Janssen Research & Development*

Clinical Protocol

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

The CREDENCE™ Trial
(Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial)

Protocol 28431754DNE3001; Phase 3
AMENDMENT INT-6

JNJ-28431754 (canagliflozin)

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	10 December 2013
Amendment INT-1	12 June 2014
Amendment INT-2	03 February 2015
Amendment INT-3	29 September 2015
Amendment INT-4	19 January 2016
Amendment INT-5	6 May 2016
Amendment INT-6	06 September 2017

Amendments below are listed beginning with the most recent amendment.

Amendment INT-6 (06 September 2017)

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 decrease the number of primary composite events required for the interim analysis from 540 to 405. In addition, 2 new secondary endpoints have been added and secondary endpoints have been reordered.

Applicable Section(s)	Description of Change(s)
Rationale: to provide clarity in the Time and Events Schedule regarding when plasma glucose monitoring is expected in accordance with the site laboratory manual and informed consent form.	
Time and Events Schedule	A row was added to the Time and Events Schedule specifying collection of fasting plasma glucose.
Rationale: to add two new secondary endpoints and adjust the hierarchical order in which secondary endpoints will be tested.	
Synopsis (Secondary Objective, Secondary Efficacy Outcomes, Secondary Efficacy Analyses); 2.1 Objectives (Secondary Objective); 9.4.1 Measures of Efficacy; 9.4.2 Efficacy Outcomes (Secondary Efficacy Outcomes); 11.3.2 Secondary Efficacy Analyses	Two secondary endpoints were added, including the composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), and non-fatal stroke (ie, 3-point major adverse cardiac event [MACE]), and the stand-alone endpoint of hospitalized congestive heart failure. The order in which secondary efficacy endpoints will be tested was adjusted to: 1) The composite endpoint of CV death and hospitalized congestive heart failure, 2) The composite endpoint of CV death, non-fatal MI, and non-fatal stroke (ie, 3-point MACE), 3) Hospitalized congestive heart failure, 4) The renal composite endpoint of end-stage kidney disease (ESKD), doubling of serum creatinine, and renal death, 5) CV death, 6) All-cause death, and 7) The CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina.

Applicable Section(s)	Description of Change(s)
Rationale: based on internal and external data of the effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on renal endpoints, the beneficial effects of canagliflozin on renal outcomes may be detected with fewer events in the primary composite endpoint.	
Synopsis (Statistical Methods: Interim Analysis); 9.3.4 Independent Data Monitoring Committee; 11.3.5 Interim Analysis; 16.1 Study-Specific Design Considerations	The interim analysis will be conducted when a fewer number of subjects meet the primary composite endpoint (ie, 405 vs 540).
Rationale: to clarify when subjects should discontinue treatment due to chronic dialysis or renal transplant.	
10.2.1 Study Drug Treatment Premature Discontinuation	Text was clarified to instruct that study medication is to be discontinued when chronic dialysis or renal transplant is "initiated" rather than "required."
Rationale: to accommodate subjects who start using a disallowed medication.	
10.2.1 Study Drug Treatment Premature Discontinuation	Changed this bullet point: "The subject requires disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)" to now read: "The subject is currently using disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)."
Rationale: to clarify that restarting study medication should not be considered for certain subjects.	
10.2.1 Study Drug Treatment Premature Discontinuation	Added this sentence: Note: Double-blind study drug should be permanently discontinued for any subject who experiences a serious adverse event of biochemically-confirmed DKA, has his/her treatment allocation formally unblinded by the investigator, or undergoes a renal transplant or initiates maintenance dialysis.
Rationale: to inform investigators of additional safety reporting requirements associated with events of pancreatitis .	
12 Adverse Event Reporting	As of October 2016, investigators were informed via an investigator letter that events of pancreatitis are designated as adverse events (AEs) of special interest to be reported to the sponsor within 24 hours of becoming aware of the event. In addition, all events of pancreatitis will require additional information to be recorded on a designated electronic case report form (eCRF) (including but not limited to fatal or hemorrhagic/necrotizing events).

Applicable Section(s)	Description of Change(s)
Rationale: to clarify and further define adverse events of interest, and adverse events of special interest, including procedures requiring reporting within 24 hours.	
12 Adverse Event Reporting	Added this heading: "Adverse Events of Interest" Revised content as noted: For adverse events of interest, investigators will be asked to provide additional information. Adverse events of interest include all malignancies, [Deleted: 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 [Added: lower extremity events], and pregnancy. Added this heading: "Adverse Events and Procedures Requiring Reporting Within 24 Hours" Revised content to now read: Ketone-related events (eg, DKA, ketoacidosis, metabolic acidosis, or acidosis) and pancreatitis events have been designated an adverse event of special interest and need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. Events with characteristics suggestive of DKA or pancreatitis will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition within the adjudication committee charters. These adverse events must be recorded on the supplemental Diabetic Ketoacidosis and Ketone-related Events or Pancreatitis eCRF to complement standard information collected on the eCRF AE/SAE page. In addition, all lower-extremity amputation procedures are considered adverse events of special interest and need to be reported to Janssen within 24 hours of becoming aware of the procedure. The underlying condition leading to the lower-extremity amputation must be recorded on the supplemental Lower-Extremity Event eCRF to complement standard information collected on the AE/SAE eCRF, and the details relating to the amputation procedure must be recorded on the Lower-Extremity Amputation eCRF. Revised content as noted: Additional information and documentation will be requested from investigators to support a detailed assessment of all deaths. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC. 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. [Added: Some events will be subject to adjudication by an ad hoc adjudication committee to standardize the diagnosis.]
Rationale: to clarify the description of a statistical method used in the Interim Analysis.	
Synopsis (Statistical Methods: Interim Analysis); 9.3.4 Independent Data Monitoring Committee; 11.3.5 Interim Analysis	Changed this sentence: "The Lan-DeMets alpha spending function approach will be used and the alpha spent in the interim analysis is 0.01." to now read: "The alpha spending function will be used and the alpha spent in the interim analysis is 0.01."

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted.	
Throughout the protocol	Throughout the protocol

Amendment INT-5 (6 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: Clarify that all potential sustained doublings of serum creatinine values are derived from a baseline average determination rather than a single baseline value.	
Synopsis (Primary Efficacy Outcomes); 3.2 Study Design rationale (Choice of Renal Efficacy Measures); 9.1.3 Double-Blind Treatment Phase; 9.2 Reporting/Adjudication of Events in the Primary and Secondary Composite Endpoints and Other Events for Adjudication; 9.4.2 Efficacy Outcomes; 11.3.1 Primary Efficacy Analysis	Added "average", "baseline average values", "average determination", and "sustained" as appropriate.
Rationale: Include guidance regarding subject management surrounding the event of lower extremity amputations.	
Time and Events Schedule footnote "c"' "h"; "m", 'n", "o"; 12.3.1 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: Address a request from a Health Authority.	
Time and Events Schedule (posttreatment); footnote "ee"	Added collection of concomitant medications, including AHAs, during the posttreatment period.
Rationale: Include new safety information and guidance regarding subject management surrounding the event of lower extremity amputations.	

Applicable Section(s)	Description of Change(s)
1.1.2.5.1 Overall Safety;	Added amputation data from IDMC.
6.1 Study Drug;	Added statement that study drug should be interrupted for subjects who develop conditions that are associated with amputation.
12 Adverse Events Reporting; 16.1 Study-Specific Design Considerations	Added a statement about additional AE of special interest "amputation".
Rationale: Exclude subjects who may be at a higher risk for lower extremity amputation.	
4.2 Exclusion criteria	Added criteria 16 to exclude history of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.
Rationale: Clarify therapy reporting for subjects who prematurely discontinue study drug.	
8 Prestudy and Concomitant Therapy	Was clarified that therapies for all subjects will be recorded on the CRF, including those subjects who prematurely discontinue study drug.
Rationale: Clarify additional safety reporting requirements associated with diabetic ketoacidosis (DKA).	
12 Adverse Events Reporting	Added a statement that events with characteristics of DKA will be adjudicated by an ad hoc adjudication committee to verify whether or not the event meets a specified definition of DKA.
Rationale: Minor errors were noted and/or corrected for clarity.	
Throughout the protocol	Minor grammatical and formatting changes were made.

Amendment INT-4 (19 January 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: Due to slower than expected recruitment early in the study and to maintain the study timeline, the sample size is being expanded to increase the likelihood of accruing endpoints within the primary composite. In addition, the cap that limits enrollment of subjects with eGFR ≥60 to <90 mL/min/1.73m^2 to approximately 25% was removed to allow more of these subjects to participate in the study. Furthermore, the number of events required for the interim analysis was increased from 420 to 540 to allow more time for renal endpoints to accrue. Two new secondary endpoints were added along with a reordering of other secondary endpoints. Lastly, if determined medically necessary, cautionary post-baseline use of mineralocorticoid antagonist (MRA) (according to local label) will be permitted to allow subjects requiring treatment with MRA to continue on double-blind study medication.

Applicable Section(s)	Description of Change(s)
Rationale: to add 2 secondary endpoints and adjust the hierarchical order in which secondary endpoints will be tested.	

Applicable Section(s)	Description of Change(s)
Synopsis (Secondary Objective, Secondary Efficacy Outcomes, Secondary Efficacy Analyses); 2.1 Objectives (Secondary Objective); 9.4.1 Measures of Efficacy; 9.4.2 Efficacy Outcomes (Secondary Efficacy Outcomes); 11.3.2 Secondary Efficacy Analyses	Two secondary endpoints were added to test the composite endpoint of CV death and hospitalized congestive heart failure and the stand alone endpoint of CV death. The order in which secondary efficacy endpoints will be tested was adjusted to 1) CV death and hospitalized congestive heart failure, 2) CV death, 3) All-cause death, 4) Renal composite, and 5) CV composite.
Rationale: to allow participation of subjects who may benefit from treatment, but may have otherwise been excluded from the study due to eGFR cap and to maintain control over the proportion of subjects enrolled in the highest eGFR category.	
Synopsis (Study Population); 3.1 Overview of Study Design (Screening to Randomization); 3.2 Study Design Rationale (Selection of Study Population); 4.2 Inclusion Criteria (Criterion #3); 5 Treatment Allocation (Randomization and Blinding Procedures)	The global cap restricting no more than approximately 25% of subjects with eGFR ≥60 to <90 mL/min/1.73m^2 has been removed. Text was added to indicate capping may occur at the regional and/or site level should the ratio of 60%:40% for chronic kidney disease (CKD) Stage 3 (eGFR ≥30 to <60 mL/min/1.73m^2; first category):CKD Stage 2 (eGFR ≥60 to <90 mL/min/1.73m^2; second category) drift substantially off target over the course of the recruitment period.
Rationale: due to slower than expected recruitment early in the study and to maintain the study timeline, the sample size is being expanded to increase the likelihood of accruing endpoints within the primary composite.	
Synopsis (Overview of Study Design, Sample Size Determination); 3.1 Overview of Study Design (Double-Blind Treatment Phase); Study Duration); 9.1.1 Overview (Blood Collection); 11.2 Sample Size Determination	The sample size was increased from 3,700 to 4,200 subjects. The projected study duration was adjusted from 5.5 years to 5 to 5.5 years to account for uncertainty in how the primary composite endpoint accrual rate will impact the study duration. In addition, assumptions regarding the duration of enrollment and overall duration of the study were updated to align with sample size calculations.
Rationale: if determined medically necessary, cautionary post-baseline use of MRA (according to local label) will be permitted, thus allowing subjects requiring treatment with MRA to continue on double-blind study medication.	
4.4 Prohibition and Restrictions; 8 Prestudy and Concomitant Therapy	Text was revised to list post-baseline use of MRAs as restricted rather than strictly prohibited. Text was added to caution investigators of the increased risk of severe hyperkalemia associated with using the MRAs in this study population taking ACEi/ARB therapy and the need for more frequent monitoring of serum potassium and management of hyperkalemia according to local MRA labeling.

Applicable Section(s)	Description of Change(s)
Rationale: based on external data, the beneficial effects of canagliflozin on renal outcomes would not be expected for at least 18 months. The timing of the existing interim analysis (ie, 420 events) would occur at a time point too early to demonstrate effects of canagliflozin on renal outcomes.	
Synopsis (Statistical Methods: Interim Analysis); 9.3.4 Independent Data Monitoring Committee; 11.3.5 Interim Analysis; 16.1 Study-Specific Design Considerations	The interim analysis will be conducted when a greater number of subjects meet the primary composite endpoint (ie, 540 vs 420). In addition, the alpha spent on the interim analysis has been increased from 0.003 to 0.01.
Rationale: to clarify text, or reconcile inconsistencies	
Throughout the protocol	Minor editorial changes were made

Amendment INT-3 (29 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 inform investigators of additional safety reporting requirements associated with diabetic ketoacidosis (DKA), which is a newly identified adverse event of special interest. In addition, background information related to bone fracture and bone mineral density already described in detail in the Investigator Brochure is added for consistency across ongoing canagliflozin study protocols.

Applicable Section(s)	Description of Change(s)
Rationale: to inform investigators of additional safety reporting requirements associated with diabetic ketoacidosis (DKA), which is a newly identified adverse event of special interest.	
1.1.2.5.1. Overall Safety; 5. Treatment Allocation; 10.2.1. Study Drug Treatment Premature Discontinuation; 12. Adverse Event Reporting; 12.3.1. All Adverse Events.	Added information, safety data and instructions on reporting related to diabetic ketoacidosis (DKA), ketoacidosis, metabolic acidosis, and acidosis.
Rationale: to exclude subjects who experience particular events outlined in Exclusion Criteria #7, #14 and #18 during the pre-treatment period prior to randomization.	
4.3. Exclusion Criteria #7, #14, #18,	Changed the event time frame from “prior to screening” to “prior to randomization” for Exclusion Criteria #7 (myocardial infarction, unstable angina, revascularization procedure [eg, stent or bypass graft surgery], or cerebrovascular accident), #14 (major surgery) and #18 (current use of an SGLT2 inhibitor).
Rationale: to provide more background information, preclinical and clinical data related to bone fracture and decrease in bone mineral density.	
1.1.2.5.1. Overall Safety.	Added more background information, preclinical and clinical data related to bone fracture and decrease in bone mineral density.

Applicable Section(s)	Description of Change(s)
Rationale: to provide further clarifications.	
1.1.2.5.1. Overall Safety; 3.2. Study Design Rationale.	Relocate the text and data related to ACEi or ARB therapy from Section 1.1.2.5.1. Overall Safety to Section 3.2. Study Design Rationale.
Time and Events Schedule (Footnote "v"); 3.1. Overview of Study Design; 3.2. Study Design Rationale; 4.3. Exclusion Criteria #9 and general note; 4.5. Repeat Testing and Subject Rescreening; 6.1. Study Drugs; 9.1.2. Pretreatment Phase; 9.5.1. Safety Evaluation; 11.3.5. Interim Analysis; 12. Adverse Event Reporting; 12.3.1. All Adverse Events; 14.5. Drug Accountability; Attachment 3; Attachment 4.	Modified text for clarity.
Rationale: Minor errors were noted.	
Throughout the protocol	Throughout the protocol

Amendment INT-2 (03 February 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: To revise inclusion criteria to allow patients with higher baseline $HbA1_c$ values who may benefit from the study treatment to participate in the study. In addition, changes to the prescreening assessment are intended to allow a wider range of measures to prescreen subjects for albuminuria/proteinuria, as well as to extend the duration of the prescreening assessment of the study. These changes should not impact the safety of subjects screened or randomized, as well as the event rates in this study.

Applicable Section(s)	Description of Change(s)
Rationale: To include subjects with higher baseline $HbA1_c$ who may be at increased risk for renal and cardiovascular events. Additionally, the higher threshold for $HbA1_c$ inclusion may help account for differences in Type 2 Diabetes Mellitus (T2DM) medical practice patterns that exist globally, and allow participation by subjects for whom available treatments are not able to achieve glycemic goals. As per Section 6.2.1 of the protocol, the background antihyperglycemic agent (AHA) regimen should be adjusted throughout the study to achieve glycemic goals, using standard local guidelines, as considered appropriate by the investigator for the individual subject. Investigators should not enroll subjects who may be considered non-compliant with study drug or who may have limited access to routine health care.	

Applicable Section(s)	Description of Change(s)
Synopsis (Study Population); 3.1 Overview of Study Design (Figure 6 Study Design Diagram, Screening to Randomization); 4.2. Inclusion Criteria (Criterion #2);	Changed the upper limit of $HbA1_c$ level from "≤10.5%" to "≤12.0%" for the study entry.
Rationale: To provide a wider range of measures for prescreening subjects for evidence of albuminuria/proteinuria.	
Synopsis (Overview of study design); 3.1. Overview of Study Design (Prescreening); 9.1.2. Pretreatment Phase (Prescreening)	Added the phrase "For the prescreening assessment where UACR is not routinely measured as per standard of care, it may be substituted by one of the following measures: albumin excretion rate >300 mg/24 hours, urine protein-to-creatinine ratio (PCR) >500 mg/g (>56.5 mg/mmol), or protein excretion rate >500 mg/24 hours."
Time and Events Schedule (Footnote "u")	Added the phrase "or other acceptable albuminuria/proteinuria measures if UACR values unavailable. For details of these additional measures refer to Section 9.1.2. Pretreatment Phase."
3.1. Overview of Study Design (Prescreening); 9.1.2. Pretreatment Phase (Prescreening)	Added guidance regarding the utility of reagent strip urinalysis (dipstick), if used as a tool for identifying subjects who may qualify prescreening criteria, that states " Note: While positive reagent strip analysis (eg, dipstick ≥2+) may be suggestive of albuminuria/proteinuria that meet the prescreening criteria, any positive reagent strip findings must be accompanied by one of the specified albuminuria/proteinuria prescreening measures listed above prior to screening with central laboratory evaluations."
Rationale: For prescreening assessments of albuminuria/proteinuria, there is no upper limit in order to allow subjects with a wider range of albuminuria/proteinuria measured at various local laboratories to continue on to a full screening visit where the UACR will be conducted by the central laboratory.	
Synopsis (Overview of study design); 3.1. Overview of Study Design (Prescreening); 9.1.2. Pretreatment Phase (Prescreening)	Removed the prescreening upper limit for UACR.
Rationale: To provide a longer timeframe in which local laboratory results may be used to prescreen subjects.	
Synopsis (Overview of study design); 3.1. Overview of Study Design (Prescreening); 9.1.2. Pretreatment Phase (Prescreening)	Revised text to indicate subjects will be prescreened on the basis of eGFR and UACR, or other acceptable albuminuria/proteinuria measurements by local laboratory within 6 months prior to screening, rather than 3 months.
Rationale: To allow subjects who fail prescreening due to local laboratory UACR and/or eGFR values to be retested.	
3.1. Overview of Study Design (Prescreening); 9.1.2. Pretreatment Phase (Prescreening)	Added the sentence "Subjects who fail local laboratory pre-screening assessments are allowed to repeat those laboratory tests."

