

Janssen Research & Development***Clinical Protocol****A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of
the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With
Type 2 Diabetes Mellitus****The CANVAS Trial
(CANagliflozin cardioVascular Assessment Study)****Protocol 28431754DIA3008; Phase 3
AMENDMENT INT-8****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).

Issue/Report Date: 5 May 2016
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-ERI-13522077:12.0 (**Legacy No.:** EDMS-PSDB-9584804)
Eudract No.: 2009-012140-16

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*.

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:

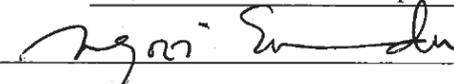
Name (typed or printed): _____
Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

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

Signature:  Date: 29 April 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.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES	6
PROTOCOL AMENDMENTS	7
SYNOPSIS	24
TIME AND EVENTS SCHEDULE	30
POSTTREATMENT TIME AND EVENTS SCHEDULE – SUBJECTS WHO PREMATURELY DISCONTINUE STUDY MEDICATION	34
ABBREVIATIONS	35
1. INTRODUCTION	37
1.1. Background.....	39
1.1.1. Brief Overview of Nonclinical Studies	39
1.1.2. Clinical Studies.....	39
1.2. Overall Rationale and Goals for the Study	44
2. OBJECTIVES AND HYPOTHESES	47
2.1. Objectives.....	47
2.1.1. Primary Objectives	47
2.1.2. Secondary Objectives	47
2.2. Hypotheses.....	48
2.2.1. Primary Hypothesis	48
2.2.2. Secondary Hypotheses	48
2.3. Substudies: Objectives and Hypotheses.....	48
2.4. Medical Resource Utilization Objective	50
3. OVERVIEW OF STUDY DESIGN	50
3.1. Study Design	51
3.2. Study Design Rationale	55
4. STUDY POPULATION.....	59
4.1. General Considerations.....	59
4.2. Inclusion Criteria.....	60
4.3. Exclusion Criteria.....	62
4.4. Prohibitions and Restrictions	64
4.5. Rescreening.....	65
5. TREATMENT ALLOCATION.....	65
6. DOSAGE AND ADMINISTRATION	67
6.1. Study Drugs.....	67
6.2. Concomitant Antihyperglycemic and Other Therapies	68
6.2.1. Management of Glycemic Control and CV Risk Factors.....	68
6.2.2. Glycemic Rescue Therapy Through Week 18 Criteria and Implementation.....	70
7. TREATMENT COMPLIANCE	70
8. PRESTUDY AND CONCOMITANT THERAPY	71
9. STUDY EVALUATIONS.....	71
9.1. Study Procedures	71
9.1.1. Overview	71

9.1.2.	Pretreatment Phase	73
9.1.3.	Double-Blind Treatment Phase	74
9.1.4.	End-of-Treatment/Early Withdrawal	75
9.1.5.	Posttreatment Phase (Follow-Up)	75
9.2.	Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication	76
9.3.	Study Management: Committees	77
9.3.1.	Academic Research Organization	77
9.3.2.	Steering Committee	77
9.3.3.	Medical Safety Review Committee	77
9.3.4.	Independent Data Monitoring Committee	77
9.3.5.	Endpoint Adjudication Committee	77
9.4.	Safety Evaluations	77
9.5.	Measures of Efficacy/Efficacy Endpoints	82
9.6.	Pharmacogenomic Evaluations	83
9.7.	Exploratory Evaluations	83
9.8.	Medical Resource Utilization	84
10.	SUBJECT COMPLETION/WITHDRAWAL	84
10.1.	Completion	84
10.2.	Withdrawal From Study Drug	84
10.3.	Reinstitution of Subjects Who Have Prematurely Discontinued Double-Blind Study Drug to Active Status	86
10.4.	Measures to Re-establish Contact in Subjects Lost to Follow-up	86
11.	STATISTICAL METHODS	87
11.1.	Analysis Sets	87
11.2.	Handling of Dose in Analysis	87
11.3.	Sample Size Determination	87
11.4.	Safety Analyses	88
11.5.	CV Outcomes and Efficacy Analyses	89
11.5.1.	CV Outcomes (Primary Efficacy Endpoint)	89
11.5.2.	Major Secondary Efficacy Endpoints	90
11.5.3.	Multiplicity Adjustment	90
11.5.4.	Additional Secondary Efficacy Endpoints	91
11.6.	Medical Resource Utilization Analyses	91
11.7.	Interim Analyses of CANVAS	91
11.7.1.	Interim Analyses for Health Authority Submissions	91
11.8.	Meta-Analysis to Support Regulatory Requirements	91
11.8.1.	Meta-Analysis Pre-Regulatory Approval	91
11.8.2.	Meta-Analysis Post-Regulatory Approval	92
11.9.	Glycemic Efficacy Substudies	93
11.9.1.	Analysis Sets	93
11.9.2.	Sample Size Determination	93
11.9.3.	Efficacy Analyses	93
11.9.4.	Multiplicity Adjustment	94
11.9.5.	Safety Analyses	95
12.	ADVERSE EVENT REPORTING	95
12.1.	Definitions	97
12.1.1.	Adverse Event Definitions and Classifications	97
12.1.2.	Attribution Definitions	98
12.1.3.	Severity Criteria	99
12.2.	Procedures	99
12.2.1.	All Adverse Events	99
12.2.2.	Serious Adverse Events	101
12.2.3.	Pregnancy	102

12.3.	Contacting Sponsor Regarding Safety	102
13.	PRODUCT QUALITY COMPLAINT HANDLING	102
13.1.	Procedures	102
13.2.	Contacting Sponsor Regarding Product Quality.....	102
14.	STUDY DRUG INFORMATION	103
14.1.	Physical Description of Study Drug(s).....	103
14.2.	Packaging	103
14.3.	Labeling	103
14.4.	Preparation, Handling, and Storage	103
14.5.	Drug Accountability.....	103
15.	STUDY-SPECIFIC MATERIALS.....	104
16.	ETHICAL ASPECTS	104
16.1.	Study-Specific Design Considerations	104
16.2.	Regulatory Ethics Compliance	107
16.2.1.	Investigator Responsibilities.....	107
16.2.2.	Independent Ethics Committee or Institutional Review Board (IEC/IRB).....	107
16.2.3.	Informed Consent.....	108
16.2.4.	Privacy of Personal Data.....	109
16.2.5.	Country Selection	110
17.	ADMINISTRATIVE REQUIREMENTS	110
17.1.	Protocol Amendments	110
17.2.	Regulatory Documentation	111
17.2.1.	Regulatory Approval/Notification	111
17.2.2.	Required Prestudy Documentation	111
17.3.	Subject Identification, Enrollment, and Screening Logs.....	112
17.4.	Source Documentation	112
17.5.	Case Report Form Completion.....	113
17.6.	Data Quality Assurance/Quality Control.....	113
17.7.	Record Retention.....	114
17.8.	Monitoring	114
17.9.	Study Completion/Termination	115
17.9.1.	Study Completion	115
17.9.2.	Study Termination	115
17.10.	On-Site Audits.....	115
17.11.	Use of Information and Publication	116
REFERENCES		118
Attachment 1:	Sulfonylurea Monotherapy Doses for Stratification Purposes	120
Attachment 2:	Hypoglycemia: Definitions, Symptoms, and Treatment.....	121
Attachment 3:	New York Heart Association Classification of Cardiac Disease	122
Attachment 4:	Optional Specimens for Exploratory Research - Sample Collection and Handling.....	123
Attachment 5:	Pharmacogenomic Sample Collection and Shipment Procedure.....	125
Attachment 6:	Clinical Laboratory Tests	126
Attachment 7:	Algorithm for Monitoring Abnormal Liver Function Tests.....	127
Attachment 8:	Candidate Gene List for Part 1 of Pharmacogenomics	128
Attachment 9:	Medical Resource Utilization Review.....	129

LAST PAGE	129
------------------------	------------

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Adverse Event Collection Requirements	79
---	-----------

FIGURES

Figure 1: Study Design Outline	52
Figure 2: Follow-up of Randomized Subjects With Respect to the GTED.....	54
Figure 3: Testing Sequences for Substudy Secondary Efficacy Endpoints	95

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	14 Aug 2009
Amendment INT-1	16 Sep 2009
Amendment INT-2	27 Apr 2010
Amendment INT-3	11 Mar 2011
Amendment INT-4	08 Sep 2011
Amendment INT-5	13 Dec 2012
Amendment INT-6	08 November 2013
Amendment INT-7	23 September 2015
Amendment INT-8	5 May 2016

Amendments are listed beginning with the most recent amendment.

Amendment INT-8 (5 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: Decision to continue adjudication of hospitalized heart failure, VTE, and fracture events.	
Section 9.2 Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication	The note that adjudication of hospitalized heart failure VTE, and fracture events would conclude with implementation of INT-6 was removed, since adjudication of these cases is continuing.
Rationale: Include guidance regarding subject management surrounding the event of lower-extremity amputations.	
Time and Events Schedule footnote “j”; footnote “v”; Time and Events Schedule (posttreatment) footnote “c”; 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 diabetic ketoacidosis will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA. In addition other categories of events (eg, renal) may undergo adjudication as necessary based on regulatory agency requests or to supplement data analyses.

Applicable Section(s)	Description of Change(s)
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.
Time and Events Schedule footnote “u”;	Added statement that study drug should be interrupted for subjects who develop conditions that are associated with or leading to amputation.
Section 9.4. Safety Evaluations; Table 1;	An additional AE of special interest was added, “amputation”.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-7 (23 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.

The overall reason for the amendment

The primary reason for the amendment is to reflect a request by Health Authorities 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: 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 and Events Schedule footnote “u”; Section, Section 9.4. Safety Evaluations; Table 1	An additional AE of interest was added, “male genital infections (balanitis, phimosis, events leading to circumcision)”, and an AE of special interest, “diabetic ketoacidosis”; “other designated forms” was added; “In addition, non-serious adverse events” was added; and 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. A directive for reporting DKA to the sponsor within 24 hours 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.
Rationale: To ensure consistency with the Investigator’s Brochure.	
Section 1.1.2. Clinical Studies	Wording updated regarding bone fracture events consistent with the Investigator’s Brochure.
Rationale: To provide clarification on drug discontinuation.	
Section 6.1. Study Drugs	Additional wording added to last paragraph to clarify study drug discontinuation.

Applicable Section(s)	Description of Change(s)
Rationale: To include a serious adverse event of biochemically-confirmed diabetic ketoacidosis (DKA) to the list of reasons for withdrawal from study drug.	
Section 10.2. Withdrawal from Study Drug	The sentence "The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) diabetic ketoacidosis (DKA)." was added.
Rationale: Consistent with changes relative to DKA.	
Section 12.2.1. All Adverse Events	A description of diabetic ketoacidosis 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: Consistent with prior reduction in amount of plasma being stored; allows potential use of smaller collection tube.	
Attachment 4	Modified the archive specimen volume collection language.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical or formatting changes were made.

Amendment INT-6 (08 November 2013)

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 for the amendment is to reflect the changes required for compliance with the United States (US) Food and Drug Administration (FDA) post-marketing requirements for canagliflozin. According to these requirements, a post-approval cardiovascular (CV) meta-analysis will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated from CANVAS plus a planned study evaluating renal events (CANVAS-R; 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; 28431754DIA4003). Per the post-marketing requirement, the FDA believes it is most appropriate to characterize CV safety based on a composite of major adverse cardiovascular events (MACE) (not MACE plus hospitalized unstable angina) and using a population at high CV risk (ie, similar to the patients currently enrolled in CANVAS). In addition to the above-mentioned meta-analysis, the US FDA is requiring enhanced pharmacovigilance on select adverse events of interest, which are now described in INT-6. Since the safety profile of canagliflozin was well-established in the Phase 3 program, adverse event collection is being limited in INT-6 to serious adverse events, adverse events that result in study drug discontinuation, and adverse events of interest (as described in the protocol).

Applicable Section(s)	Description of Change(s)
Rationale:	This change was made to comply with US FDA post-marketing requirements for canagliflozin.
Synopsis; 1.2. Overall Rationale and Goals for the Study; 3. Overview Of Study Design; 11.3. Sample Size Determination; 11.8.2. Meta-Analysis Post-Regulatory Approval	The post-approval meta-analyses across all Phase 3 studies for assessment of CV safety when 500 and 700 events in the CV composite endpoint occur will no longer be done. Instead the post-approval CV meta-analysis will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated from the CANVAS (28431754DIA3008) study plus a planned study evaluating renal outcomes (CANVAS-R; 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; 28431754DIA4003). The projected date of occurrence (April 2017) of the total number of required events was added.
Synopsis; 2.1.1. Primary Objectives	A statement was added indicating that the data from CANVAS (28431754DIA3008) will be combined with CANVAS-R (28431754DIA4003) to meet US FDA post-marketing requirements for canagliflozin.
Rationale:	This section was updated to reflect the current status of the study.
Synopsis; 1.2. Overall Rationale and Goals for the Study	The description of the pre-approval CV meta-analysis was modified indicating that it has already been conducted.
Rationale:	Hospitalized unstable angina is no longer part of the pre-specified CV composite endpoint, which now focuses only on MACE events (ie, CV death, nonfatal myocardial infarction, and nonfatal stroke). Hospitalized heart failure events observed in the ongoing CANVAS study occur infrequently due to the nature of the population enrolled which contains no subjects with NYHA Class IV heart failure and few subjects with NYHA Class III.
	With respect to venous thromboembolism and fracture events, there is a high concordance rate between investigator-reported events and adjudication committee confirmed events, such that the adjudication of these events does not impact the assessment of these events. Nevertheless, all reported venous thromboembolism and fracture events will be reported and captured by investigators.
	It is not anticipated that proposed changes to adjudication will impact procedures conducted by investigators. Data collection remains unchanged, with investigators still being required to provide the same level of data.
	Safety analyses will be conducted using investigator-reported safety results for hospitalized unstable angina, hospitalized heart failure, venous thromboembolism, and fracture events.
9.2. Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication; Synopsis; 9.4. Safety Evaluations; 12. Adverse Event Reporting	For events of hospitalized unstable angina and hospitalized heart failure, adjudication will conclude with implementation of amendment INT-6. However, investigators will continue to report such events that are serious or that lead to study drug discontinuation on the eCRF. For events of venous thromboembolism and fractures, adjudication will conclude. However, investigators will continue to report all events of venous thromboembolism and fractures on the eCRF. The implementation date to end adjudication of these events will be documented in an update to the adjudication charter(s).

Applicable Section(s)	Description of Change(s)
Rationale:	This change is consistent with US FDA post-marketing requirements for canagliflozin, and the circumstances outlined in INT-5.
Synopsis	The text describing the safety and tolerability assessments was modified to specify that CV safety will be assessed as part of the meta-analysis of CANVAS and CANVAS-R.
Rationale:	Because the safety profile of canagliflozin was well-established in the Phase 3 program, adverse event collection is being limited in INT-6 to serious adverse events, adverse events that result in study drug discontinuation, and events of interest specified by the US FDA in their post-marketing requirements for canagliflozin. In addition, this process is consistent with the protocol (Section 9.4), which previously indicated (as of INT-2), “After the decision to re-open enrollment (and recruit Cohort B), for subjects continuing from the initial cohort (Cohort A) and subjects entered in the subsequent cohort (Cohort B), only serious adverse events, adverse events resulting in study drug discontinuation, and selected adverse events will be collected on CRFs.”
Time and Events Schedule (new footnote “u”); 3. Overview Of Study Design; 9.4. Safety Evaluations; 11.4. Safety Analyses; 12. Adverse Event Reporting	<p>Only serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest will be recorded on eCRFs.</p> <p>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, and pregnancy. Information on these events of interest will also be recorded on a supplemental electronic case report form (eCRF) for any event that is serious or that leads to study drug discontinuation. The only exceptions to the adverse event collection described above are for malignancies, photosensitivity reactions, fractures, and venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental eCRF pages (in addition to the information collected on serious adverse events and adverse events leading to study drug discontinuation).</p> <p>Also, as noted above, events of hospitalized unstable angina and hospitalized heart failure, will be reported the adverse event/serious adverse event eCRF if such events are serious or lead to study drug discontinuation (see Section 9.4. Safety Evaluations).</p>
Rationale:	This change is consistent with US FDA post-marketing requirements for canagliflozin in that only serious hypoglycemia events and those resulting in study drug discontinuation will be collected. This decision also reflects the fact that extensive safety data regarding hypoglycemia were collected in the canagliflozin Phase 3 program. The focus going forward will be on more clinically relevant hypoglycemia events and not all events. As noted above, because the safety profile of canagliflozin was well-established in the Phase 3 program, adverse event collection is being limited in INT-6 to serious adverse events, adverse events that result in study drug discontinuation, and events of interest specified by the US FDA in their post-marketing requirements for canagliflozin. In addition, this process is consistent with the protocol (Section 9.4), which previously indicated (as of INT-2), “After the decision to re-open enrollment (and recruit Cohort B), for subjects continuing from the initial cohort (Cohort A) and subjects entered in the subsequent cohort (Cohort B), only serious adverse events, adverse events resulting in study drug discontinuation, and selected adverse events will be collected on CRFs.”
12.2.4. Hypoglycemia; related text in Section 11.4. Safety Analyses	Section or text regarding hypoglycemia was deleted.

Applicable Section(s)	Description of Change(s)
Rationale:	The decision to stop routine annual central ECGs was made due to there being no ECG signal from the extensive Phase 3 program.
Synopsis; Time and Events Schedule; 3.1. Overview of Study Design; 9.4. Safety Evaluations; 11.4. Safety Analyses	Routine central ECGs will no longer be collected after Week 52.
Rationale:	The urine pregnancy test requirement was removed, but the provision remains for investigators to continue testing if locally required or clinically warranted for individual subjects.
Time and Events Schedule; 9.4. Safety Evaluations; 11.4. Safety Analyses	Urine pregnancy testing will no longer be required on a routine basis post-baseline, but the provision remains for investigators to continue testing women of childbearing potential if locally required or clinically warranted for individual subjects.
Rationale:	The total blood collection was decreased because the collection volumes for exploratory samples have been decreased based on the projected need for minimal additional retention samples.
16.1. Study-Specific Design Considerations	The total blood volume collected over the course of the study was lowered from 875 mL to 850 mL.
Rationale:	More recent information regarding canagliflozin has become available since the CANVAS protocol was drafted. The description of pharmacokinetic, pharmacodynamic, efficacy, and safety information was outdated.
Introduction	<p>The introduction was updated to reflect the current benefit/risk profile of canagliflozin and its marketing approval in the United States and other countries.</p> <p>The background section was updated to describe the exposure in the Phase 1, 2, and 3 studies as of the end of 2012. The pharmacokinetic, pharmacodynamic, efficacy, and safety information was updated with current information.</p>
Rationale:	This change was made to correct a typographical error in INT-5 and clarify that the primary objective will be assessed using the ITT analysis set. Selected secondary objectives may be assessed using the mITT analysis (if appropriate) to comply with US FDA post-marketing requirements for canagliflozin.
Synopsis; 3. Overview of Study Design; 11.1. Analysis Sets; 11.4. Safety Analyses	<p>The modified intent-to-treat (mITT) analysis set definition is now randomized subjects who receive at least one dose of study drug (original definition) <i>plus</i> their data occurring between first dose and last dose plus 30 days.</p> <p>A statement was added that alignment of the analysis of the secondary endpoints with the ITT and mITT analysis sets will be detailed in the study statistical analysis plan (SAP).</p>
Rationale:	This section was updated to allow investigators more flexibility in scheduling subject contacts.
Time and Events Schedule	Visits at 13-week in-clinic visits after Week 52 are no longer required and will now be performed as a telephone contact. An in-clinic visit at 13-week intervals may be performed at the investigator's discretion to resupply study drug.

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, spelling or template changes were made.

Amendment INT-5 (13 December 2012)

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 CANVAS (DIA3008) study is being modified because the sponsor has been unblinded to the results of the analysis of the study's primary cardiovascular (CV) endpoint (MACE events), which was part of a cross-program CV meta-analysis. Originally, the cross-program CV meta-analysis results (and results from CANVAS) were only to be unblinded to the canagliflozin program Independent Data Monitoring Committee (IDMC) and a limited number of sponsor personnel not involved with the canagliflozin program, and then submitted to Health Agencies (who were to be requested to avoid public disclosure). The release of these CV meta-analysis results to the sponsor was based upon the observed small dose-related increase in LDL-cholesterol (4.4% and 8.0% for canagliflozin 100 mg and 300 mg, respectively, relative to placebo) observed in Phase 3 studies. This allowed an assessment by the sponsor of the LDL-C changes in the context of the CV meta-analysis results, including the hazard ratio (HR) for the composite MACE plus hospitalized unstable angina endpoint. Due to the release of the unblinded CV endpoint results from CANVAS, the study Steering Committee has determined that the second cohort (Cohort B), originally planned for future enrollment in CANVAS, would not be conducted; this decision was based upon the assessment that the unblinding interim primary endpoint (MACE CV HR) data from the ongoing CANVAS study did not allow a definitive assessment of the study objective. The Steering Committee indicated that a separate CV outcome study should be conducted to provide a definitive assessment of CV risk. After review of the CV HR results, the Steering Committee in concert with the sponsor (and after IDMC review) has recommended continuing CANVAS with the original cohort (Cohort A, which completed enrollment in March 2011) so as to provide an initial assessment of the study's primary objective of CV benefit. This initial assessment will provide important information supporting a subsequent separate CV outcome study, and will also support assessment of other study objectives.

Applicable Section(s)	Description of Change(s)
Rationale: Comprehensive follow-up of subjects who discontinue is important for analysis of the study results; these changes provide mechanisms for enhancing follow-up.	
Synopsis; Time and Events Schedule	Added mention of provision for alternative posttreatment follow-up options; added specific mention of 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, and the use of locator agencies and checking public records, as allowed by local law.

Rationale: Refer to overall reason for amendment.

