINUATION OF TREATMENT, LOSS TO FOLLOW-UP AND WITHDRAWAL OF CONSENT

10.1. Subject Completion

A subject will be considered as having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until a time point between the notification of the GTED and the GTED (eg, subjects who complete the treatment need to have a final posttreatment follow-up visit; subjects who withdraw early from the treatment need to have a final contact after the notification of the GTED), or at the time of death for subjects who die prior to the GTED. The occurrence of a nonfatal MI, nonfatal stroke or any other safety or efficacy outcome does not comprise study completion and is not a criterion for withdrawal from the study or study drug.

10.2. Premature Discontinuation of Study Medication

A subject will discontinue study medication for any of the following reasons:

- The investigator believes that for safety or tolerability reasons it is essential for the subject to stop treatment
- The investigator formally unblinds the subject's treatment allocation
- The subject becomes pregnant (study therapy should be immediately discontinued based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β -hCG test)
- The subject's eGFR is <15 mL/min/1.73m² (as reported by the central laboratory).

Note: the central laboratory will alert the investigator for eGFR falls to <15 mL/min/1.73m². A repeat determination should be performed within 2 weeks, and study treatment discontinued if the repeat eGFR is <15 mL/min/1.73m² (unless a reversible cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the short-term illness).

- Subject requires dialysis or renal transplantation
- Subject requires disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)
- The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA.

Premature discontinuation of study treatment does not comprise study completion and is not a criterion for withdrawal from the study. All subjects who prematurely discontinue study treatment should continue study follow-up, although the nature of follow-up may be modified (see Section 9.1.4 and the Time and Events Schedule). Treatment should be recommenced wherever possible and routinely considered at every visit following discontinuation.

Subjects who decide to withdraw from double-blind study drug must be interviewed by the investigator so as to determine if a specific reason for withdrawal can be identified. Withdrawing

subjects should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented. If the subject elects to withdraw due to an adverse event, the event should be recorded as the reason for withdrawal, even if the investigator's assessment is that the adverse event would not require study drug withdrawal. The reason for withdrawal is to be documented in the eCRF and in the source documentation. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Reinstitution of Treatment for Subjects Who Have Prematurely Discontinued Double-Blind Study Drug to Active Status

Subjects for whom study drug is interrupted as a result of an adverse event, a life event (eg, temporary relocation to care for an ill family member), or other unforeseen circumstance should be encouraged to recommence study drug unless there is a clear contraindication at the discretion of the investigator, with concurrence from the sponsor's medical monitor.

Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

10.4. Lost to Follow-up

If a subject is lost to follow-up, all possible efforts must be made by the study site personnel to contact the subject and to achieve as complete follow-up as possible until after the site notification of the GTED. The measures taken to achieve follow-up are discussed in Section 10.5, Circumstances for Reduced Follow-up, and must be documented. The informed consent form will stipulate that even if double-blind study drug is discontinued, he/she will agree to continue follow-up.

10.5. Circumstances for Reduced Follow-up

There may be circumstances in which a reduced follow-up schedule is required and the options for this are described in Section 9.1.6, Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits. If one of these regimens is not possible, it will be necessary for the site investigator to contact the Sponsor representative to indicate the reasons why no further follow-up is necessary. It is important to note that a subject declining further follow-up does not constitute withdrawal of consent and the alternate follow-up mechanisms that the participant agreed to when signing the consent form will still apply (eg, searches of databases, use of locator agencies at study completion) as permitted by local regulations.

In this regard, the subject will be asked as a condition of entry into the study to agree to grant permission for the investigator to consult family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's status with respect to the CV safety composite endpoint, in the event the subject is not reachable by conventional means (eg, office visit, telephone, e-mail, or certified mail). The subject is also to be advised that if the site of the study doctor closes, and the study doctor cannot reach the subject to inform him/her, the contact information will be transferred to another site where a new study doctor will consult with family members, the subject's physicians

and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status.