Applicable Section(s)	Description of Change(s)
Rationale: To provide clarification on management of background standard care medications	
4.2 Inclusion Criteria (Criterion #5)	Added the word "stable" into the criterion, stating "All subjects must be on a stable, maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization.".
Synopsis (Overview of study design); 3.1. Overview of Study Design (Screening to Randomization); 6.2.3. Management of Medications That May Impact Serum Creatinine Levels; 9.1.2. Pretreatment Phase;	Provided instruction that "Investigators are encouraged to keep other anti-hypertensive, lipid-lowering and antihyperglycemic therapies dose stable for approximately 4 weeks prior to randomization. In addition, investigators are encouraged to keep medications that are known to impact serum creatinine levels (eg, NSAIDs, trimethoprim, cimetidine, probenecid, aminoglycosides, amphotericin, ketoconazole, and clofibrate) stable during the screening period and for approximately 2 weeks before any serum chemistry measurement during the course of the study."
Time and Events Schedule (Footnote "ff"); 8. Prestudy and Concomitant Therapy	Removed the content related to "AHAs taken within 12 months of screening will be recorded."
Rationale: To provide additional instructions on eligibility of subjects for study enrollment.	
4.3 Exclusion Criteria (Criterion #19)	Changed the sentence "Current or prior participation in another canagliflozin study" to "Current participation in another canagliflozin study or previously exposed to canagliflozin in a prior canagliflozin study." to allow subjects who received placebo or non-canagliflozin active control treatment in previous canagliflozin study to participate in the CREDENCE study.
4.3. Exclusion Criteria (Criterion #17)	Added the sentence "**Note:** If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with MRA or DRI during screening. Subjects who are off therapy with MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrollment."
Rationale: To provide clarification to study procedures	
4.3. Exclusion Criteria (Criterion #14)	Removed example of major surgery to provide more discretion to investigators. Major surgery ~~(ie, requiring general anesthesia)~~ within 12 weeks before screening, or has not fully recovered from surgery. ~~**Note**: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.~~
Synopsis (Stratification, Primary efficacy analysis); 3. Study Design and Rationale; 5, Treatment Allocation; 9.1.3. Double-blind Treatment Phase (Day 1/Day of Randomization);11.3.1. Primary Efficacy Analysis	Clarified that stratification will be based on pretreatment eGFR value most proximate to the baseline visit (eg, screening, unscheduled, or Week -2), since, in addition to the screening eGFR value, other eGFR values may be obtained during the pretreatment phase of the study.

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of study design); 3.1. Overview of Study Design (Screening to Randomization); 9.1.2. Pretreatment Phase	Clarified the screening period extension process, stating "…the screening period may be extended, up to a total of 8 weeks (inclusive of the 2-week single-blind placebo run-in period); however, an additional 2 weeks of screening time may be allowed, if considered medically appropriate. Extension beyond this period of time would require concurrence with the sponsor's medical monitor."
3.1. Overview of Study Design (End of Treatment Visit); 9.14. Post-Treatment Follow-up; 10.1. Subject Completion;	Clarified the process of announcement of the predicted Global Trial End Date (GTED), end of treatment/final on-site visit, 30 day telephone follow-up contact and the actual GTED.
Time and Events Schedule (Footnote "j")	Modified footnote "j" to provide greater flexibility for the time frame when the Optional Exploratory Research Consent may be signed.
6.1. Study Drugs (Two-week Single-Blind Placebo Run-in Period following Screening); 9.1.2. Pretreatment Phase	Clarified that subjects should take the last dose of single-blind placebo study drug on the day prior to the Baseline (Day 1) visit.
9.1.3. Double-Blind Treatment Phase	Removed "ESKD" from the list of events with which subjects will continue to receive double-blind study drug.
Rationale: To increase consistency, and be compliant with the current protocol template.	
3.2. Study Design Rationale (Choice of Renal Efficacy Measures)	Deleted the last paragraph in sub-section "Choice of Renal Efficacy Measures" for consistency with Time and Events Schedule as well as other section of the protocol. ~~In the present study, duplicate first morning void urine collections on consecutive days, made by subjects at home (collection of the first urine void after the individual awakes from sleep), are being used to monitor changes of UACR overtime. 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.~~
10.3.2. Withdrawal of Consent	Modified text that describes reasons subjects may be discontinued from study medication to maintain consistency with the response options available in the eCRF.
12.2.1. Adverse Event Definitions and Classifications	Modified text under "Serious Adverse Event" to be complaint with the language in current protocol template.
12.3.3. Pregnancy	Added examples for abnormal pregnancy outcomes considered as serious adverse events according to the current protocol template.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, spelling or formatting changes were made.

Amendment INT-1 (12 June 2014)

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 to the protocol is to reflect recommendations from the United States (US) Food and Drug Administration (FDA) for study 28431754DNE3001.

Applicable Section(s)	Description of Change(s)
Rationale:	To further reinforce standards of care for glycemic, blood pressure and lipid goals in both treatment arms.
6.2.1. Management of Glycemic Control; 6.2.2. Management of Renal and CV Risk Factors; 15. Study Specific Materials	Added text to inform study sites about the individualized metrics reports for glycemic, blood pressure and lipids control that will be prepared for the sites approximately biannually and about the independent data monitoring committee (IDMC) monitoring of the same data in unblinded fashion by the treatment group. Added text stating that investigators will be provided American Diabetes Association (ADA) guidance as a reference for standards of care in the management glycemic, blood pressure and lipids control, but are encouraged to use similar local guidelines if they exist.
Rationale:	To refine the specific definition of the endpoint event of renal death.
Synopsis, Primary Efficacy Outcomes; 3.2. Study Design Rationale; 9.4.2. Efficacy Outcomes	The definition of renal death was clarified as death in subjects who have reached end-stage kidney disease (ESKD), die without initiating renal replacement therapy, and no other cause of death is determined via adjudication.
Rationale:	To clarify the time frame in laboratory measurements for endpoint events.
11.3.1. Primary Efficacy Analysis;	The date of confirmed doubling of serum creatinine was clarified as being the date when the first doubling from baseline is detected from local or central laboratory determinations. Additionally, clarifications were added to indicate the endpoint of doubling of serum creatinine may be triggered by a central or local laboratory results.
Synopsis, Primary Efficacy Outcomes; 3.2. Study Design Rationale; 9.4.2 Efficacy Outcomes	The time window for confirmation of the initial estimated glomerular filtration rate (eGFR) value and doubling of serum creatinine via the central laboratory was clarified as being ≥30 days and preferably within 60 days of the initial value.
Rationale:	To clarify the definition of and the procedure for baseline serum creatinine.
11.3.1. Primary Efficacy Analysis;	Additional details were added to instruct that the baseline serum creatinine will be determined using the average of 2 pre-treatment measures up to 4 weeks apart.
T&E Schedule, footnote "v"; 9.1.2. Pretreatment Phase	To instruct that an additional serum chemistry collection for serum creatinine will be made at the run-in visit (Week -2) for subjects who have an extended screening period (ie, >2 weeks between the screening visit and run-in (Week -2) visit.
Rationale:	To include an assessment of stroke disability to evaluate stroke outcomes.
9.5.2. Study Outcomes; Attachment 6	Text was added instructing study sites that for subjects who experience a stroke during the study, a modified Rankin Scale (mRS) assessment will be conducted, and the mRS assessment form is provided in Attachment 6 of the protocol.

Applicable Section(s)	Description of Change(s)
Rationale:	To use general standards for management of hyperkalemia in place of specific hyperkalemia management guidance, since there is no evidence of excess risk for hyperkalemia associated with the canagliflozin 100 mg dose used in this study.
8. Prestudy and Concomitant Therapy; 9.5.1. Safety Evaluation; 15. Study Specific Materials	References to the specific hyperkalemia management guidance were removed.
Rationale:	To clarify prescreening.
T&E Schedule, footnote "k"; 9.1.2. Pretreatment Phase;	Added details regarding the collection of the latest 3 pre-study local laboratory serum creatinine values if available.
T&E Schedule, footnote "i"; 9.1.2. Pretreatment Phase; 16.2.3. Informed Consent:	Added an optional separate abbreviated prescreening-specific informed consent form to allow study sites to conduct the prescreening assessments of urinary albumin-to-creatinine ratio (UACR) and eGFR.
Rationale:	To provide more clarity.
Synopsis, Sample Size Determination; 11.2. Sample Size Determination;	Sample size calculation was clarified to account for the effect of treatment discontinuation.
T&E Schedule, footnote "n"; 9.5.1. Safety Evaluation;	Added clarification regarding the frequency of the focused physical examination.
4.1. General Considerations;	Added clarification regarding repeat laboratory measures.
4.2. Inclusion Criteria;	Added clarification to definition of tubal occlusion to Inclusion Criterion# 6.
4.3. Exclusion Criteria;	Added clarification regarding reassessment of blood pressure in Exclusion Criterion#5. Removed previous history of hyperkalemia from Exclusion Criterion#6.
4.5. Repeat Testing and Subject Rescreening;	Clarified instructions for repeating blood pressure and laboratory result, as well as procedures for rescreening subjects.
5. Treatment Allocation;	Clarified that urine glucose results will not be reported by central laboratories and that investigators avoid performing local urinalysis with dipstick.
9.2.Reporting/Adjudication of Events in the Primary and Secondary Composite Endpoints and Other Events for Adjudication;	Clarified circumstance for recording local serum creatinine laboratory results.

Applicable Section(s)	Description of Change(s)
10.1. Subject Completion;	Clarified study completion date.
10.2.1. Study Drug Treatment Premature Discontinuation	Clarified when study drug should be discontinued as result of endpoint being reached.
Throughout the protocol	Added SI units for UACR. Minor grammatical, spelling or formatting changes were made.

SYNOPSIS

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

EUDRACT number: 2013-004494-28

PREAMBLE

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). Canagliflozin has been approved by several Health Authorities including the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The goal of this study is to assess whether canagliflozin has a renal and vascular protective effect in reducing the progression of renal impairment relative to placebo in subjects with T2DM, Stage 2 or 3 chronic kidney disease (CKD) and macroalbuminuria, who are receiving standard of care including a maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

OBJECTIVES AND HYPOTHESES

Primary Objective

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

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

Secondary Objectives

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

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

Exploratory Objectives

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

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

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

- Changes in estimated glomerular filtration rate (eGFR) over time (as calculated by the Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] equation)
- Changes in albuminuria over time

Safety Objectives

To assess the overall safety and tolerability of canagliflozin.

Hypotheses

Canagliflozin reduces the risk of the composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death, relative to placebo, in subjects with T2DM, Stage 2 or 3 CKD, and macroalbuminuria who are receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter study that will include a total of approximately 4,200 subjects. The study will have a pretreatment phase, consisting of a prescreening assessment and a screening period (up to 8 weeks), inclusive of a 2-week single-blind placebo run-in period. Subjects will be prescreened on the basis of eGFR, and urinary albumin-to-creatinine ratio (UACR). Only subjects with an eGFR of ≥30 to <90 mL/min/1.73m^2 and a UACR of level >300 mg/g (>33.9 mg/mmol), as confirmed by a local laboratory within 6 months prior to screening will be eligible for screening by the central laboratory. For the prescreening assessment where UACR is not routinely measured as per standard of care, it may be substituted by one of the following measures: albumin excretion rate >300 mg/24 hours, urine protein-to-creatinine ratio (PCR) >500 mg/g (>56.5 mg/mmol), or protein excretion rate >500 mg/24 hours.

Subjects must be on a stable maximum tolerated labeled daily dose of an ACEi or ARB for a period of at least 4 weeks prior to randomization. To reach this requirement, the screening period may be extended up to a total of 8 weeks (inclusive of the 2-week single-blind placebo run-in period); however. An additional 2 weeks of screening time may be allowed, if considered medically appropriate. Extension beyond this period of time would require concurrence of the sponsor's medical monitor. Investigators are encouraged to keep other anti-hypertensive, lipid-lowering and antihyperglycemic therapies dose stable for approximately 4 weeks prior to randomization. In addition, investigators are encouraged to keep medications that are known to impact serum creatinine levels stable during the screening period and for approximately 2 weeks before any serum chemistry measurement during the course of the study.

Qualified subjects will enter the single-blind placebo run-in phase at Week -2. During this phase, subjects will be instructed to take one capsule daily in order to assess their compliance with study drug. Subjects who are compliant during the single-blind placebo run-in period will be randomly assigned in a 1:1 ratio to canagliflozin or matching placebo group and will enter the double-blind treatment phase at the randomization visit (Day 1). Subjects randomized to canagliflozin will receive 100 mg canagliflozin, to be taken once daily (QD).

After randomization, subjects will return to the clinic at Week 3, Week 13, Week 26, and every 26 weeks thereafter for laboratory assessments, concomitant medication review, adverse event collection and determination of clinical endpoints. At Week 39 and at the midpoint between office visits after Week 52, telephone contact will be made to check the subject status, including discussing study diary entries, concomitant medication use, adverse events, and determining clinical endpoints. All subjects treated by the investigator will be managed to reach their glycemic, blood pressure and lipid goals according to established local and regional guidelines, with medical therapies used according to approved local labels. A post-treatment follow-up contact will take place following the treatment phase. Subjects who discontinue study medication prematurely should continue to attend all subsequent study visits and be

followed to the global trial end date (GTED). This event-driven study is estimated to have a total duration of approximately 5 to 5.5 years.

DOSAGE SELECTION RATIONALE

The 100 mg dose of canagliflozin was chosen for this study based on the clinical effect of canagliflozin 100 mg in reducing macroalbuminuria and a favorable benefit to risk ratio for subjects who had a baseline eGFR of ≥30 to <90 mL/min/1.73m^2 and macroalbuminuria in the Phase 3 development program. This included an examination of expected reductions in blood pressure and UACR as well as safety considerations (eg, volume depletion adverse events, adverse events leading to discontinuation, and lab findings suggestive of hyperkalemia) where the balance favored canagliflozin 100 mg over 300 mg in the population of subjects with renal impairment.

STUDY POPULATION

Subjects who are ≥30 years of age and diagnosed with T2DM with the following laboratory values (as determined by the central laboratory at the screening visit): an HbA_{1c} level ≥6.5% to ≤12.0%, an eGFR of ≥30 to <90 mL/min/1.73m^2, and a UACR of >300 mg/g to ≤5000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol), who are receiving standard of care including a stable maximum tolerated labeled daily dose of an ACEi or ARB for at least 4 weeks and who meet all other enrollment criteria will be eligible for randomization.

An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (eGFR ≥30 to <60 mL/min/1.73m^2; first category):CKD Stage 2 (eGFR ≥60 to <90 mL/min/1.73m^2; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, the entry of subjects with Stage 2 CKD (ie, eGFR ≥60 to <90 mL/min/1.73m^2) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.

STRATIFICATION

Eligible subjects will be stratified according to their pretreatment eGFR value most proximate to the baseline visit (eg, screening, unscheduled, or Week -2) and will be randomized within the following 3 strata: 1) ≥30 to <45 mL/min/1.73m^2, 2) ≥45 to <60 mL/min/1.73m^2, 3) ≥60 to <90 mL/min/1.73m^2.

DOSAGE AND ADMINISTRATION

Study Drugs

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

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

EFFICACY OUTCOME/DEFINITIONS/EVALUATION

Primary Efficacy Outcomes

The primary efficacy outcome is reduction in a composite endpoint of the first occurrence of ESKD, doubling of serum creatinine, and renal or CV death.

Definitions for each component of the primary composite endpoint are:

- ESKD: Initiation of maintenance dialysis for at least 1 month, or renal transplantation, or a sustained eGFR of <15 mL/min/1.73m^2 (by CKD-EPI formula and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days)
- Doubling of serum creatinine: from the baseline average determination (sustained and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days)
- Renal death: death in subjects who have reached ESKD, die without initiating renal replacement therapy, and no other cause of death is determined via adjudication
- CV death: death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed above (eg, aneurysm, peripheral vascular disease [PVD])

Confirmatory data for all potential study endpoints will be collected from study investigators and will be adjudicated by a blinded Independent Endpoint Adjudication Committee.

Secondary Efficacy Outcomes

The secondary efficacy outcomes are reduction in the composite endpoint of CV death and hospitalized congestive heart failure; the composite endpoint of CV death, non-fatal MI, and non-fatal stroke (ie, 3-point MACE); hospitalized congestive heart failure; the renal composite endpoint of ESKD, doubling of serum creatinine and renal death; CV death; all-cause death; and the CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina.

The definitions for each component of the CV composite endpoint are defined in the endpoint adjudication charter.

Confirmatory data for the CV composite endpoint will be collected from study investigators and will be adjudicated by a blinded Independent Endpoint Adjudication Committee.

Exploratory Efficacy Outcomes

The exploratory efficacy outcomes are reduction in the composite endpoint of ESKD and renal or CV death, reductions in the individual components of the renal and CV composite endpoints (ESKD, doubling of serum creatinine, renal death, CV death, fatal or non-fatal MI, fatal or non-fatal stroke, hospitalized congestive heart failure, hospitalized unstable angina), as well as changes in eGFR and albuminuria over time.

SAFETY OUTCOMES/EVALUATION

The safety outcomes include the overall safety and tolerability of canagliflozin. The safety evaluations include the collection of adverse events, laboratory tests, vital signs (pulse, blood pressure), physical examination, and body weight.

PHARMACOGENOMIC AND BIOMARKER EVALUATIONS

A pharmacogenomic blood sample and plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for pharmacogenomic and biomarker analyses that could help to further explain and examine the efficacy and safety findings in this study.

STATISTICAL METHODS

Analysis Sets

The intent-to-treat (ITT) analysis set includes all randomized subjects. The assessment of the primary and secondary endpoints will be based upon this analysis set.

Sample Size Determination

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

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

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

Primary Efficacy Analysis

The primary efficacy measure will be the time from randomization to the first occurrence of ESKD, doubling of serum creatinine, and renal or CV death. The comparison of the treatment groups will be assessed by means of a stratified Cox proportional hazard model with terms of treatment and strata defined by pretreatment eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73m^2). The primary analysis will be based on the ITT analysis set up to GTED. Subjects will be analyzed according to the treatment group that they are randomized, regardless of actual treatment received.