1.2. Overall Rationale and Goals for the Study; 2.3. Substudies:	In light of overall reason for amendment, removed mention of Cohorts A and B.
---	---

Applicable Section(s)	Description of Change(s)
Objectives and Hypotheses 3. Overview of Study Design; 3.1. Study Design; 3.2. Study Design Rationale; 4. Study Population; 4.1. General Considerations; 5. Treatment Allocation; 6.1. Study Drugs; 6.2.1. Management of Glycemic Control and CV Risk Factors; 6.2.2. Glycemic Rescue Therapy; 9.1.2. Pretreatment Phase; 9.1.3. Double-Blind Treatment Phase; 9.1.4. End-of-Treatment/Early Withdrawal; 9.4. Safety Evaluations; 9.8. Medical Resource Utilization; 10.2. Withdrawal from the Study; 11. Statistical Methods; 12.2.2 Serious adverse experiences	
Rationale: Refer to overall reason for amendment.	
Synopsis; 3. Overview of Study Design; 3.1 Study Design; 11.3 Sample Size Determination; 11.8.2. Meta-Analysis Post-Regulatory Approval	In light of overall reason for amendment, removed mention of Cohorts A and B and associated statements in the analysis; revised wording regarding meta-analyses to meet the CI <1.3 requirement for the upper bound of the 95% CI for the CV HR.
Rationale: Comprehensive follow-up of subjects who discontinue is important for analysis of the study results; these changes provide mechanisms for enhancing follow-up	
Synopsis; Time and Events Schedule; 9.1.4 End-of-Treatment/Early Withdrawal; 10.2 Withdrawal From the Study	Provided for subject to allow contacting physicians and medical records to follow-up subjects who cannot be contacted; added provision 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.

Applicable Section(s)	Description of Change(s)
9.8 Medical Resource Utilization	Removed erroneous mention of collecting hospitalization information on MRU forms.
<p>Rationale: The sponsor has been unblinded to the results of the analysis of the study's primary cardiovascular endpoint (MACE events), which was part of a cross-program CV meta-analysis. Originally, the cross-program CV meta-analysis results (and results from CANVAS) were only to be unblinded to the canagliflozin program Independent Data Monitoring Committee and a limited number of sponsor personnel not involved with the canagliflozin program, and then submitted to Health Authorities. Since the scope of unblinding within the sponsor organization is broader than originally planned, a more limited firewall is implemented involving individuals within the sponsor responsible for submitting events to the Endpoint Adjudication Committee.</p>	
11.8.1. Meta-analysis Pre-Regulatory Approval	Description of the firewall to maintain data integrity has been edited.
<p>Rationale: Study drug supplies may be supplied in bottles rather than blister packs in the future.</p>	
14.2. Packaging	Provided for use of bottles.
<p>Rationale: Company name and sponsorship statement updated due to the recent change in various legal entity names.</p>	
Title Page; Attachment 4	Changed name from Johnson and Johnson Pharmaceutical Research and Development to Janssen Research and Development.

Amendment INT-4 (8 September 2011)

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 overall reasons for the amendment are (1) to remove the pre-planned adaptation to re-estimate the sample size for Cohort B and (2) to specify that an interim analysis of the ongoing CANVAS (DIA3008) study will be required for reporting of safety data in the initial canagliflozin marketing applications.

Applicable Section(s)	Description of Change(s)
<p>Rationale: In discussions between the sponsor and the CANVAS Steering Committee, a fixed sample size approach has been chosen as this is a more statistically and analytically sound approach, relative to adaptation, to re-estimate sample size.</p>	
Synopsis; 1.2. Overall Rationale and Goals for the Study; 3. Overview of Study Design; 3.2. Study Design Rationale; 11.9. Feasibility Assessment	The pre-planned adaptation to re-estimate the sample size for Cohort B will no longer be conducted. The description of the prior adaptive design was modified to reflect the fixed sample size of the 2 sequential cohorts.

Applicable Section(s)	Description of Change(s)
	<p>Rationale: Since CANVAS (DIA3008) contributes a substantial amount of placebo-controlled, safety data in a high-risk population to the overall canagliflozin development program, health authorities will be expecting to review unblinded data from this study in order to make a determination of overall safety and efficacy of this compound and ultimately a decision on the approvability of canagliflozin.</p>
11.7.1. Interim Analyses for Health Authority Submissions	New section added. Text added to the protocol indicating that an unblinded interim analyses of CANVAS data will be done to prepare an interim safety report in support of the initial health authority filing.
	<p>Rationale: Recently published literature with other drugs in the SGLT2 inhibitor class suggest that the observed standard deviation with respect to HbA_{1c} change from baseline in subjects taking sulfonylureas is less than originally anticipated in the protocol. The new data would allow for an assessment of the primary substudy endpoint (ie, change in HbA_{1c} from baseline) in the sulfonylurea substudy using a smaller samples size than originally planned, ie, approximately 50 subjects per group (instead of 86 subjects per group) while retaining adequate power.</p>
11.10.2. Sample Size Determination; References	Added a reference to support the analysis of the sulfonylurea substudy with at least 50 subjects per group.
	<p>Rationale: An evaluation of intermediate endpoints to assess the feasibility in enrolling Cohort B involves modeling the effects on surrogate markers, such as blood pressure, body weight, and fasting lipids, in order to derive a predicted HR. Such an evaluation is beyond the current scope of the IDMC's responsibility, which is focused on ensuring the safety of subjects enrolled in the study.</p>
Synopsis; 4.1. General Considerations; 11.3.2. Subsequent Cohort (Cohort B); 11.7.2. Interim Analysis to Assess the Feasibility in Initiating Cohort B; 11.9. Feasibility Assessment	A CV risk factor evaluation committee was formed to evaluate the effects of canagliflozin on intermediate outcomes (eg, blood pressure, fasting lipids, body weight).
	<p>Rationale: The investigator should be allowed to retain some autonomy in their clinical diagnoses which may or may not coincide with the Adjudication Committee's clinical diagnosis.</p>
12. Adverse Event Reporting	Added a stipulation that any nonfatal CV event in the composite endpoint initially classified as a serious adverse event, but subsequently determined by the Endpoint Adjudication Committee as meeting the definition of a study endpoint, will be reviewed on an individual basis by the sponsor to determine whether or not such an event should be reported by the investigator on the CV events eCRF page (and removed from the adverse event/serious adverse event eCRF page).

Amendment INT-3 (11 Mar 2011)

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 overall reasons for the amendment are (1) to describe procedures associated with the use of rosiglitazone in light of recent regulatory actions and (2) to add to the follow-up provisions for subjects who discontinue double-blind study drug prior to completion of the study.

Applicable Section(s)	INT-3 Description of Change(s)
-----------------------	--------------------------------

Rationale: Addition of new nonclinical study results.

1.1.1. Brief Overview of Nonclinical Studies	The results of genotoxicity and carcinogenicity studies in rats were included.
--	--

Rationale: Rosiglitazone has been withdrawn or restrictions have been placed on its use in several markets worldwide.

2.3. Substudies: Objectives and Hypotheses (Cohort A); 3.1. Study Design; 4.1. General Considerations; 4.2. Inclusion Criteria; 5. Treatment Allocation	Rosiglitazone was removed from the list of approved background AHAs.
---	--

4.1. General Considerations	Procedures for handling subjects taking rosiglitazone were added.
-----------------------------	---

4.3. Exclusion Criteria – Medications/ Therapies	Rosiglitazone was added to the list of exclusionary medications.
--	--

Rationale: Additional follow-up measures for subjects who discontinue double-blind study drug early will allow for a more comprehensive safety dataset.

Posttreatment Time & Events Schedule	Added new Posttreatment Time & Events Schedule for subjects who prematurely discontinue study medication.
--------------------------------------	---

Rationale: Additional information regarding superficial genital adverse events in men will be collected in the canagliflozin development program to better characterize this recently identified adverse drug reaction.

3.1. Study Design; 3.2. Study Design Rationale; 12. Adverse Event Reporting	Superficial genital adverse events in men were added to the list of selected adverse events.
--	--

Applicable Section(s)	INT-3 Description of Change(s)
	Rationale: The exclusion criterion related to thyroid stimulating hormone (TSH) was modified in INT-2, and measurement of TSH at Run-in is no longer necessary.
Time & Events Schedule; Attachment 6	Thyroid stimulating hormone was removed as a procedure at the Week -2 (Run-in Start) visit.
	Rationale: Pharmacogenomic samples will continue to be collected as planned; however, the analyses of those samples will not be prespecified in the statistical methods section of the protocol.
11.11. Pharmacogenomic Analyses	This section was removed from the protocol.
	Rationale: Updates need to align with other canagliflozin Phase 3 protocols.
3.2. Study Design Rationale; 9.1.1. Overview; 9.7. Exploratory Evaluations	Description of the exploratory samples was aligned with the global canagliflozin Phase 3 protocols.
3.1. Study Design; 3.2. Study Design Rationale; 12. Adverse Event Reporting	Hypoglycemia was removed from the list of selected adverse events for editorial reasons because additional information is collected on all hypoglycemic episodes, irrespective of whether the episode is considered an adverse event.
	Rationale: Flexibility for first morning void collection was needed for subjects with atypical sleep patterns.
Time & Events Schedule; 9.4. Safety Evaluations	Added a clarification that for subjects working a night shift, or who otherwise have atypical sleep patterns, the first morning void collection should be made at the end of the subject's usual sleep period.
	Rationale: Clarification of blood pressure and body weight measurements were needed.
9.4. Safety Evaluations	Specified that blood pressure will be measured 3 times in both arms at the screening visit.
	Specified that if disrobing for weighing is logistically impossible, the subject must be dressed as lightly as possible, with consistency from visit to visit.
	Rationale: 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 another unforeseen circumstance may need to return to active status (ie, re-start double-blind study drug).
10.3. Reinstitution of Subjects who Have Prematurely Discontinued Double-blind Study Drug to Active Status	New section added.

Applicable Section(s)	INT-3 Description of Change(s)
Rationale: The per-protocol analysis set definition was too restrictive based upon ICH definition of major protocol deviations.	
11.10.1. Analysis Sets	Clarified that having no major protocol deviations to be included in the per-protocol analysis set means having no deviations that may affect the interpretation of the primary efficacy endpoint.
Rationale: Follow-up telephone contact may not always be possible.	
Throughout the protocol	Noted that if a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic means.

Amendment INT-2 (27 April 2010)

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 overall reasons for the amendment are to (1) add additional data that demonstrated no clinically meaningful photosensitizing potential of canagliflozin in humans and to remove the photoprotection prohibition; and (2) add additional data of co-administration of digoxin and canagliflozin and the removal of digoxin as a prohibited medication.

Applicable Section(s)	INT-2 Description of Change(s)
Rationale: Additional studies that evaluated the photosensitizing potential of canagliflozin in humans have been completed.	
1.1.2. Clinical Studies; 3.2. Study Design Rationale	Findings of the photosensitivity studies in Caucasian subjects were added, demonstrating that canagliflozin 100 mg or 300 mg once daily, the clinical doses used in the Phase 3 studies, had no delayed photosensitizing effect at any wavebands representing the terrestrial solar spectrum.
4.4. Prohibitions and Restrictions	Instructions that subjects should use photoprotective measures were removed.
16.1. Study-Specific Design Considerations	Instructions that subjects should use photoprotective measures were removed. Text stating that the photosensitivity studies support safe participation of subjects in these Phase 3 studies without specific photoprotection precautions was added.
Rationale: A Phase 1 drug-drug interaction study with digoxin has been completed.	
1.1.2. Clinical Studies	A description of the main pharmacokinetic findings from the study was added.
4.3. Exclusion Criteria; 4.4. Prohibitions and Restrictions	Digoxin was removed as a prohibited medication and subjects will no longer be excluded for taking this medication.

Applicable Section(s)	INT-2 Description of Change(s)
Rationale: Study oversight committee structure and responsibilities were modified with input from Steering Committee.	
9.3.4. Executive Committee; throughout the protocol	Section removed. “Executive” Committee changed to “Steering” Committee throughout the protocol.
Rationale: Clarification regarding the meta-analysis for pre-regulatory approval could occur with as few as 80 events and as many as 160 events.	
11.8.1. Meta-analysis Pre-Regulatory Approval	The maximum number of expected events in the first meta-analysis for CV safety was modified from 140 to an approximate range of 140 to 160 (with the number from the CANVAS study changed from 100 to a range of 110 to 120). In no event would the meta-analysis to support regulatory approval occur with fewer than 80 events.
Rationale: Follow-up contact in other Phase 3 protocols is 30 days after last dose of study drug in accordance with requirements for SAE reporting.	
Throughout the protocol	Follow-up contact after last dose of study drug was changed from 28 to 30 days. The collection time frame after last dose of study medication for CV events for the CV analysis was changed from 28 to 30 days. The time frame for reporting SAEs after last dose of study drug was changed from 28 to 30 days.
12.2.1. All Adverse Events	Corrected the time point at which the 30-day reporting period for SAEs starts (changed to the “last dose of study medication” instead of “last follow-up contact”).
Rationale: Description of events that require additional data collection was revised to be consistent with program-wide data collection.	
3.1. Study Design; 3.2. Study Design Rationale; 9.4. Safety Evaluation; 12. Adverse Events	Events of increased ALT \geq 3-fold the upper limit of normal (ULN) were removed from the events that require a separate section in the eCRFs for collection of additional information. Clarification was added that investigators may be contacted and requested to provide additional information regarding such events and that subjects will be monitored and managed according to the algorithm in Attachment 7.
Rationale: Additional Phase 1 studies have been completed.	
1.1.2. Clinical Studies	The number of subjects who participated in the Phase 1/1b studies was updated.
Rationale: Single-blind placebo capsules were described as “tablets” in error.	
Synopsis; 3.1. Study Design; 4.2. Inclusion Criteria; 6.1. Study Drugs; 9.1.2. Pretreatment; 9.1.3. Double-blind Treatment	Single-blind placebo “tablets” were changed to single-blind placebo “capsules.” Clarification was added that subjects are to take one single-blind capsule once daily during the 2-week run-in period.
Rationale: Hematology was not originally included at end-of-treatment/early withdrawal visit, but is needed for optimal safety monitoring.	
Time and Events Schedule	Hematology was added at end-of-treatment/early withdrawal visit.

Applicable Section(s)	INT-2 Description of Change(s)
Rationale: Input from the Steering Committee was received after further review of data from other CV outcomes trials.	
4.2. Inclusion Criteria	The blood pressure criterion was modified to clarify that the value should be an average of 3 readings recorded at the screening visit.
Rationale: The standard exclusion criteria wording has been modified in other issued canagliflozin Phase 3 protocols.	
4.3. Exclusion Criteria	Thyroid exclusion criterion was modified for consistency with the other protocols.
4.3. Exclusion Criteria	The laboratory exclusion criterion for subjects taking metformin was modified to a serum creatinine level of ≥ 1.4 mg/dL (124 $\mu\text{mol/L}$) for men or ≥ 1.3 mg/dL (115 $\mu\text{mol/L}$) for women and with no contraindication to the use of metformin (including eGFR) based on the label of the country of the investigational site.
4.3. Exclusion Criteria; 5. Treatment Allocation	The definition of a stable dose of insulin was modified from a $\leq 10\%$ change to a $\leq 15\%$ change.
Rationale: The standard prohibition and restrictions wording has been modified in other canagliflozin Phase 3 protocols.	
4.4. Prohibitions and Restrictions	A bullet was added with instructions that subjects should not collect first morning void during acute illness with fever.
Rationale: For consistency with standards of care for glycemic rescue in clinical trials and with other canagliflozin Phase 3 protocols.	
6.2.2. Glycemic Rescue Therapy Through Week 18 for Initial Cohort (Cohort A): Criteria and Implementation	The time points for rescue were modified: “Week 4” was changed to “Week 6.”
Rationale: Health authorities have requested that a “firewall” be established to ensure data integrity in the CANVAS study.	
11.8.1. Meta-analysis Pre-Regulatory Approval	Description of the firewall to maintain data integrity has been added.
Rationale: Additional canagliflozin Phase 3 protocols have been issued and program-wide wording and standards have been established for consistency.	
Throughout the protocol	Updates were made for consistency with the other Phase 3 protocols.
Section 1. Introduction; References	References added.

Amendment INT-1 (16 September 2009)

The overall reason for the amendment: Protocol was amended to further clarify the interim analysis and adaptation plan for the study.

Applicable Section(s)	INT-1 Description of Change(s)
-----------------------	--------------------------------

Rationale: Description of the criteria for adaptation and the potential for enrollment of a second cohort of subjects was clarified. In addition, the roles of the Independent Data Monitoring Committee (IDMC) and Executive Committee in the interim analysis and adaptation of the study were clarified.

Synopsis Overview of Study Design; 1.2. Overall Rationale; 3. Overview of Study Design; 3.1. Study Design; 3.2 Study Design Rationale; 9.3.5. IDMC; 11.3 Sample Size Determination; 11.7 Interim Analysis	Updated Text
---	--------------

Rationale: Description of the initial cohort (referred to as Cohort A) and the subsequent cohort (referred to as Cohort B) was modified for clarity.

Throughout the protocol	Previously described as Cohort A and Cohort B; now described as initial cohort (Cohort A) and subsequent cohort (Cohort B).
-------------------------	---

Rationale: First morning void urine collection was added to run-in visit to provide additional baseline data for comparison with treated values.

Time and Events Schedule	
--------------------------	--

Rationale: Description of the inclusion and exclusion criteria and prohibitions and restrictions were aligned with other Phase 3 studies in the canagliflozin development program for consistency.

4.1. Inclusion Criteria; 4.2. Exclusion Criteria; 4.4 Prohibitions and Restrictions	Minor changes to the text were made.
---	--------------------------------------

Rationale: The study drug kit number will be automatically recorded.

5. Treatment Allocation	Deleted statement that the study drug kit number will be entered in the electronic case report form (CRF) when the drug is assigned.
-------------------------	--

Rationale: Clarification regarding urinalysis by a local laboratory for safety reasons was needed.

5. Treatment Allocation	Added a statement that if 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).
-------------------------	--

Applicable Section(s)	INT-1 Description of Change(s)
<p>Rationale: Consideration was needed for subjects who do not meet screening adjustment/optimization of lipid altering or blood pressure-lowering medications.</p>	
<p>9.1.1. Overview, 9.1.2. Pretreatment</p>	<p>Added text stating that if additional time in run-in is required for adjustment/optimization of lipid altering or blood pressure-lowering medications, (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks (note: the single-blind placebo package contains sufficient drug supply for additional time period)</p>
<p>Rationale: Exploratory samples were under 2 different informed consents; modifications to the description were made to simplify the consent process and include the samples for exploratory research under a single informed consent.</p>	
<p>9.1.1. Overview; Attachment 4</p>	<p>Modified text to clarify that one set of plasma, serum, and urine samples will be collected at baseline and all 52-week intervals from subjects who consent to this component of the study to allow for exploratory research related to canagliflozin or biomarker analyses.</p>
<p>Rationale: Hypoglycemic events will be captured as non-serious adverse events in addition to recording the information on the hypoglycemia section of the eCRF.</p>	
<p>9.4. Safety evaluations; 12.2.4. Hypoglycemia</p>	<p>Added text stating that information on possible hypoglycemic events will be collected on a separate hypoglycemia eCRF page, and hypoglycemic events should be recorded on the adverse event eCRF, if considered an adverse event by the investigator.</p>
<p>Rationale: Clarification of certain procedures and corresponding analyses was needed.</p>	
<p>9.4. Safety evaluations; 9.5. Efficacy Evaluations; 11. Statistical Methods</p>	<ul style="list-style-type: none"> • Physical examinations elaborated; estimated glomerular filtration rate (eGFR) evaluations moved from safety to efficacy; Medical Resource Utilization evaluation removed from follow-up telephone contact procedures.

SYNOPSIS

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (CANVAS: CANagliflozin cardioVascular Assessment Study)

EUDRACT number: 2009-012140-16

Canagliflozin (JNJ-28431754) is an orally active inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that is being developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). Canagliflozin is selective for inhibition for SGLT2 relative to sodium-glucose co-transporter 1 (SGLT1). The initial goals of this study (CANVAS) were to assess the overall safety and tolerability of canagliflozin and to demonstrate a reduction in major adverse cardiovascular events (MACE) with canagliflozin treatment.

Prior clinical studies of canagliflozin in patients with T2DM have demonstrated improvements in glycemic control (with reductions in hemoglobin A_{1c} [HbA_{1c}] and fasting plasma glucose [FPG]), reduction in body weight, and trends towards improvements in other cardiovascular (CV) disease risk factors (including increases in high-density lipoprotein cholesterol [HDL-C], decreases in triglyceride levels, and decreases in blood pressure, especially at the 300-mg dose), with generally good tolerance and appropriate safety to support continued clinical development of this medication. With improved glycemic control, which itself may provide a benefit in CV risk, and the trends towards benefit on other CV risk factors including body weight, the potential for a benefit of long-term treatment with canagliflozin on CV disease is raised.

The present study was intended to assess if treatment of subjects with T2DM with canagliflozin reduces CV risk for MACE (including CV death, nonfatal myocardial infarction [MI], and nonfatal stroke) and to achieve a number of other important goals. These include the assessment of overall safety and tolerability, glycemic efficacy (in the overall study population and in subjects on specific AHAs), long-term effects on beta-cell function, and long-term effects on renal function with canagliflozin treatment. This study also provides key support for a cross-canagliflozin program assessment of CV safety, examining a composite endpoint of MACE plus hospitalized unstable angina (pre-approval CV safety assessment) and MACE (post-approval CV safety assessment). Subsequent to the initial plan it has been necessary to modify the design of the study.

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-R; 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; 28431754DIA4003) in a pre-specified meta-analysis of CV safety outcomes, to satisfy post-approval United States (US) Food and Drug Administration (FDA) post-marketing requirements for canagliflozin.

OBJECTIVES AND HYPOTHESES

Primary Objectives

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

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

The data from this study will be combined with the data from CANVAS-R in a pre-specified meta-analysis of CV safety outcomes to satisfy US FDA post-marketing requirements for canagliflozin.

Secondary Objectives

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

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

- fasting measures of beta-cell function (homeostasis model assessment [HOMA]-B and the proinsulin/insulin ratio) (Note: this assessment will be conducted in a subset of subjects at sites that elect to participate, including only subjects who are not receiving insulin at randomization).
- the proportion of subjects with progression of albuminuria (progression defined as ≥ 1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria)
- the urinary albumin/creatinine ratio
- renal function (as measured by the change from baseline in estimated glomerular filtration rate [eGFR])
- to assess the effect of canagliflozin relative to placebo after 18 weeks and at the end of the treatment period on:
 - glycemic efficacy (HbA_{1c} and FPG)
 - body weight
 - blood pressure (systolic and diastolic)
 - fasting plasma lipids (triglycerides, HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses

Primary hypothesis

In subjects with T2DM with inadequate glycemic control who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV risk (as measured by the HR for a composite endpoint including CV death, nonfatal MI, and nonfatal stroke).