10.6. Withdrawal of Consent

Withdrawal of consent should be a very unusual occurrence in a clinical trial. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence. In many instances where withdrawal of consent could potentially be recorded, the subject could be expected to be followed-up through one of the alternative follow-up mechanisms discussed in Section 10.5, Circumstances for Reduced Follow-up.

Withdrawal of consent in this trial may only be logged in the eCRF after a discussion between the investigator and the appropriate sponsor representative.

For subjects truly requesting withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing.

If a subject had previously withdrawn consent but decides to retract that withdrawal, the subject will be reconsented. The investigator will be responsible for making all required notifications to the IRB or Ethical Committee.

11. STATISTICAL METHODS

11.1. Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects who are randomized via the Interactive Web Response System (IWRS). The assessment of the primary and most of the secondary objectives will be based upon this analysis set.

The modified intent-to-treat (mITT) or On-Treatment analysis set includes all subjects who are randomly assigned to a treatment group and receive at least one dose of double-blind study. It will be used in the analyses assessing on-treatment effects, e.g. time slope of on-treatment eGFR.

Efficacy data will be analyzed according to the initial randomization assignment regardless of actual treatment received.

11.2. Sample Size Determination

Based on the interim data from the CANVAS study, where ACR was measured periodically at scheduled visits, it is projected that the annual progression rate for the CANVAS-R study will be approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month accrual period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it is estimated that 693 events will be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression is 90.5%, with type I error rate of 0.05 (two-sided).

11.3. Efficacy Analyses

11.3.1. Primary Efficacy Analysis

In this study, duplicate urine specimens will be collected for all ACR measurements. At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analysis unless otherwise specified.

Subjects will be classified as having normoalbuminuria (urinary ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥ 3.5 mg/mmol [≥ 30 mg/g] and ≤ 35 mg/mmol [≤ 300 mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]).

The primary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of albuminuria progression relative to placebo.

The time from first study drug administration to first visit date observing progression (ie, not using the visit date of the repeat sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The model will include treatment and baseline albuminuria status as covariates. The hazard ratio between canagliflozin and placebo will be provided, including its 95% confidence interval. The observation period for this time-to-event analysis will include all available measurements from first study drug administration to the visit date of the last ACR measurement. Subjects with no progression will be censored at the visit date of the last albuminuria measurement.

As a sensitivity analysis, the actual onset time of progression of albuminuria can be determined to lie within an interval from a sequence of examination times (ie, data are interval censored). As a supportive analysis, the accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring. The dependent variable in AFT model is logarithm of time to progression of albuminuria. The model will include treatment group and baseline albuminuria status as covariates. We can use speed of progression to interpret AFT model. For any time (t), the probability of a subject on placebo progression-free beyond time t is the probability of a subject on canagliflozin progression-free beyond t/α , where α is the acceleration factor which can be estimated from the model. Additional sensitivity analyses will be specified in the study SAP.

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

11.3.2. Secondary Efficacy Analyses

The secondary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of the following CV events relative to placebo.

- Composite of CV death or hospitalization for heart failure
- CV death

The analysis of these CV endpoints will be based on the time to first occurrence of the events using the ITT analysis set. The hazard ratio of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factor.

11.3.3. Exploratory Efficacy Analyses

Regression of albuminuria will be analyzed in a similar fashion as the analysis for progression of albuminuria.

For change in eGFR from baseline to the off-treatment measurement, an analysis of covariance (ANCOVA) model will be used with treatment as a fixed effect and adjusting for the baseline eGFR value. The treatment difference in the least-squares means and their 2-sided 95% CI will be estimated.

Since the distribution of ACR is highly skewed, the log-transformed ACR values for all the post-baseline and scheduled visits will be modeled using a linear mixed-effect model. The model will include treatment group and logarithm of baseline ACR value, visit, and treatment-by-visit interaction as fixed effects. The percentage treatment difference can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1.