Estimates of RRR, hazard ratio and the corresponding 95% CI will be derived from the model. Kaplan-Meier estimates for the event curve will be provided for the 2 treatment groups.

In addition, ratios of cause-specific hazards between the treatment groups will be obtained for each component of the primary efficacy composite endpoint (ESKD, doubling of serum creatinine, renal death, or CV death), with stratification of the baseline hazard by pretreatment eGFR group as in the analysis of the primary efficacy composite endpoint. Sensitivity analysis using a stratified log-rank test will be conducted to assess the robustness of the primary efficacy analysis.

Secondary Efficacy Analyses

The time from randomization to the first occurrence of the secondary endpoint events will be analyzed separately in a similar fashion as the primary analysis. If superiority of canagliflozin 100 mg over placebo in reducing the risk of the primary efficacy endpoint is established, the treatment effects in secondary endpoints will be tested subsequently in the following hierarchical order:

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

- CV death
- All-cause death
- CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina

Statistical significance is required before testing the next hypothesis in the hierarchical test procedure.

Exploratory Efficacy Analyses

The time from randomization to the first occurrence of composite endpoint events of ESKD and CV death or renal death will be analyzed similar to the primary efficacy analysis.

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

Similar modeling analysis will be performed for UACR. Since the distribution of UACR value is highly skewed, log transformation of UACR values will be made prior to the modeling.

When the trial is fully recruited, the baseline characteristics of the subjects (including those which may be imbalanced) will be examined and can be considered in exploratory analyses. A more detailed description of the analyses for all outcomes will be pre-specified in the Statistical Analysis Plan (SAP) for this study.

Safety Analyses

Subjects in the safety analysis set will be included in the denominators for the summaries of adverse event, exposure, and concomitant medication data.

Multiplicity Adjustment

A closed testing procedure will be implemented to control the overall type I error rate at 5% for primary and secondary endpoints.

Interim Analysis

An interim analysis will be conducted when the primary efficacy events have been observed in approximately 405 subjects. The analysis method for primary efficacy endpoint will be used for the interim analysis. The assumptions behind the sample size calculation of the study will be examined and the study duration may be prolonged in order to attain the target number of events. In addition, if the conditional power (based on the assumption that the hazard ratio in the remaining study is 0.80) is 10% or lower, the study may be stopped for futility. The alpha spending function will be used and the alpha spent in the interim analysis is 0.01. Detailed stopping guidelines will be specified in the charter of Independent Data Monitoring Committee (IDMC).

TIME AND EVENTS SCHEDULE

Protocol Activity[a]	Pretreatment[a]			Double-Blind Treatment[a]									Posttreatment[a]
	Pre-Screening	Screening	Run-In[b]	Baseline	Treatment							End of Treatment	
	Pre-Screening	Week -10 to -3	Week -2	Day 1	Week 3	Week 13	Week 26	Week 39 (TC)[c]	Week 52 and at 52-week intervals thereafter[d]	Week 65 and at 26-week intervals thereafter (TC)[e c]	Week 78 and at 52-week intervals thereafter[f]	EOT, EOS or EW[g]	Follow-Up Contact[h]
Screening/Administrative													
Informed Consent[i]	X	X											
Informed Consent for optional samples[j i]				X									
Inclusion/Exclusion Criteria		X	X	X									
Medical history and demographics		X											
Assess compliance with single-blind placebo run-in				X									
Record pre-study serum creatinine				X[k]									
Randomization				X									
Pretreatment Procedures													
Study Drug													
Dispense single-blind placebo			X										
Administer/dispense double-blind study drug[l]				X		X	X		X[l]		X[l]		
Procedures													
Initial physical examination/Vitals and weight, foot examination			X[m]										
Follow-Up /Vitals, foot examination[n]									X			X	

Protocol Activity[a]	Pretreatment[a]			Double-Blind Treatment[a]									Posttreatment[a]
	Pre-Screening	Screening	Run-In[b]	Baseline	Treatment							End of Treatment	
	Pre-Screening	Week -10 to -3	Week -2	Day 1	Week 3	Week 13	Week 26	Week 39 (TC)[c]	Week 52 and at 52-week intervals thereafter[d]	Week 65 and at 26-week intervals thereafter (TC)[e c]	Week 78 and at 52-week intervals thereafter[f]	EOT, EOS or EW[g]	Follow-Up Contact[h]
Brief Visit w/vitals, weight, foot examination[o]		X[p]		X	X	X	X				X		
Height			X										
12-lead electrocardiogram[q]			X										
Clinical Laboratory Assessments													
Follicle stimulating hormone, if necessary per inclusion criteria)		X											
Hemogram (CBC) w/ Plate & Auto Diff[r]		X		X					X			X	
Urinalysis[r]		X		X					X			X	
Serum chemistry[s t r]	X[u]	X	X[v]	X	X	X	X		X[s]		X[s]	X	
Fasting plasma glucose[r]		X		X		X	X		X[ii]		X	X	
Glycated Hemoglobin (HbA_{1c})[s]		X		X		X	X		X[s]		X[s]	X	
Fasting lipid profile[w r]		X		X					X			X	
First morning void for albumin/creatinine ratio[s x r]	X[u]	X		X			X		X[s]		X[s]	X	
Archived samples (plasma, serum, and urine samples) for exploratory analysis[r]				X					X			X	
Pharmacogenomic specimen[y]				X									
Urine Pregnancy Test, Qualitative[z]				X									

Protocol Activity[a]	Pretreatment[a]			Double-Blind Treatment[a]									Posttreatment[a]
	Pre-Screening	Screening	Run-In[b]	Baseline	Treatment							End of Treatment	
	Pre-Screening	Week -10 to -3	Week -2	Day 1	Week 3	Week 13	Week 26	Week 39 (TC)[c]	Week 52 and at 52-week intervals thereafter[d]	Week 65 and at 26-week intervals thereafter (TC)[e c]	Week 78 and at 52-week intervals thereafter[f]	EOT, EOS or EW[g]	Follow-Up Contact[h]
Subject Counseling and Assessments													
Diet and exercise counseling[aa]			X										
Dispense glucose testing supplies and first study diary[bb cc]			X				X[bb]		X[bb]		X[bb]		
Review/discuss subject diary and SMBG results[dd]			X	X	X	X	X	X	X	X	X	X	
Review Concomitant Medications[ee]		X[ff]	X[ff]	X	X	X	X	X	X	X	X	X	X
Endpoints and Adverse Events Assessment[gg]		X	X	X	X	X	X	X	X	X	X	X	X[hh]

[a] EOS = end-of-study; EOT = end-of-treatment; EW=early withdrawal; HbA_{1c} =hemoglobin A_{1c}; CBC = complete blood count; SMBG = self-monitored blood glucose; TC = telephone contact.

[b] 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, Repeat Testing and Subject Rescreening.

[c] At Week 39 and at the midpoint between office visits after Week 52, telephone contact will be made to check the subject's status, including discussing the subject's diary entries, concomitant medications, and adverse events, including those events in the primary composite endpoint and those included in the secondary endpoints. In addition, investigators should ask subjects about any foot problems and remind all subjects about routine preventative foot care and early intervention for foot problems (see Section 12.3.1 All Adverse Events for further detail).

[d] This visit will occur at Week 52, 104, 156, 208, and 260.

[e] This telephone contact will occur at Week 39, 65, 91, 117, 143, 169, 195, 221, 247, and 273.

[f] This visit will occur at Week 26, 78, 130, 182, 234 and 286.

[g] End-of-treatment/end-of-study/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 should attend all subsequent visits and will be continually monitored according to the Time and Events Schedule for the duration of the study, until completion of the study (ie, the global trial end date [GTED]).

[h] A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 30 days (+/- 12 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 means. At this telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

[i] For subjects who require additional local laboratory assessment solely for the purpose of prescreening, either the optional prescreening-specific or full informed consent must be obtained before collecting UACR and eGFR values. If an optional prescreening-specific informed consent is obtained, and the subject is eligible to enter the screening period, the full informed consent must be obtained before screening is initiated. See Section 16.2.3, Informed Consent, for details.

[j] Subject participation in the pharmacogenomics and exploratory biomarker research is optional. The Optional Exploratory Research Consent may be obtained after signing the full consent and at any point prior to collecting the sample, including after randomization.

[k] The latest 3 pre-study serum creatinine values, when available, collected within a year prior to screening in an outpatient setting, and at least 30 days apart, will be recorded in the eCRF.

[l] Study drug is dispensed every 26 weeks after the first year.

[m] 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. 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 12.3.1 All Adverse Events for further detail).

[n] Focused physical examination will be performed at the follow-up visits occurring at Week 52, and every 52 weeks thereafter, and will include targeted examinations based on the subject's specific complaints, signs or symptoms of a disease. 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 12.3.1 All Adverse Events for further detail).

[o] Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart); the average of the 3 blood pressure readings will be recorded on eCRF. 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 12.3.1 All Adverse Events for further detail).

[p] Please refer to Section 9.5.1. Safety Evaluation.

[q] Electrocardiograms will be conducted at the local investigator site or affiliated facility.

[r] Specific details about specimen collection, storage, packaging, and shipping will be provided in Attachment 4. For fasting plasma glucose 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 subjects who consent to the optional exploratory analysis will be collected at each specified time point. The urine collections for routine urinalyses and exploratory specimens should be obtained from a spot urine specimen in the clinic.

[s] The test is performed every 26 weeks after the first year.

[t] For serum creatinine and eGFR values to be considered as a component of composite endpoint, the results need to be confirmed by central laboratory repeat test ≥30 days and preferably within 60 days.

[u] Prescreening local laboratory test will be performed and does not require a first morning void sample. These tests include eGFR and UACR, or other acceptable albuminuria/proteinuria measures if UACR values unavailable. For details of these additional measures refer to Section 9.1.2. Pretreatment Phase.

[v] A serum chemistry determination should be made at the Week -2 visit **ONLY** for subjects who have an extended screening period (ie, >2 weeks between the screening visit and the run-in visit) or who do not have a central serum chemistry value determined within the 2 weeks prior to the Week -2 visit. For subjects no longer meeting entry criteria for serum creatinine or eGFR based on this extra serum chemistry determination, an extension of the 2-week single-blind placebo run-in period may be required to accommodate a one-time repeat at the discretion of the investigator (see Section 4.5, Repeat Testing and Subject Rescreening).

[w] 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.

[x] 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.

[y] 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 after randomization if not obtained at baseline. Specific details about DNA samples collection, storage, packaging, and shipping will be provided in Attachment 5.

[z] Urine pregnancy testing will be performed by local laboratories for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. Additional serum or urine pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. If positive, the subject is not eligible to enter or continue in the study.

[aa] Subjects should be counseled to maintain a diet and exercise regimen consistent with those outlined in treatment guidelines for T2DM (eg, the American Diabetes Association guideline).
[bb] The supplies are dispensed every 26 weeks after randomization.
[cc] Subjects will be provided with and instructed on the use of a home blood glucose monitoring system. In addition, a diary and glucose testing supplies will also be provided as necessary.
[dd] See Section 9.1.1, Overview, for diary procedures.
[ee] Concomitant therapy consists of all medications, including AHAs, taken after the initiation of double-blind study medication (Day 1).
[ff] Record as prestudy therapy any medications taken from 30 days before screening.
[gg] This review will also include subjects' blood glucose level, lipid profile and blood pressure as well as the use of blood pressure medications. Assessments on adverse events and study endpoints will also be performed.
[hh] Serious adverse events and potential endpoint events will be assessed (refer to Section 9.1.4. Post-Treatment Follow-up).
[ii] Only at Week 52.

ABBREVIATIONS

ACEi	angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ARO	Academic Research Organization
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum concentration (during a dosing interval)
CV	cardiovascular
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DRI	direct renin inhibitor
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GTED	global trial end date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEAC	Independent Endpoint Adjudication Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
LS	least squares
MACE	major adverse cardiac event
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
MSRC	Medical Safety Review Committee
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PCR	protein-to-creatinine ratio
PDLC	predefined limit of change
Pgp	P glycoprotein
PG	plasma glucose
PK	pharmacokinetics
PPARγ	peroxisome proliferator activated receptor

PQC	Product Quality Complaint
RRR	relative risk reduction
QD	once daily
RT_G	renal threshold for glucose
SAP	statistical analysis plan
SBP	systolic blood pressure
SGLT1/SGLT2	sodium-glucose co-transporter 1/sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
SNGFR	single nephron glomerular filtration rate
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TGF	tubuloglomerular feedback
t_{max}	time to reach the maximum plasma concentration
UACR	urinary albumin/creatinine ratio
UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
UTI	urinary tract infection

1. INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) has been rapidly rising over the past decades 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. Diabetic nephropathy is one of the microvascular complications of diabetes mellitus (DM) and is characterized by persistent albuminuria and a progressive decline in renal function.

The prevalence of diabetic nephropathy (microalbuminuria or worse) in patients with T2DM was 28% by 15 years after diagnosis, with a projected prevalence of 38% by 25 years after diagnosis (UKPDS 1998); for macroalbuminuria or worse, the prevalence was 7% after 15 years and 12% after 25 years (Adler 2003). Approximately 20% of subjects with T2DM and nephropathy will have progressed to end-stage kidney disease (ESKD) after 20 years (ADA 2004). Once ESKD has developed in these patients, the 5-year survival rate for patients on dialysis is 36% (NKUDIC 2012). Long-term dialysis or kidney transplantation for ESKD is associated with a high cost of care, which was estimated to be about 17 billion dollars in the United States (US) or 0.77 billion pounds in the United Kingdom (UK) for managing diabetic nephropathy in patients with DM in 2004 (Gordois 2004).

The clinical progression of diabetic nephropathy is well characterized (Mogensen 1998). Initially, hyperfiltration is accompanied by increases in glomerular filtration rate (GFR) and increased renal plasma flow. A meta-analysis found that the presence of hyperfiltration in patients with type 1 diabetes mellitus (T1DM) more than doubled the risk of developing micro- or macroalbuminuria (Magee 2009). This phase is followed by reductions in GFR and the development of microalbuminuria (defined as urinary albumin excretion of ≥30 mg/day or 20 μg/min and ≤300 mg/24 h or ≤200 μg/min), which may be accompanied by increases in blood pressure, later progresses to further GFR decline, overt proteinuria (ie, macroalbuminuria, defined as urinary albumin excretion of >300 mg/day or >200 μg/min) and associated with worsening hypertension, continually leads to ESKD with a possible need for renal replacement therapy, and eventually to a renal death, or cardiovascular (CV) death.

Hyperglycemia is an important contributor to the onset and progression of diabetic nephropathy. A significant relationship was seen between hemoglobin A_{1c} (HbA_{1c}) levels and risk of developing and progression of diabetic nephropathy in patients with T1DM (DCCT 1995; DCCT 2000; Lachin 2007). Similarly, intensive control of blood glucose reduced the risk of the development and progression of diabetic nephropathy in patients with T2DM (UKPDS 1998; ADVANCE 2008; Perkovic 2013). The relationship between hyperglycemia and risk of diabetic nephropathy was also confirmed in a recent meta-analysis (Coca 2012).

In addition, inhibition of the renin-angiotensin pathway by angiotensin receptor blocker (ARB) or by angiotensin-converting enzyme inhibitor (ACEi) has been demonstrated to reduce the progression of diabetic nephropathy in subjects with T2DM (Parving 2001; Lewis 2001;

HOPE 2000; Viberti 2002) and T1DM (Bjorck 1990; Lewis 1993). The renal-protective effects by ACEi or ARB appear to be beyond those that can be attributed to blood pressure lowering. Thus, agents acting by a unique hemodynamic mechanism in addition to the renin-angiotensin system may exert further renal protection and possibly reduce adverse CV outcomes in diabetic nephropathy.

Canagliflozin is an orally active inhibitor of sodium-glucose co-transporter 2 (SGLT2) that is being developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with T2DM.

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). In patients with T2DM, the RT_G is elevated, leading to increased glucose reabsorption despite hyperglycemia, which likely contributes to sustained elevation in serum glucose concentrations (DeFronzo 2009). Glucose reabsorption in the renal tubules, determining the renal threshold is largely due to 2 key glucose transporters: sodium glucose co-transporter 2 (SGLT2) and sodium glucose co-transporter 1 (SGLT1). Sodium glucose co-transporter 2 is a high-capacity and low-affinity glucose transporter exclusively expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules. Sodium glucose co-transporter 2 is responsible for the majority of filtered glucose reabsorption from the lumen. Sodium-glucose co-transporter 1 expressed in the S3 segment, a low capacity and high-affinity transporter, is also involved in reabsorption of filtered glucose from the lumen (Wright 2001). Sodium-glucose co-transporter 1 is also highly expressed in the intestine and is responsible for intestinal glucose and galactose absorption.

Pharmacologic inhibition of SGLT2 is a novel mechanism to decrease renal glucose reabsorption, as it lowers RT_G and leads to an increase in urinary glucose excretion (UGE), thereby directly lowering plasma glucose in individuals with elevated glucose concentrations. Canagliflozin is an orally active inhibitor of SGLT2. This agent has much higher potency for SGLT2 relative to SGLT1; at the plasma drug concentrations achieved with the doses in this study, canagliflozin would be expected to provide significant systemic inhibition of SGLT2 and not of SGLT1. In addition to lowering plasma glucose concentrations, the increased renal glucose excretion with SGLT2 inhibition also translates to a loss of calories, leading to a net negative energy balance and the potential for weight loss as well as an osmotic diuretic effect, which can lead to reductions in blood pressure and osmotic diuresis- and volume depletion-related adverse events.

In patients with T2DM, the clinical progression of diabetic nephropathy is variable, primarily due to the multiple renal insults, including not only hyperglycemia, but also hypertension and vascular pathology resulting in ischemic renal injury. However, hyperfiltration at the level of the single nephron, proximal tubular glycotoxicity and a stimulus for tubular cell growth as a result of enhanced sodium coupled glucose transport into tubular cells are common features in patients with T2DM.

In streptozotocin-treated diabetic rats, single nephron GFR (SNGFR), glomerular plasma flow and mean glomerular transcapillary pressure were elevated and preceded the onset of diabetic nephropathy (Zatz 1985). The increase in glomerular capillary pressure is a consequence of decreased resistance of the afferent glomerular arteriole and increased resistance of the efferent glomerular arteriole (Hostetter 1995). Brenner and coworkers (1996) demonstrated in animal models that as nephrons are progressively destroyed, glomerular filtration and nephron size increases in a compensatory manner in the remaining nephrons (increase in SNGFR, however decrease in total GFR). The increases in glomerular filtration eventually result in glomerular damage and focal sclerosis (O'Bryan 1997).