Secondary hypotheses

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

- improves beta-cell function (change from baseline in HOMA-B)
- reduces progression of albuminuria (ie, proportion of subjects with a ≥ 1 -step progression of albuminuria measured by the urine albumin/creatinine ratio)

(See protocol body for objectives and hypotheses for substudies examining the efficacy and safety of canagliflozin in combination with specific AHAs.)

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM, on a wide range of antihyperglycemic therapies, who have either a history or high risk of CV disease. Although the effects of canagliflozin on several CV risk factors (eg, glycemic control, body weight, blood pressure) appear favorable in short-term studies, the longer-term benefits on CV risk factors are currently unknown; in addition, Phase 3 results demonstrated a small increase in LDL-C, without a change in the LDL-C to HDL-C ratio. Note that results from this study, integrated with cross-Phase 3 program results, were included in a pre-approval meta-analysis to evaluate CV safety (as required by the US FDA Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes) by examining the composite of MACE plus hospitalized unstable angina (referred to as the pre-approval CV safety endpoint). This CV meta-analysis was conducted in 2012 (addressing the US FDA filing requirement that the upper bound of the 2-sided 95% confidence interval (CI) around the CV HR is < 1.8); this meta-analysis confirmed the requirement, showing the upper bound was < 1.8 .

This study was originally designed to include 2 sequential cohorts, with up to 18,500 subjects and a study duration for individual subjects of up to approximately 8 years. The study will now recruit only the initial 4,330 subjects who were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg)

or placebo, in a 1:1:1 ratio. The study's last subject last visit will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies which is projected to occur prior to April 2017.

The study was modified (as of amendment INT-5) because the cross-program meta-analysis of the pre-approval CV safety endpoint was unblinded to the sponsor to prepare regulatory submissions (originally this was to be unblinded to the study IDMC only); this was done based upon a decision by the sponsor, so that the impact of the small dose-related increase in LDL-C observed with canagliflozin treatment in Phase 3 program on the CV HR could be evaluated. Due to the unblinding of these CV endpoint results, the study Steering Committee noted that the addition to the CANVAS trial of the planned second cohort of subjects would not provide a robust assessment of the primary CV protection hypothesis.

The CANVAS study has additional objectives including the assessment of overall safety and tolerability of canagliflozin. The study also includes several substudies intended to provide additional information about the efficacy and safety of canagliflozin compared to placebo in combination with specific AHAs.

In this study, investigators will be counseled to assure appropriate management of CV risk factors (eg, blood pressure and lipids) according to standard guidelines (eg, the American Diabetes Association [ADA] or other local diabetes guidelines) for the care of patients with T2DM. In addition, after a relatively brief period during which the subject's antihyperglycemic regimen is to be kept stable (described in the section below), investigators will attempt to achieve good glycemic control, consistent with standard diabetes guidelines, individualized as considered clinically appropriate, with up-titration or stepwise addition of AHA therapies. Thus, this study will examine the impact on CV risk, and the safety and tolerability of treatment with canagliflozin along with standard of care for CV risk factor and glycemic management relative to placebo with standard of care management.

STUDY POPULATION

Men or women with T2DM who have inadequate glycemic control ($HbA_{1c} \geq 7.0$ and $\leq 10.5\%$), not on an AHA or on an AHA in monotherapy or combination therapy, and who have known CV disease or who have 2 or more risk factors for CV events are eligible.

STRATIFICATION FOR SUBSTUDIES

Subjects will have within-subgroup balanced (1:1:1) randomization to each of the 3 treatment groups within 6 predefined strata based upon AHA medication(s) that the subject is receiving at the run-in visit and will be continuing at entry into the double-blind treatment phase (the strata are defined in the main body of the protocol).

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 administered once-daily).

Subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. Subjects will be counseled to take their dose of canagliflozin or matching placebo once daily, before the first meal of the day, according to their randomized treatment assignment, for the duration of the study or until early discontinuation.

Concomitant Antihyperglycemic and Other Therapies

Detailed instructions are provided in the main protocol for management of (1) glycemic control and CV risk factors, and (2) glycemic rescue therapy through Week 18.

EFFICACY AND SAFETY OUTCOME DEFINITIONS/EVALUATION CRITERIA

Primary MACE Outcome

The hypothesis of CV risk reduction for canagliflozin will be evaluated based upon the events in the CV composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). An independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and

only those events where the committee, using methodology and definitions defined in the committee's charter, determines a specified endpoint has occurred will be included in the primary analysis. The independent Endpoint Adjudication Committee will apply the endpoint definitions contained in its charter and classify the outcome events while blinded to treatment assignment.

Secondary Efficacy Endpoints

Secondary measures of efficacy include beta-cell function (HOMA-B; in subjects who are not receiving insulin) and progression of albuminuria (based upon categories determined by urinary albumin/creatinine ratio).

Additional efficacy endpoints of interest will include the following: changes from baseline to end-of-treatment in the proinsulin/insulin ratio (in a subset of subjects), urinary albumin/creatinine ratio, and eGFR; changes from baseline to Week 18 in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight; and percent change from baseline to Week 18 in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C).

Measurements to assess HOMA-B and the proinsulin/insulin ratio will be collected in a subset of subjects of approximately 1,200 subjects (at sites that elect to participate) who are not receiving insulin at baseline.

Safety and Tolerability Assessments

The safety and tolerability assessments will include an evaluation of serious adverse events, adverse events of interest, discontinuation due to adverse events, clinical laboratory tests, vital signs (pulse, blood pressure), and body weight. Cardiovascular safety will be assessed as a part of the meta-analysis of CANVAS and CANVAS-R.

STATISTICAL METHODS

Analysis Sets

The ITT analysis set includes all subjects who are randomly assigned to a treatment group. The assessment of the primary objective will be based upon this analysis set. The primary CV analysis will be based on the time to the first occurrence of any component of the MACE composite endpoint. The modified ITT (mITT) analysis set includes the randomized subjects who receive at least one dose of study drug and their data occurring between first dose and last dose plus 30 days.

The alignment of the analysis of the secondary endpoints with the ITT and mITT analysis sets will be detailed in the study statistical analysis plan (SAP).

Sample Size Determination

The sample size for the recruitment of the initial 4,500 subjects was based upon having a sufficient number of participants to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed pre-approval assessment of the safety and tolerability of canagliflozin. Data from this initial cohort were exported and integrated with data from other Phase 3 well-controlled studies to support a planned, pre-approval meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI for the CV HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) was <1.8, as part of the current US regulatory requirements for filing. The FDA post-marketing requirements for canagliflozin demand a subsequent estimate of CV safety that will be performed on data from CANVAS and CANVAS-R, when sufficient events have occurred to demonstrate that the upper bound of the 95% CI HR is <1.3 based on MACE (excluding hospitalized unstable angina).

The assumed per annum event rate is 2.25% and the per annum dropout rate is 5% with an enrollment period of 1.5 years, 4,500 randomized subjects were projected to contribute sufficient CV events to support the pre-approval meta-analysis. The original phased recruitment strategy allowed for an interim assessment of study feasibility to demonstrate the primary hypothesis of CV benefit using the results of the interim analysis. Results from the interim analysis (after approximately 2 to 4 years from study initiation, eg, at approximately the time of US regulatory approval) were planned to be evaluated by a CV risk factor evaluation committee to assess the effect of canagliflozin on CV risk factors (to predict the likely effect of canagliflozin on CV events) and determine the point estimate for the HR for MACE. The data on the observed point estimate for the CV HR for MACE were to have been reviewed by the IDMC only and not

made more broadly available. Re-opening of enrollment was to have proceeded if the effects on the intermediate outcomes (ie, CV risk factors) suggested that canagliflozin compared with placebo would result in an HR of 0.85 or less (for MACE) and if the observed HR was 0.95 or less. If recruitment did proceed, an additional 14,000 subjects would have been enrolled into Cohort B. However, for the reason outlined above, this second cohort will no longer be recruited.

Without the recruitment of the second cohort of 14,000 subjects, CANVAS study power is reduced from the originally planned 90% power to detect a HR of 0.85 or less. It is now projected that at the completion of the study there will be about 400 MACE events recorded within CANVAS, which will provide 33% power to detect a HR of 0.85 or less, 55% power to detect a HR of 0.80 or less, and 76% power to detect a HR of 0.75 or less using a 2-sided test with 0.05 alpha.

Safety and Tolerability Analysis

Safety and tolerability will be evaluated by summarizing and comparing the incidence of serious adverse events and adverse events of interest, discontinuation rate due to adverse events, clinically important changes in clinical laboratory tests, vital signs (pulse, blood pressure), and body weight between randomized groups. There will be no imputation for missing values for clinical laboratory test results or vital sign measurements in the analyses.

CV Outcomes (Primary Efficacy Endpoint)

The primary endpoint for CV benefit will be time to MACE, which is calculated as the time from randomization to the first occurrence of MACE. The statistical hypothesis will be:

$H_{0(1.0)}$: the HR =1.0, versus $H_{1(1.0)}$: the HR \neq 1.0.

The primary analysis will be based on the ITT analysis set based upon events determined by the EAC to meet prespecified criteria. The primary comparison of canagliflozin to placebo will be based on the HR estimate derived from a Cox proportional hazards model with terms for treatment and history of a previous CV event as fixed effects.

The assumption of the proportional HR will be examined. In case the assumption is deemed not reasonable, sensitivity analyses that do not rely on the constant HR assumption will be conducted to verify the results of the primary analysis. Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For individual components of the composite CV endpoint, the HR and its 2-sided 95% CIs of canagliflozin combined doses relative to placebo will also be assessed.

Sensitivity analyses including CV endpoint events that occur within 30 days of the last dose of blinded study medication will be done.

The effects of different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, key concomitant therapy use, and region) on the primary endpoint will be explored; a detailed discussion of subgroup analyses will be provided in a SAP for this study which will be finalized before the first interim analysis.

Major Secondary Efficacy Analysis

Changes from baseline in the continuous variables of HOMA-B and the proinsulin/insulin ratio, HbA_{1c}, FPG, blood pressure, body weight, albuminuria, and eGFR, and percent change in fasting lipids will be analyzed using an analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg, canagliflozin 300 mg, or placebo), and stratification factors as a fixed effect and the corresponding baseline value as a covariate. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The analyses for beta-cell function will be conducted on subjects not receiving insulin at randomization and, for subjects who are started on insulin during the study, the last data point before the initiation of insulin will be included for these analyses.

The categorical secondary efficacy endpoint is the proportion of subjects with progression of albuminuria (defined as ≥ 1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria). The proportion of subjects with progression of albuminuria will be analyzed using

the logistic model with treatment (canagliflozin 100 mg, canagliflozin 300 mg or placebo) and stratification factors as a fixed effect.

Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in this study is at most 5%, a gatekeeping procedure will be applied in testing the primary and secondary hypotheses.

Interim Analysis

Interim analyses of CANVAS will be done to prepare: (1) an interim safety report in support of the initial health authority filing, (2) the 18-week substudy reports, and (3) the CV safety meta-analyses (based on adjudicated data). The interim data from the CANVAS study will primarily supplement the safety and tolerability data generated from other studies in the canagliflozin development program.

TIME AND EVENTS SCHEDULE (CONTINUED)

- ^a Following the run-in visit, there will be a single-blind, placebo run-in period, during which therapy for diabetes should remain stable and therapy for CV risk factors (eg, blood pressure, fasting lipids) will be optimized as needed, at the investigator's discretion. Subjects who fail protocol-specified screening criteria for study entry may be rescreened, at the discretion of the investigator as described in Section 4.5, Rescreening.
- ^b End-of-treatment/early withdrawal evaluations will be performed when the double-blind treatment phase of the study is ended or at the time the subject discontinues the double-blind study drug or is withdrawn from the study. Evaluations will be performed as soon as possible after stopping the study drug. Subjects who discontinue double-blind treatment for any reason will have a posttreatment follow-up contact and visits according to the Posttreatment Time and Events Schedule for the duration of the study, until completion of the study. 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, and the use of locator agencies and checking public records, as allowed by local law.
- ^c A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 30 days (and no more than 42 days) after the last dose of study drug. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.
- ^d After Week 65, on those occasions when the 13- 26-, and/or 52-week-interval visits overlap each other, the visit with the more comprehensive procedures will be followed.
- ^e Telephone contact (or an optional, unscheduled site visit, at the discretion of the investigator) will be made at Weeks 2, 4, and 9 to check the subject's status, including discussing the subject's diary entries and any CV events or adverse events. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.
- ^f See Section 16.2.3, Informed Consent, for details. The informed consent form must be signed before any study procedure is performed.
- ^g Record as prestudy therapy any medications taken from 30 days before screening (except for AHAs; record AHAs taken within 12 months of screening).
- ^h Subjects will receive information regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia (and concurrent fingerstick glucose measurement, if available) should be captured in the subject diary, which should be brought to the study center for review by research study staff.
- ⁱ Full physical examination will include a full review of body systems (vital signs, as below, head and neck, eyes, chest and lungs, breast, CV, extremities and back, abdomen, and neurological examination). A pelvic/genitourinary system examination (ie, prostate, rectal, and gynecologic examinations) should be performed if considered clinically appropriate by the investigator.
- ^j 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). 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 All Adverse Events for further detail).
- ^k Only required before a 52-week interval visit, regardless of whether the subject is coming for in-clinic visits every 13 or 26 weeks.
- ^l Medical resource utilization (MRU) data should be collected in the subject diary. A sample list of MRU questions contained in the diary is provided in Attachment 9.
- ^m Specific details about specimen collection, storage, packaging, and shipping will be provided in operations manuals. For fasting plasma glucose, insulin, proinsulin, C-peptide, and lipids, subjects must be fasting for at least 8 hours before blood sample collection, except for the screening visit when nonfasting blood samples may be collected. The first morning void specimens will be used to measure albumin and creatinine. A set of plasma, serum, and urine samples for exploratory analysis will be collected at each specified time point. (Specific details about specimen collection, storage, packaging, and shipping are provided in Attachment 4.) The urine collections for routine urinalyses and exploratory specimens should be obtained from a spot urine specimen in the clinic.

(Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

- ⁿ If the subject is fasting at the screening visit, the lipid profile can be obtained at that time point; otherwise, fasting lipid profile should be obtained at the Week -2 visit.
- ^o C-peptide, insulin, and proinsulin measurements will be performed on a subset of subjects (at sites that elect to participate) who are not receiving insulin at baseline; if a subject starts insulin therapy after baseline, no further assessments of these analytes will be made for that subject.
- ^p The subject will provide a urine specimen from the first morning void on the morning of the clinic visit. If the subject does not provide the morning void collection 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.
- ^q Subject participation in the pharmacogenomics component of the study is optional. A 10-mL blood sample will be collected only from subjects who give informed consent for the pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). A sample may be collected at any point in time during the study if not obtained at baseline.
- ^r If positive, the subject is not eligible to enter or continue in the study. A urine pregnancy test will be performed at all specified pre-randomization clinic visits, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations. Serum or urine pregnancy tests may be performed in women (unless they are surgically sterile or unless there is a documented history of their postmenopausal status), as determined by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the study.
- ^s See Section 9.1.1, Overview, for diary procedures.
- ^t Concomitant therapy includes all medications taken 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.
- ^u Only serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest will be recorded on eCRFs. 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 a supplemental eCRF 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, venous thromboembolic events, and male genital infections (balanitis, phimosis, events leading to circumcision) and amputation 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 DKA, ketoacidosis, metabolic acidosis or acidosis need to be reported to the sponsor 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. Amputation has also been designated as an adverse event 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. Details regarding adverse event collections are provided in Section 9.4, Safety Evaluations.
- ^v Every 13-week in-clinic visits are no longer required and may be changed to every 26-week in-clinic visits (at the option of the investigator). Accordingly, study drug may be supplied every 13 or 26 weeks. If in-clinic visits are changed to a every 26 week frequency, a telephone contact should occur in between the 26-week in-clinic visits such that there will be a contact with the subject every 13 weeks (in-clinic visit alternating with telephone contacts). At each telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

POSTTREATMENT TIME AND EVENTS SCHEDULE – SUBJECTS WHO PREMATURELY DISCONTINUE STUDY MEDICATION

Phase	Double-Blind Visit Schedule (Posttreatment)										
	- Starting at the nearest post-randomization week after the Follow-up					Contact Visit -					
Procedures and Evaluations											
Week ^a	2, 4 (TC) ^b	6	(TC) ^b	9	12	18	26	39	52	78 to end ^e	104 to end ^e
Procedures											
Vital signs, weight, Foot examination ^c		X		X	X	X	X	X	X	X	X
Provide container for urine collection for first morning void		X						X		X (foot examination only)	X
Serum creatinine		X			X	X	X	X	X		X
HbA _{1c}			X	X	X	X	X	X	X		X
Fasting serum lipids				X	X	X	X	X	X		X
First morning void urine for albumin/creatinine ratio ^d				X	X	X	X	X	X		X
Ongoing review											
Serious adverse events and adverse events of fracture	X	X	X	X	X	X	X	X	X	X	X
AHA agents after study drug discontinuation											At final visit or contact
Events in CV composite endpoint	X	X	X	X	X	X	X	X	X	X	X

^a After Week 78, on those occasions when the 26- and/or 52-week-interval visits overlap each other, the visit with the more comprehensive procedures will be followed.

^b Telephone contact (or an optional, unscheduled site visit, at the discretion of the investigator) will be made at Weeks 2, 4, and 9 to check the subject's status, including discussing the subject's diary entries and any CV events or adverse events. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.

^c 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). At each visit or telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

^d Specific details about specimen collection, storage, packaging, and shipping will be provided in operations manuals. The first morning void specimens will be used to measure albumin and creatinine. The subject will provide a urine specimen from the first morning void on the morning of the clinic visit. If the subject does not provide the morning void collection 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.

^e 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, and the use of locator agencies and checking public records, as allowed by local law.

Note: Alternate follow-up provisions may be used by the investigator if necessary (see Section 9.1.4).

CV=cardiovascular; TC=telephone contact.

ABBREVIATIONS

ADA	American Diabetes Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARO	Academic Research Organization
AST	aspartate aminotransferase
BMI	body mass index
CPK	creatine phosphokinase
CI	confidence interval
CV	cardiovascular
CYP	cytochrome P450
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase 4
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GTED	global trial end date
HbA _{1c}	hemoglobin A _{1c}
HDL-C	high-density lipoprotein cholesterol
HOMA	homeostasis model assessment
HR	hazard ratio
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS/IWRS	interactive voice response system/interactive web response system
LCT	Leydig cell tumor
LDL-C	low-density lipoprotein cholesterol
LOCF	last-observation-carried-forward
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
mITT	modified intent-to-treat
MRU	Medical Resource Utilization
MSRC	Medical Safety Review Committee
NAG	N-acetyl glucosaminidase
NYHA	New York Heart Association
PG	plasma glucose
PP	per-protocol
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
SU	sulphonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
UVA/UVB	ultraviolet A/ultraviolet B

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 the 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.

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in subjects with T2DM. As of 01 May 2013, approximately 1,840 subjects (including healthy subjects, non-diabetic subjects with specific diseases [eg, renal or hepatic disease], and subjects with T2DM), have completed studies in the Phase 1 program conducted by the sponsor. In addition, 1,106 subjects in three Phase 2 studies and 10,961 subjects in 10 Phase 3 studies have completed or are participating in clinical studies conducted by the sponsor.

A Phase 3 development program provided 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 indicate that canagliflozin has the potential to be a useful addition to currently available AHAs.

Canagliflozin was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in the United State (29 March 2013), Australia (12 September 2013) and Mexico (23 October 2013). On 19 September 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for canagliflozin.

An ongoing clinical program designed to continue research on the effects of the agent on renal and CV outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on CV events.

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. Brief Overview of 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 Investigator's Brochure.

1.1.2. Clinical 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, 2 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 dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 agonists.

Glycemic Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing hemoglobin A_{1c} (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 fasting plasma glucose (FPG) as well as in the post-prandial glucose (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, 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 urinary tract infection (mostly lower tract infections) was observed with canagliflozin relative to control, without an increase in serious adverse events of urinary tract infection.

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 there was a low incidence across treatment groups of renal cell cancers without imbalance.

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 cardiovascular study of 4,327 subjects with known or at high risk for cardiovascular disease (Study DIA3008), the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 subject-years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other T2DM studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 subjects, no difference in fracture risk was observed relative to control (Investigator's Brochure).

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 (HR) of 0.91 for a pre-specified composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina (95% confidence interval [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, DKA is considered a rare adverse drug reaction.

During a routine review of unblinded interim data from the ongoing CANVAS study, 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 to 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 amputation included 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. New therapies are needed that can provide improved glycemic control—which has been shown to reduce microvascular complications—and lower the risk of macrovascular complications.

Prior clinical studies of canagliflozin in patients with T2DM have demonstrated improvements in glycemic control (with reductions in HbA_{1c} and FPG), reduction in body weight, and trends towards improvements in other CV disease risk factors (including increases in HDL-C, decreases in triglyceride levels, and decreases in blood pressure, especially at the 300-mg dose), with generally good tolerance and appropriate safety to support continued clinical development of this medication. With improved glycemic control, which itself may provide a benefit in CV risk (Ray 2009), and the trends towards benefit on other CV risk factors including body weight, the potential for a benefit of long-term treatment with canagliflozin on CV disease is raised.

The present study was intended to determine if treatment of subjects with T2DM with canagliflozin reduces CV risk for major adverse cardiovascular events (MACE, including CV death, nonfatal MI, and nonfatal stroke) and also was intended to achieve a number of other important goals. These include the assessment of overall safety and tolerability, glycemic efficacy (in the overall study population and in subjects on specific AHAs), long-term effects on beta-cell function, and long-term effects on renal function with canagliflozin treatment. This study also provides key support for a cross-canagliflozin program assessment of CV safety, examining a composite endpoint of MACE plus hospitalized unstable angina (pre-approval CV safety assessment) and MACE (post-approval CV safety assessment). Subsequent to the initial plan it was necessary to modify the design of the study.