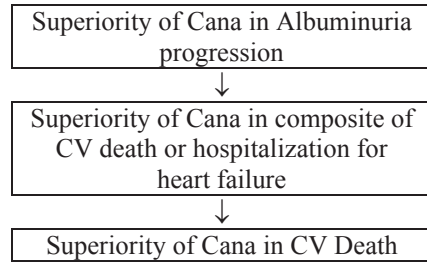
For on-treatment eGFR measurements, a linear mixed effects model will be fitted to eGFR as a dependent variable, including treatment, baseline eGFR value, time (as a continuous variable), and treatment time interaction as fixed effects and including subject effect as a random intercept and time as a random slope. The parameter of interest is the coefficient for treatment and time interaction term, which measures the slope difference between canagliflozin and placebo.

The effect of canagliflozin relative to placebo on changes in HbA_{1c} over time will be evaluated using a linear mixed effects model. The use of AHA therapy over time will also be summarized by treatment group.

11.3.4. Multiplicity Adjustment

A testing sequence for the CV program consisting of the integrated database of CANVAS and CANVAS-R is specified. The testing of the endpoints in CANVAS-R is specified as part of the sequence. To control the type I error in the CV program, testing of the hypotheses in CANVAS-R will not proceed until the hypothesis tests related to the integrated database are significant. When the hypotheses in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to CANVAS-R. The primary and the key secondary endpoints will be tested as follows.

Hypothesis



For other efficacy endpoints assessed in CANVAS-R, nominal p-values will be reported.

There are no interim analyses planned.

11.4. Safety Analyses

The safety analysis will be based on all randomized subjects who receive at least one dose of double-blind study medication (ie, the same as the mITT analysis set). There will be no imputation for missing values for clinical laboratory test results and vital sign measurements.

The study objective regarding safety and tolerability will be assessed based upon a review of the incidence of overall and specific adverse events, discontinuations due to adverse events, laboratory results, and other safety and tolerability measurements.

Major Adverse Cardiac Event (MACE)

Time to the MACE composite of non-fatal myocardial infarction, non-fatal stroke, or CV death occurring post-randomization will be analyzed via a stratified Cox proportional hazards model treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factor. The hazard ratio estimate and the 95% CI will be derived from the model.

For supplementary purpose, the CV risk ratio will be assessed at the early treatment phase. The MACE events occurring within the first 30 days and 90 days post-randomization will be analyzed in a similar fashion.

Adverse Events

The original terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least one occurrence of the given event will be summarized by treatment group. An adverse event will be considered to be a treatment-emergent event if it occurs within 30 days of the last date of blinded study medication. The percentage of subjects with specific treatment-emergent adverse events will be summarized by severity and relationship to study drug, as classified by the investigators, for each treatment group.

Further analyses, described in the SAP for this study, will be conducted on the prespecified adverse events for which additional information is collected from the investigators (refer to Section 9.4, Safety Evaluations).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Normal reference ranges will be provided. Criteria for markedly abnormal laboratory values will be prespecified in the SAP. The percentage of subjects with markedly abnormal results will be summarized for each laboratory analyte. Descriptive statistics will be reported for each laboratory analyte at baseline and at each scheduled time point and for change from baseline.

Vital Signs, Weight

Descriptive statistics for pulse and sitting blood pressure (systolic and diastolic), weight values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All deaths and events that are assessed by the investigator as being one of the components of the CV safety composite endpoints (ie, CV deaths, nonfatal MI, nonfatal stroke) should be handled as follows:

Investigator Responsibilities:

All SAEs must be reported to the sponsor within 24 hours of knowledge of the event. This reporting timeline is also applicable to CV events. The investigator will record the event on the AE eCRF and will submit an SAE report to the Sponsor. For CV events, an adjudication package will also be submitted; details on assembly and submission of adjudication packages will be provided in an Adjudication Manual.

Sponsor Responsibilities:

Nonfatal MACE Events (ie, nonfatal stroke, nonfatal myocardial infarction):

- The sponsor will submit non-fatal MACE events for adjudication to the Endpoint Adjudication Committee.
- Nonfatal events that are adjudicated to be components of the primary endpoint will not be unblinded or reported to either Health Authorities (HAs) or investigators as safety reports. These events will be included in the final analysis which will be unblinded and submitted to HAs.