Augmentation of proximal tubular sodium reabsorption stimulates increased filtration via systemic volume expansion, as well as decreased tubuloglomerular feedback (Bank 1990; Ditzel 1983; Vallon 1999). Given the coupling between glucose and sodium transport by SGLT2 in the proximal tubule, increases in glucose filtered at the glomerulus will increase sodium reabsorption in the proximal tubule causing salt and water retention, and volume expansion. The increased proximal tubule reabsorption reduces the delivery of sodium to the distal tubule. The macula densa responds to reduced sodium in the distal tubule by decreasing afferent glomerular arteriole tone, which increases filtration until distal salt delivery is restored. Thus in hyperglycemic states, the increase in GFR may, in part, be a consequence of reduced tubuloglomerular feedback (TGF), a mechanism coupling tubular reabsorption of sodium and fluid with glomerular filtration (Thomson 2012; Gilbert 2013).

SGLT2 inhibitors, such as canagliflozin, increase the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose reabsorption thereby increasing tubuloglomerular feedback, which is associated with a decrease in hyperfiltration in preclinical models of diabetes and clinical studies (Cherney 2013; Thomson 2012).

A Phase 3 development program including 9 controlled studies was conducted providing evidence for the effectiveness of canagliflozin both as monotherapy and in combination with approved, commonly prescribed AHA therapies in T2DM. These 9 studies spanned a range of clinical uses (as monotherapy or as combination therapy) to treat T2DM. Three of the Phase 3 studies evaluated canagliflozin in special populations, including older adults with T2DM, subjects with T2DM who had moderate renal impairment, and subjects with T2DM who had or were at high risk for CV disease. The extensive Phase 3 clinical development program studied approximately 10,285 subjects with T2DM and including nearly 6,650 subjects treated with 100 mg or 300 mg doses of canagliflozin. A 1,090 subject-year exposure through 31 December 2012 was reported with median duration of follow-up experience (safety, efficacy and serial chemistry measurements) of 93 weeks. Across all of the studies, clinically meaningful reductions in HbA_{1c} and fasting plasma glucose (FPG) were seen. Statistically significant (relative to placebo) reductions in body weight (predominantly fat mass) were also achieved with canagliflozin 100 mg and 300 mg across the spectrum of T2DM patients evaluated in the Phase 3 program. Canagliflozin also showed benefit in improving other clinical endpoints associated with diabetic comorbidities, including systolic and diastolic blood pressure (SBP and DBP), and some lipid parameters (high-density lipoprotein cholesterol [HDL-C], and triglyceride). Improvements in beta-cell function, presumably through an indirect effect, such as reductions in glucotoxicity

and insulin secretory demand, were also seen with canagliflozin treatment. Canagliflozin has been approved by several Health Authorities including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

In the Phase 3 program, a pooled population of 1,085 subjects with a baseline eGFR ≥30 to <60 mL/min/1.73m^2 was defined as moderate renal impairment and analyzed separately. This population also included all 272 subjects in a Phase 3 study (28431754DIA3004) that only enrolled subjects with T2DM and renal impairment with a baseline eGFR ≥30 to <50 mL/min/1.73m^2. Among all 1,085 subjects with renal impairment, 703 subjects were treated with 100 mg or 300 mg doses of canagliflozin. Results of analyses showed that canagliflozin reduced HbA_{1c}, body weight, and blood pressure relative to placebo in this pooled population. Furthermore, there were 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. In addition, the safety profile of canagliflozin appeared to be acceptable in this population.

The goal of this study is to assess whether canagliflozin has a renal protective effect in reducing the progression of diabetic nephropathy relative to placebo in subjects with T2DM, Stage 2 or 3 Chronic Kidney Disease (CKD) and macroalbuminuria, who are receiving standard of care, as defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) consensus guidelines (NKF 2007; NKF 2012), including a maximum tolerated labeled daily dose of ACEi or ARB.

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 (IB) for canagliflozin (IB JNJ-28431754).

1.1.1. Nonclinical Studies

For a complete review of the findings and discussions regarding implications for human risk, please refer to the current version of the canagliflozin IB. Results of alterations in renal injury and function with SGLT2 inhibitors in preclinical models of diabetic nephropathy are described below.

After 12 weeks, diabetic db/db mice treated with a selective SGLT2 inhibitor, JNJ-39933673, other than canagliflozin, improved glycemic control and reduced urinary ACR (207±5 mg/g in treated group versus 745±36 mg/g in control group, p<0.001). JNJ-39933673 treatment also reduced histologic changes characteristic of diabetic nephropathy such as mesangial expansion, accumulation of fibronectin and type IV collagen, podocyte loss as well as prevented renal

accumulation of macrophages and renal neutral lipid accumulation (Qiu 2013). Similar reductions in blood glucose levels and urinary albumin excretion were seen with another selective SGLT2 inhibitor (T-1095) in another rodent model of diabetes (streptozotocin treated rats) (Adachi 2000). It should be noted that improved glycemic control in these rodent models will also reduce the decline in renal function. Thus, in these studies it was not possible to dissect the impact of improved glycemic control from that of a hemodynamic effect on renal outcomes.

Several publications have reported results of nonclinical renal studies with SGLT2 inhibitors. The effects of luseogliflozin, a novel SGLT2 inhibitor, lisinopril (an ACEi) and the combination of lisinopril and luseogliflozin, or vehicle were examined in diabetic rat model of diabetic nephropathy. Rats treated with vehicle exhibited progressive proteinuria, a decline in GFR, focal glomerulosclerosis, renal fibrosis, and tubular necrosis. Lisinopril, as well as luseogliflozin when administered alone, prevented the fall in GFR and reduced the degree of glomerular injury, renal fibrosis, and tubular necrosis. In contrast, treatment with insulin had no effect on the progression of renal disease in T2DM rats. Combination therapy reduced the degree of glomerular injury, renal fibrosis, and tubular necrosis to a greater extent than administration of either drug alone. These results suggest that SGLT2 inhibition slows the progression of diabetic nephropathy more than that seen with insulin, and combination therapy with an SGLT2 inhibitor and an ACEi is more renoprotective than administration of either compound alone (Kojima 2013).

A renal micropuncture study in diabetic Wistar rats was conducted to assess the hemodynamic effects of dapagliflozin, a selective SGLT2 inhibitor, on early diabetic nephropathy. Dapagliflozin treatment increased the delivery of sodium to the distal tubule and reduced the diabetes-related increases in SNGFR (eg, reduced hyperfiltration) (Thomson 2012).

Although the mechanisms have yet to be elucidated, results from these rodent studies suggest that SGLT2 inhibition may reduce glomerular hyperfiltration and delay the onset and reduce the progression of diabetic nephropathy.

1.1.2. Clinical Studies

1.1.2.1. Overview

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 3 Phase 2 studies and 10,961 subjects in 10 Phase 3 studies have completed or are participating in clinical studies conducted by the sponsor.

This included a total of 1,085 subjects with T2DM and moderate renal impairment in the Phase 3 program. Two-hundred seventy-two (272) of these subjects were from a Phase 3 study (28431754DIA3004) that only enrolled subjects with T2DM and renal impairment (ie, baseline eGFR of ≥30 to <50 mL/min/1.73m^2). The total exposure through 31 December 2012 for subjects with moderate renal impairment was 1090 subject-years with a median duration of follow-up experience (safety, efficacy and serial chemistry measurements) of 93 weeks.

1.1.2.2. 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. Enzyme inducers (such as St. John's wort [Hypericum perforatum], rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) may give rise to decreased exposure of canagliflozin. Following co administration of canagliflozin with rifampicin (an inducer of various active transporters and drug metabolizing enzymes), 51% and 28% decreases in canagliflozin systemic exposure (AUC) and peak concentration (C_{max}) were observed. These decreases in exposure to canagliflozin may decrease efficacy. For patients who are tolerating 100 mg canagliflozin the dose should be increased to 300 mg canagliflozin if therapy with a UGT enzyme inducer is initiated.

Canagliflozin is transported by P glycoprotein (Pgp) and Breast cancer Resistance Protein. 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 effect of concomitant administration of canagliflozin (a weak Pgp inhibitor) on dabigatran etexilate (a Pgp substrate) has not been studied. As dabigatran concentrations may be increased in the presence of canagliflozin, monitoring (looking for signs of bleeding or anemia) should be exercised when dabigatran is combined with canagliflozin. Cholestyramine may potentially reduce canagliflozin exposure. Dosing of canagliflozin should occur at least 1 hour before or 4 to 6 hours after administration of a bile acid sequestrant to minimize possible interference with their absorption.

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.

A single-dose Phase 1 study (28431754DIA1003) with canagliflozin in non-diabetic subjects with various degrees of renal function (including ESKD on hemodialysis) was performed.

Median t_{max} values for canagliflozin were similar across all renal function groups. Exposure (AUC_∞ and C_{max}) of canagliflozin was higher in subject groups with impaired renal function ranging from mild to severe impairment. In subjects with mild, moderate, and severe renal impairment, C_{max} values were approximately 13%, 29%, and 29% higher while AUC_∞ values were approximately 17%, 63%, and 50% higher, respectively, compared with subjects with normal renal function. Mean renal clearance for canagliflozin was lower in subjects with reduced renal function, while mean half-life was slightly prolonged for the renally impaired groups compared with subjects with normal renal function. Increases in canagliflozin AUC of the magnitude seen with renal impairment are not deemed to be clinically relevant.

In subjects with ESKD (pre-dialysis and after a 4-hour hemodialysis session [post-dialysis]), the systemic exposure of canagliflozin was similar to that in subjects with normal renal function. Similar systemic exposure in subjects with ESKD compared with subjects with normal renal function has previously been reported for other drugs for which the PK was altered in proportion to the degree of renal impairment (De Martin 2006; Shi 2004). It was speculated that this may be due to the removal of uremic substances by dialysis that might decrease the drug's intrinsic clearance by inhibiting metabolic enzymes and transporters (Nolin 2008; Zhang 2009). Mean arterial canagliflozin concentrations were similar to venous concentrations at each time point during hemodialysis. Only a small fraction of administered dose (<1% of canagliflozin and <1.2% of metabolites [M5 and M7]) was removed in the dialysate fluid following a 4-hour hemodialysis session. These results indicate that hemodialysis has a minimal effect on plasma concentrations and the PK of canagliflozin, and that the metabolites were negligibly dialyzable.

1.1.2.3. 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 $UGE_{0\text{-}24h}$, with mean $UGE_{0\text{-}24h}$ 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 plasma glucose (PG) levels associated with hypoglycemia and because very little UGE occurs whenever PG is below the RT_G, canagliflozin, itself, is not expected to pose a risk for hypoglycemia.

1.1.2.4. 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 (PPARγ) 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: ie, subjects with renal impairment (eGFR of ≥30 to <50 mL/min/1.73m^2); subjects with or at high risk for CV complications; and older subjects.

The dose of canagliflozin in the Phase 3 program is 100 mg and 300 mg. The 100 mg dose of canagliflozin was chosen for this study based on the clinical efficacy and safety information

available in the moderate renal impairment group of subjects who participated in the Phase 3 development program (see Section 3.2, Study Design Rationale). The efficacy section below will be focused on the results of 100 mg canagliflozin in 3 sets of subjects with T2DM: those involved in 9 completed Phase 3 studies, those included in a pooled population with moderate renal impairment, and those who participated in a 52-week Phase 3 study (28431754DIA3004) with moderate renal impairment (eGFR of ≥30 to <50 mL/min/1.73m^2).

1.1.2.4.1. Glycemic Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing HbA_{1c} in a broad range of subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and in combination therapy. In the monotherapy study, an HbA_{1c} reduction of -0.91% was observed for canagliflozin 100 mg relative to placebo. 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 canagliflozin 100 mg (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 compared with subjects with lower baseline values. In subjects with moderate renal impairment (ie, baseline eGFR's between 30 to 60 mL/min/1.73m^2), the mean, placebo-subtracted reduction in HbA_{1c} was -0.38% on canagliflozin 100 mg. A total of 24% of subjects achieved a target HbA_{1c} <7% at the end of treatment on canagliflozin 100 mg relative to 17% of subjects on placebo.

In a 52-week Phase 3 study in 272 adult subjects with T2DM who were inadequately controlled on their current diabetes treatment regimen (ie, HbA_{1c} of ≥7.0% and ≤10.5%) and had renal impairment (eGFR ≥30 and <50 mL/min/1.73m^2), the mean, placebo-subtracted reduction in HbA_{1c} was -0.27% on canagliflozin 100 mg (with the 95% CI for the between-group difference for the canagliflozin 100 mg and placebo including "0"). Results at Week 26 were similar to those observed at Week 52 (28431754DIA3004).

1.1.2.4.2. Weight Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo, with -1.4% to -2.7% reductions observed with canagliflozin 100 mg relative to placebo.

In the pooled moderate renal impairment population, as observed for HbA_{1c}-lowering response, and anticipated based upon canagliflozin mechanism of action, the placebo-subtracted least squares (LS) mean percent change from baseline to the primary assessment timepoint in body weight was somewhat attenuated for the canagliflozin 100 mg dose (-1.6%) relative to subjects

with higher baseline eGFRs, but the same (-1.6%) to those seen in the study of subjects with renal impairment (ie, baseline eGFR of ≥30 to <50 mL/min/1.73m^2).

In the Phase 3 study in subjects with T2DM and moderate renal impairment (28431754DIA3004), body weight was meaningfully reduced over the 52-week study with canagliflozin (placebo-subtracted change from baseline difference of -1.5% for the canagliflozin 100 mg dose)

1.1.2.4.3. Blood Pressure Effects

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

In a pooled analysis of subjects with moderate renal impairment in the Phase 3 program, the LS mean reduction from baseline in SBP with canagliflozin 100 mg was -4.4 mmHg and a slightly lesser reduction from baseline in DBP (-1.8 mmHg) was observed at Week 26. In the placebo group, smaller decreases from baseline SBP and DBP were observed at Week 26 (-1.6 mmHg and -1.1 mmHg, respectively). Results were generally similar regardless of concomitant use of ACEi/ARB or diuretics

In the Phase 3 study in subjects with T2DM and moderate renal impairment (28431754DIA3004), SBP was reduced over the 52-week study with canagliflozin 100 mg, with a placebo-subtracted change from baseline difference of -5.49 mmHg observed.

1.1.2.5. Safety

1.1.2.5.1. Overall Safety

Based on PK data showing higher exposure of canagliflozin in subject groups with mild to severe renal impairment, a robust summary of safety data, including data from both the 100 mg and 300 mg dose of canagliflozin studied in the Phase 3 program is provided below.

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 well tolerated overall. The incidence of discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific ADRs, described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

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

In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals and in those with a past history of genital mycotic infections, generally did not lead to discontinuation from the study. Circumcision was performed in 17/3569 (0.5%) and 3/1924 (0.2%) of men treated with canagliflozin and control, respectively. In women, genital mycotic infections (including candidal vulvovaginitis) occurred more commonly in women with a prior history of genital mycotic infections and did not generally lead to discontinuation. A modest increase in the incidence of adverse events of UTI (mostly lower tract infections) was observed with canagliflozin relative to control, without an increase in serious adverse events of UTI.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension.

Risk factors for volume-related adverse events on canagliflozin treatment were ≥75 years of age, eGFR ≥30 to <60 mL/min/1.73m^2 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.

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.

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 apolipoprotein B, non-HDL-C, and LDL particle number were approximately half as large as the rise in LDL-C. In subjects with moderate renal impairment, the degree of increase in LDL-C was smaller than that seen in subjects with mildly impaired or normal renal function. 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 triglycerides were also observed with canagliflozin.

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

During a routine review of unblinded interim data from an ongoing Phase 3 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 Phase 3 study Independent Data Monitoring Committee (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.

1.1.2.5.2. Safety Related to Renal Function

Canagliflozin safety information related to general renal function in the clinical program can be found in the IB (IB Section 4.6.2.5, Effect of Canagliflozin on Renal Function). Effects of canagliflozin on albuminuria and eGFR in the Phase 3 program are also summarized in this protocol Section 1.2, Overall Rationale and Goals for the Study.

In summary, treatment with canagliflozin leads to small reductions from baseline in eGFR that were generally stable or improved with continued treatment. Analyses of eGFR post-discontinuation showed reversibility of the initial reductions seen on canagliflozin. The biomarker of renal injury, the UACR, did not increase in subjects treated with canagliflozin who were normoalbuminuric at baseline, and decreased in subjects with baseline albuminuria (either micro- or macroalbuminuria). The incidence of renal-related serious adverse events was similar across treatment groups. Data from clinical studies with canagliflozin does not suggest an increased risk of renal injury.

1.1.2.5.3. Safety in Renal Impairment Population

1.1.2.5.3.1. Safety in Moderate Renal Impairment

A total of 1,085 subjects from the pooled analysis of subjects with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73m^2) were included and analyzed in the Moderate Renal Impairment Dataset. Overall, the exposure for this dataset was 503 patient-years, and 16% of subjects discontinued before the primary study endpoint, with a numerically higher proportion in the placebo group (19%) compared with the combined canagliflozin group (15%).

Baseline demographic characteristics were generally similar across treatment groups. The median age of subjects was 67 years, with 38% of subjects between the ages of 35 to 64 years, 45% between the ages of 65 and 74 years, and 17% older than 75 years. Men comprised 58% of the subjects. Consistent with the regions of the world in which subjects were recruited, 78% of the subjects were white, 13% of subjects were Asian, and 3% of subjects were black or African-American. The mean BMI was 32.5 kg/m^2 and more than half of the subjects (64%) were obese (BMI ≥30 kg/m^2).

Baseline diabetes characteristics were generally similar across treatment groups. The median eGFR was 50.0 mL/min/1.73m^2, the mean was 48.2 mL/min/1.73m^2, and the range was 30.0 to 59.9 mL/min/1.73m^2. Approximately one-third of subjects had an eGFR <45 mL/min/1.73m^2. Most subjects had mild to moderate hyperglycemia at baseline (baseline mean HbA_{1c} of 8.0-8.1%), with 18% of total subjects poorly controlled (HbA_{1c} ≥9%). The median duration of diabetes was 15.0 years in the combined canagliflozin group and 13.6 years in the placebo group. Overall, 59% of subjects had a history of 1 or more microvascular complications, a substantial proportion having 2 complications (21%). Microvascular complications included neuropathy (37%), nephropathy (35%), and retinopathy (25%).