To evaluate the effect of canagliflozin on CV risk, this study was to recruit up to 18,500 subjects with T2DM who are at increased risk for CV events, in 2 separate cohorts, including an initial cohort of 4,500 subjects and a subsequent cohort of 14,000 subjects (recruited after an interim analysis of results from the initial cohort). The study will now continue with the initial 4,330 randomized subjects.

The study was modified (as of amendment INT-5) because the cross-program meta-analysis of the pre-approval CV safety endpoint was unblinded to the sponsor to prepare regulatory submissions (originally this was to be unblinded to the study IDMC only); this was done based upon a decision by the sponsor, so that the impact of the small dose-related increase in LDL-C observed with canagliflozin treatment in Phase 3 program on the CV HR could be evaluated. Due to the unblinding of these CV endpoint results, the study Steering Committee noted that the addition to the CANVAS study of the planned second cohort of subjects would not provide a robust assessment of the primary CV protection hypothesis.

As part of the safety and tolerability objective, the study was originally designed to be able to show, within 4 years of marketing approval in the US, that the upper bound of the CV HR for MACE plus unstable angina events was <1.3. Upon approval of canagliflozin for marketing, the US FDA required that the 1.3 requirement be met with MACE events (ie, CV death, nonfatal MI, and nonfatal stroke, and excluding hospitalized unstable angina), and that additional subjects with high CV risk be recruited to explore events occurring within the first 30 days after initiation of therapy. Accordingly, it was not possible to fulfill these requirements solely with the ongoing CANVAS study within the 4 year post-approval timeframe required by FDA, and therefore another large-scale study of the effects of canagliflozin compared to placebo (CANVAS-R; 28431754DIA4003) with 5,700 subjects is being initiated to meet the FDA CV safety requirement.

The primary objective of the CANVAS-R study is to evaluate the effects of canagliflozin relative to placebo on albuminuria progression. The CANVAS and CANVAS-R studies will share similar inclusion and exclusion criteria and will enroll similar patient

populations. Both studies will require a standardized collection and evaluation of MACE endpoint events by the same Endpoint Adjudication Committee (see Section 9.3.5).

The original CANVAS cohort of 4,330 subjects who were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio will continue to be followed. The data from CANVAS will be combined with the data from CANVAS-R in a pre-specified meta-analysis of CV safety outcomes to satisfy US FDA post-marketing requirements for canagliflozin. The details of the meta-analysis are described in a separate statistical analysis plan (SAP).

The study's last subject last visit is targeted to occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies, which is projected to occur prior to April 2017. In both studies, the effects of canagliflozin are being 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.

Assessment of glycemic efficacy of canagliflozin – overall and in key subgroups

The present study is also intended to provide important information on the glycemic efficacy of this medication. To achieve this goal, subjects will enter an 18-week AHA regimen stable period to provide an opportunity to characterize the glycemic efficacy of canagliflozin relative to placebo in this high CV risk population, and support important analyses aimed at understanding the response to this medication in patient subgroups defined by key demographic and anthropometric components, disease characteristics, and concomitant AHA treatments. After this 18-week AHA regimen stable period, and for the remainder of the double-blind treatment phase, investigators will adjust the subject's AHA regimen with the goal of achieving individualized, target glycemic control.

Embedded within this study are 3 substudies which will compare the glycemic efficacy and assess the safety of canagliflozin relative to placebo in subjects receiving regimens with (1) insulin as monotherapy or in combination therapy, (2) sulfonylurea monotherapy, or (3) pioglitazone and metformin combination therapy. These substudies are being conducted to better characterize the safety, tolerability, and efficacy profile of canagliflozin when used in conjunction with these specific glucose-lowering therapies.

Assessment of long-term effects of canagliflozin on beta-cell function and renal function

Patients with T2DM usually have a progressive deterioration in glycemic control, with the need for stepwise added therapies. Underlying this progressively worse glucose control is a progressive deterioration in beta-cell function. Canagliflozin, by increasing UGE and possibly improving insulin sensitivity through weight loss, may “unload” the beta-cells, lowering secretory demand and potentially improving function over time, and

potentially providing good durability. In addition, improved glycemic control itself, through reversal of so-called “glucotoxicity,” may also improve beta-cell function. Analysis of results from a Phase 1 study in subjects with T2DM did show an improvement in a model-based assessment of beta-cell function, and HOMA-B, a measure of fasting beta-cell insulin secretion, was improved in the Phase 2b study of subjects with T2DM. To assess the effect on beta-cell function over time in the present study, standard fasting measures of beta-cell function (HOMA-B, proinsulin/insulin ratio) will be evaluated.

Another 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 micro-albuminuria that may progress to macro-albuminuria and eventually loss of renal function. By virtue of its improvement in glycemic control, which has been shown to reduce micro-albuminuria progression in prior studies (ADVANCE 2008), and possible effects to reduce blood pressure (if confirmed in larger studies), canagliflozin may slow the progression of diabetic nephropathy. Additionally, proximal tubule inhibition of SGLT2 by canagliflozin is predicted to increase the distal delivery of sodium which could, via the macula densa, lead to a reduction in intraglomerular pressure and a decrease in glomerular damage (Vallon 1999). For these reasons, the study will also examine the potential benefit of canagliflozin on albuminuria.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

2.1.1. Primary Objectives

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

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

The data from this study will be combined with the data from CANVAS-R in a pre-specified meta-analysis of CV safety outcomes to satisfy US FDA post-marketing requirements for canagliflozin.

2.1.2. Secondary Objectives

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

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

- fasting measures of beta-cell function (HOMA-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at sites that elect to participate, including only subjects who are not receiving insulin at randomization)
- the proportion of subjects with progression of albuminuria (progression defined as ≥ 1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria)
- the urinary albumin/creatinine ratio
- renal function (as measured by the change from baseline in eGFR)
- to assess the effect of canagliflozin relative to placebo after 18 weeks and at the end of the treatment period on:
 - glycemic efficacy (HbA_{1c} and FPG)
 - body weight
 - blood pressure (systolic and diastolic)
 - fasting plasma lipids (triglycerides, HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

2.2. Hypotheses

2.2.1. Primary Hypothesis

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV risk (as measured by the HR for a composite endpoint including CV death, nonfatal MI, and nonfatal stroke).

2.2.2. Secondary Hypotheses

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

- improves beta-cell function (change from baseline in HOMA-B)
- reduces progression of albuminuria (ie, proportion of subjects with a ≥ 1 -step progression of albuminuria measured by the urine albumin/creatinine ratio)

2.3. Substudies: Objectives and Hypotheses

The three 18-week substudies will be conducted and are intended to assess the safety and tolerability and efficacy of canagliflozin in subjects with T2DM, with inadequate glycemic control in each of the 3 specific subgroups of subjects receiving (1) insulin ≥ 20 units/day monotherapy or in combination with other AHA(s), (2) sulfonylurea monotherapy at protocol-specified doses ([Attachment 1](#)), or (3) pioglitazone ≥ 30 mg/day plus metformin $\geq 2,000$ mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHA. The following

objectives and hypotheses will apply to each of these substudies. These are separate and distinct from the main study hypothesis testing.

Primary Substudy Objectives

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

- to assess the HbA_{1c}-lowering efficacy (change from baseline in HbA_{1c}) of canagliflozin relative to placebo after 18 weeks of treatment
- to assess the safety and tolerability of canagliflozin

Primary Substudy Hypothesis

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, after 18 weeks of treatment, canagliflozin provides a greater improvement in HbA_{1c} relative to placebo (change from baseline in HbA_{1c}).

Secondary Substudy Objectives and Hypotheses

Objectives

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

- to assess the effect of canagliflozin relative to placebo after 18 weeks on:
 - body weight
 - FPG-lowering efficacy
 - proportion of subjects reaching HbA_{1c} <7.0%
 - systolic and diastolic blood pressure
 - fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)
- to assess the effect of canagliflozin relative to placebo after 52 weeks on:
 - glycemic efficacy (HbA_{1c} and FPG)
 - body weight
 - systolic and diastolic blood pressure
 - fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses

After 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, relative to placebo, canagliflozin:

- reduces body weight

- reduces FPG
- leads to a greater proportion of subjects achieving HbA_{1c} <7%
- reduces systolic blood pressure
- increases HDL-C concentrations
- lowers triglyceride concentrations

2.4. Medical Resource Utilization Objective

To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this protocol).

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM, on a wide range of antihyperglycemic therapies, who have either a history or high risk of CV disease. Although the effects of canagliflozin on several CV risk factors (eg, glycemic control, body weight, blood pressure) appear favorable in short-term studies, the longer-term benefits on CV risk factors are currently unknown; in addition, Phase 3 results demonstrated a small increase in LDL-C, without a change in the LDL-C to HDL-C ratio.

Note that results from this study, integrated with cross-Phase 3 program results, were included in a pre-approval meta-analysis to evaluate CV safety (as required by the US FDA Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes) by examining the composite of MACE-plus hospitalized unstable angina (referred to as the pre-approval CV safety endpoint). This CV meta-analysis was conducted in 2012 (addressing the US FDA filing requirement that the upper bound of the 2-sided 95% CI around the CV HR is <1.8); this meta-analysis confirmed the requirement, showing the upper bound was <1.8.

This study was originally designed to include 2 sequential cohorts, with up to 18,500 subjects and a study duration for individual subjects of up to approximately 8 years. The study will now recruit only the initial 4,330 subjects who were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio.

The study's last subject last visit will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies, which is projected to occur prior to April 2017.

The study was modified because the cross-program meta-analysis of the pre-approval CV safety endpoint was unblinded to the sponsor to prepare regulatory submissions (originally this was to be unblinded to the study IDMC only); this was done based upon a decision by the sponsor, so that the impact of the small dose-related increase in LDL-C observed with canagliflozin treatment in the Phase 3 program on the CV HR could be evaluated. Due to the unblinding of these CV endpoint results, the study Steering Committee noted that the addition to the CANVAS trial of the planned second cohort of subjects would not provide a robust assessment of the primary CV protection hypothesis.

The CANVAS study has additional objectives including the assessment of overall safety and tolerability of canagliflozin.

The study also includes several substudies intended to provide additional information about the efficacy and safety of canagliflozin compared to placebo in combination with specific AHAs.

In this study, investigators will be counseled to assure appropriate management of CV risk factors (eg, blood pressure and lipids) according to standard guidelines (eg, the American Diabetes Association [ADA] or other local diabetes guidelines) for the care of patients with T2DM. In addition, after a relatively brief period during which the subject's antihyperglycemic regimen is to be kept stable (described in the section below), investigators will attempt to achieve good glycemic control, consistent with standard diabetes guidelines, individualized as considered clinically appropriate, with up-titration or stepwise addition of AHA therapies. Thus, this study will examine the impact on CV risk, and the safety and tolerability of treatment with canagliflozin along with standard of care for CV risk factor and glycemic management relative to placebo with standard of care management.

3.1. Study Design

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

Screening/Run-in Period Management

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

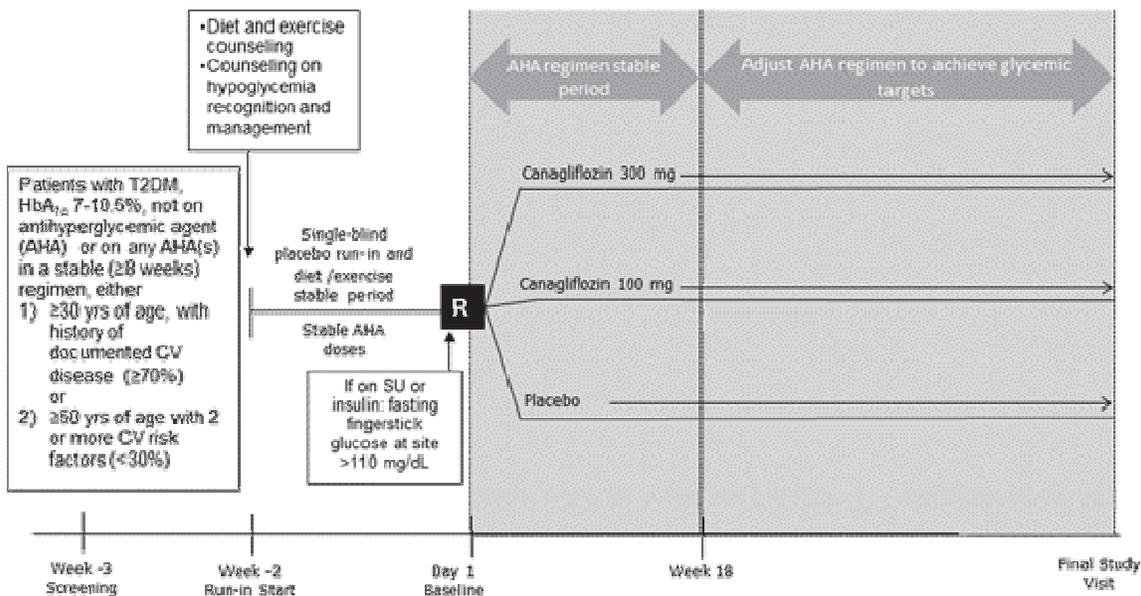
A subject meeting initial enrollment criteria at the screening visit will return to the investigational site at Week -2 (single-blind run-in start visit) to complete the evaluation of enrollment criteria. At this visit, subjects continuing to be eligible will enter a 2-week single-blind placebo, diet/exercise, and CV risk factor (eg, blood pressure and lipids) management optimization period. All subjects will receive diet/exercise counseling *at*

entry into the 2-week single-blind run-in period, be counseled on hypoglycemia recognition and management, be dispensed single-blind placebo capsules, and be given a monitor and materials for self-monitored blood glucose (SMBG) measurements. If additional time in run-in is required for adjustment/optimization of lipid-altering or blood pressure-lowering medications (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks.

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, will be randomized to treatment with canagliflozin 100 mg, 300 mg, or matching placebo administered once daily (in a 1:1:1 ratio). Approximately 4,500 subjects will be randomized. Subjects will remain on a stable regimen (medications and doses) of their current AHA regimen (if on AHA) from screening entry until the Week 18 visit of the double-blind treatment phase (see “Double-blind Treatment Phase Management” below for details).

An overview of the study design is illustrated in [Figure 1](#).

Figure 1: Study Design Outline



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

Double-blind Treatment Phase Management

Subjects will remain on a stable regimen (medications and doses) of their current AHA regimen through Week 18 of the double-blind treatment phase, unless down-titration is required to manage or avoid hypoglycemia, or unless glycemic rescue criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy Through Week 18: Criteria and Implementation). After the AHA regimen stable period is completed at Week 18, the investigator should adjust the subject's AHA regimen so as to achieve target glycemic control, per standard diabetes care guidances, individualized as considered appropriate by the investigator. *Adjustments in the AHA regimen should be carefully implemented throughout the study to avoid events of hypoglycemia.*

Planned Meta-analyses (CANVAS and Other Canagliflozin Studies)

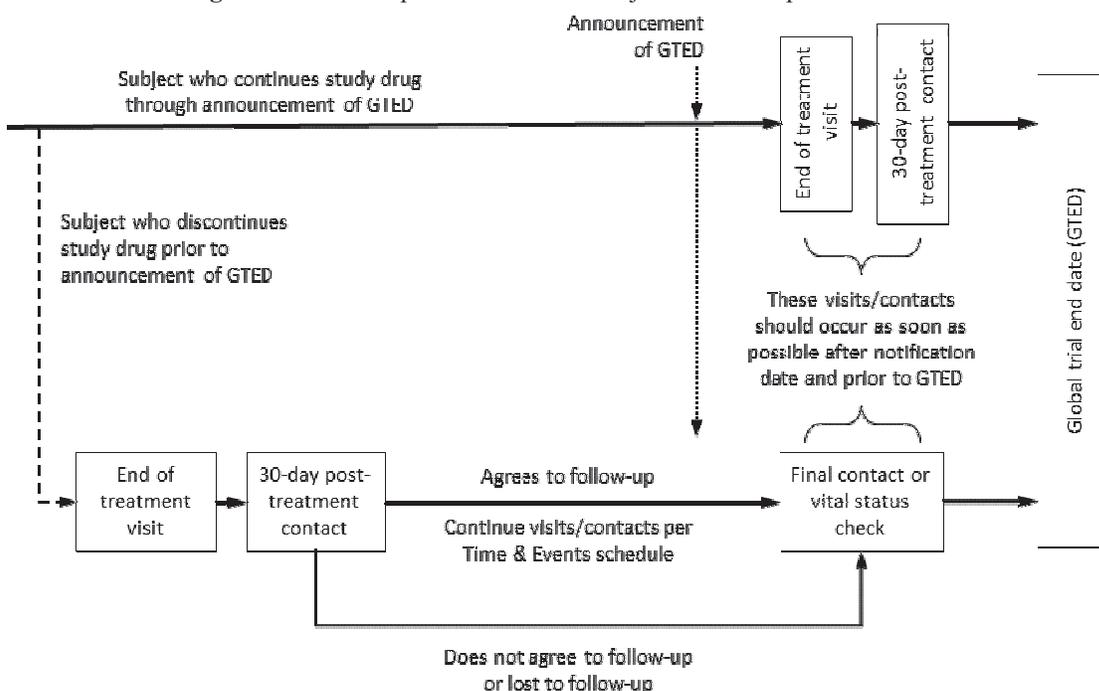
As described in Section 11.8, Meta-analyses to Support Regulatory Requirements, during the conduct of this study, data from CANVAS will be exported and integrated with data from other large, well-controlled, double-blind, randomized studies of canagliflozin to support meta-analysis to assess the rate of important CV events in a prespecified composite endpoint.

Study Duration

Subjects are expected to be followed for a maximum of approximately 7.25 years with the last visit for the last subject targeted to occur when at least 688 MACE events are accumulated between the CANVAS and CANVAS-R studies. All sites will be notified of the projected global trial end date (GTED) which is projected to occur prior to April 2017. The GTED is the stopping date of the study (ie, targeted date when the last subject completes last study visit), which will be announced to investigators at a time point when the actual accrual of events approaches the number of events required for the analysis; the announcement of the GTED may occur approximately 3 months prior to the GTED. 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 2 shows the intended follow-up of randomized subjects with respect to the GTED.

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

Collection of Study Endpoints and Safety Measures

Events in the CV composite endpoint: Investigators will be counseled to report any event that they assess as potentially to be a component of the study CV composite endpoint (refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication).

Collection of Information After Early Withdrawal: Early withdrawal (for subjects prematurely discontinued)/end-of-treatment (for subjects completing the study) evaluation will be performed at the time the subject discontinues double-blind study drug or when the study ends (refer to Sections 9.1.4, End-of-Treatment/Early Withdrawal, and 9.1.5, Posttreatment Phase [Follow-Up] for collection of information on CV events and other assessments). In subjects that prematurely discontinue study drug, events in the CV composite endpoint, all deaths, serious adverse events and adverse events of fractures should continue to be collected until study completion.

Safety Evaluations and Adverse Events Requiring Collection of Additional Information: See Section 3.2, Safety Evaluations, for details around safety assessments and adverse events requiring collection of additional information. 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 IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee).

Pharmacogenomic Blood Sample: A pharmacogenomic blood sample should be collected on Day 1 (or at a subsequent visit if not collected on Day 1) from subjects who consent separately to the pharmacogenomic component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in pharmacogenomic research is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study.

Substudies – Add-on Use with Specific AHAs

Randomized subjects on specific concomitant AHAs, listed below, will be included in 3 substudies. These substudies will assess the glycemic efficacy and safety of canagliflozin in subjects on one of the following concomitant AHAs: insulin ≥ 20 units per day as monotherapy or in combination with other AHA(s); sulfonylurea monotherapy (at doses specified in [Attachment 1](#)); or pioglitazone ≥ 30 mg plus metformin $\geq 2,000$ mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHAs. These subjects will follow the same procedures and assessments as described for the overall study (refer to the Time and Events Schedule that follows the Synopsis); no additional procedures or assessments are required for subjects in these substudies. Results from subjects in these substudies will be analyzed based upon prespecified objectives and hypotheses (refer to [Section 2.4](#), Substudies: Objectives and Hypotheses).

[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 designed in general accordance with the FDA and European Medicines Agency (EMA) guidances on the development of medications and clinical investigations for the treatment and prevention of diabetes mellitus (FDA 2008; EMA 2002, 2008), and will contribute CV events (for a prespecified meta-analysis) to meet the requirements of the FDA guidance for industry on evaluating CV risk in new AHAs to treat type 2 diabetes issued in December 2008 (Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes).

The study was to have 2 sequential cohorts, with the decision to recruit further subjects (ie, re-open enrollment) based upon a protocol-specified interim analysis of results from the initial cohort planned approximately 4 years after study initiation, around the time of US regulatory agency approval. However, the study will now only recruit the initial 4,330 subjects randomized for the reason discussed in [Section 3](#). Randomization and blinding will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups. Blinded

treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of the active treatment.

The 2-week single-blind placebo period before randomization allows sufficient time for investigators to assess whether subjects demonstrate compliance with study procedures, and to study medication, and provides an opportunity to adjust treatment for other CV risk factors, by titration or addition of background medications at the investigator's discretion, before randomization.

The stable AHA regimen period of 18 weeks was chosen because it is sufficiently long to evaluate the effect of canagliflozin on HbA_{1c}. Maintaining stable background AHAs, permits an assessment of the effect of canagliflozin not confounded by changes in other agents, and hence supports the determination of glycemic efficacy of this potentially valuable medication across the entire study population as well as in the substudies.

Study Population

The study population includes subjects on a variety of different AHAs, with a range of baseline glycemic control—from mildly elevated to more moderately elevated HbA_{1c} values—and at higher risk of or having documented CV disease. This population was selected to provide a broad experience with canagliflozin so as to enhance the characterization of this new medications efficacy, safety, and tolerability profile, and to support assessment of the effect of treatment with this agent on CV risk. The substudy populations were selected to provide information on concurrent use of canagliflozin with important AHAs that are not being assessed in separate Phase 3 studies.

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

The once daily oral therapy is an acceptable dosage regimen given the half-life of canagliflozin.