- Non-fatal events that are adjudicated NOT to be components of the primary endpoint, and are considered possibly, probably or definitely related by the investigator will be unblinded and subject to reporting requirements to both HAs and investigators. The reporting timeline starts when the Adjudication Committee notifies the sponsor of the decision.

Fatal Events:

- The sponsor will submit all deaths for adjudication to the Endpoint Adjudication Committee.
- Fatal events will be submitted to HAs but to protect the integrity of the trial, the event will not be unblinded prior to review of the death by the EAC. The US FDA has agreed to receive these fatal cases blinded. These will also be submitted blinded to other HAs worldwide, if allowed by local regulation (eg, where local regulations do not allow for submission of blinded safety reports, those regulations should be followed).
- Fatal events that are adjudicated to be a component of the primary endpoint (ie, CV death) will remain blinded and will not be reported to either HAs or investigators as safety reports. These events will be included in the final analysis which will be unblinded and submitted to HAs.
- Fatal events that are adjudicated NOT to be a component of the primary endpoint (ie, non-CV death) and considered possibly, probably or definitely related will be unblinded and subject to reporting requirements to both HAs and investigators. The reporting timeline starts when the Adjudication Committee notifies the sponsor of the adjudication decision.

For specific adverse events of interest, investigators will be asked to provide additional information so as to support more detailed analyses.

Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance

concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Additional information and documentation will be requested from investigators to support a detailed assessment and all deaths. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

See above for handling of components of the composite CV endpoint other than CV deaths.

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted adverse event is one for which the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Procedures

12.2.1. All Adverse Events

For this study, all serious adverse events, nonserious adverse events that result in study drug discontinuation and other selected adverse events as specified later in this section are to be reported from the time a signed and dated informed consent form is obtained until completion of the study (including subjects who withdraw prematurely). For specific adverse events of interest, a supplemental eCRF page or other designated form will be used to collect additional information. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Data will be collected in source documents and on the eCRF for these adverse events.

Serious adverse events, including those spontaneously reported to the investigator must be reported using a Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Adverse events, regardless of severity or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

Study research staff should make study subjects aware of potential signs and symptoms of diabetic ketoacidosis such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to diabetic ketoacidosis (even if the subject’s blood glucose levels are less than 250 mg/dL [13.9 mmol/L]), testing for urine or blood ketones should be considered.

Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems. Specifically:

- Provide or ensure that all subjects have had general foot self-care education.
- Perform a comprehensive foot evaluation at each visit to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet.
- Subjects who have a history of prior lower extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease should be referred to foot care specialists for ongoing preventive care.

For all study participants, there should be a clinical evaluation at every visit to assess the presence of any sign or symptom suggestive of volume depletion (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), which if present should be adequately treated either by decreasing dose or eliminating use of diuretics or other antihypertensive medications or interrupting study drug until the condition resolves.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug, according to standard operating procedures and the requirements outlined in this protocol. These events will be reported blinded to the investigator when and where possible. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a “study card” indicating the name of the investigational study drug, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Nonfatal MI and nonfatal stroke events will be reported on the AE eCRF pages; the entry must be completed within 24 hours of the investigator staff's knowledge of the event. Events that are adjudicated as not meeting with charter-specified event definitions by the Endpoint Adjudication Committee will be subject to standard reporting requirements, but the reporting time limit will start when the sponsor learns that the event is not a CV safety event as per the Endpoint Adjudication Committee.

All serious adverse events that have not resolved by the end of the study, or that have not resolved after a reasonable time following the discontinuation of study drug, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study or a procedure to treat or explore a non-worsened pre-existing condition (eg, elective knee replacement, routine coronary angiogram without intervention, elective bariatric surgery); the non-worsening of the pre-existing condition must be documented in the source documents and the eCRF.