The incidence of subjects who experienced any adverse event, prior to use of rescue medication, was higher in the canagliflozin 100 mg and 300 mg groups (73.1% and 74.5%, respectively) compared with the placebo group (68.3%). The incidence of subjects who experienced adverse events leading to discontinuation was higher in the canagliflozin 300 mg group (7.4%) relative to the canagliflozin 100 mg (4.7%) and placebo groups (5.0%). Overall, most adverse events were reported by the investigators as mild or moderate in intensity.

The incidence of serious adverse events, including results after initiation of glycemic rescue therapy, was 19.6%, 13.3% and 14.8% in placebo, canagliflozin 100 mg and canagliflozin 300 mg groups, respectively. The incidence of subjects with serious adverse events that led to discontinuation was low, with similar incidences in the combined canagliflozin group and the placebo group (3.0% and 3.7%, respectively). The incidence of subjects with serious adverse events that were considered related to study drug was also low, with similar incidences in the combined canagliflozin and placebo groups (1.3% and 1.6%, respectively). The incidence of events occurring in any particular specific adverse event term was low, with no particular specific adverse event having an incidence of more than 1.1% (>4 subjects) in either canagliflozin group and most reported in only 1 subject (0.3%).

The incidence of adverse events that led to discontinuation of study drug, including results after initiation of glycemic rescue therapy, was slightly higher in the canagliflozin 300 mg group (7.7%) compared with the canagliflozin 100 mg group (5.6%) and the placebo group (5.8%). The majority of specific adverse events that led to discontinuation resulted in the discontinuation of only 1 subject. Adverse events of renal failure acute, renal impairment, and blood creatinine increased each resulted in discontinuation of 2 (0.3%), 4 (0.6%), and 3 (0.4%) subjects, respectively, in the combined canagliflozin group and 0, 3 (0.8%), and 2 (0.5%) subjects, respectively, in the placebo group.

Fourteen subjects died, with deaths occurring in 3 (0.9%) subjects and 5 (1.4%) subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 6 (1.6%) subjects in the placebo group. None of the deaths was considered related to study drug by the investigator. No deaths related to an adverse event in the Renal and urinary disorders SOC were reported.

Selected Adverse Events

The incidence of volume depletion adverse events was higher in the combined canagliflozin group (6.8%) relative to the placebo group (2.6%). The incidence was higher in the canagliflozin 300 mg group (8.5%) relative to the canagliflozin 100 mg group (5.0%). Volume depletion-related adverse events were serious in 4 (0.6%) subjects in the combined canagliflozin group and 5 (1.3%) subjects in the placebo group, and led to discontinuation in 3 (0.4%) subjects in the canagliflozin groups and no subjects in the placebo group. Relative to the placebo and canagliflozin 100 mg groups, volume depletion adverse events in the canagliflozin 300 mg group tended to occur earlier in the studies, as indicated by a greater proportion of subjects with events in the first 30 days.

The incidence of osmotic diuresis-related adverse events was higher in the combined canagliflozin group (4.0%) relative to placebo (3.7%). The specific adverse event terms most

commonly reported with canagliflozin were adverse events of pollakiuria (2.3%) and thirst (1.0%). There were no adverse events related to osmotic diuresis that led to study discontinuation in any treatment group and none of the events was serious.

The incidence of UTI adverse events was higher in the canagliflozin 300 mg group (7.4%) relative to the placebo group (6.0%), whereas the incidence in the canagliflozin 100 mg group (6.2%) was similar to the placebo group. The incidence of discontinuations due to UTI adverse events was 0.5% (2 subjects) and 0.3% (1 subject) in the placebo and 100 mg canagliflozin groups, respectively. No subjects discontinued due to a UTI adverse event in the 300 mg canagliflozin group. Serious UTI adverse events occurred in 3 (0.8%) subjects (preferred terms: urinary tract infection [2 subjects] and urosepsis [1 subject]) and 1 (0.3%) subject (preferred term: urinary tract infection) in placebo and 100 mg canagliflozin groups, respectively. No serious UTI adverse events occurred in the 300 mg canagliflozin group.

The incidence of documented hypoglycemic episodes in subjects receiving a sulphonylurea and/or insulin was moderately higher in the canagliflozin 100 mg (41.9%) and the canagliflozin 300 mg group (43.8%) relative to the placebo group (29.2%). The incidence rate per subject-year exposure was similar in the canagliflozin 100 mg and 300 mg groups (1.13 and 1.19, respectively), and higher relative to the placebo group (0.83). The incidence of subjects experiencing severe hypoglycemic episodes was higher in the pooled canagliflozin group (2.6%), with no dose relationship, relative to the placebo group (1.2%). The hypoglycemia event rates per subject-year exposure in subjects not receiving background AHA associated were similar in canagliflozin 100 mg and placebo groups (0.47 and 0.45, respectively) and greater relative to the canagliflozin 300 mg group (0.06).

The incidence of acute renal failure (by SMQ) adverse events was higher in the canagliflozin 100 mg group (3.8%) and canagliflozin 300 mg group (3.0%) relative to the placebo group (2.1%). The incidence of events that led to discontinuation of study drug or were considered related to study drug by the investigator was higher in the canagliflozin 300 mg group relative to the canagliflozin 100 mg and placebo groups. The incidence of serious events was similar in all groups.

Selected Laboratory Findings

As part of an outlier analysis of all Phase 3 studies in subjects with moderate renal impairment, the incidence of subjects who met the eGFR predefined limit of change (PDLC) criterion of <80 mL/min/1.73m^2 and a decrease >30% from baseline to “any” post-baseline value was higher in the canagliflozin 100 mg and 300 mg groups (9.3% and 12.2%, respectively) relative to the placebo group (4.9%). In contrast, the incidence of subjects meeting this PDLC criterion to the last value measured while on study drug was similar in the canagliflozin 100 mg and placebo groups (3.0% and 3.3%, respectively) and was 4.0% in the canagliflozin 300 mg group.

The incidence of subjects with any serum potassium value meeting PDLC criteria (>ULN and >15% increase from baseline) was similar in the canagliflozin 100 mg and placebo groups, 7.2% and 7.9%, respectively, and higher in the canagliflozin 300 mg group, 12.0%. Potassium elevations were transient, with no notable difference in the incidence of subjects meeting the

PDLC criteria across groups at the last value. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, medications that interfere with the renin-angiotensin-aldosterone system, angiotensin-converting-enzyme inhibitors, and angiotensin receptor blockers. Adverse events of hyperkalemia occurred with a similar incidence across treatment groups: 1.5% and 2.2% in the canagliflozin 100 mg and 300 mg groups, respectively, and 1.6% in the placebo group. These events were considered as serious adverse events in 3 subjects (1 subject in the canagliflozin 100 mg and 2 subjects in the canagliflozin 300 mg group, and led to discontinuation in 2 subjects (in the canagliflozin 300 mg group). The adverse event of blood potassium increased was reported in 0.9% and 1.1% of subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and not reported in the placebo group. None of the adverse events of blood potassium increase were considered as drug-related, and none were serious or led to discontinuation.

For low serum bicarbonate, the incidence of subjects meeting PDLC criteria (value <16 mmol/L) at any time was 7.2% in the combined canagliflozin group, without notable dose dependent differences, and 2.7% in the placebo group. For the last value, the incidences of subjects meeting the PDLC criterion were 1.6% and 0.3%, in the combined canagliflozin group and non canagliflozin group, respectively

For increases in serum magnesium, the incidence of subjects with any post-baseline value meeting PDLC criteria (>ULN and >25% increase from baseline) was 1.5% and 2.3% in the canagliflozin 100 mg and 300 mg groups, respectively, and not observed in the placebo group. A lower incidence of subjects meeting PDLC criteria for the “last” value was seen: 0.6% and 1.4% of subjects in the canagliflozin 100 mg and 300 mg groups, respectively. Increases in serum magnesium meeting the PDLC criteria were generally mild, with modest increases from baseline, and with no values reaching the range considered to reflect hypermagnesemia (ie, >1.5 mmol/L).

For increases in serum phosphate, the incidence of subjects with any value meeting PDLC criteria (>ULN and >25% increase from baseline) was 2.7% and 5.1% in the canagliflozin 100 mg and 300 mg groups, respectively, and 0.3% in the placebo group. A lower incidence of subjects met the PDLC criteria for the last value: 0.6% and 1.4%, in the canagliflozin 100 mg and 300 mg groups, respectively, with no subjects in the placebo group meeting the criterion. No adverse events of hyperphosphatemia or increased blood phosphate were reported in the canagliflozin groups, suggesting that these transient, mild increases in serum phosphate. No subject required treatment for increases in phosphate.

A higher proportion of subjects in the canagliflozin groups relative to the placebo group met the PDLC criteria for increases in serum sodium: 4.5% and 4.8% of subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 2.2% of subjects in the placebo group.

1.1.2.5.3.2. Findings in Subjects With eGFR <30 mL/min/1.73m^2

In the CANagliflozin cardioVascular Assessment Study (CANVAS), subjects were eligible for randomization if their eGFR was ≥30 mL/min/1.73m^2 and were discontinued from the study if their eGFR decreased to <15 mL/min/1.73m^2; thus safety information, albeit limited, is available

for 149 subjects in this population with severe renal impairment. SBP decreases were noted in the population of subjects treated with canagliflozin who had an eGFR <30 mL/min/1.73m^2 at any time while on study drug, with SBP changes of -7.7 mmHg and -7.5 mmHg in the canagliflozin 100 mg and 300 mg treatment groups, respectively, relative to a mean change of -3.1 in the comparator group noted after eGFR dropped below 30 mL/min/1.73m^2.

While only a limited number of subjects experienced a reduction at some point in the study to an eGFR <30 mL/min/1.73m^2, no notable differences were seen between canagliflozin and non-canagliflozin groups in adverse event reporting. Due to the limited ability of canagliflozin to increase urinary glucose excretion in subjects with an eGFR of less than 30 mL/min/1.73m^2 (due to the severe decrease in functioning nephrons), it may have been expected that adverse events related to increased urinary glucose excretion (eg, osmotic diuresis, decreases in intravascular volume) would be minimal in this population.

While in subjects with an eGFR <45 mL/min/1.73m^2 minimal to no improvement in blood glucose control will be expected, the safety profile of canagliflozin as assessed by adverse event reporting appears to be acceptable with no clinically important differences seen relative to the non-canagliflozin group. It should be noted that the ability of canagliflozin to increase delivery of sodium to the distal tubule and enhance tubuloglomerular feedback in the remaining nephrons in these subjects should be intact, allowing these subjects to potentially benefit in terms of reducing progression of diabetic nephropathy in response to canagliflozin treatment.

1.2. Overall Rationale and Goals for the Study

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

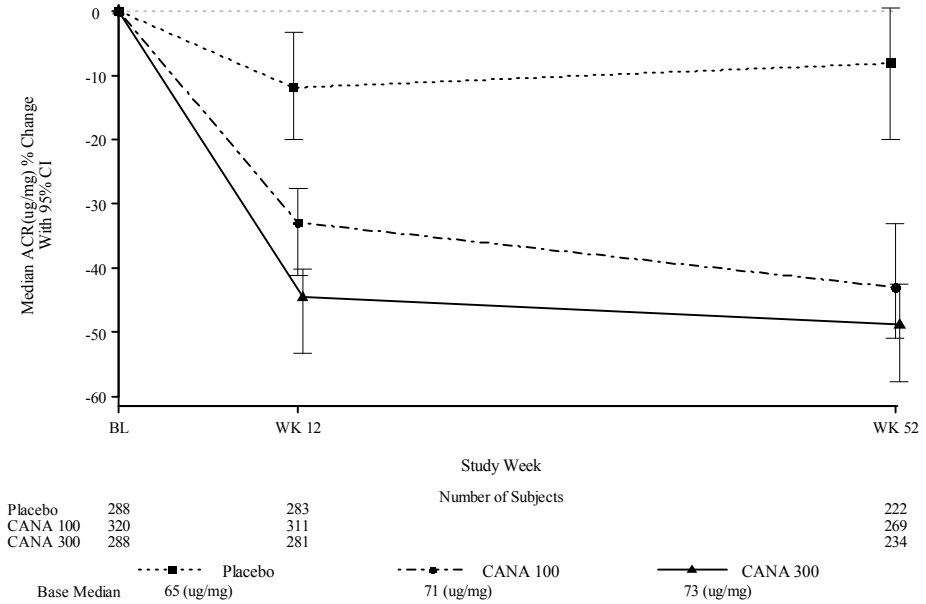
Hyperglycemia increases glucose levels delivered to the proximal tubule, which is reabsorbed, predominantly via an SGLT-2-dependent mechanism (Vallon 1999). Increased proximal tubule resorption of glucose results in increases in the proximal tubule reabsorption of sodium and reduces the delivery of sodium to the distal tubule (DeFronzo 2009). Decreases in sodium levels in the distal tubule reduce macula densa-dependent tubuloglomerular feedback, which results in afferent glomerular arteriole vasodilation and increases in glomerular pressure (Vallon 1999; Gilbert 2013). Increases in glomerular pressure are believed to be an important factor in the onset and progression of diabetic nephropathy (Anderson 1986; ADA 2004). ACEi and ARB decrease glomerular pressure by stimulating efferent glomerular arteriole vasodilation and reduce albuminuria and the progression of diabetic nephropathy (IDNT Study, Lewis 2001; RENAAL Study, de Zeeuw 2004).

In preclinical diabetic rodent models, SGLT2 inhibition increases tubuloglomerular feedback and reduces SNGFR, consistent with an increase in tubuloglomerular feedback leading to a decrease in glomerular pressure (Vallon 2011). In a Phase 1 study in subjects with T1DM who exhibited glomerular hyperfiltration (eGFR 172 mL/min/1.73m^2), an 8-week treatment with empagliflozin, a selective SGLT2 inhibitor, significantly reduced glomerular hyperfiltration (eGFR 139 mL/min/1.73m^2) (Cherney 2013 ADA poster). The reduction in hyperfiltration was associated with increases in renal vascular resistance and reductions in renal blood flow, both consistent with an increase in afferent glomerular arteriole tone. Thus, in preclinical and clinical models, SGLT2 inhibition reduces glomerular pressure, a factor known to be associated with the onset and progression of diabetic nephropathy.

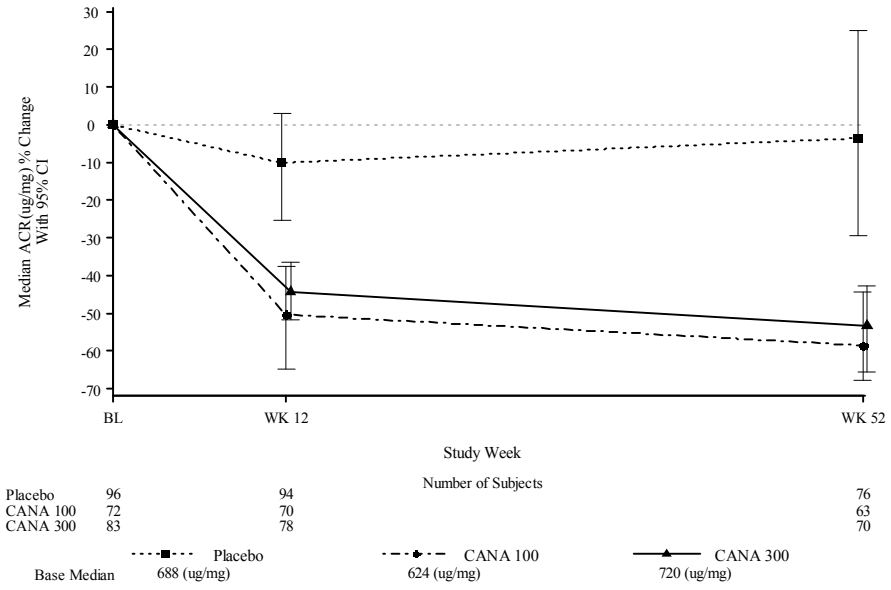
In the canagliflozin Phase 3 program, albuminuria (measured as first morning void urinary albumin/creatinine ratio) was assessed in several studies. After 52 weeks of treatment in the CANVAS study, reductions in albuminuria were seen with canagliflozin treatment in subjects with micro- and macroalbuminuria at baseline (Figure 1).

Figure 1: Micro- and Macroalbuminuria: Change from Baseline in Albumin/Creatinine Ratio in CANVAS (28431754DIA3008) through 01 July 2012

A. Microalbuminuria:



B. Macroalbuminuria:



In subjects with macroalbuminuria in CANVAS, the median percent change from baseline in UACR at Week 52 was -3.6% in the placebo group, -58.6% in the canagliflozin 100 mg group, and -53.3% in the canagliflozin 300 mg group. Notably this effect was seen on the background of ACEi and ARB use (82% of subjects in CANVAS were taking ACEis or ARBs at baseline). In a 52-week study (28431754DIA3004) in subjects with moderate renal impairment (ie, baseline eGFR ≥30 to <50 mL/min/1.73m^2), median percent reductions in albuminuria were also observed in subjects treated with canagliflozin 100 mg and 300 mg (-16.4% and -28%, respectively) relative to an increase in placebo (19.7%).

The categorical endpoint of the proportion of subjects with progression of albuminuria (defined as ≥1 step increase in category of albuminuria [ie, none to micro- or macro-, or micro- to macroalbuminuria]) according to the categorizations defined in the National Kidney Foundation KDOQI Guideline 1 (NKF 2007) was assessed. The definition of microalbuminuria is a UACR ≥30 to ≤300 mg/g and the definition of macroalbuminuria is a UACR >300 mg/g. In a post-hoc analysis in CANVAS, 253/1390 (18.2%) placebo-treated subjects showed albuminuria progression (defined by albuminuria status change and 30% increase in UACR from baseline) relative to baseline versus 221/1406 (15.7%) with canagliflozin 100 mg, 191/1397 (13.7%) with canagliflozin 300 mg, and 412/2803 (14.7%) with canagliflozin overall. Relative to placebo, the hazard ratio was 0.81 (95% CI: 0.68 to 0.97) for canagliflozin 100 mg and 0.71 (95% CI: 0.59 to 0.85) for canagliflozin 300 mg.

In the Phase 3 program, treatment with canagliflozin was associated with a dose-dependent, reversible reduction in eGFR that was maximal at the first post baseline visit and was either stable or attenuated with continued treatment. The time course of eGFR changes over 52 weeks in CANVAS (28431754DIA3008, Figure 2), over a 52-week study in subjects with moderate renal impairment (28431754DIA3004, Figure 3), as well as over a 104-week period in an active comparator study (28431754DIA3009, add-on to metformin, Figure 4) are shown below. These acute, modest declines in eGFR that do not progress and may attenuate over time are consistent with a hemodynamically mediated effect somewhat not unlike the effects seen with ACEi and ARB therapy (Holtkamp 2011).