Based on findings from the Phase 2b diabetes study, 100 mg once daily is deemed to be the lowest dose providing clearly sufficient efficacy in terms of HbA_{1c}-lowering for approval as an AHA and 300 mg once daily is deemed to provide an incremental improvement in glycemic efficacy and possibly weight loss and blood pressure lowering, greater than that achieved with the 100 mg once daily regimen. The safety and tolerability profile of these 2 doses appeared to be generally similar. In Phase 1 studies of canagliflozin, at doses above 200 mg, a decrease in incremental glucose and an increase in the time to peak glucose were observed after a meal challenge when study drug was administered before the meal. The mechanism of this reduction in post-meal glucose is not known, but could relate to inhibition of SGLT1 gut glucose transport based upon transiently high gut concentrations of canagliflozin after dose administration. If this effect on post-meal glucose is established, it may provide an additional mechanism of

glucose-lowering benefit. In the present study, double-blind study drug is to be taken before the first meal of the day so as to obtain this potential benefit of canagliflozin. Additional studies in the canagliflozin program will evaluate this effect on post-meal glucose.

Both the 100 and 300 mg doses of canagliflozin are being evaluated in this study.

Collection of Additional Information for Selected Adverse Events

The safety profile of canagliflozin has been well-established in the Phase 3 program, which included approximately 10,000 subjects from randomized, controlled clinical trials. As a condition of approval certain health authorities (eg, US FDA) are requesting enhanced pharmacovigilance on selected adverse events of interest (see Section 9.4, Safety Evaluations, for additional details).

Choice of Cardiovascular Outcome Composite Endpoint

To evaluate the study's primary hypothesis of CV benefit (ie, a reduction in CV risk), the endpoint of MACE (CV death, nonfatal MI, nonfatal stroke) will be used. This has become the standard composite endpoint utilized for this purpose, and hence was selected for use in the current study. The effect of canagliflozin relative to placebo on the HR of the individual components of these endpoints will also be characterized. To support the planned meta-analysis of integrated results from this and other large, well-controlled, double-blind, randomized studies of canagliflozin), the pre-approval composite endpoint included MACE *and* hospitalized unstable angina. This endpoint was utilized to support the pre-approval CV safety of canagliflozin, evaluating the hypothesis (in the separate meta-analysis SAP) of no unacceptable increase in CV risk (ie, rule out an upper bound of 1.8 or greater). The event of hospitalized unstable angina was included in this composite to cast a wider net, given the importance of such events, and their close relationship to, and prediction of, progression of coronary artery disease.

Choice of Renal Efficacy Measures

The onset and progression of nephropathy is a major morbidity outcome in diabetic patients. Hyperglycemia, possibly through production of advanced glycation endproducts (Diabetes Control and Complications Trial [DCCT], Brownlee 2001), systemic hypertension (DCCT), and increases in intraglomerular pressure (Anderson 1986; ADA 2004) are known to be risk factors for the onset and progression of diabetic nephropathy.

In the Phase 2b diabetes study, canagliflozin improved glycemic control, with a trend towards reduced blood pressure in the 300 mg once daily group. By virtue of its mechanism, canagliflozin will reduce the increased glucose flux across the proximal tubule and through the interstitium to be reabsorbed into the bloodstream. The reduced glucose flux within the kidney could lead to a reduction in renal advanced glycation endproduct accumulation resulting in a delay in the onset and/or progression of diabetic

nephropathy. Because SGLT2 in the proximal tubule cotransports both sodium and glucose, SGLT2 inhibition by canagliflozin will increase the distal delivery of sodium, which could lead to a reduction in intraglomerular pressure via the macula densa and a decrease in glomerular damage (Vallon 1999).

The development and progression of renal disease in people with diabetes follows a clearly defined pathway starting with micro-albuminuria, progressing to macro-albuminuria, 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 albumin/creatinine ratio in the first morning void was selected as a key secondary 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 micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macro-albuminuria is 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, first morning void urine collections 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.

Choice of Beta-cell Function Measures

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by the progressive loss of beta-cell function and insulin secretory capacity (UKPDS 1998). In large clinical trials, HOMA-B is a well-accepted means of assessing fasting beta-cell function (Wallace 2004). Homeostasis model assessment (HOMA)-B is calculated using fasting insulin or C-peptide and glucose levels (Wallace 2004). Because C-peptide is not, but insulin is, extracted by the liver, the use of C-peptide to calculate HOMA-B is not confounded by increased hepatic extraction such as that which can occur in conditions of improved hepatic insulin sensitivity. Given that canagliflozin is predicted to cause weight loss, which could lead to improved hepatic insulin sensitivity, C-peptide was chosen to be used for HOMA-B calculations, which will be assessed in a subset of subjects who are not receiving insulin at baseline; if a subject starts insulin therapy after baseline, no further assessments of these analytes will be made for that subject. Approximately 1,200 subjects (400 per treatment group) will be studied in this subset, at sites that elect to participate.

In this subset of subjects, fasting proinsulin and insulin will also be measured to assess beta-cell function. Elevated proinsulin/insulin ratios reflect increasing degrees of impairment in beta-cell function in T2DM (Roder 1998).

DNA Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence glucose and lipid metabolism, and supporting interpretation of dynamic effects measured in the study or to characterize genes potentially affecting drug absorption, distribution, metabolism, or excretion of canagliflozin. DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies in the future. Details are provided in Section 9.6, Pharmacogenomic Evaluations.

Archive Samples for Exploratory Research and Specimens for Biomarker Assessment

Numerous biomarkers have been studied as potentially important surrogate measures of CV and overall health in subjects with T2DM (Ridker 2004). Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for the analysis of important biomarkers (not prespecified) that could help to further explain and examine the efficacy and safety findings in this study. See [Attachment 4](#) for details of specimen collection.

Medical Resource Utilization

Should canagliflozin reduce the risk of CV events, the risk of onset and progression of nephropathy and improve beta-cell function, the utilization of medical resources such as physician visits (outside of protocol-specified), hospitalizations, and medication requirements may be lower in the canagliflozin group than in the standard care group. To assess this, information will be collected in order to characterize differences in the need for additional medical interactions (eg, physician visits, hospitalizations).

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 disease. Approximately 4,500 subjects will be randomized.

Subjects must have inadequate glycemic control (as defined by $HbA_{1c} \geq 7.0$ 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. Subjects receiving AHA therapy must be on a stable dose of that therapy for at least 8 weeks before the screening visit. Subjects taking rosiglitazone within 8 weeks before the prescreening or screening visit may not enter the study. Subjects taking rosiglitazone

who are already in screening are not eligible for randomization. Subjects who have been randomized before implementation of Protocol 28431754DIA3008 Amendment INT-3 and are taking rosiglitazone should be evaluated in a timely manner to determine how to modify their rosiglitazone-containing antihyperglycemic regimen, if clinically appropriate and in accordance with local regulatory requirements.

As noted, subjects must also either have a prior history of documented CV disease or be at high risk of CV disease (on the basis of 2 or more specific CV risk factors). For details, refer to Section 4.2, Inclusion Criteria, below.

Subjects will be recruited from centers in Asia-Pacific, North America, Latin America, Europe, and possibly other regions for this study.

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 disease defined on the basis of either:
 - Age ≥ 30 years with documented symptomatic atherosclerotic CV disease: 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 macro-albuminuria (see Section 3.2, Study Design Rationale, for definition), or documented HDL-C of <1 mmol/L (<39 mg/dL).

Note: An overall 70%:30% target ratio for CV history (first category): risk factors (second category) will be implemented (with a maximum of approximately 40% in the second category). This ratio is intended to be a global ratio and may

vary by region. The proportion of subjects in these categories will be monitored centrally.

- 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 serum follicle stimulating hormone (FSH) level >40 IU/L, or
 - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation), 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 must have a negative urine β -human chorionic gonadotropin (β -hCG) pregnancy test at screening and baseline (predose, Day 1).
- 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.
- To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.

Inclusion Criterion for Randomization

- Subjects must have taken $\geq 80\%$ of their single-blind placebo capsules during the 2-week run-in period at 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 DKA, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On an AHA and not on a stable regimen (ie, agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period

Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and $\leq 15\%$ change in the total daily dose of insulin (averaged over 1 week to account for day to day variability).

- Fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1
- *For patients on a sulfonylurea agent or on insulin:* fasting fingerstick glucose at home or at investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1

Note: at the investigator's discretion, based upon an assessment of recent SMBG values, subjects meeting either of these fingerstick glucose exclusion criteria may continue the single-blind placebo and return to the investigational site within 14 days and may be randomized if the repeat fasting fingerstick value no longer meets the exclusion criterion. Subjects with fingerstick glucose >270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted, and be rescreened once on a stable regimen for at least 8 weeks.

- History of one or more severe hypoglycemic episode within 6 months before screening

Note: a severe hypoglycemic episode is defined as an event that requires the help of another person. Refer to [Attachment 2](#), Hypoglycemia: Definitions, Symptoms, and Treatment, for a definition of severe hypoglycemia.

- 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; refer to [Attachment 3](#), New York Heart Association Classification of Cardiac Disease, for a description of the classes

- Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)

Gastrointestinal

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

Laboratory

- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m² at screening (provided by the central laboratory)
- *For subjects taking metformin:* at screening, serum creatinine ≥ 1.4 mg/dL (124 μ mol/L) for men or ≥ 1.3 mg/dL (115 μ mol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site
- ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening, 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 use of other SGLT2 inhibitor; use of rosiglitazone within 8 weeks of screening. (Note: subjects taking rosiglitazone who are already in screening are not eligible for randomization.)

- 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 or received at least one dose of canagliflozin in a prior study

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:

- Women of childbearing potential who are heterosexually active must use a highly effective method of birth control throughout their participation in the study (refer to Section 4.2, Inclusion Criteria)(refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test)
- Prohibited medications include other SGLT2 inhibitors; 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 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 one time if the reason for non-eligibility relates to duration (eg, time from an MI, or duration on a stable dose of thyroid hormone, or duration on a stable AHA regimen), or appropriate clinical management leads to study eligibility (eg, HbA_{1c} >10.5% that prompts adjustment of the subject's AHA regimen, or subject is on a medication not allowed per local prescribing information [eg, on metformin with eGFR below level permitted per label], and the subject's treatment regimen is being adjusted as clinically appropriate to be consistent with local prescribing information).

Rescreening for an abnormal laboratory value is only allowed as indicated for the specific laboratory exclusion criterion. Typically, rescreening will require that all screening and/or run-in 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 documented, pre-existing CV disease—the highest risk group—approximately 70% (minimum of 60%) of subjects (globally) are targeted to be in this group.

Stratification for Substudies

Subjects will have within-subgroup balanced (1:1:1) randomization to each of the 3 treatment groups within the following 6 predefined strata, which are based upon AHA medication(s) that the subject is receiving at the run-in visit and will be continuing at entry into the double-blind treatment phase:

- Stratum 1: insulin monotherapy ≥ 20 units per day, on stable doses at least 10 weeks before the run-in visit
- Stratum 2: insulin ≥ 20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy
- Stratum 3: insulin ≥ 20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit
- Stratum 4: sulfonylurea monotherapy (at doses specified in [Attachment 1](#)), on stable doses at least 10 weeks before the run-in visit
- Stratum 5: pioglitazone ≥ 30 mg/day plus metformin $\geq 2,000$ mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit
- Stratum 6: subjects not in one of the above AHA subgroups

Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and $\leq 15\%$ change in the average total daily dose of insulin (as averaged over one week).

The stratification process will be handled via queries in the Interactive Voice Response System (IVRS) or after logging on to the Interactive Web Response System (IWRS) being used for the study, described below.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified based on the use of specific concomitant antihyperglycemic medications at baseline (as noted above). 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 telephoning into the IVRS or after logging on to the IWRS designated by the sponsor. The requestor must use his/her own user identification (ID) and personal identification number (PIN) when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IVRS/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 IVRS/IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IVRS/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 will be identical in appearance and will be packaged in identical containers.

The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IVRS/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 the IVRS or 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 IVRS. 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 eCRF and in the source documents. The documentation received from the IVRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, 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.

Subjects who have had their treatment assignment unblinded by the investigator will be discontinued (refer to Section 10.2, Withdrawal from the Study).

Randomization codes will be released based upon protocol-specified interim or meta-analyses, and after completion of the study. At the time of these analyses, the translation of randomization codes into treatment and control groups will be disclosed only to those authorized and only for those subjects included in the interim analysis (refer to Section 11.7, Interim Analyses of CANVAS and Section 11.8, Meta-analysis to Meet Regulatory Requirements).

To maintain the treatment blind, the FPG and HbA_{1c} values after baseline and before Week 18 will be masked to the study sites unless: (1) the FPG meets specific glycemic criteria for the initiation of rescue therapy (as described in Section 6.2.2, Glycemic Rescue Therapy Through Week 18: Criteria and Implementation), or (2) glycemic rescue therapy has been initiated.

Urine glucose measurements will not be performed on first morning void urine specimens, or on urinalyses during the study, as an additional step to ensure the maintenance of the treatment blind. Unless required by urgent subject management, investigators should obtain all urinalyses through the central laboratory and not by a local laboratory so as to avoid potential for unblinding related to urine glucose results (which will not be reported by the central laboratory). 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

Run-in Period Single-Blind Placebo

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 administered once daily).

Double-Blind Study Medication

Subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo.

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 will take the first dose of study drug at the study center on Day 1.

On the days of study visits when fasting blood samples are collected (refer to the Time and Events Schedule that follows the Synopsis), subjects will be instructed to refrain from taking the study drug before the clinic visit. The subject will be instructed to take the dose of study drug before the subject's next meal.

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-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Study drug treatment may be interrupted (eg, for safety and/or tolerability reasons such as hospitalizations for major surgical procedure or serious medical illness). Study drug treatment interruptions, occurring for any reason and lasting 7 days or longer, will be documented in source documents at the site. Study drug may be reinstated at the investigator's discretion once the subject has recovered and the safety and/or tolerability concern is no longer present (provided the subject has not been off study drug for >90 days).

For subjects who develop conditions that are associated with amputations, 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

Run-in Period Management

Subjects will receive diet/exercise counseling at entry into the 2-week run-in period and will remain on a stable regimen (medications and doses) of their current AHA regimen (if on an AHA[s]), except as described below. During the run-in period, investigators will

counsel subjects to perform regular fasting SMBG determinations, in general at least 2 measurements per week, with additional measurements as considered clinically appropriate by the investigator.

Double-blind Treatment Phase Glycemic Management

Subjects should remain on a stable AHA regimen (doses and medications) from screening to Week 18, unless a down-titration is considered necessary to manage or avoid hypoglycemia, or if glycemic rescue criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy Through Week 18: Criteria and Implementation). From Week 18, the AHA regimen should be adjusted to achieve glycemic goals, using standard guidances, and as considered appropriate by the investigator for the individual subject. *Adjustment to the AHA regimen (from Week 18) should be carefully implemented so as to avoid events of hypoglycemia.*

Adjustment of AHA therapy will be performed by the investigator, consistent with standard diabetes guidances: no specific AHA treatment algorithm is utilized in this study. Treatment may include reinforcement of lifestyle counseling, up-titration to maximum labeled doses of current AHAs, the addition of oral AHAs, addition of GLP-1 analogue, or the initiation and up-titration of insulin (intermediate or long-acting insulin and subsequent short-acting, pre-meal insulin, if needed). 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. All adjustments to the AHA regimen should be documented in the appropriate eCRF.

Use of AHAs and adjustments to the AHA regimen (dose or agents) should be consistent with the labeled use of the AHA within the country of the investigational site.

During the double-blind treatment period, investigators will counsel subjects to perform regular fasting SMBG determinations; in general, the guidance should be for subjects to perform at least 2 measurements per week, with additional measurements as considered clinically appropriate by the investigator, although it is recognized that subjects may not always be compliant with this guidance for various reasons.

Therapeutic Management of CV Risk Factors

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

During the 2-week single-blind placebo run-in period, investigators should adjust the subject's regimen as needed to optimize the subject's CV risk factors and thereby to reduce the need for adjustments of medications after randomization. If additional time in

run-in is required for adjustment/optimization of lipid-altering or blood pressure-lowering medications (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks.

6.2.2. Glycemic Rescue Therapy Through Week 18 Criteria and Implementation

So as to avoid poorer glycemic control during the 18-week AHA dose-stable period, glycemic rescue criteria will be applied. After Week 18, investigators will determine subject's glycemic goals and the need for adjustments in the AHA regimen.

From Day 1 to Week 18, the criteria for starting glycemic rescue therapy are based on an FPG value exceeding the glucose cutpoints shown in the table below. Subjects should be counseled to contact the site if their SMBG consistently exceeds these values and an FPG measurement (ie, venous blood collection) to determine eligibility for initiation of glycemic rescue therapy should be obtained.

Rescue Criteria Through Week 18	
Time point	Glucose
After Day 1 through Week 6	>270 mg/dL (15 mmol/L)
After Week 6 through Week 12	>240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	>200 mg/dL (11.1 mmol/L)

Glycemic rescue therapy should be as determined to be clinically appropriate by the investigator: either up-titration of current AHA medications or the stepwise addition of non-insulin antihyperglycemic agent(s) and then insulin therapies. After initiation of rescue therapy, the glycemic goals will be based upon standard diabetes guidances, individualized for the subject, as considered appropriate by the investigator.

Investigators must complete the appropriate eCRF page (documenting initiation of therapy) for subjects starting on rescue medication. From Week 18, adjustment of the subject's diabetes treatment regimen is permitted per protocol, and hence such adjustments are not considered as rescue (and therefore the eCRF for rescue therapy does not need to be completed).

Double-blind study drug is to be continued after initiation of rescue therapy.

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 taking the study drug (based on capsule counts) should receive counseling on the importance of dosing compliance and may continue in the study, at the investigator's discretion.

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 completing the diary, as required.

8. PRESTUDY AND CONCOMITANT THERAPY

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

Prestudy therapies administered up to 30 days before screening (and up to 12 months before screening for AHA) and up to the time of the first dose of double-blind study drug must be recorded.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug to 30 days after the last dose of study drug.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded as prestudy therapy (before the first dose of double-blind study drug) or as concomitant therapy (after the first dose of double-blind study drug) on the eCRF.

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

Disallowed Therapies

Other SGLT2 inhibitors may not be used concurrently, and subjects should not take any other investigational agents during the study (however, please note the guidance for subjects in posttreatment follow-up in Section 4.4).

The sponsor must be notified in advance (or as soon as possible thereafter) 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

A screening visit should occur 1 to 2 weeks before the run-in start visit. The single-blind placebo run-in period should be 2 weeks in length (with a recommended visit window of ± 4 days). If additional time in run-in is required for adjustment/optimization of

lipid-altering or blood pressure-lowering medications (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks.

Subsequent scheduled study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization), Weeks 6, 12, 18, 26, 39, and 52. After the first year, scheduled (in-clinic) study visits may occur at 13-week or 26-week intervals (at the option of the investigator). If in-clinic visits are changed to an every 26-week frequency, a telephone contact should occur in between the 26-week interval in-clinic visits such that there will be contact with the subject every 13 weeks (in-clinic visits alternating with telephone contacts) (see the Time and Events Schedule). For each post-baseline visit up through Week 26, the recommended visit window is ± 7 days. After Week 26, the recommended visit window is ± 14 days. After Week 65, on those occasions when the 26- and/or 52-week-interval visits overlap, the visit with the more comprehensive procedures (as outlined in the Time and Events Schedule that follows the Synopsis) will be followed.

Telephone contacts, or optional site visits, should be conducted at Weeks 2, 4, and 9. Refer to the Time and Events Schedule that follows the Synopsis for further details. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as closely 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. The study visits at Week 52, and annual visits, should occur as closely as possible to this scheduled time.

Pregnancy Testing

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).

Subject Diary: Collection of Self-Monitoring of Blood Glucose (SMBG), Possible Hypoglycemic Event Information, Medical Resource Utilization Information

A standard, protocol-specified diary will be provided to each subject. Routine SMBG measurements may be recorded in the diary, and all events of possible hypoglycemia that are serious adverse events or that lead to study drug discontinuation should be documented as well as associated fingerstick glucose measurements, if available.

The diary may also be used to keep track of medications and/or medication changes at the investigator's discretion. In addition, the diary should be used for the subject to record

health-care provider visits (other than protocol-specified study visits), emergency care, and hospital visits (refer to Section 9.8, Medical Resource Utilization).

The diary should be reviewed by study research staff at each scheduled visit.

Collection of Other Endpoints: Optional Specimens for Exploratory Research

A set of fasting plasma, serum, and urine samples will be collected at the time points specified in the Time and Events Schedule from subjects who consent to this component of the study to allow for exploratory research related to canagliflozin and biomarker analyses that may provide further understanding regarding the diagnosis and treatment of T2DM or obesity (where local regulations permit). Subject participation in this component of the study is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study. Refer to Section 9.7, Exploratory Evaluations, for further details. Refer to Attachment 4, Optional Specimens for Exploratory Research - Sample Collection and Handling, for further information regarding the collection and handling of exploratory blood and urine samples.

Pharmacogenomic Testing

A blood sample will be collected on Day 1 (or any time after Day 1 if the specimen is inadvertently missed on Day 1) from subjects who have consented to participate in the pharmacogenomic component of the study. Refer to Attachment 5, Pharmacogenomic Sample Collection and Shipment Procedures, for details on collecting and handling blood samples for pharmacogenomic research. In the event of DNA extraction failure, a replacement pharmacogenomic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample.

9.1.2. Pretreatment Phase

Screening Visit (Week -3)

Potential subjects will be seen at a screening visit, approximately 3 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 key laboratory studies (including serum chemistry and HbA_{1c}, and fasting lipids [if subject is fasting at the screening visit]) will be obtained.

Run-in Visit (Week -2)

At the Week -2 run-in visit, a complete medical history will be obtained and a physical examination and additional laboratory evaluations (including hematology, urinalysis, FPG, fasting lipids [if not obtained at screening visit]), and an ECG will be performed, per the Time and Events Schedule that follows the Synopsis.

At this visit, subjects who continue to meet enrollment criteria may then be dispensed single-blind placebo capsules (through IVRS or IWRS, refer to Section 5, Treatment Allocation) and enter the 2-week single-blind placebo run-in period. An assessment of the subjects' adherence to protocol procedures during the run-in 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), and having a stable diet and exercise regimen.