12.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must immediately discontinue further study treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Canagliflozin will be supplied for this study as over encapsulated 100- or 300-mg tablets in a gray-colored, hard, gelatin capsule. The over encapsulated tablet will be backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

Matching placebo capsules will consist of microcrystalline cellulose within a gray-colored, hard, gelatin capsule.

14.2. Packaging

The study drug will be packaged as individual bottles. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be

packaged according to the randomization code and each unit will be labeled with a medication ID number.

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 15°C to 30°C (59°F to 86°F) and kept out of reach of children.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects, or their legally-acceptable representative where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and partially used study drug returned by the subject (if applicable), must be available for verification by the sponsor's or sponsor-delegated site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or partially used study drug returned for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- IWRS manual and worksheets

- eCRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding CV events, documentation required, and adjudication-related procedures
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution (optional by country/region)
- Materials to promote healthy dietary and exercise habits
- Laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This study is being conducted under U.S. FDA IND regulations as part of a post-approval commitment. The protocol was submitted to and reviewed by the FDA prior to implementation.

The primary ethical concern of this study is that, though the safety profile of canagliflozin has been demonstrated in a clinical program involving more than 10,000 subjects, long-term safety data under conditions of extensive market use have not yet been established. Thus, subjects may be placing themselves at an increased risk of unexpected adverse events by participating in this study, and that subjects with T2DM who have not achieved optimal glycemic control at study entry could fail to achieve optimal glycemic control for a prolonged period. The investigator is asked to appropriately manage glycemic control and CV risk according to standard guidelines across the study. The potential risks in the present study include exposure to study drug, with the potential for side effects (Section 1.1.2, “Safety”) and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors. As per Section 9.3.4, an IDMC is commissioned for this study to review unblinded safety information on a periodic basis during the study.

Based on data from clinical studies with canagliflozin and the theoretical possibilities associated with SGLT2 and intestinal SGLT1 inhibition, potential human adverse effects may occur (Section 1.1.2, “Safety”). The following adverse of interest have been identified for follow-up in post-marketing studies by the US FDA: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and

venous thromboembolic events. for which information on non-serious adverse events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. These events will be recorded and analyzed in this study, as will all serious adverse events, adverse events that result in study drug discontinuation, all deaths, nonfatal MI and nonfatal stroke. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Clinical and laboratory evaluations will be performed throughout the study (according to the Time and Events Schedule that follows the Synopsis) to monitor the safety of subjects. HbA_{1c} will be measured approximately every 6 months.

Subjects will be followed after prematurely discontinuing study drug until scheduled study completion in line with the Time and Event Schedule to obtain comprehensive information about their health and well-being. The investigator will be provided with detailed information about the study to ensure that the study research staff is fully informed. Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Subjects will sign an informed consent form before any study-related procedure is performed.

The maximum blood volume that would be collected if a subject were to continue in the study for about 3.5 years would be approximately 300 mL. The maximum amount that would be collected at a single visit would be approximately 30 mL. These volumes are considered to be well within the normal range for this subject population over this time frame according to blood donation standards (American Red Cross).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By

signing the informed consent form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (refer to Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medications of interest; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within 3 working days of the subject's visit or in the time frame specified in the clinical trial agreement. The electronic file will be considered to be the eCRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query. A query is generally to be answered within 5 days of generation of the query or in the time frame specified in the clinical trial agreement.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field data correction form [DCF]) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the sponsor, and transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor and ARO designated by the sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be

available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit/contact of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit/contact at that site, 3 days after the subject's visit/contact (query generation and resolution excluded), or in the time frame specified in the clinical trial agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding canagliflozin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of canagliflozin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of pharmacogenomic results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted

to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

REFERENCES

ADA 2004. American Diabetes Association. Nephropathy in Diabetes. *Diabetes Care* 2004;27(1):S79-83.

ADVANCE 2008. The ADVANCE collaborative Group. Intensive blood glucose control and vascular outcomes in patients with Type 2 Diabetes. *N Engl J Med* 2008;358:2560-72.