Figure 2: eGFR (mL/min/1.73m^2) (28431754DIA3008): Mean Change from Baseline Over Time (Safety) – Regardless of Rescue Medication – Within 2 Days After Last Study Medication

(Study 28431754DIA3008: Safety Analysis Set)

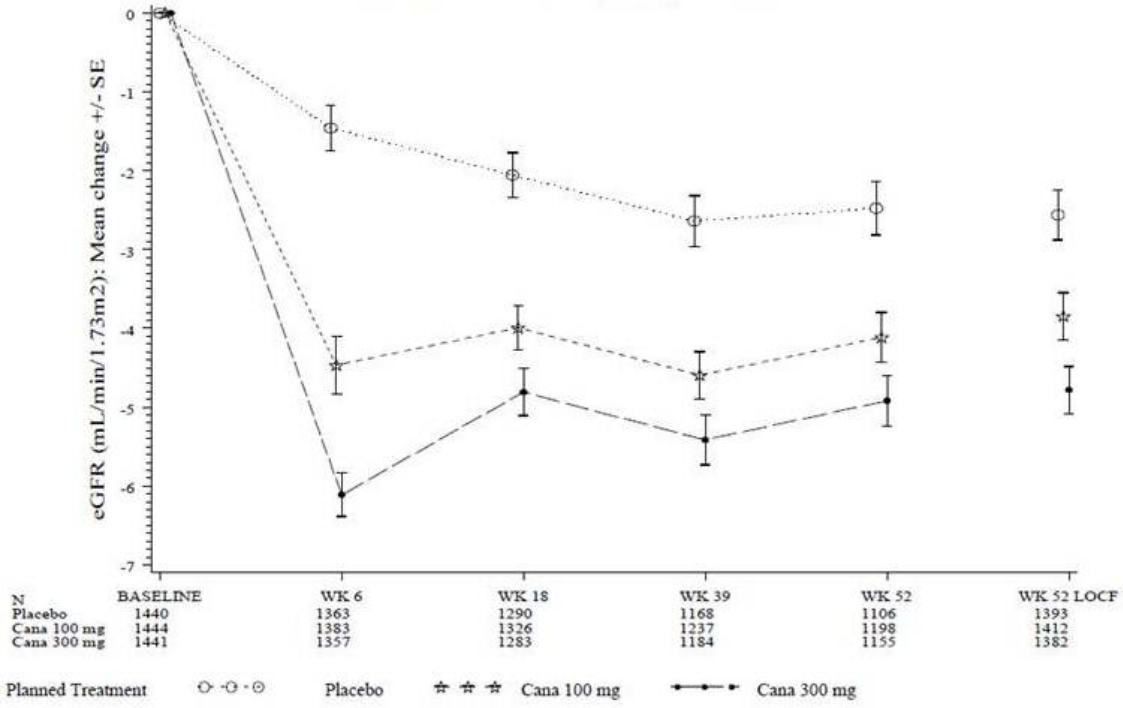


Figure 3: eGFR (mL/min/1.73m^2) (28431754DIA3004): Mean Change from Baseline Over Time (Safety)

(Study 28431754DIA3004: Safety Analysis Set)

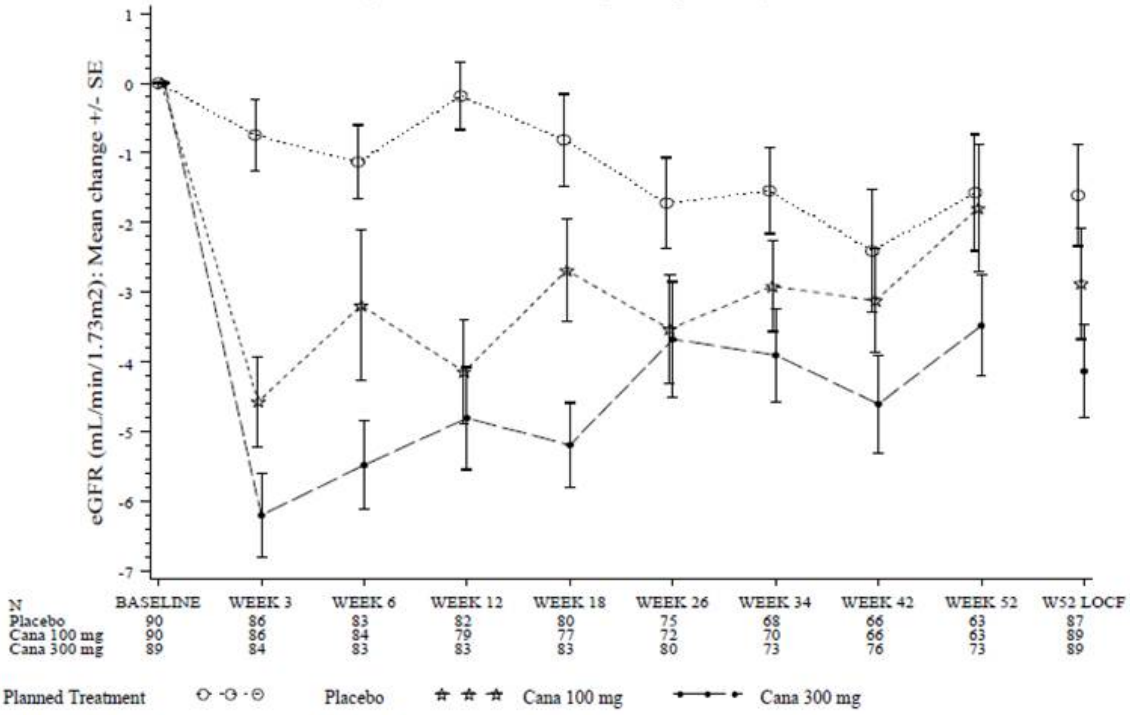
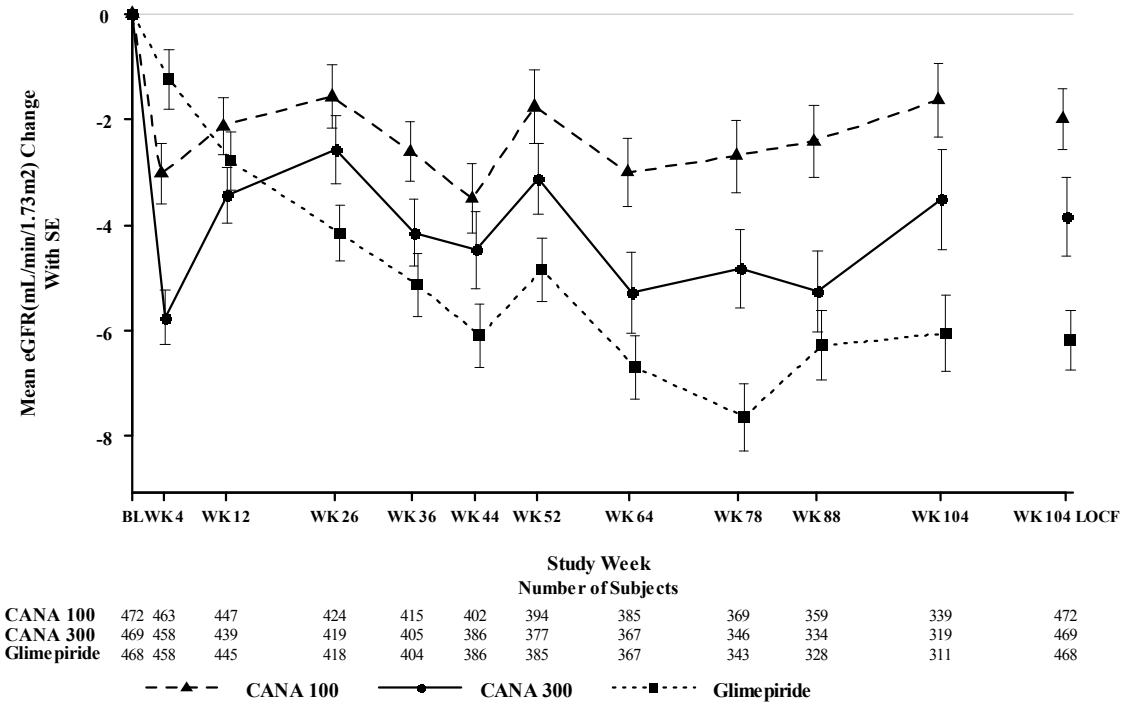


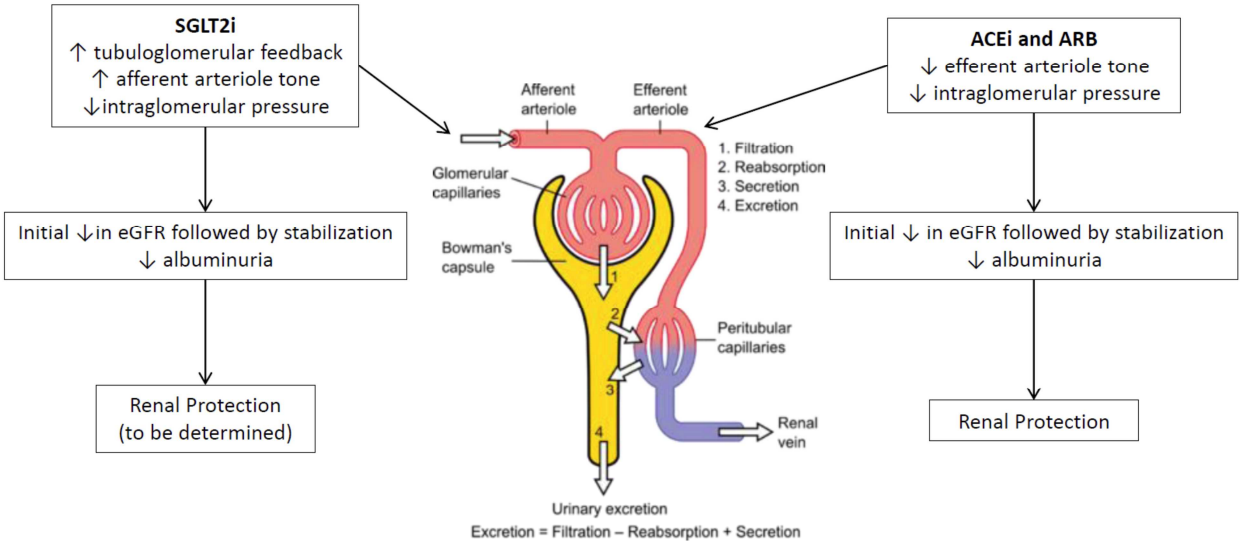
Figure 4: eGFR (mL/min/1.73m^2) (28431754DIA3009): Mean Change from Baseline Over Time (Safety) – Regardless of Rescue Medication – Within 2 Days After Last Study Medication

(Study 28431754DIA3009: Safety Analysis Set)



Based on these data, it is hypothesized that SGLT2 inhibition with canagliflozin will reduce glomerular pressure by increasing afferent glomerular arteriole tone, which will lead to a hemodynamically mediated decrease in glomerular pressure, as reflected by an acute, mild decrease in GFR. The reduction in glomerular pressure is hypothesized to mediate the reduction in albuminuria seen with canagliflozin treatment and to potentially lead to a reduction in progression of diabetic nephropathy. A schematic of these hypotheses and the effect of ACEi and ARBs on the progression of diabetic nephropathy is shown in Figure 5.

Figure 5: Hypotheses Regarding the Effect of ACEi and ARBs on the Progression of Diabetic Nephropathy



The present study is intended to determine whether canagliflozin treatment has a renal protective effect in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care, as defined in KDOQI consensus guidelines (NKF 2007; NKF 2012) and treatment with an ACEi or ARB. The renal protective effect of canagliflozin relative to placebo is measured by the reduction in progression to ESKD, doubling of serum creatinine, and renal or CV death. The study will also assess the effects of canagliflozin on reducing renal events (ESKD, doubling of serum creatinine and renal death), or CV events (CV death, non-fatal MI, non-fatal stroke, hospitalized unstable angina, and hospitalized congestive heart failure), and all-cause death. Additionally, the study will explore the clinically important renal and CV events (ESKD and renal or CV death), each component of the primary and secondary composite endpoints, as well as changes in eGFR and albuminuria over time.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objective

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

- The composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death

Secondary Objectives

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

- The composite endpoint of CV death and hospitalized congestive heart failure

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

Exploratory Objectives

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

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

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

- Changes in eGFR over time
- Changes in albuminuria over time

Safety Objective

To assess the overall safety and tolerability of canagliflozin.

2.2. Hypotheses

Canagliflozin reduces the risk of the composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death, relative to placebo, in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria who are receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

3. STUDY DESIGN AND RATIONALE

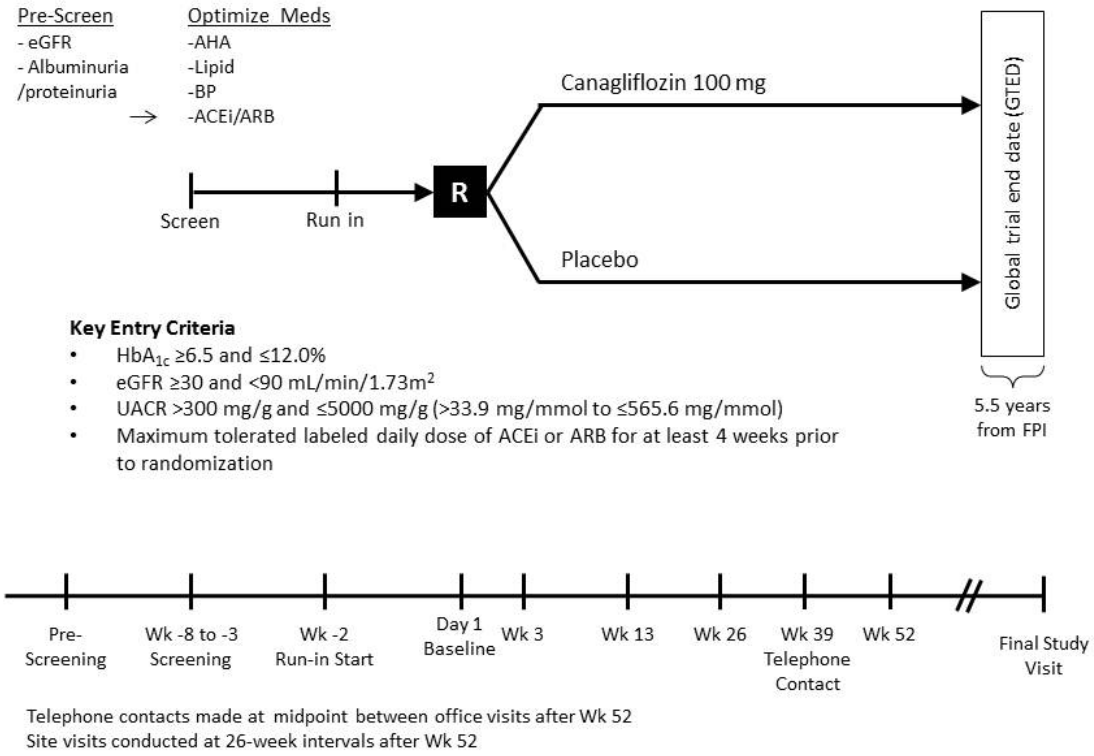
3.1. Overview of Study Design

This is a randomized, double-blind, event-driven, placebo-controlled, parallel-group, 2-arm, multicenter study to evaluate the effects of canagliflozin relative to placebo on progression to ESKD, doubling of serum creatinine, renal or CV death in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care including a maximum tolerated labeled daily dose of an ACEi or ARB.

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

An overview of the study design is illustrated in Figure 6.

Figure 6: Study Design Diagram



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

Prescreening

Subjects will be prescreened on the basis of eGFR and UACR. Only subjects with an eGFR ≥30 to <90 mL/min/1.73m^2 and a UACR >300 mg/g (>33.9 mg/mmol), as confirmed by a local laboratory within 6 months prior to screening, will be eligible for screening by the central laboratory. For the prescreening assessment where UACR is not routinely measured as per standard of care, it may be substituted by one of the following measures: albumin excretion rate >300 mg/24 hours, urine protein-to-creatinine ratio (PCR) >500 mg/g (>56.5 mg/mmol), or protein excretion rate >500 mg/24 hours. Subjects who fail local laboratory pre-screening assessments are allowed to repeat those laboratory tests.

Note: While positive reagent strip analysis (eg, dipstick ≥2+) may be suggestive of albuminuria/proteinuria that meet the prescreening criteria, any positive reagent strip findings must be accompanied by one of the specified albuminuria/proteinuria prescreening measures listed above prior to screening with central laboratory evaluations.

Information related to the management of subjects' blood pressure, including the use of an ACEi or ARB, will also be collected to ensure it meets the study's requirement (ie, dose stable for at least 4 weeks prior to randomization).

Screening to Randomization (up to 8-10 weeks, inclusive of the 2-week single-blind placebo run-in period)

Subjects will undergo a screening visit for a preliminary determination of eligibility between Week -8 and Week -3. Men or women ≥30 years of age, diagnosed with T2DM with HbA_{1c} level ≥6.5% to ≤12.0% at screening are eligible to enroll. Eligible subjects must have an eGFR of ≥30 to <90 mL/min/1.73m^2 and UACR of >300 mg/g to 5,000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol).

Subjects who meet inclusion criteria in the screening period must be on the stable maximum tolerated labeled daily dose of an ACEi or ARB for a period of at least 4 weeks prior to randomization. To reach this requirement, the screening period may be extended up to a total of 8 weeks (inclusive of the 2-week single-blind placebo run-in period); however, an additional 2 weeks of screening time may be allowed, if considered medically appropriate. Extension beyond this period of time would require concurrence of the sponsor's medical monitor. Investigators are encouraged to keep other anti-hypertensive, lipid-lowering and antihyperglycemic therapies dose stable for approximately 4 weeks prior to randomization. In addition, investigators are encouraged to keep medications that are known to impact serum creatinine levels stable during the screening period (for details see Section 6.2.3, Management of Medications That May Impact Serum Creatinine Levels).