Subjects who do not meet all inclusion criteria or meet a study exclusion criterion based upon the results of the screening or run-in visit laboratory studies should be excluded from the study, and discontinue single-blind placebo.

At the run-in visit and during the 2-week run-in period (ie, at additional visits as considered appropriate), investigators should evaluate CV risk factors (eg, blood pressure, and fasting lipid levels) and adjust therapies, if necessary (refer to Section 6.2.1, Management of Glycemic Control and CV Risk Factors). At the run-in visit (Week -2), subjects who continue to be eligible will be provided with a glucose meter and testing supplies and instructed on the performance of SMBG. In addition, a standard, protocol-specified diary will be provided to each subject. Subjects will also receive counseling regarding diet and exercise consistent with standard diabetes guidance recommendations (eg, ADA), and will be counseled regarding recognition and management of hypoglycemia, including recording of possible hypoglycemic events on the subject diary along with concurrent fingerstick glucose measurements. Subjects should be counseled by the study research personnel regarding the importance of good compliance with all study procedures throughout the study.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Potential subjects who return for the Day 1 (baseline), who have taken $\geq 80\%$ of the scheduled single-blind placebo capsules during the run-in period, and who meet the enrollment criteria will be randomly assigned in a 1:1:1 ratio to once daily treatment with canagliflozin 100 mg, canagliflozin 300 mg, 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).

In addition, pharmacogenomic informed consent will be obtained (only from those subjects who agree to participate in this component).

Visits Following Randomization

Subjects will be seen in the clinic at visits or contacted by telephone 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 events in the CV composite endpoint (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.

9.1.4. End-of-Treatment/Early Withdrawal

The end-of-treatment/early withdrawal evaluation will be performed when the double-blind treatment phase of the study is ended or at the time the subject is withdrawn from the study. The evaluation should be performed as soon as possible after stopping the study drug.

Refer to the Time and Events Schedule that follows the Synopsis for procedures at the End-of-Treatment/Early Withdrawal evaluation.

Subjects who prematurely discontinue double-blind treatment will have follow-up contact as described in Section 9.1.5, Posttreatment Phase (Follow-Up) and in the Posttreatment Time and Events Schedule. If it becomes no longer possible for a subject to continue to make site visits for posttreatment measurement of vital signs and laboratory specimen collection, the investigator may revert to telephone contacts (with the subject or, as a last resort, with relatives or a family physician) or other available medical records to assess and collect information regarding serious adverse events, CV events, and fractures on the timelines described in the Time and Events Schedule, and forego the clinic visits. Alternately, at the investigator's discretion, less frequent in-clinic visits may be interspersed with other forms of contact, including telephone, email, letters, social media sources, fax, or other electronic or non-electronic means.

9.1.5. Posttreatment Phase (Follow-Up)

All subjects should have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) (if a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means) approximately 30 days (but no more than 42 days) after the last dose of study drug to collect:

- Nonfatal CV events in the primary composite endpoint (nonfatal MI, nonfatal stroke)
- Death from any cause
- Nonfatal serious adverse events
- Adverse events of fracture

Subjects who discontinue treatment early for any reason (other than withdrawal of consent for follow-up contacts) will be contacted according to the Posttreatment Time and Events Schedule (or more frequently if necessary based on the investigator's knowledge of the subject) until completion of the overall study, with the goal of collecting any CV outcome events (ie, nonfatal events in the CV composite endpoint), deaths from any cause, adverse events of fracture, and any serious adverse events. Subjects who discontinue treatment less than 26 weeks before the completion of the study will be contacted by telephone at the end of the study to collect any of the events in the list above.

9.2. Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication

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

For events of hospitalized unstable angina, adjudication will conclude with implementation of amendment INT-6. However, investigators will continue to report such events that are serious or that lead to study drug discontinuation on the eCRF.

Investigators will complete a separate eCRF for potential events in the CV composite endpoints and 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 all events that could potentially contribute to the specified CV endpoints and only those events that the committee, using methodology defined in the committee's charter, determines are prespecified endpoint events will be included in the analysis. The Endpoint Adjudication Committee will classify the outcome events while blinded to treatment assignment. The same Endpoint Adjudication Committee will adjudicate events from all of the studies that will contribute to the meta-analysis of the pooled large, well-controlled, randomized studies of canagliflozin (including CANVAS).

Note that events assessed by the investigator as an event in the CV composite endpoint, with the exception of CV death, should not be reported as adverse events/serious adverse events (refer to Section 12, Adverse Event Reporting). If the event is adjudicated by the Endpoint Adjudication Committee as **not** meeting the event definition, *then the event should be reported as an adverse event/serious adverse event* (with reporting timelines starting at the time of notification of this by the Endpoint Adjudication Committee).

With the implementation of INT-6, hospitalized unstable angina events should now be reported as adverse events/serious adverse events (see Section 9.4, Safety Evaluations).

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 monitoring for a portion of the sites.

9.3.2. Steering Committee

A 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 will be 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 include 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

An IDMC will be commissioned for this study to review accumulated, unblinded safety information during the study. Details of the composition, roles, and responsibilities will be documented in its charter.

The IDMC will also have responsibility for review of the primary CV endpoints for this study as well as across the canagliflozin clinical development program.

9.3.5. Endpoint Adjudication Committee

An independent Endpoint Adjudication Committee composed of external specialists, blinded to treatment assignment, will be commissioned to review case information on potential MACE events. The operations, processes, and endpoint definitions to be employed by the committee will be defined in its charter.

9.4. Safety Evaluations

Only serious adverse events, non-serious adverse events resulting in study drug discontinuation, and adverse events of interest (see below) will be recorded on eCRFs.

Safety and tolerability will include an evaluation of serious adverse events, adverse events of interest, discontinuation due to adverse events, clinical laboratory tests, vital

signs (pulse, blood pressure), and body weight. Cardiovascular safety will be assessed as part of the meta-analysis of CANVAS and CANVAS-R.

Refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication, for reporting and adjudication of events in the CV composite endpoint.

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 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, venous thromboembolic events, male genital infections (balanitis, phimosis, events leading to circumcision), and amputations 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 as an adverse event of special interest and therefore adverse events related to DKA, ketoacidosis, metabolic acidosis or acidosis need to be reported to the sponsor 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. Amputation has also been designated as an adverse event 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. (see [Table 1](#))

Table 1: Adverse Event Collection Requirements

Collect all (serious or non-serious):	Collect if serious or if adverse event causes discontinuation:
<ul style="list-style-type: none"> • Malignancies (especially renal cell cancer, pheochromocytoma, Leydig cell tumor) • Photosensitivity • Venous thromboembolic events • Fractures • Male genital infections (balanitis phimosis, events leading to circumcision) • Amputations • Diabetic ketoacidosis • Any pregnancy 	<ul style="list-style-type: none"> • Fatal pancreatitis and hemorrhagic/necrotizing pancreatitis • Severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome) • Serious adverse events of hepatic injury • Nephrotoxicity/acute kidney injury • Any other event

Detailed collection of information on serious adverse events of hypoglycemia or adverse events of hypoglycemia that lead to study drug discontinuation will be performed on supplemental eCRFs. For selected specific adverse events (ie, vulvovaginal adverse events, superficial genital adverse events in men, and adverse events of urinary tract infection), investigators will be asked to provide additional information, on separate eCRFs, so as to support more detailed analyses for events that are serious or that lead to study drug discontinuation.

All deaths will undergo adjudication by the Endpoint Adjudication Committee to determine cause of death and whether CV disease was a proximate or underlying cause.

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.

Adverse Events

Adverse events as noted above 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 when the informed consent is signed. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

For purposes of reporting serious adverse events for this study, the components of the CV composite endpoints (with the exception of CV death) will not be considered adverse events or serious adverse events. Events in the CV composite endpoints will not be considered as unexpected but as disease-related, and as such will not be

unblinded. Refer to Section 12, Adverse Event Reporting, for details regarding the handling of components of the CV composite endpoints (note: hospitalized unstable angina, previously considered a component of the CV composite endpoint, will now be considered as a serious adverse event and should be recorded on the adverse event/serious adverse event eCRF page).

Information for all adverse events will be collected in source documents (eg, progress notes) retained at the investigative sites.

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time of end-of-treatment or early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached, or until further follow-up is no longer considered by the investigator to be clinically meaningful. For details on the end-of-treatment or early withdrawal evaluations, and posttreatment follow-up collection of information, see Section 9.1.4, End-of-Treatment/Early Withdrawal, and Section 9.1.5, Posttreatment Phase (Follow-Up).

Clinical Safety Laboratory Tests

Subjects will be monitored with safety laboratory measurements (hematology, chemistry, and urinalysis [with urine glucose not measured to avoid unblinding]) as described in [Attachment 6](#).

In subjects with elevations in ALT ≥ 3 -fold ULN, subjects will be monitored and managed using the algorithm in [Attachment 7](#).

Alerts will be provided to investigators by the central laboratory identifying important laboratory changes or key out-of-range values, so the investigator can follow up as necessary. For creatine phosphokinase (CPK) elevations, the investigator should determine if follow-up evaluation is clinically appropriate to exclude a potential cardiac event. The review of such alerts should be documented by the investigator as soon as possible after receipt of the results.

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.

Urine samples from first morning void on day of designated visits will be collected for urine albumin and creatinine determinations. If the subject does not provide the morning void collection 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.

The urine collections for exploratory analysis, as well as the routine urinalyses, should be obtained from a spot urine specimen in the clinic.

Urine glucose will not be measured in the first morning void urine specimens or urinalyses.

For SMBG monitoring during the study, see Section 6.2.1, Management of Glycemic Control and CV Risk Factors.

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 a properly calibrated automated blood pressure monitor; if neither of these is available, a high-quality aneroid sphygmomanometer calibrated according to manufacturer specifications will be acceptable. 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.

In addition, blood pressure will be measured 3 times in both arms at the screening visit; if there is a difference between arms of >10 mmHg in either the mean systolic or diastolic pressure, the arm with the higher pressure should be used to measure blood pressure and *should be used for all subsequent blood pressure measurements during 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 the same calibrated scale at each visit. The study center will be responsible for calibrating the scale before the first subject enrolled in the study at the site is weighed and then at approximately 12-week intervals during the study. Calibration must be documented in a calibration log. 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 must be dressed as lightly as possible, with consistency from visit to visit); subjects will be asked to urinate before being weighed.

Urine Pregnancy Testing

Serum or urine pregnancy tests may be performed in women (unless they are surgically sterile or unless there is a documented history of their postmenopausal status), 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). Supplies for urine and serum pregnancy testing will be provided by the central laboratory, where possible.

9.5. Measures of Efficacy/Efficacy Endpoints

The primary measure of efficacy is the HR of the composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). Secondary measures of efficacy include beta-cell function (HOMA-B; in subjects who are not receiving insulin) and progression of albuminuria (based upon categories determined by urinary albumin/creatinine ratio).

The primary efficacy endpoint, the hypothesis of CV benefit for canagliflozin, will be evaluated based upon the events in the CV composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). As previously described, an independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and only those events where the committee, using methodology and definitions defined in the committee's charter, determines a specified endpoint has occurred will be included in the analysis. The independent Endpoint Adjudication Committee (refer to Section 9.3.5) will apply the endpoint definitions contained in its charter and classify the outcome events while blinded to treatment assignment.

The secondary efficacy endpoint of change in HOMA-B will be assessed in a subset of subjects (approximately 1,200 subjects at sites that elect to participate) who are not receiving insulin at baseline. Homeostasis model assessment-B will be assessed based upon C-peptide and fasting glucose; for subjects who initiate therapy with insulin during the study, data from the last proinsulin, insulin, and C-peptide measurement before initiation of insulin will be utilized for beta-cell function analyses.

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

Additional efficacy endpoints of interest will include the following: changes from baseline to end-of-treatment in the proinsulin/insulin ratio (in a subset of subjects), urinary albumin/creatinine ratio, and eGFR; changes from baseline to Week 18 in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight; and percent change from baseline to Week 18 in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C). The eGFR will be calculated using the Modification of Diet in Renal Disease [MDRD] equation (Levey 2006).

Refer to Section 11.5, CV Outcomes and Efficacy Analyses, for the evaluation of efficacy criteria.

9.6. Pharmacogenomic Evaluations

There are 2 parts to the pharmacogenomic component of this study.

Analysis Related to the Study (Part 1)

Part 1 of pharmacogenomic research allows for the analysis of genes that may be relevant to help to better understand canagliflozin, or T2DM or obesity. Candidate genes will only be genotyped, if it is hypothesized that this may help resolve issues with the clinical data. Analyses may involve the analysis of known candidate genes or the analysis of genetic variants throughout the genome (genome-wide association analysis), both in relation to canagliflozin, or T2DM or obesity (provided in Attachment 8). Genotyping of any of these candidate genes would be performed on identifiable samples.

Additional genes may be analyzed on identifiable samples if these genes are hypothesized to be relevant to canagliflozin, or T2DM or obesity between the time that the clinical protocol has been issued and the samples have been made nonidentifiable.

DNA Storage for Future Research (Part 2)

Part 2 of the pharmacogenomic research allows for the storage of DNA samples for future genetic research related to canagliflozin or the indication(s) for which it is developed. Stored DNA samples and relevant clinical data will be made nonidentifiable after the Clinical Study Report has been issued. This involves removing personal identifiers and replacing the study subject identifier with a new number to limit the possibility of linking genetic data to a subject's identity.

Subjects will be given the option to participate in Part 1 only, Part 2 only, both parts, or neither part of the pharmacogenomic component of this study (where local regulations permit).

9.7. Exploratory Evaluations

A set of fasting plasma, serum, and urine samples will be collected (where local regulations permit) at the time points specified in the Time and Events Schedule for the following:

- exploratory analysis that may be done to provide insight into the actions of canagliflozin or assist in understanding of adverse events possibly associated with the compound. Samples may also be used for future exploratory research to improve understanding of the pathophysiology of T2DM or obesity or to assess other pharmacodynamic effects of canagliflozin, and
- to develop biomarkers that may provide further understanding regarding the risk of development of diabetes-related complications.

This exploratory evaluation is optional and will only be performed in subjects who give informed consent for this specific component of the study.

9.8. Medical Resource Utilization

Subjects will be requested to collect information in a protocol-specified diary on information related to their utilization of medical resources (see [Attachment 9](#)). This MRU data from the subject diaries will then be documented in the eCRF by the investigator and study research staff for all subjects at each visit throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses.

No cost data will be collected in this study.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has experienced a clinical endpoint that precludes further study (eg, early mortality due to CV event) or when the study ends. Note that occurrence of a nonfatal event in the CV composite endpoint (ie, nonfatal MI, nonfatal stroke) is not a study withdrawal criteria. Subjects with these events should be continued in the study, on study drug, unless they meet a study withdrawal criterion (see [Section 10.2, Withdrawal From the Study](#)). Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind treatment phase will not be considered to have completed the study.

10.2. Withdrawal From Study Drug

A subject will be withdrawn from the study drug for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent (subject withdrew consent for treatment and refuses any further follow-up)
- Subject is persistently in poor compliance with study treatment or procedures
- The investigator believes that for safety or tolerability reasons (eg, an adverse event) it is in the best interest of the subject to stop treatment
- 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 values <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 has liver function test abnormalities meeting criteria for permanent discontinuation of study drug as outlined in [Attachment 7](#)
- The investigator formally unblinds the subject's treatment allocation
- Subject initiates 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.

The end-of-treatment evaluations should be performed as soon as possible after stopping the study drug (see Section 9.1.4, End-of-Treatment/Early Withdrawal, and the Time and Events Schedule that follows the Synopsis for procedures to be performed). For posttreatment follow-up contacts, refer to Section 9.1.5, Posttreatment Phase (Follow-up).

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. 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.

When a subject withdraws from double-blind study drug before completing the study, 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.

A subject who elects to withdraw consent for the biomarker specimen collections will not have further collections made after withdrawing consent, and has the following options:

- to allow the previously collected specimens to remain for biomarker analysis, or
- to request that the previously collected specimens be destroyed.

A subject who withdraws from the main part of the study will have the following options regarding pharmacogenomic research:

- The DNA extracted from the subject's blood will be retained and used in accordance with the subject's original pharmacogenomic informed consent.
- The subject may withdraw consent for pharmacogenomic research, in which case the DNA sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the pharmacogenomics representative to execute sample destruction. If requested, the

investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal from Pharmacogenomic Research Only

The subject may withdraw consent for pharmacogenomic research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed. The sample destruction process will proceed as described above. However, all samples will be made nonidentifiable after the Clinical Study Report is issued and thereafter cannot be identified for destruction. If the sample has already undergone conversion to the nonidentifiable format, the sponsor will notify the investigator in writing.

10.3. Reinstitution of 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 may return to active status (ie, re-start double-blind study drug) in the study at the discretion of the investigator, with concurrence from the sponsor's medical monitor, even if previously withdrawn from the study or off study drug for up to 90 days. Subjects off study drug for more than 90 days, or subjects who meet the conditions that require withdrawal (eg, unblinding), should not be returned to active status. If the 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.

10.4. Measures to Re-establish Contact in Subjects 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 determine endpoint status and the reason for discontinuation/withdrawal.** The measures taken to follow-up must be documented. The informed consent form will stipulate that even if a subject decides to discontinue double-blind study drug, he/she will agree to be contacted periodically by the investigator to assess his/her endpoint status (refer to the Posttreatment Time and Events Schedule for subjects that prematurely discontinue double-blind study drug). Furthermore, the subject will be asked 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 endpoint status, in the event the subject is not reachable by conventional means (eg, office visit, telephone, email, or certified mail). The subject is informed 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.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

11.1. Analysis Sets

The ITT analysis set includes all subjects who are randomly assigned to a treatment group. The assessment of the primary objective will be based upon this analysis set. The primary CV analysis will be based on the time to the first occurrence of any component of the CV composite endpoint.

The modified intent-to-treat (mITT) analysis set includes randomized subjects who receive at least one dose of study drug and their data occurring between first dose and last dose plus 30 days.

The alignment of the analysis of the secondary endpoints with the ITT and mITT analysis sets will be detailed in the study SAP.

11.2. Handling of Dose in Analysis

The primary comparison, to assess CV risk reduction, will be between canagliflozin (100 and 300 mg groups combined) versus placebo. Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin.

11.3. Sample Size Determination

The sample size for the recruitment of the initial 4,500 subjects was based upon having a sufficient number of participants to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed pre-approval assessment of the safety and tolerability of canagliflozin. Data from this initial cohort were exported and integrated with data from other Phase 3 well-controlled studies to support a planned pre-approval meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI for the CV HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) was <1.8 ; the current US regulatory requirements for filing. The FDA post-marketing requirements for canagliflozin demand a subsequent estimate of CV safety that will be performed on data from CANVAS and CANVAS-R, when sufficient events have occurred to demonstrate that the upper bound of the 95% CI HR is <1.3 based on MACE (excluding hospitalized unstable angina).

The assumed per annum event rate is 2.25% and the per annum dropout rate is 5%. With an enrollment period 1.5 years, 4,500 randomized subjects were projected to contribute sufficient CV events to support the pre-approval CV meta-analysis.

The original phased recruitment strategy allowed for an interim assessment of study feasibility to demonstrate the primary hypothesis of CV benefit using the results of the interim analysis. Results from the interim analysis (conducted after approximately 2 to

4 years from study initiation, eg, at approximately the time of US regulatory approval) were planned to be evaluated by a CV risk factor evaluation committee to assess the effect of canagliflozin on CV risk factors (to predict the likely effect of canagliflozin on CV events) and determine the point estimate for the HR for MACE. The data on the observed point estimate for the CV HR for MACE were to have been reviewed by the IDMC only and would not have been made more broadly available. Re-opening of enrollment was to have proceeded if the effects on the intermediate outcomes (ie, CV risk factors) as determined by appropriate models (to be prespecified before the interim analysis) that canagliflozin compared to placebo would result in an HR of 0.85 or less (for MACE) and if the observed HR (for MACE) is 0.95 or less. If recruitment did proceed, an additional 14,000 subjects would have been enrolled into Cohort B. However, for the reason outlined above (see Section 3), this second cohort will no longer be recruited.

Without the recruitment of the second cohort of 14,000 subjects, CANVAS study power is reduced from the originally planned 90% power to detect a HR of 0.85 or less. It is now projected that at the completion of the study there will be about 400 MACE events recorded within CANVAS, which will provide 33% power to detect a HR of 0.85 or less, 55% power to detect a HR of 0.80 or less, and 76% power to detect a HR of 0.75 or less using a 2-sided test with 0.05 alpha.

11.4. Safety Analyses

The safety analysis will be based on the mITT analysis set. The mITT analysis set includes all subjects who are randomly assigned to a treatment group and have received at least one dose of study drug and their data occurring between first dose and last dose plus 30 days. There will be no imputation for missing values for clinical laboratory test results or vital sign measurements in the analyses.

Safety and tolerability will be evaluated by summarizing and comparing the incidence of serious adverse events and adverse events of interest, discontinuation rate due to adverse events, clinically important changes in clinical laboratory tests, vital signs (pulse, blood pressure), and body weight between randomized groups. There will be no imputation for missing values for clinical laboratory test results or vital sign measurements in the analyses.

Adverse Events

The verbatim terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest 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.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, who experience a serious adverse event, or who experience an adverse event of interest.

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

Descriptive statistics for pulse and sitting blood pressure (systolic and diastolic) 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.

11.5. CV Outcomes and Efficacy Analyses

11.5.1. CV Outcomes (Primary Efficacy Endpoint)

The primary endpoint for CV benefit will be time to MACE, which is calculated as the time from randomization to the first occurrence of MACE. The statistical hypothesis will be:

$H_{0(1.0)}$: the HR = 1.0, versus $H_{1(1.0)}$: the HR \neq 1.0.

The primary analysis will be based on the ITT analysis set and the MACE events determined by the EAC to meet prespecified criteria. The primary comparison of canagliflozin to placebo will be based on the HR estimate derived from Cox proportional hazards model with terms for treatment, history of a previous CV event as fixed effects.