American Red Cross. American Red Cross Website. <http://www.redcrossblood.org/donating-blood/donation-faqs>. Accessed March 3, 2011.

Anderson S (1986), Brenner B. The role of intraglomerular pressure in the initiation and progression of renal disease. *J Hypertension Suppl.* 1986;4(5):S236-8.

Brownlee M (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813-820.

Clinical Study Report CANVAS; 28431754DIA3008; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus. Janssen R&D (13 Dec 2012).

de Zeeuw D, Remuzzi G, Parving HH, Keane W, Zhang Z, Shahinfar S, Snapinn S, Cooper M, Mitch W, Brenner B. Albuminuria, a Therapeutic Target for Cardiovascular Protection in Type 2 Diabetic Patients With Nephropathy. Dallas, TX. American Heart Association, 2004. The online version is located on the <http://circ.ahajournals.org/content/110/8/921>.

DCCT 1993. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Eng J Med.* 1993;329(14):977-986.

Ganong W (2005) Review of Medical Physiology. McGraw-Hill Professional. 2005.

IB-JNJ-28431754 Edition 6. Document ID No. EDMS-PSDB-5839974. Johnson & Johnson Pharmaceutical Research and Development, L.L.C. Investigator's Brochure (2 June 2009).

KDOQI 2007. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI). *American Journal of Kidney Diseases* 2007;49(2, Suppl 2):S1-S180.

Levey AS (2006), Coresh J, Greene T, Stevens LA, Zhang Y. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. *Ann Int Med* 2006;145:247-55.

Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New England Journal of Medicine.* 2001;345:851-860.

Rave K (2006), Nosek L, Posner J, Heise T, Roggen K, van Hoogdalem EJ. Renal glucose excretion as a function of blood glucose concentration in subjects with type 2 diabetes - results of a hyperglycaemic glucose clamp study. *Nephrol Dial Transplant.* 2006;21:2166-2171.

Seifter J (2005), Sloane D, Rather A: Concepts in Medical Physiology. Lippincott Williams & Wilkins, 2005.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

UKPDS 1998. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

Vallon V (1999), Richter K, Blantz RC, Thomson S, Osswald, H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. *J Am Soc Nephrol* 1999;10:2569-2576.

Vallon V (2011), Platt KA, Cunard R, Schroth J, Whaley J, Thomson SC, Koepsell H, Rieg T. SGLT2 mediates glucose reabsorption in the early proximal tubule. *J Am Soc Nephrol* 2011;22(1):104-112.

Witte EC (2009), Lambers Heerspink HJ, de Zeeuw D, Bakker SJL, de Jong PE, Gansevoort R. First morning voids are more reliable than spot urine samples to assess microalbuminuria. *J Amer Soc Nephrol* 2009;20:436-443.

Wright EM (2001). Renal Na⁺-glucose cotransporters. *Am J Physiol Renal Physiol* 2001;280:F10-F18.

Zinman B (2015), Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117-2128.

Attachment 1: Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and a baseline random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF and take appropriate action (eg, repeating abnormal laboratory result or further evaluation as considered clinically appropriate). The following tests will be performed by the central laboratory.

- Hematology Panel
 - hemoglobin
 - hematocrit
 - white blood cell (WBC) count with differential
 - platelet count
 - red blood cell (RBC) count
- Serum Chemistry Panel
 - sodium
 - potassium
 - chloride
 - bicarbonate
 - blood urea nitrogen (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)*
 - specific gravity
 - pH
 - protein
 - blood
 - ketones
 - bilirubin/urobilinogen
 - nitrite
 - leukocyte esterase

*Urine glucose will not be measured by the central laboratory

Central laboratory will report the 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:

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

For creatinine in μmol/L:

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

INVESTIGATOR AGREEMENT

JNJ-28431754: Canagliflozin

Clinical Protocol 28431754DIA4003 – Amendment INT-5

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____
Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____
Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Ngozi Erundu, MD, PhD
Institution: Janssen Research & Development

Signature: _____ Date: 1-Sept-2016
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.