Qualified subjects will enter the single-blind placebo run-in phase at Week -2. During this phase, subjects will be instructed to take one capsule daily in order to assess their compliance with study drug. The study site staff should not disclose to the subject that during the single-blind placebo run-in period subjects will receive placebo capsules. At the Week -2 visit, subjects should also be counseled to perform self-monitored blood glucose (SMBG) determinations, according to standard guidelines. The frequency of SMBG determinations will be at investigator's discretion based on individualized standard of care. Subjects will also receive diet/exercise counseling and instructions on hypoglycemia recognition and management, as well as counseling on renal and CV risk factor medication. This counseling may be reinforced as needed throughout the study.

Double-Blind Treatment Phase

Subjects who complete the 2-week single-blind placebo run-in period with ≥80% compliance (by pill count), will be stratified according to their pretreatment eGFR value most proximate to the baseline visit (eg, screening, unscheduled, or Week -2) and will be randomized within the following 3 strata: 1) ≥30 to <45 mL/min/1.73m^2, 2) ≥45 to <60 mL/min/1.73m^2, 3) ≥60 to <90 mL/min/1.73m^2. They will be randomly allocated to treatment with canagliflozin 100 mg or matching placebo (in a 1:1 ratio). Double-blind study drug will be administered once daily (ie, one capsule taken before the morning meal). A total of approximately 4,200 subjects will be randomized.

Office visits will occur 3 times during the first 13 weeks (ie, Day 1 [randomization], Week 3, and Week 13]). Subjects will then be seen at Week 26 and then every 26 weeks thereafter for an office visit with laboratory assessment, concomitant medication review, adverse event collection and determination of clinical endpoints. Study drug will be dispensed on Day 1 and at Week 13 and Week 26, and every 26 weeks thereafter. Telephone contact will be made at Week 39 and at the midpoint between office visits after Week 52, to check the subject's status, including discussing the subject's diary entries, concomitant medications, and adverse events, including those events in the primary and secondary outcomes. Clinical evaluations and laboratory tests using local laboratory facilities may be performed more frequently, as clinically appropriate, and abnormalities determined by the investigator to be clinically important should be recorded on the local laboratory eCRF.

Blood pressure, lipid, and glucose control should be managed according to local standard of care guidelines (such as National Kidney Foundation) in this population. Local laboratory findings that prompt adjustment to medical treatment, require protocol-specified monitoring (ie, potassium), or are associated with adverse events should be documented in the specified eCRF.

End of Treatment Visit

The study has an end of treatment (EOT) visit as soon as possible after the sponsor announces the projected GTED. Subjects are expected to remain in the double-blind treatment phase until the sponsor-announced GTED. The date is based on study site local time. The study sites will be notified of the projected GTED, at which time subjects will be scheduled to return to the study site for the EOT visit. Subjects should remain on double-blind study drug up until their EOT visit. Efficacy and safety outcomes will be collected at the EOT visit.

Subjects who permanently discontinue the study drug before the announcement of the projected GTED will complete the EOT/Early Withdrawal (EW) visit as soon as possible after the last dose of study drug (or when it is known the subject will be permanently discontinuing study drug). In addition, these subjects will return for all scheduled visits in the same way as the subjects still on study drug treatment. If these subjects refuse office visits, the investigator is asked to encourage the subjects to allow regular contact until study end, according to the Time and Events Schedule, either with them, or with a legally acceptable representative, a close friend or relative, or their primary care physician to determine vital status and if an efficacy or safety outcome event has occurred.

Vital status will be collected for all subjects who permanently discontinue study drug early, withdraw from study, or are lost to follow-up at the EOT visit either by telephone or in person, or if applicable, by a review of subject's medical or public records unless this contact is not allowed by local regulations.

A Steering Committee, a Medical Safety Review Committee (MSRC), an Independent Data Monitoring Committee (IDMC), and an Independent Endpoint Adjudication Committee (IEAC) will be commissioned for this study. Refer to Section 9.3, Study Management Committee, for details.

Study Duration

Assuming the study endpoints occur as planned, the total study duration is estimated to be 5 to 5.5 years, including a subject accrual phase of approximately 2 to 2.5 years. Subjects are expected to be followed for approximately 4.5 years on average, with the last visit for the last subject targeted to occur when all subjects have at least 3 to 3.5 years of follow-up. All study sites will be notified of the projected GTED (projected to occur in the fourth quarter of 2019). Immediately after the projected GTED notification is sent, for subjects who remain on double-blind study drug, study sites will be required to schedule the last on treatment visits.

Collection of Data Related to Renal and Cardiovascular Safety Outcomes

Investigators will be required to report any renal or CV event that they consider could possibly be an endpoint or a component of the primary or secondary composite endpoint, (refer to Section 9.2, Reporting/Adjudication of Events in the Primary and Secondary Composite Endpoints and Other Events for Adjudication), as well as all deaths. Additional information and documentation will be requested from investigators for all such events to support a detailed assessment of these outcomes by the IEAC.

Collection of Information After Early Discontinuation of Randomized Treatment

It is the intent that subjects who discontinue treatment with the study drug will continue in the study according to the visit schedule described in the Time and Events Schedule. After early discontinuation of randomized treatment, subjects will continue to be followed in the same way as those who are on study drug treatment.

Participants who prematurely discontinue study drug will require an immediate follow-up assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) as well as a follow-up assessment approximately 30 days (±12 days) after last dose, after which they should continue to be followed for the full duration of their originally scheduled study visits. The follow-up regimen for these individuals will be the same as those individuals who continue with randomized therapy, ie, requiring study site visits every 26 weeks with phone/e-mail contact occurring at the midpoint between study site visits (refer to Section 9.1.4, Post-Treatment Follow-up, and Section 9.1.5, Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits, for collection of information on renal and CV events and other assessments). The investigator will make every effort to ascertain the vital status of all subjects at the end of the study (GTED), 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 (see Section 10.4, Circumstances for Reduced Follow-up).

Safety Evaluations

Safety evaluations will include the monitoring of all adverse events, clinical laboratory tests, physical examination, vital sign measurements, and measurement of body weight. Further details can be found in Section 9.5.1, Safety Evaluation. For adverse events of interest, investigators will be asked to provide additional information on separate electronic case report forms (eCRFs). The detailed information on collection and reporting of all adverse events is also described in

Section 9.5.1, Safety Evaluation. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC, IEAC or IDMC (Section 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events. Section 9.3, Study Management Committees, provides details regarding the committees commissioned to provide oversight for the management of this study.

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.

Biomarker Research Sample

Plasma, serum, and urine archive samples will be collected (where local regulations permit and in subjects who consent to provide these samples) annually as described in the Time and Events Schedule to allow for exploratory biomarkers analyses that could help to further explain and examine the efficacy and safety findings in this study. Subject participation in the exploratory biomarker research is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study.

3.2. Study Design Rationale

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

This study was designed based on the guidelines for the identification and management of kidney disease (NICE 2008; NKF 2012), in general accordance with the US FDA and EMA guidance on the development of medications and clinical investigations for the treatment and prevention of diabetes mellitus (FDA 2008; EMEA 2012), and in consultation with Health Authorities.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment, improving the precision of the assessments of both efficacy and safety. Since canagliflozin has blood glucose- and blood pressure lowering effects and can alter lipids, all subjects are required to be under standard care including anti-hypertensive, lipid lowering and antihyperglycemic therapies. Antihyperglycemic, lipid lowering and anti-hypertensive therapies can be adjusted any time during the study as needed.

The pretreatment phase allows sufficient time for study-related procedures to be performed and for determining subject eligibility based on the study entry criteria and test results. During the pretreatment phase, adjustment of therapy to reach the stable maximum tolerated labeled daily dose of an ACEi or ARB before at least 4 weeks prior to randomization may be performed.

The 2-week single-blind placebo run-in period will allow sufficient time for investigators to assess whether subjects demonstrate compliance with study procedures, including compliance with administration of study drug.

Eligible subjects will be stratified according to their pretreatment eGFR value most proximate to the baseline visit (eg, screening, unscheduled, or Week -2) and will be randomized within the following 3 strata: 1) ≥30 to <45 mL/min/1.73m^2, 2) ≥45 to <60 mL/min/1.73m^2, 3) ≥60 to <90 mL/min/1.73m^2. The cut-off threshold for eGFR strata was based on the potential differences in the primary event rate and in the relative contribution of the components of the composite primary endpoint between the three eGFR strata.

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, and to maximize the likelihood that the study precisely and reliably addresses the questions it is designed to answer.

Selection of Study Population

The study population is selected to ensure a sufficiently high rate of deterioration of renal function occurring in the study, which will allow the study to reach the primary aim in a reasonable amount of time.

This study includes subjects with T2DM on a variety of different AHAs with a range of different levels of baseline glycemic control.

To be eligible for enrollment, subjects must also have Stage 2 or 3 CKD with an eGFR ≥30 to <90 mL/min/1.73m^2 (as determined by CKD-EPI equation) and macroalbuminuria with a UACR >300 mg/g to ≤5000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol).

An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (ie, eGFR ≥30 to <60 mL/min/1.73m^2; first category):CKD Stage 2 (ie, eGFR ≥60 to <90 mL/min/1.73m^2; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, entry of subjects with Stage 2 CKD (ie, eGFR ≥60 to <90 mL/min/1.73m^2) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.

Use of ACEi or ARB

All subjects are also required to be receiving the maximum tolerated labeled daily dose of ACEi or ARB. This requirement is aligned with current guidelines which recommend the use of ACEi or ARB for patients with CKD and diabetes (KDIGO 2013). The rationale for this requirement is based on the observation that inhibition of the renin-angiotensin pathway by ACEi or ARB reduces the progression of diabetic nephropathy in subjects with T2DM (see Section 1, Introduction) and the hypothesis that canagliflozin may exert its renal protective effect through a

unique hemodynamic mechanism different from that by ACEi or ARB (see Section 1, Introduction). Thus, this requirement will allow the study to address whether canagliflozin can provide further renal protection in diabetic nephropathy in addition to standard of care ACEi or ARB therapy.

Combination therapy with an ACEi and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy (Fried 2013). Therefore, combination use of ACEi and ARB, use of mineralocorticoid receptor antagonists or direct renin inhibitors are prohibited during this study.

In the canagliflozin Phase 3 program, it was not common for subjects on ACEi or ARBs to down-titrate doses or discontinue the ACEi or ARB therapy. There were a total of 236 subjects with baseline eGFR ≥30 to <90 mL/min/1.73m^2 and UACR >300 mg/g in the Phase 3 program who were treated with ACEi or ARBs at baseline. The number of subjects who permanently discontinued therapy with ACEi or ARB before the end of the study was 6 of 65 (9.2%), 6 of 77 (7.8%), and 3 of 94 (3.2%) in the canagliflozin 100 mg, 300 mg and comparator groups, respectively.

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

Canagliflozin has been filed with health agencies for marketing approval based on the results of the clinical program, and has been approved for marketing in some countries. As per the US Package Insert (USPI) and EU Summary of Product Characteristics (SmPC), the recommended starting dose of canagliflozin is 100 mg. Canagliflozin should be taken once daily before the first meal of the day.

The 100 mg dose of canagliflozin was chosen for this study in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria who are receiving standard of care, mainly based on a favorable benefit to risk ratio and clinical data available in the moderate renal impairment group of subjects (ie, with baseline eGFR ≥30 to <60 mL/min/1.73m^2) who participated in the Phase 3 development program. This included an examination of expected reductions in blood pressure (the mean reduction from baseline in SBP for placebo, canagliflozin 100 mg and 300 mg groups was -1.6 mmHg, -4.4 mmHg and -6.0 mmHg, respectively) and UACR (ie, in subjects with macroalbuminuria in CANVAS study [28431754DIA3008], the median percent change from baseline in UACR at Week 52 for placebo, canagliflozin 100 mg and 300 mg groups was -3.6%, -58.6%, and -53.3% respectively) as well as safety considerations in the pooled population with moderate renal impairment (eg, volume depletion adverse events [incidence rates for placebo, canagliflozin 100 mg and 300 mg groups were 2.6%, 5.0% and 8.5%, respectively], adverse events leading to discontinuation [incidence rates for placebo, canagliflozin 100 mg and 300 mg groups were 5.0%, 4.7% and 7.4%, respectively], and lab findings of hyperkalemia [incidence rates for placebo, canagliflozin 100 mg and 300 mg groups were 7.9%, 7.2% and 12.0%, respectively]) where the balance favored canagliflozin 100 mg over 300 mg in the population of subjects with moderate renal impairment.

Choice of Renal Efficacy Measures

The development and progression of renal disease in people with diabetes follows a clearly defined pathway: Initially, hyperfiltration (elevated GFR) significantly increases the risk for development of microalbuminuria, which progresses to macroalbuminuria, associated with reduction in renal function (lower glomerular filtration rate), which eventually leads to renal failure with the need for dialysis or transplantation, and finally to death (Mogensen 1998; Magee 2009).

The renal components in the composite endpoint (ESKD, doubling of serum creatinine, and renal death) are all clinically meaningful and represent different manifestations of the same underlying pathophysiologic process. They are widely accepted endpoints indicative of severity of renal impairment and have been used in other renal-related outcome trials (Ninomiya 2009; Parving 2012; de Zeeuw 2013). Diabetic nephropathy increases the risk of CV disease and leads to a poorer prognosis (Aso 2008). In addition, CV death is included in the primary composite because it is an important competing risk in this patient population (Amin 2013). These endpoint events can be clearly defined (definitions are provided in the protocol Section 9.4, Efficacy Evaluations and Outcomes) and quantitatively measured. To further ensure the study objectivity, all the major efficacy endpoint events will be adjudicated by a blinded IEAC.

Sustained doubling of baseline average serum creatinine values will be confirmed by central laboratory repeat test ≥30 days and preferably within 60 days from the index event. Doubling of serum creatinine as a marker of a significant progression of renal disease has been shown to be an appropriate parameter in the assessment of renal outcomes and disease progression that correlated positively with important CV and renal outcomes in a large outcomes studies (IDNT, RENAAL) in patients with T2DM (Lewis 2001; Brenner 2001). Not unlike the effects seen with ACEi and ARB therapy (Holtkamp 2011), the hemodynamically mediated effects of canagliflozin are associated with acute, modest declines in renal filtration with a concomitant increase in serum creatinine that do not progress over time and attenuate with cessation of treatment.

ESKD is defined as initiation of maintenance dialysis (confirmed by continued need for dialysis for at least one month), renal transplantation, or an eGFR <15 mL/min/1.73m^2 (determined by the central laboratory using the CDK-EPI formula and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days).

Renal death is defined as death in subjects who have reached ESKD, die without initiating renal replacement therapy, and no other cause of death is determined via adjudication. The endpoint of "renal death" in the composite is to capture and account for any subjects who died with renal failure but did not have renal replacement therapy applied (because of medical or social reasons). This component of the composite endpoint has been used in other renal-related outcome studies (Parving 2012; de Zeeuw 2013). These renal death events will be adjudicated by a blinded IEAC.

As exploratory endpoints, changes in eGFR and albuminuria over time will be monitored. The slope of the eGFR decline is strongly correlated with adverse clinical endpoints including ESKD and all-cause mortality (Turin 2012; 2013). The CKD-EPI equation was chosen for estimating

GFR in this study. The CKD-EPI equation has been found to be generally more accurate than the Modification of Diet in Renal Disease Study (MDRD) equation and is preferred in the most recent clinical practice guidelines (KDIGO 2013). An analysis using pooled data sets with measured GFR across multiple studies (including subjects with diabetes) found the CKD-EPI equation to be superior to the MDRD study equation across a wide range of GFRs and patient types (Levey 2009). The CKD-EPI equation has also been shown to be superior to MDRD in elderly subjects (Kilbride 2013) and can better categorize subjects as to long-term clinical risk than the MDRD study equation (Matsushita 2010).

Choice of Cardiovascular Efficacy Measures

Patients with T2DM with reduced eGFR and albuminuria are at increased risk of CV death and adverse renal outcomes (Amin 2013). Therefore, an intervention that would be expected to reduce the progression of diabetic nephropathy might reduce the incidence of CV death. In addition, CV death also serves as a competing risk for renal-related endpoints. CV deaths would be expected to account for approximately two thirds of the deaths in this subject population (Packham 2012), and this component of the composite endpoint has also been used in other renal-related outcome studies (Parving 2012; de Zeeuw 2013). Other causes of death (such as malignancy, infection, or injuries) would not be expected to be influenced by changes in nephropathy progression. In addition to CV death, other clinically important CV events are also monitored in this study, including non-fatal MI, non-fatal stroke, hospitalized CHF, or hospitalized unstable angina. These events are clearly defined in the charter of the IEAC and will be adjudicated by an IEAC.

Archive Samples for Exploratory Research and Specimens for Biomarker Assessment

Numerous biomarkers have been studied as potentially important surrogate measures of renal or CV events and overall health in subjects with T2DM (Ridker 2004). Fasting plasma, serum, and urine samples will be collected (where local regulations permit) and archived to allow for the analysis of important biomarkers (not prespecified) and could help to further explain and examine the efficacy and safety findings in this study. Details are provided in Section 9.7, Exploratory Biomarker Evaluations.

Pharmacogenomic (DNA) Samples Collection

It is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis (Parsa 2013). Pharmacogenomic research may help to explain variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of collecting DNA samples in this study is to allow the identification of genetic factors that may influence the efficacy of canagliflozin in the study population. Details are provided in Section 9.6, Pharmacogenomic Evaluations.

4. STUDY POPULATION

4.1. General Considerations

The study will include subjects with a diagnosis of T2DM with Stage 2 or 3 CKD and macroalbuminuria. 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 study representative before enrolling the subject in the study.

Note: For laboratory test values, a one-time repeat measurement is allowed, at the discretion of the investigator, if the screening value is not consistent with prior values and the repeat is considered clinically appropriate. For more information, refer to Section 4.5. Repeat Testing and Subject Rescreening.

4.2. Inclusion Criteria

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

Inclusion Criteria at Screening Visit

1. Man or woman ≥30 years-old with a clinical diagnosis of T2DM
2. HbA_{1c} ≥6.5% to ≤12.0%
3. eGFR ≥30 to <90 mL/min/1.73m^2 (as determined using the CKD-EPI equation)

   Note: An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (ie, eGFR ≥30 to <60 mL/min/1.73m^2; first category):CKD Stage 2 (ie, eGFR ≥60 to <90 mL/min/1.73m^2; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, entry of subjects with Stage 2 CKD (ie, eGFR ≥60 to <90 mL/min/1.73m^2) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.

4. Urinary albumin-to-creatinine ratio >300 mg/g to ≤5,000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol).
5. All subjects must be on a stable maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization.