The assumption of the proportional HR will be examined. In case the assumption is deemed not reasonable, sensitivity analyses that do not rely on the constant HR assumption will be conducted to verify the results of the primary analysis.

Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For individual components of the composite CV endpoint, the HR

and its 2-sided 95% CIs of canagliflozin combined doses relative to placebo will also be assessed.

Sensitivity analyses including CV endpoint events that occur within 30 days of the last dose of blinded study medication will be done.

The effects of different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, key concomitant therapy use, and region) on the primary endpoint will be explored; a detailed discussion of subgroup analyses will be provided in a SAP for this study, which will be finalized before the first interim analysis.

11.5.2. Major Secondary Efficacy Endpoints

The continuous secondary efficacy endpoint, change from baseline in HOMA-B will be analyzed using an analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg, canagliflozin 300 mg or placebo) and stratification factors as fixed effects and the corresponding baseline value as a covariate. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The analyses for beta-cell function will be conducted on subjects not receiving insulin at randomization and, for subjects who are started on insulin during the study, the last data point before the initiation of insulin will be included for these analyses.

The categorical secondary efficacy endpoint is the proportion of subjects with progression of albuminuria (defined as ≥ 1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria). The proportion of subjects with progression of albuminuria will be analyzed using the logistic model with treatment (canagliflozin 100 mg, canagliflozin 300 mg or placebo), and stratification factors as a fixed effect. Albuminuria 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 micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macro-albuminuria is albumin/creatinine ratio greater than 300 mg/g.

For the secondary endpoints of HOMA-B and proportion of subjects with progression of albuminuria, the analyses will compare the dose groups, *combined* and *individually*, relative to placebo.

11.5.3. Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in this study is at most 5%, a gatekeeping procedure will be applied in testing the primary and secondary hypotheses. The superiority of the canagliflozin combined doses over placebo in time to MACE will be tested first. If statistically significant, the procedure will proceed to test the secondary endpoints of the proportion of subjects with progression of albuminuria and HOMA-B for

each canagliflozin dose versus placebo. Details of the gatekeeping procedure will be contained in the SAP.

11.5.4. Additional Secondary Efficacy Endpoints

Additional efficacy endpoints of interest will include the following:

- changes from baseline to end-of-treatment in the proinsulin/insulin ratio (in a subset of subjects), urinary albumin/creatinine ratio, and eGFR
- changes from baseline to Week 18 in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight
- percent change from baseline to Week 18 in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

The continuous secondary efficacy endpoints, changes from baseline in the proinsulin/insulin ratio, HbA_{1c}, FPG, body weight, blood pressure, albuminuria, and eGFR and percent change in fasting lipids will be analyzed in the same manner as the secondary efficacy endpoint, change from baseline in HOMA-B.

For the assessment of change from baseline in HbA_{1c} at Week 18, subgroup analyses (described in detail in the SAP for this study) will be conducted to enhance understanding of factors that might impact glycemic response to canagliflozin.

11.6. Medical Resource Utilization Analyses

Medical Resource Utilization data analyses will be descriptively summarized by primary outcome variable (ie, those with a CV event versus those without) regardless of treatment group. These data may be used in future economic modeling to be done outside of the protocol.

11.7. Interim Analyses of CANVAS

11.7.1. Interim Analyses for Health Authority Submissions

Interim analyses of CANVAS will be done to prepare: (1) an interim safety report in support of the initial health authority filing, (2) the 18-week substudy reports, and (3) the CV safety meta-analyses (based on adjudicated data). The interim data from the CANVAS study will primarily supplement the safety and tolerability data generated from other studies in the canagliflozin development program.

11.8. Meta-Analysis to Support Regulatory Requirements

11.8.1. Meta-Analysis Pre-Regulatory Approval

To support submissions for marketing approval, the CV event data and other safety and efficacy results in this study will be exported and integrated with the data from other large, well-controlled, double-blind, randomized studies in the canagliflozin clinical development program. A meta-analysis of the integrated CV data will be conducted to compare canagliflozin with active or placebo control (eg, current FDA guidance requires

exclusion of the upper bound of the 2-sided 95% CI around the HR of 1.8 or greater). It is projected that the meta-analysis to support regulatory approval would be conducted when an approximate range of 140 to 160 composite events of MACE (CV death, nonfatal MI, nonfatal stroke) and hospitalized unstable angina are observed across the canagliflozin clinical development program (including CANVAS). In no case would a meta-analysis to support regulatory approval occur with fewer than 80 events. Note that the primary composite endpoint to show CV risk reduction in the present study includes MACE, while the pre-approval meta-analysis to rule out harm utilizes a composite endpoint that includes MACE plus hospitalized unstable angina.

If the meta-analysis occurs with 140 to 160 events, 30 to 40 are expected to be observed in the other large, well-controlled, double-blind, randomized studies that will be included in the meta-analysis and 110 to 120 observed from the CANVAS study.

Sponsor personnel will be unblinded to the data during the submission of data from this analysis; however, blinding to the subject's treatment allocation will be maintained for the subjects, investigators, Endpoint Adjudication Committee, and sponsor site-monitoring personnel throughout the study. In order to maintain data integrity with respect to endpoint adjudication, individuals within the sponsor responsible for submitting events to the Endpoint Adjudication Committee will handle the review and submission of adjudication packages in a completely blinded fashion.

The meta-analysis will be the subject of a separate SAP in which the objectives, hypotheses, and analytic strategy are described.

11.8.2. Meta-Analysis Post-Regulatory Approval

To meet US regulatory requirements post-approval (refer to Section 1.2, Overall Rationale and Goals for the Study), results from this study will be exported and integrated with results from CANVAS-R to demonstrate that the upper bound of the 95% CI around the HR for important CV events (MACE) is <1.3. The primary objective of the CANVAS-R study is to evaluate the effects of canagliflozin relative to placebo on albuminuria progression. The CANVAS and CANVAS-R studies will share similar inclusion and exclusion criteria and will enroll similar patient populations. Both studies will require a standardized collection and evaluation of MACE endpoint events by the same Endpoint Adjudication Committee (see Section 9.3.5).

A CV meta-analysis was conducted with 201 MACE plus events. The pre-approval condition was met by demonstrating that the upper bound of the 2-sided 95% CI for the HR was <1.8. The post-approval condition for the exclusion of HR of 1.3 was then tested with 0.001 alpha, and was not met.

As part of the post-approval CV safety requirement, a meta-analysis based on the data from this study and the data from another large-scale study, CANVAS-R, will be conducted when at least 688 MACE events are accumulated in the 2 studies, which is

projected to occur prior to April 2017. With at least 688 MACE events, the power to show the HR <1.3 is about 90% with a 2-sided significance level of 0.05.

The ‘Statistical Analysis Plan for the Post-Marketing Requirement for the CV Risk Assessment of Canagliflozin (CANVAS and CANVAS-R)’ was finalized and submitted to FDA.

11.9. Glycemic Efficacy Substudies

11.9.1. Analysis Sets

The mITT analysis set includes all subjects who are randomly assigned to a treatment group and received at least one dose of study medication. The per-protocol (PP) analysis set will consist of all mITT subjects who completed 18 weeks of treatment, and have no protocol deviations that may affect the interpretation of the primary efficacy endpoint (to be defined in the SAP before database lock and unblinding of the treatment groups) and have not received glycemic rescue therapy. The primary efficacy analysis will be based on the mITT set. The efficacy data measured after the initiation of rescue therapy will be treated as missing. Analysis based on the PP set will also be conducted as a sensitivity analysis.

Efficacy data will be analyzed according to the randomization assignment, regardless of actual treatment received. Safety data will be analyzed according to actual treatment received. The approaches to handle study treatment deviations will be detailed in the SAP.

11.9.2. Sample Size Determination

The primary objectives of the substudies are to compare the HbA_{1c}-lowering efficacy of canagliflozin with placebo after 18 weeks of treatment, in subjects on specific AHAs.

With the exception of the sulfonylurea substudy, assuming a group difference of 0.50% and a common SD of 1.0% with respect to change in HbA_{1c}, and using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it is estimated that 258 randomized subjects (86 subjects in each of the 3 treatment groups) would provide 90% power.

Recently published literature with another SGLT2 inhibitor (Strojek 2010) suggest that the observed standard deviation with respect to HbA_{1c} change from baseline in subjects taking sulfonylureas is less than originally anticipated in the protocol (ie, SD was reported to be 0.75% instead of 1.0%). These new data would allow for an assessment of the primary substudy endpoint (ie, change in HbA_{1c} from baseline) in the sulfonylurea substudy using a smaller sample size in this substudy, ie, 150 randomized subjects (50 subjects in each of the 3 treatment groups) would provide 90% power.

11.9.3. Efficacy Analyses

For each substudy, except the sulfonylurea substudy as noted above, the primary efficacy analysis will only be performed when sufficient subjects (≥ 258) in the subpopulation are

randomized in each of the 3 treatment groups (≥ 86 per group). The analysis will be conducted when the sponsor prepares for the regulatory submissions. For the sulfonylurea substudy, the primary efficacy analysis will only be performed when sufficient subjects (≥ 150) in the subpopulation are randomized in each of the 3 treatment groups (≥ 50 per group).

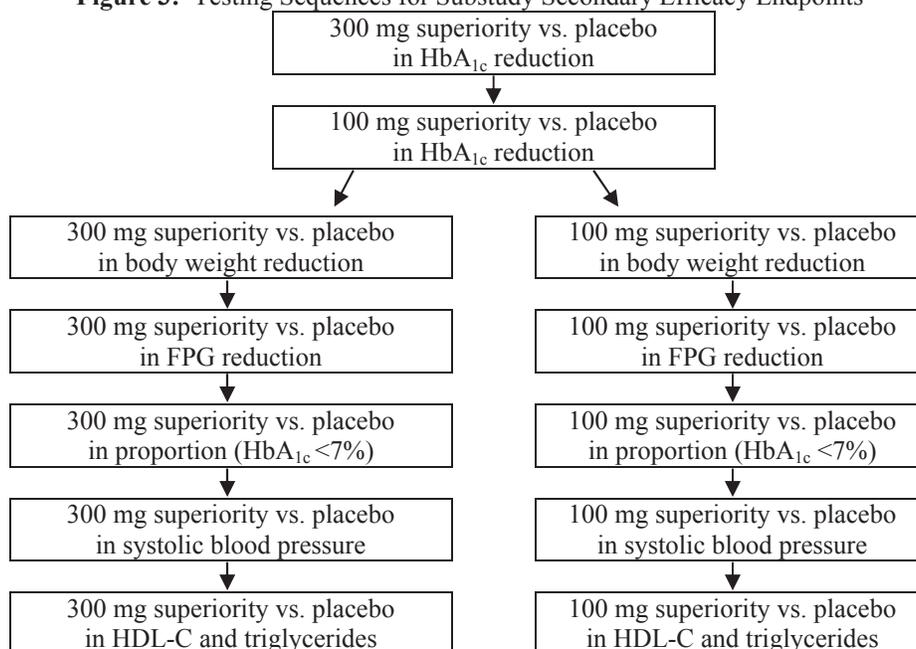
The primary efficacy endpoint will be the change in HbA_{1c} from baseline through Week 18. The LOCF method will be applied when the Week 18 values are missing. In subjects receiving rescue therapy, their measurements made before rescue will be used as the last observation. An ANCOVA model with treatment as a fixed effect and the corresponding baseline value as covariate will be used. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

As a supportive analysis, change from baseline in HbA_{1c} will be analyzed using a restricted maximum likelihood (REML) based on repeated measures approach. The analysis will be based on observed data and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-subject errors. The treatment comparisons will be made between each dose of canagliflozin and placebo at Week 18 and significance tests will be based on the difference of the least-squares means.

The secondary efficacy evaluations of change in body weight, FPG, and systolic and diastolic blood pressure, and percent change in fasting plasma lipids will be analyzed using an ANCOVA model similar to that used in the primary efficacy analysis. The percentage of subjects with HbA_{1c} $< 7\%$ at Week 18 will be assessed by means of a logistic model with treatment and stratification factors as fixed effects and baseline HbA_{1c} as a covariate.

11.9.4. Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in each substudy is at most 5%, a gatekeeping procedure will be applied in testing the hypotheses in the substudy. The superiority over placebo in HbA_{1c} reduction will be tested sequentially for the descending doses of canagliflozin. After the superiority of the 2 doses on HbA_{1c} is concluded, the hypothesis of the secondary endpoints will be tested via 2 testing sequences as illustrated in [Figure 3](#). The alpha level will be split evenly for the 2 sequences.

Figure 3: Testing Sequences for Substudy Secondary Efficacy Endpoints

Testing in each sequence stops as soon as any hypothesis in the sequence is failed to be rejected. The Hochberg procedure will be applied for the 2 lipid parameters at the end of the testing sequence. Note that the alpha level in the main study and the alpha level in each substudy are separately controlled.

11.9.5. Safety Analyses

The safety analysis for the substudies will follow the methodology as outlined in Section 11.4, Safety Analyses.

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 composite endpoints* (ie, CV deaths, nonfatal MI, nonfatal stroke) should be handled as follows:

- Events in the CV composite endpoints will be captured on an eCRF page specifically designed to record endpoint events (note: hospitalized unstable angina events which were previously recorded on the CV eCRF page will now be recorded on the AE/SAE eCRF page) (note: with the implementation of INT-6, hospitalized unstable angina is

no longer part of the CV safety composite endpoint and should now be recorded on the adverse event/serious adverse event eCRF page. This type of event will no longer undergo adjudication as discussed in Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication).

- Because these events in the CV composite endpoint are not unexpected in this high CV risk population (and are considered part of the natural history of the disease), these events, *with the exception of CV deaths (and hospitalized unstable angina)*, will *not* be reported (or recorded) as adverse events (ie, not recorded in the adverse event or serious adverse event eCRF page).
- All deaths, including CV deaths, will be reported as serious adverse events, and submitted for adjudication to the Endpoint Adjudication Committee. These events will be subject to expedited reporting to health authorities by the sponsor, *but will not be subject to unblinding* (unless it is determined by the Adjudication Committee that the death was non-CV related).

*Note that for the study primary hypothesis of CV benefit, the post-approval CV composite endpoint includes MACE (CV death, nonfatal MI, nonfatal stroke); the composite endpoint to assess pre-approval CV safety (as part of a meta-analysis of events from pooled large, well-controlled, randomized studies including CANVAS to assess CV safety) includes MACE plus hospitalized unstable angina (refer to Section 3.2, Study Design Rationale).

- Events that are *initially* reported by the investigator as a study endpoint event, but which are determined by the Endpoint Adjudication Committee as *not* meeting the definition of a study endpoint, will be reported as an adverse event or a serious adverse event upon the sponsor's receipt of this determination by the Endpoint Adjudication Committee (with the sponsor reporting timeline starting from the time of notification by the Adjudication Committee). Such serious adverse events will be handled as per serious adverse event reporting guidelines, when the sponsor is notified by the Endpoint Adjudication Committee. The sponsor will notify the investigator to immediately report the event as a serious adverse event.
- Nonfatal CV events in the composite endpoint that, due to a reporting error or other reason, are initially classified as a serious adverse event, but which are subsequently determined by the Endpoint Adjudication Committee as meeting the definition of a study endpoint, will be reviewed on an individual basis by the sponsor regarding whether the case should be recorded only on the specific endpoint eCRF page and removed from the database as an adverse event or serious adverse event; clear and appropriate documentation of any changes will be maintained.

Deaths or events with an outcome of death will be reported as outcome events if within the composite (ie, if considered a CV death) and the cause of death will also be reported as a serious adverse event (and hence managed per serious adverse event reporting guidelines).

Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the study IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee).

Refer to Section 9.4, Safety Evaluations, for additional information on the adverse events of interest.

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 Harmonisation [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).

Change in Adverse Event Collection with the Implementation of INT-6

Only serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest will be recorded on eCRFs. Details regarding adverse event collections are provided in Section 9.4, Safety Evaluations.

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.

As described in the section above, nonfatal events in the CV composite endpoint (nonfatal MI and nonfatal stroke) will not be considered or reported as adverse events, but collected as study endpoints, subjected to adjudication, and only reported as adverse events if the Endpoint Adjudication Committee determines that the event does not meet the prespecified criteria for an endpoint event.

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. For a comparator product or baseline therapy with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the approved label for the product.

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**

All adverse events, whether serious or non-serious, will be collected in source documents from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety).

Data will be collected on the eCRF for serious adverse events, adverse events that result in study drug discontinuation, and adverse events of interest described in Section 9.4, Safety Evaluations.

Serious adverse events, including those spontaneously reported to the investigator within 30 days (with the exception of those components of the clinical primary composite endpoints) after the last dose of study drug, 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, as specified in Section 9.4, Safety Evaluations, 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 DKA 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 DKA (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) must 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. For purposes of reporting serious adverse events for this study, the components of the clinical primary composite endpoints (with the exception of CV death, which, as with all deaths, will be reported as a serious adverse event; see Section 12, Adverse Event Reporting) will not be considered adverse events or serious adverse events and will not be considered as unexpected but as disease-related, and as such will not be unblinded. These events will be captured on the eCRF as endpoint events only and will not be unblinded or subject to expedited reporting.

Events that are adjudicated as non-endpoints 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 an endpoint 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 upon discontinuation of the subject's participation in the study, 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)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

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:

- Related to a component of the clinical primary composite endpoints
- Social reasons in absence of an adverse event

- Surgery or procedure planned before entry into the study (must be documented in 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 within 24 hours 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.

It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

The study drug will be packaged either as individual blister cards or 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 20°C to 25°C (68°F to 77°F) and kept out of reach of children. Where applicable, excursions from 15°C to 30°C (59°F to 86°F) are allowed.

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. The study drug administered to the subject must be documented on the drug accountability form. 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 at the study site 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
- IVRS/IWRS manual and worksheets
- eCRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding endpoints, endpoint documentation required, and adjudication-related procedures
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution
- Diary card
- Materials to support diet and exercise counseling
- Standardized ECG recording devices and instruction manual
- Laboratory 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

The primary ethical concerns of this study are that the safety profile of canagliflozin has not been fully established so that 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. In this study, there is no requirement to discontinue prestudy medications. The investigator is asked not to change the antihyperglycemic regimen during the first 18 weeks of the study, but rescue criteria are

specified. The potential risks that are apparent in the present study include exposure to study drug, with the potential for side effects and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors.¹

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, including osmotic diuresis due to increased UGE, alterations in serum or urine electrolytes, gastrointestinal intolerance, hypoglycemia, changes in bone formation and/or bone resorption and in the hormones controlling calcium homeostasis, abnormalities in renal function, photosensitivity, or vulvovaginal adverse events. Data from the Phase 1 studies as well as from Phase 2b studies involving over 1,200 subjects indicates that canagliflozin is generally well tolerated and serious adverse events are uncommon.

Results from the photosensitivity studies demonstrate that canagliflozin has no clinically relevant photosensitizing effect at the doses studied in the Phase 3 studies (100 mg or 300 mg once daily), and support safe participation of subjects in these Phase 3 studies without specific photo-protection precautions.

As described in Section 1.1.2, Clinical Studies, women subjects may be at an increased risk for vulvovaginal adverse events. Also, because of the modest magnitude of the observed increase of serum CTx levels and the biologic variability associated with this marker as well as it not being associated with changes in other markers of bone turnover, the increase in serum CTx levels is of uncertain significance; nonetheless, this will be monitored in Phase 3 studies by careful collection of information on any fractures and additional assessments in selected Phase 3 studies. Renal glomerular and tubular integrity were assessed using several biomarkers in Phase 2b studies. A urinary NAG increase noted could be secondary to increased flow in the proximal tubule or to glucosuria. Based on the preclinical, theoretical, and clinical experience to date, appropriate safety measures have been included to help in the selection of subjects as defined in the inclusion and exclusion criteria in Sections 4.2 and 4.3, respectively.

This study will provide scientific guidance on using canagliflozin in a T2DM subject population requiring improved glycemic control, and it should answer important questions about canagliflozin. Subjects will be randomly assigned to either canagliflozin 100 or 300 mg, both of which have shown glucose-lowering activity in Phase 1 and Phase 2b clinical studies, or placebo. The use of placebo as a comparator in this study does not represent an ethical compromise because subjects will be allowed to remain on a

¹ The study-specific design considerations are reflective of the available data at the time the protocol was originally designed. For updated information regarding canagliflozin, please refer to the current version of the Investigator's Brochure.

background of standard care for diabetes or to add other agents as the investigator considers necessary according to established treatment guidelines.

One of the objectives of this study is to demonstrate safety in subjects treated with the compound. Safety will be evaluated on a frequent and ongoing basis, and all adverse events will be treated according to standard medical practice. Hypoglycemia is considered to be a side effect of treatment in T2DM. It occurs most frequently with insulin therapy, but hypoglycemia can occur with the use of other agents as well. Because canagliflozin does not alter the regulation of glucose-dependent insulin secretion, hypoglycemia is not intrinsic to the mechanism of action of canagliflozin and should not be a frequent occurrence in subjects treated with this agent.

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 3 months. Subjects will be required to report episodes of hypoglycemia and encouraged to report any changes in their clinical condition to the investigator.

Subjects will be followed after discontinuing study drug and early withdrawal from the study by a follow-up contact to evaluate adverse events and concomitant therapy use, and to document CV events.

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 7.25 years would be approximately 850 mL. The maximum amount that would be collected at a single visit would be approximately 80 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 (as required by local regulations):

- 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.

Approval for the pharmacogenomic research component of the clinical study and for the pharmacogenomic informed consent form must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of approval for pharmacogenomic research.

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
- 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 or Periodic 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.

Subjects will be asked to consent to participate in a pharmacogenomic research component of the study where local regulations permit. After informed consent for the clinical study is appropriately obtained, the subject will be asked to sign and personally date a separate pharmacogenomic informed consent form indicating agreement to participate in optional pharmacogenomic research. A copy of the signed pharmacogenomic informed consent form will be given to the subject. Refusal to participate will not result in ineligibility for the clinical study.

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.

For those subjects who gave consent to store DNA samples for future genetic research (Part 2), samples and corresponding relevant clinical data will be made nonidentifiable by the removal of personal identifiers. Samples will be stored until completely used. Only research related to the drug or the indications for which the drug is developed will be done on stored samples. For data generated on identifiable samples (Part 1), the sponsor will provide the individual raw data, through the investigator, to subjects who submit a written request. The sponsor cannot make decisions as to the significance of any findings resulting from this pharmacogenomic research, and cannot, therefore, provide genetic counseling. Genotypic data generated on nonidentifiable samples (Part 2) cannot be returned to individual subjects.

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, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

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 (or sealed, where appropriate per local regulations) 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 subinvestigators
- Documentation of subinvestigator 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 medication; 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 electronic eCRF, and transmitted in a secure manner to the sponsor within 3 working days of the subject's visit. 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 study-site personnel 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.

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, handling, storage, and shipment of 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 and consistency with the data sources.

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 (ie, GTED) 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 study 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 and clinical laboratory data from a central laboratory via direct transmission into the sponsor's data base. 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 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.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. 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.
- DCCT (1993). The Diabetes Control and Complications Trial (DCCT) Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 1993; 329:977-86.
- de Zeeuw D (2004), Remuzzi G, Parving H-H, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation.* 2004;110:921-927.
- EMA 2002. The European Medicines Agency. Committee for Proprietary Medicinal Product (CPMP). Note For Guidance On Clinical Investigation Of Medicinal Products In The Treatment Of Diabetes Mellitus (30 May 2002).
- EMA 2008. The European Medicines Agency. Committee for Proprietary Medicinal Product (CPMP). Concept Paper on the Need for Revision of the Note For Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (30 May 2008). <http://www.emea.europa.eu/pdfs/human/ewp/17634808en.pdf>
- FDA 2008. U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008).
- Friedewald WT (1972), Levy RI, and Fredrickson DS. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. *Clinical Chemistry* 1972;18;499-502.
- Ganong W (2005) Review of Medical Physiology. McGraw-Hill Professional. 2005
- IB JNJ-28431754 Edition 12. Document ID No. EDMS-ERI-13482463. Johnson & Johnson Pharmaceutical Research and Development, L.L.C. Investigator's Brochure (08 September 2014).
- 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.
- 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.

Ray KK (2009), Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009;373:1765–72.

Ridker PM (2004), Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* 2004;109:Suppl 1:IV6-IV19.

Roder ME (1998), Porte D, Schwartz RS, Kahn SE. Disproportionately elevated proinsulin levels reflect the degree of impaired β cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. *J Endocrinol Metab* 1998;83:604-8.

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

Strojek K (2010), Hrubá V, Elze M, Langkilde A, Parikh S. Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and inadequate glycaemic control on glimepiride monotherapy. European Association for the Study of Diabetes Annual Meeting (Stockholm, Sweden). Presentation 870. Session A. PS 079 SGLT-2 inhibitors. September 2010.

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.

Wallace TM (2004), Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;27(6):1487-95.

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.

Attachment 1:
Sulfonylurea Monotherapy Doses for Stratification Purposes

Monotherapy consisting of one of the following:

- glipizide ≥ 20 mg/day
- glipizide extended release ≥ 10 mg/day
- glyburide/glibenclamide ≥ 10 mg/day
- glimepiride ≥ 4 mg/day
- gliclazide ≥ 160 mg/day
- gliclazide modified release ≥ 60 mg/day

Attachment 2: **Hypoglycemia: Definitions, Symptoms, and Treatment**

Hypoglycemia is defined and classified as follows:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose (PG) concentration ≤ 70 mg/dL (3.9 mmol/L)

Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG concentration ≤ 70 mg/dL (3.9 mmol/L)

Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination.

Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer a carbohydrate, glucagon, or other resuscitative actions. A subject is considered to "require assistance" if he/she is unable to help himself/herself. An act of kindness to assist a subject when it is not necessary does not qualify as "requiring assistance". These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.

Symptoms

Subjects will receive information regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia and other specific details should be captured in the subject diary, which should be returned to the study center for review by research study staff at each visit. The following list of symptoms is not meant to be exhaustive but represents the more common symptoms associated with hypoglycemia:

- Seizure
- Loss of consciousness
- Headache
- Tremor
- Hunger
- Sweating
- Nervousness
- Palpitations
- Light headedness
- Blurred vision
- Disorientation
- Dizziness
- Feeling faint

Treatment

The treatment of hypoglycemia requires the ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Therefore, glucose (15 to 20 g) is the preferred treatment for hypoglycemia. Although pure glucose may be the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose and may be used. Adding protein to a carbohydrate does not affect the glycemic response and does not prevent subsequent hypoglycemia. However, adding fat may retard and then prolong the acute hypoglycemic response. Treatment effects should be apparent within 15 minutes although the effects may only be temporary. Therefore, PG should be retested in approximately 15 minutes, as additional treatment may be necessary.

Attachment 3:
New York Heart Association Classification of Cardiac Disease

The following table represents the NYHA classification of cardiac disease:

Functional capacity	Objective assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain	A. No objective evidence of cardiovascular disease
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain	B. Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

Source: 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.

Attachment 4:**Optional Specimens for Exploratory Research - Sample Collection and Handling****Materials and Labeling**

- The central laboratory will provide the study site with blood collection tubes, storage tubes, preprinted Janssen Research and Development labels (or tubes labeled with preprinted labels), and related supplies for the collection and shipment of exploratory samples.
- The central laboratory will provide the study site with urine collection containers, storage tubes, and preprinted Janssen Research and Development labels (or tubes labeled with preprinted labels), for the collection and shipment of urine exploratory samples.
- Use of alternative materials will not result in a protocol amendment if preapproved by the Bioanalysis Scientist.
- Detailed information regarding the collection and storage containers will be provided in the laboratory manual from the central laboratory.

Preparation of Exploratory Plasma Samples

- Collect one full blood sample into the K₂EDTA-containing collection tube (eg, Vacutainer[®]) provided (10 mL or 5 mL) at the appropriate time point.
- Immediately after draw, gently invert the plasma tube 8 times (up-down-up=1 inversion) to completely mix tube contents. Place tubes at room temperature, 15°C to 25°C, until processed.
- Record the exact date and time of sampling in the eCRF or laboratory requisition form, as appropriate.
- Centrifuge blood sample at room temperature within 1 hour of collection in a clinical centrifuge according to the specifications in the laboratory manual.
- The following steps should be done separately for each blood sample that was collected. Do not combine the plasma. Keep aliquots separate.
- Immediately after centrifugation, transfer all separated plasma with a clean disposable plastic pipette to a prelabeled storage tube. Gently mix the tube by inversion.
- Dispense the plasma (0.5 to 1.0 mL aliquots) into two prelabeled microfuge tubes or cryovials (1.5- to 2-mL size) and securely cap.
- Store the plasma samples in an upright position in a freezer at –70°C or colder until transfer to the central laboratory. Record the exact time of storage in the eCRF or laboratory requisition form, as appropriate. Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at –70°C or colder.
- The time between blood collection and freezing the plasma must not exceed 2 hours.
- Ship specimens on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory plasma specimens should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 4: (Continued)**Optional Specimens for Exploratory Research - Sample Collection and Handling****Preparation of Exploratory Serum Samples**

- Collect one 8.5 mL of blood into the appropriate plastic collection tube (Serum SST; SST with clot accelerator and gel barrier, also called Red & Black Tiger top) at the appropriate time point.
- Immediately after draw, gently invert the serum tube 5 times (up-down-up=1 inversion) to completely mix tube contents. Place tube at room temperature, 15°C to 25°C, for a minimum of 30 minutes or until processed.
- Record the exact date and time of sampling in the eCRF or laboratory requisition form, as appropriate.
- Centrifuge blood sample at room temperature within 45 min of collection in a clinical centrifuge according to the specifications in the laboratory manual.

The following steps should be done separately for each blood sample that was collected. Do not combine the serum. Keep aliquots separate.

- Immediately after centrifugation, transfer all separated serum with a clean disposable plastic pipette to a pre-labeled storage tube. Gently mix the tube once by inversion.
- Dispense the serum (0.5-1.0 mL aliquots) into two prelabelled microfuge tubes or cryovials (1.5 to 2 mL size) and securely cap.
- Store serum samples in an upright position in a freezer at -70° C or colder until transfer to the central laboratory. Record the exact time of storage in the eCRF or laboratory requisition form, as appropriate.
- Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at -70° C or colder.
- The time between blood collection and freezing the serum must not exceed 2 hours.
- Ship specimens on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory serum specimens should be addressed to the contact person for the sponsor.

Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Preparation of Exploratory Urine Samples

- Collect voided urine in the appropriate urine collection container at the time designated in the protocol.
- Thoroughly mix the urine.
- Transfer one 3-mL aliquot into a labeled cryovial.
- Store the urine sample in an upright position in a freezer at -70° C or colder until transfer to the central laboratory. Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at -70° C or colder.
- The time between urine collection and freezing should not exceed 1 hour.
- Ship specimen on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory urine sample should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 5:
Pharmacogenomic Sample Collection and Shipment Procedure

Pharmacogenomic Sample Supplies and Labeling

The central laboratory will provide the investigational site with pre-labeled 10 mL blood collection tubes containing potassium or sodium EDTA. Detailed information is provided in the laboratory manual from the central laboratory.

Preparation of Pharmacogenomic Samples

Pharmacogenomic samples should be prepared as follows:

- Invert the tube 10 to 15 times immediately after collection, to prevent coagulation.
- DO NOT centrifuge the sample.
- Freeze the samples at or below -20°C in an upright position immediately after collection

Pharmacogenomic Sample Shipment

Once collected, the blood samples must immediately be frozen at or below -20°C in an upright position. Samples must remain at this temperature until shipment to the central laboratory. All samples must then be shipped with sufficient dry ice to ensure samples remain frozen during shipment. Detailed information will be provided in the laboratory manual from the central laboratory.

The following guidelines should be adhered to:

- Shipment of the frozen pharmacogenomic blood samples should be arranged with other clinical study samples. If this is not possible, a separate shipment for these blood samples should be organized, using the courier recommended by the central laboratory.
- Notify the courier, at least 24 hours in advance of the planned shipment. Provide the courier with the appropriate account number to be used, if applicable.
- Package the samples in sufficient dry ice to ensure that the samples remain frozen during shipment.
- Label the package with the study number and all other information required by the central laboratory.
- Include a return address (that includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment, in the study files.
- The blood samples should be shipped to the name and address indicated in the central laboratory manual.

NOTE: If there are changes regarding the courier or location to which samples are shipped during the course of the clinical study, written notification will be provided to the investigator; a protocol amendment will not be required.

Attachment 6:
Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected for the tests listed below. The investigator must review the laboratory report, document this review, and record any clinically relevant changes (in the investigator's judgment) occurring during the study in the adverse event section of the eCRF.

The following tests will be performed by the central laboratory (the use of local laboratory studies should be limited to situations in which immediate availability of laboratory study results are necessary for appropriate care of the subject):

Hematology Panel	Chemistry Panel		Urinalysis*
Hemoglobin	Sodium, potassium, chloride,	Uric acid	Specific gravity
Hematocrit	bicarbonate	Calcium	pH
RBC count	Blood urea nitrogen (BUN)	Phosphate	Protein
WBC with automated differential	Serum creatinine	Albumin	Blood
Platelet count	Glucose	Total protein	Ketones
	Aspartate aminotransferase (AST)	Magnesium	Bilirubin/urobilinogen
	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)	Nitrate
	Gamma-glutamyl transferase (GGT)		Leukocyte esterase
	Total bilirubin		
	Alkaline phosphatase		
	Lactic acid dehydrogenase (LDH)		

Fasting lipid profile: triglycerides, HDL-C, LDL-C (using Friedewald [1972] equation), total cholesterol (Note, C-peptide, insulin, proinsulin are collected as efficacy assessments as described in Section 9.5)

*Urine glucose will not be measured by the central laboratory

At run-in visit: Follicle stimulating hormone (FSH) only for women >45 years of age with amenorrhea for at least 6 months and <18 months before screening

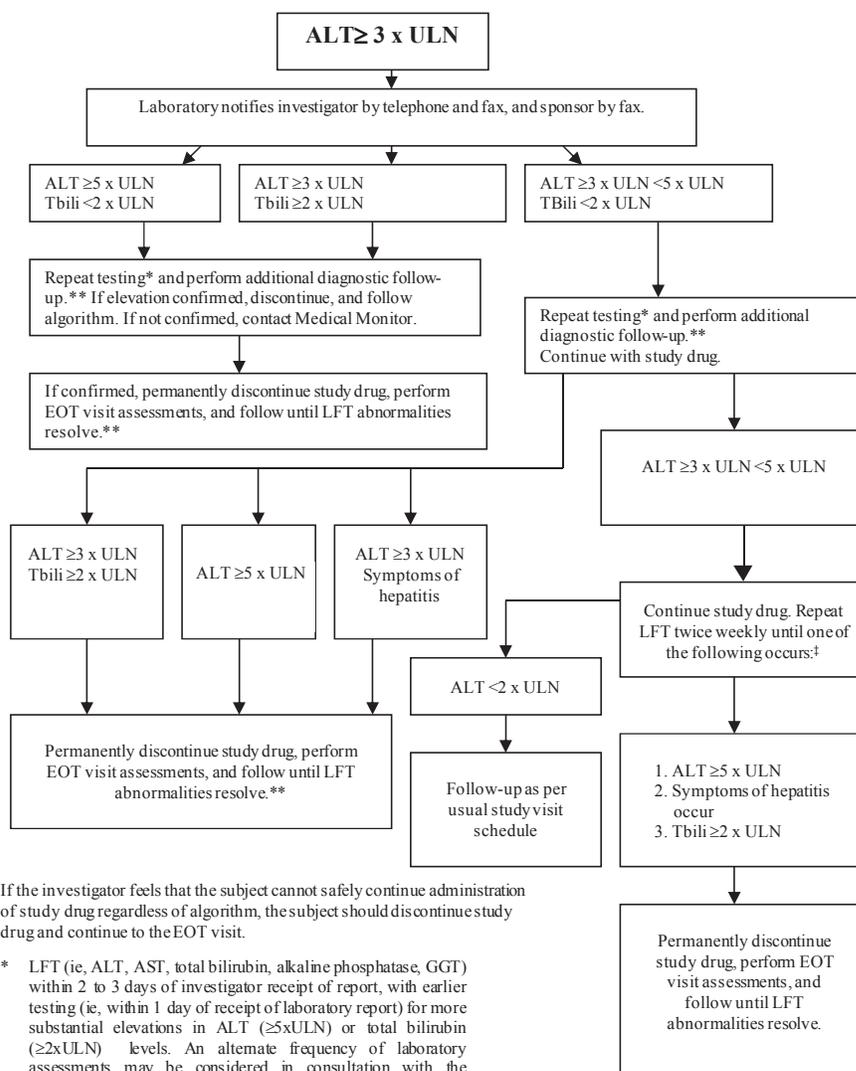
Central laboratory will report the eGFR according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured.

The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

For creatinine in mg/dL:

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

Attachment 7:
Algorithm for Monitoring Abnormal Liver Function Tests



If the investigator feels that the subject cannot safely continue administration of study drug regardless of algorithm, the subject should discontinue study drug and continue to the EOT visit.

* LFT (ie, ALT, AST, total bilirubin, alkaline phosphatase, GGT) within 2 to 3 days of investigator receipt of report, with earlier testing (ie, within 1 day of receipt of laboratory report) for more substantial elevations in ALT ($\geq 5 \times \text{ULN}$) or total bilirubin ($\geq 2 \times \text{ULN}$) levels. An alternate frequency of laboratory assessments may be considered in consultation with the sponsor's medical monitor.

** Focused medical history (including review of prior history of liver or biliary disorders, concurrent symptoms, review of all concomitant medications [eg, acetaminophen-containing medications, over-the-counter or herbal medications, nutritional supplements] including any changes in medications, detailed review of alcohol use and a complete physical examination); liver ultrasound and follow-up imaging as appropriate; hepatitis serology (anti-HAV, HBsAg, anti-HBs, anti-HB core, anti-HCV, HCV RNA, EBV and CMV screen) and autoantibodies (eg, ANA, anti-smooth muscle antibody) should be obtained as appropriate, with additional evaluation as clinically indicated. The extent of the evaluations should be made in consultation with the sponsor's medical monitor.

† If the subject's ALT value is $\geq 2 \times \text{ULN}$ and $< 3 \times \text{ULN}$ upon retest, then repeat LFT weekly until one of the subsequent events occurs. An alternate frequency of laboratory assessments may be considered in consultation with the sponsor's medical monitor.

Key: ALT=alanine aminotransferase; EOT=End of Treatment; GGT= gamma-glutamyl transferase; LFT=liver function test; Tbil=total bilirubin; ULN=upper limit of normal

Attachment 8:
Candidate Gene List for Part 1 of Pharmacogenomics

Absorption, Distribution, Metabolism, and Excretion Genes: *ABCB family, ABCC family, ABCG2, ADH family, AHR, ALDH family, AOX1, ARNT, ATP7A, ATP7B, BDH2, CDA, CHST family, COMT, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1A1, CYP1A2, CYP1B1, CYP20A1, CYP21A2, CYP24A1, CYP26A1, CYP27A1, CYP2A13, CYP2A6, CYP2A7, CYP2B6, CYP2B7, CYP2C family, CYP2D6, CYP2E1, CYP2J2, CYP2S1, CYP39A1, CYP3A family, CYP46A1, CYP4B1, CYP4F family, CYP4Z1, CYP51A1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, DHRS family, DHRSX, DPYD, EPHX1, EPHX2, FMO family, FOM3, GPX family, GSR, GSS, GSTA family, GSTCD, GSTK1, GSTM family, GSTO1, GSTO2, GSTP1, GSTP2, GSTT1, GSTT2, GSTZ1, HAGH, HNMT, MAOA, MAOB, MGST1, MGST2, MGST3, MPO, NAT1, NAT2, NFE2L2, NNMT, NQO1, NR1H2, NR3C1, POR, PPARA, PPARB, PPARG, RALBP1, RLIP76, SLC10A1, SLC10A2, SLC13A1, SLC15A1, SLC15A2, SLC16A1, SLC19A1, SLC22A family, SLC28A family, SLC29A1, SLC29A2, SLC5A6, SLC7A5, SLC7A7, SLCO1A2, SLCO1B1, SLCO1B3, SLCO1C1, SLCO2A1, SLCO2B1, SLCO3A1, SLCO4A1, SLCO4C1, SLCO5A1, SLCO6A1, SPG7, STE, SULT1A1, SULT1A2, SULT1B1, SULT1C1, SULT2A1, SULT2B1, SULT4A1, TPMT, UGT1A family, UGT2A1, UGT2B family, UGT8, XDH.*

Target related genes: *SGLT gene family (SLC5 family), GLUT gene family (SLC2 family).*

Diabetes related genes: *ABCA1, ABCC8, ABCG5, ACE, ACPI, ACTN4, ADA, ADAMTS9, ADIPOQ, ADRB3, AKR1B1, ALB, ALMS1, ALX4, ANGPTL4, APOA1, APOA4, APOA5, APOB, APOC3, APOE, ARG1, ASIP, ASPN, BBS4, BCHE, CAMK1D, CAPN10, CART, CCK, CCKAR, CCL2, CD36, CD59, CDC123, CDKAL1, CDKN2A-2B, CELSR2, CETP, CIDEA, CILP2, COL2A1, CPE, CTLA4, CTNBL1, CXCL12, CYP19A1, DF, DIANPH, DOCK7, DPP4, ENPP1, ESR1, EXT2, FABP10, FABP2, FABP4, FABP5, FADS1-3, FASN, FOLH1, FOXC2, FRZB, FTO, FXN, GADI, GAD2, GAL, GALNT2, GCG, GCGR, GCK, GCKR, GDF8, GHI, GH2, GHRL, GIP, GIPR, GNB3, GPD2, GPKOW, GYS1, HBA1, HFE, HHEK1, HHEX-IDE, HK1, HK2, HK3, HLA-DQA1, HLA-DQB1, HMGA2, HMGCR, HNF4A, HSD11B1, HSD17B7, IAPP, IDE, IGF1, IGF1R, IGF2BP2, IKBKB, IL1R1, IL gene family, INS, INSIG2, INSR, IPF1, IRS1, IRS2, IRS4, ISL1, JAZF1, JPH3, KCNJ11, KCNJ9, KCNQ1, KIF11, LACT, LDLR, LEP, LEPR, LGR5, LIPC, LIPE, LIPG, LMNA, LPA, LPAL2, LPL, LRPAP1, MADD, MANT3, MAPK8, MAPK8IP1, MBL2, MC3R, MC4R, MIA3, MKKS, MLXIPL, MMAB, MMP13, MVK, NEGR1, NEUROD1, NEUROG3, NFKB1, NOS3, NOTCH2, NPY, NR0B2, NR3C1, NUCB2, PBX1, PCSK1, PCSK9, PDE3B, PFKF, PGC, PGR, PLG, PLIN, PNPLA3, POMC, PON1, PON2, PPARG, PPARGC1A, PPARGC1B, PPP1R1A, PPP1R3A, PRL, PSRC1, PTPN1, PTPRN, RBP4, REG1A, RETN, RPS6KB1, SCARB1, SERPINE1, SH2B1, SIM1, SLC2A1, SLC2A10, SLC2A2, SLC2A4, SLC30A8, SORBS1, SORT1, SPINK1, SREBF1, SST, TCF1, TCF2, TCF7L2, TGFB1, TH, THADA, TMEM18, TNF, TRAPPC2, TRIP1, TSPAN8, TUB, TULP2, UCN, UCP1, UCP2, UCP3, VDR, WFS1, WRN, XBPI, ZDHHC23 and ZFP36.*

Attachment 9:
Medical Resource Utilization Review

The questions below are representative but may not be exact wording of those that will be asked in the Diary.

When To Use Your Diary:

- Complete this diary any time you seek medical care that is not part of your study visit.

How To Use Your Diary:

- Do not list medical care received during an overnight hospitalization.
- Please indicate whether the medical care is planned
- Please be as accurate and complete as you can.

Sample Medical Care Visit Chart

Visit Date	Health-Care Provider Type	Planned	Location of Visit
05 February 2010	Primary Care Doctor	Yes	Home
11 March 2010	ER Doctor	No	Emergency Room
13 March 2010	Cardiologist	No	Doctor's Office

Medical Care Chart

Visit Date	Health-Care Provider Type	Planned	Location of Visit

LAST PAGE