   Note: A maximum tolerated labeled daily dose of an ACEi or ARB is defined as the maximum approved labeled dose for diabetic nephropathy (for agents with an approved indication for diabetic nephropathy in patients with T2DM, ie, losartan and irbesartan) or the maximum approved dose for hypertension (for agents without an approved indication for diabetic nephropathy), unless side effects or adverse events limit the use of the maximum approved dose. For subjects who are not on a maximum labeled daily dose of an ACEi or ARB, investigators will be required to document why a higher dose should not be used.

6. 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 <18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or

– surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), 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, and consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, 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.

7. Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above), regardless of age, must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations.

   Note: A serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations.

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol
9. 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. Each subject must also sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

Inclusion Criterion for Randomization

10. Subjects must have ≥80% compliance (by pill count) with single-blind placebo.

4.3. Exclusion Criteria

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

Diabetes-Related/Metabolic

1. History of diabetic ketoacidosis or T1DM.
2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

3. Known medical history or clinical evidence suggesting non-diabetic renal disease
4. 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.

5. Uncontrolled hypertension (systolic BP ≥180 and/or diastolic BP ≥100 mmHg) by Week -2.

   Note: Subjects not fulfilling blood pressure criteria at the initial screening visit may have their blood pressure lowering medication regimen adjusted, followed by re-evaluation up to the Week -2 run-in period (the ACEi or ARB regimen must be stable for at least 4 weeks before Day 1 to be eligible).

6. Blood potassium level >5.5 mmol/L during screening.

   Note: Subjects in whom hyperkalemia was associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), beta-blockers, or mineralocorticoid receptor antagonists (eg, spironolactone or eplerenone), who have been withdrawn from these drugs, and in whom usage of these drugs is not indicated in the view of the treating physician, may be included in the study.

7. Myocardial infarction, unstable angina, revascularization procedure (eg, stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomization, or a revascularization procedure is planned during the trial.
8. Current or history of heart failure of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association). See Attachment 2.
9. ECG findings within 12 weeks before randomization that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance).

Gastrointestinal

10. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis).

Laboratory

11. Alanine aminotransferase (ALT) levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.

Other conditions

12. 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).
13. History of human immunodeficiency virus antibody positive.
14. Major surgery within 12 weeks before randomization, or has not fully recovered from surgery.

15. Any condition that in the opinion of the investigator or sponsor's medical monitor would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments.
16. History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.

Medications/ Therapies

17. Combination use of ACEi and ARB.
18. Use of mineralocorticoid receptor antagonists (MRA) or a direct renin inhibitor (DRI).

    Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with MRA or DRI during screening. Subjects who are off therapy with MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrollment.
19. Current use of an SGLT2 inhibitor (within 12 weeks prior to randomization).
20. Current participation in another canagliflozin study, or previously exposed to canagliflozin in a prior canagliflozin study.
21. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug[s]).
22. Received an active investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks before Day 1/baseline.

General

23. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.
24. 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 ensure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since the time of the initial screening visit. Before randomization, subjects whose clinical status changes after screening such that they now meet an exclusion criterion, should be excluded from participation.

4.4. Prohibitions and Restrictions

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

- Prohibited medications include other SGLT2 inhibitors (including commercially available canagliflozin); subjects must not take any other investigational agents during the study (if a subject prematurely discontinues from the study medication but continues in the posttreatment follow-up phase, entering another investigational trial is discouraged but is not prohibited; however, entering another canagliflozin trial is prohibited).
- Combination use of ACEi and ARB will not be permitted.

- Use of direct renin inhibitors (DRIs) will not be permitted.
- If determined medically necessary, cautionary post-baseline use of MRA is permitted. As per labeling of MRA therapy, concomitant use of an MRA with ACEi (or ARB) therapy may significantly increase the risk of hyperkalemia. Thus, enhanced potassium monitoring must be carefully considered if starting an MRA post-randomization. Contraindications, Warnings, and Precautions specified in local product labeling of MRAs must be strictly adhered to, such as avoiding use of an MRA in subjects treated with other potassium-conserving diuretics and in subjects with acute renal insufficiency, with significantly compromised renal function, or subjects with heart failure and proteinuria.
- Subjects should not collect first morning void urine specimens during acute illness with fever. The collection and respective visit should be postponed until the subject is recovered from the acute illness.
- Strenuous exercise may affect safety laboratory results; for this reason, strenuous exercise should be avoided within 72 hours before planned study visits.

4.5. Repeat Testing and Subject Rescreening

During the screening period, a disqualifying blood pressure measurement or laboratory test may be repeated one time at the discretion of the investigator and where there is a clinical reason to do so. In subjects for whom a one-time repeat measure is deemed clinically appropriate, the repeat measure should be assessed within the screening period and prior to recording the subject as having failed screening.

Subjects who do not satisfy entry criteria based on a physical or laboratory measurement either during the initial screening assessment or following an allowable one-time repeat assessment will be reported as having failed screening and may, at the discretion of the investigator and with concurrence of the sponsor's medical monitor, be rescreened after appropriate clinical management. Rescreening will require that all screening parameters be repeated, including the signing of a new informed consent form and the completion of a full screening visit with a comprehensive central laboratory review. Rescreened subjects must meet all entry criteria to be considered eligible for the study. Generally, a subject may only be rescreened once, but one additional rescreening may be allowed with concurrence of the sponsor's medical monitor.

5. TREATMENT ALLOCATION

Stratification

Eligible subjects will be stratified according to their pretreatment eGFR value most proximate to the baseline visit (eg, screening, unscheduled, or Week -2) and will be randomized within the following 3 strata: 1) ≥30 to <45 mL/min/1.73m^2, 2) ≥45 to <60 mL/min/1.73m^2, and 3) ≥60 to <90 mL/min/1.73m^2.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor before the study. The randomization will be balanced by using

randomly permuted blocks and will be stratified by pretreatment eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73m^2). 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, medication numbers, and treatment code, which is linked to the randomization schedule, will be assigned after logging on to the interactive web response system (IWRS) designated by the sponsor. The requestor must use his/her own user identification (ID) and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and study drug kit for the subject. As subjects are randomly assigned to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IWRS is contacted for dispensing additional study drug. The randomization (or initial subject allocation) number at baseline will be the identifying number linking all subsequent kits to the individual subject.

The study drugs, whether canagliflozin or placebo, will be identical in appearance and will be packaged accordingly to maintain the blind.

The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. However, the treatment blind may be broken to provide unblinded information to the study 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 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 the IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source documents. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, in a sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. For the purpose of the interim analysis, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

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

Unless required for urgent medical management, investigators should obtain all post-baseline urinalyses through the central laboratory and not by a local laboratory. Urine glucose results will not be reported by the central laboratory. Investigators will be counseled to avoid performing local urinalysis with dipstick unless required for urgent medical management (eg, DKA or other safety concerns). If a urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

6. DOSAGE AND ADMINISTRATION

6.1. Study Drugs

Two-week Single-Blind Placebo Period Following Screening

Upon completion of initial screening, all eligible subjects will receive single-blind placebo capsules and will be instructed to take one capsule prior to the first meal of the day for a total of 2-weeks to assess compliance.

Subjects will take the last dose of single-blind placebo study drug on the day prior to the Baseline (Day 1) visit. The investigational site staff should avoid disclosing to the subject that the run-in period drug is placebo.

Double-Blind Study Medication

On Day 1, subjects will be randomly assigned in a 1:1 ratio to canagliflozin 100 mg or matching placebo.

On Day 1, the first dose of double-blind study drug will be administered at the study site **after** all baseline procedures have been completed.

After Day 1, subjects will be counseled to take one capsule of canagliflozin 100 mg or matching placebo once daily, before the first meal of the day, for the duration of the study or until early discontinuation.

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed.

If a subject does not take a dose of study drug within 12 hours after its scheduled time (ie, before the first meal of the day), the dose of study drug should be skipped for that day, and the subjects should be instructed to take their usual dose of study drug on the following morning at its regularly scheduled time.

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 on the

eCRF. Study drug should be reinstituted once the subject has recovered and the safety and/or tolerability concern is no longer present.

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

For subjects who develop conditions that are associated with amputation such as a lower extremity infection, skin ulcer, osteomyelitis, gangrene, or critical limb ischemia, study drug should be interrupted until the condition has resolved in the opinion of the investigator. In the event of an amputation, restarting of dosing with study drug 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

Subjects will receive diet/exercise counseling at the single-blind placebo run-in visit (Week -2) for their glycemic control. During this visit, subjects should also be counseled to perform fasting SMBG determinations, according to standard local guidelines, and to enter results into the protocol-specified study diary that will be provided to each subject, as described in Section 9.1.1.

The background AHA regimen may be adjusted at any time during the study to achieve glycemic goals, using standard local guidelines, and as considered appropriate by the investigator for the individual subject. As a reference of one possible standards of care guidance that study sites can use, the current American Diabetes Association (ADA) Standards of Medical Care in Diabetes will be provided to the sites (Section 15, Study Specific Materials). Adjustment to the AHA regimen should be carefully implemented so as to avoid events of hypoglycemia.

For optimization of glycemic control among the study participants, study sites will be informed, approximately biannually, about the proportion of subjects in their Country and/or Region who are meeting treatment targets, along with a benchmark of other Countries/Regions and the global on-average performances for the CREDENCE™ study sites worldwide.

To monitor whether additional measures are needed to ensure that treatment targets are being reached in both treatment arms, the IDMC will review unblinded glycemic data by treatment group.

6.2.2. Management of Renal and CV Risk Factors

Subjects will receive counseling at the single-blind placebo run-in visit (Week -2) for their renal and CV risk factor medication.

Before randomization and throughout the study, investigators should carefully consider the management of hyperlipidemia and hypertension based upon standard local guidelines for the care of subjects with T2DM. As a reference of one possible standards of care guidance that study sites can use, the current ADA Standards of Medical Care in Diabetes will be provided to the sites (Section 15, Study Specific Materials).

In line with monitoring for the glycemic parameters described in Section 6.2.1, an individual site report will include metrics on the proportion of subjects reaching treatment targets for systolic blood pressure as well as the proportion of subjects being treated with HMG-CoA reductase inhibitors (statin). The IDMC will review unblinded blood pressure and lipid management data by treatment group.

6.2.3. Management of Medications that May Impact Serum Creatinine Levels

Investigators are encouraged to keep medications that are known to impact serum creatinine levels (eg, NSAIDs, trimethoprim, cimetidine, probenecid, aminoglycosides, amphotericin, ketoconazole, and clofibrate) stable during the screening period and for approximately 2 weeks before any serum chemistry measurement during the course of the study.

7. TREATMENT COMPLIANCE

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

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with making required clinic visits. The initial compliance will be assessed during the 2-week single-blind placebo run-in period.

8. PRESTUDY AND CONCOMITANT THERAPY

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

Prestudy therapies taken from 30 days before screening and up to the time of the first dose of double-blind study drug must be recorded on the eCRF.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; non-pharmacologic 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 concomitant therapy (after first dose of double-blind study drug) on the eCRF, including in subjects who prematurely discontinue study drug.

Concomitant therapies will not be provided by the sponsor.

For subjects requiring a downward adjustment of blood pressure medication, other background therapy (eg, diuretics) should be modified prior to adjusting the dose of ACEi or ARB, and prior to interruption/discontinuation of study drug.

Subjects who experience a volume depletion adverse event or a meaningful change in eGFR should have concomitant medications reviewed by the investigator with adjustments made as clinically appropriate. Guidance for the management of volume depletion adverse events or eGFR changes will be provided in a separate document (see Section 15, Study Specific Materials).

There is no evidence of excess risk for hyperkalemia associated with the canagliflozin 100 mg dose used in this study (see Section 3.2, Study Design Rationale). Therefore, general standards for management of hyperkalemia should be applied in case of an elevation in serum potassium.

Prohibited and Restricted Post-Baseline Therapies

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited and restricted post-baseline therapies are administered. In addition, prohibited medication must be immediately recorded in RAVE.

Prohibited therapies include:

- **Other SGLT2 inhibitors (including concurrent use of canagliflozin)**

  Note: Subjects should not take any other investigational agents during the study. If the use of another SGLT2 inhibitor or investigational agent is reported during the study, the subject's physician should be contacted, the other agent discontinued, and the subject should continue in the study.

- **Combination use of ACEi and ARB**
- **Direct renin inhibitors**

Restricted therapy includes:

- **Mineralocorticoid receptor antagonists**

  Note: if post-baseline treatment with an MRA is determined medically necessary over the course of the double-blind treatment period, more frequent monitoring of serum potassium and more aggressive medication management should occur as per the local label. For example, if spironolactone is prescribed and the potassium values exceed 5.0 mEq/L (mmol/L) (as per US label for spironolactone), consideration should be made to first discontinue or interrupt treatment with spironolactone, followed by other medications that may be suspected to have contributed to hyperkalemia (eg, ACEi/ARB, double-blind study drug).

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 8 weeks before the single-blind placebo run-in visit (Week -2). The single-blind placebo run-in period should be 2 weeks in length, with a recommended visit window of ±4 days.

During the post-randomization period, subsequent scheduled study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization) and Weeks 3, 13, 26, and 52. A telephone contact will be conducted at Week 39 to collect information related to subjects' concomitant medications, adverse events and events in the primary and secondary composite endpoints. After the first year, scheduled in-clinic study visits should occur at 26-week intervals with telephone contacts approximately midway between in-clinic visits.

For the visits at Weeks 3, 13 and 26, the recommended visit window is ±7 days. After Week 26, the recommended visit window is ±14 days.

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 means.

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

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

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

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

Pregnancy Testing

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

Subject Diary: Collection of Self-Monitoring of Blood Glucose and Possible Hypoglycemic Event Information

A standard, protocol-specified study diary will be provided to each subject. Routine self-monitored blood glucose (SMBG) measurements may be recorded in the diary, and all episodes of possible hypoglycemia should be documented as well as associated fingerstick glucose measurements, if available.

The study diary may also be used to keep track of medications and/or medication changes at the investigator's discretion. In addition, the study diary should be used for the subject to record health-care provider visits (other than protocol-specified study visits), emergency care, and hospital visits.

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

Collection of 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 diabetic nephropathy (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 Biomarker 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. 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 9.6, Pharmacogenomic Evaluations, for further details. Refer to Attachment 5, Pharmacogenomic Sample Collection and Shipment Procedures, for details on collecting and handling blood samples for pharmacogenomic research.

Blood Collection

The estimated total blood volume that will be collected for a subject who completes the study (including all procedures outlined in the pretreatment and double-blind treatment phases over approximately 5 to 5.5 years) will be approximately 340 mL with the maximum amount collected in a single visit being approximately 40 mL. For details please see Attachment 3.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Pretreatment Phase

Prescreening Assessment

Potential subjects will sign an informed consent form before any study-related procedures are performed.

Subjects will be prescreened on the basis of eGFR and UACR. Only subjects with an eGFR ≥30 to <90 mL/min/1.73m^2 and a UACR >300 mg/g (>33.9 mg/mmol), as confirmed by a local laboratory within 6 months prior to screening, will be eligible to proceed to a full screening visit including central laboratory assessments. For the prescreening assessment where UACR is not routinely measured as per standard of care, it may be substituted by one of the following measures: albumin excretion rate >300 mg/24 hours, urine protein-to-creatinine ratio (PCR) >500 mg/g (>56.5 mg/mmol), or protein excretion rate >500 mg/24 hours. Subjects who fail local laboratory pre-screening assessments are allowed to repeat those laboratory tests.

Note: While positive reagent strip analysis (eg, dipstick ≥2+) may be suggestive of albuminuria/proteinuria that meet the prescreening criteria, any positive reagent strip findings must be accompanied by one of the specified albuminuria/proteinuria prescreening measures listed above prior to screening with central laboratory evaluations.

In addition, when available, the latest 3 pre-study serum creatinine values collected within a year prior to screening in an outpatient setting, and at least 1 month apart, will be recorded in the eCRF.

For subjects who require additional local laboratory assessment solely for the purpose of prescreening, either the optional prescreening-specific or full informed consent must be obtained. For detailed description of the informed consent forms see Section 16.2.3. Informed Consent.

During the prescreening assessment, a focused review and initial assessment of subjects' use of an ACEi or ARB will be performed to ensure that all subjects assessed for enrollment have been (or will be) on a stable, maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization.

Screening Visit (Week -10 to Week -3)

If an optional prescreening-specific informed consent is obtained, and the subject is eligible to enter the screening period, the full informed consent must be obtained before screening is initiated.

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

During the screening period, the investigator should adjust/optimize the subject's medications as necessary according to local standard guidelines, including antihyperglycemic, lipid-lowering, and anti-hypertensive therapy (with exception of ACEi or ARB which should remain stable after the maximum tolerated dose is achieved). Investigators are encouraged to keep these medications dose stable for approximately 4 weeks prior to randomization. In addition, investigators are encouraged to keep medications that are known to impact serum creatinine levels (eg, NSAIDs, trimethoprim, cimetidine, probenecid, aminoglycosides, amphotericin, ketoconazole, and clofibrate) stable during the screening period.

Subjects must be on a stable maximum tolerated labeled daily dose of an ACEi or ARB for a period of at least 4 weeks prior to randomization. To reach this requirement, the screening period may be extended, up to a total of 8 weeks (inclusive of the 2-week single-blind placebo run-in period); however, an additional 2 weeks of screening time may be allowed, if considered medically appropriate. Extension beyond this period of time would require concurrence of the sponsor's medical monitor. Subjects who have an extended screening period (ie, >2 weeks between the screening visit and the run-in Week -2 visit) for any reason (eg, undergoing ACEi or ARB therapy adjustments during the pre-randomization period) must undergo an additional serum chemistry test at the run-in visit (Week -2) to facilitate the calculation of a baseline average serum creatinine value, using the values from the Week -2 and randomization visits (see Time and Events Schedule, footnote "v"). The baseline average serum creatinine value for subjects who do not have an extended screening period will be calculated using the serum creatinine values from the screening and randomization visits.

At the Week -2 visit, potential eligible subjects will be counseled to take one capsule of single-blind placebo once daily, before the first meal of the day, for a duration of 2 weeks. Subjects should be instructed to take their last dose of single-blind placebo study drug on the day prior to the Baseline (Day 1) visit. The study site staff should not disclose to the subject that during the single-blind placebo run-in period subjects will receive placebo capsules. An assessment of the subjects' adherence to protocol procedures during this period will be made at the end of the period, before randomization, and will provide investigators with an opportunity to assess subjects' compliance with taking the single-blind placebo (by counting capsules).

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

The screening visit and the 2-week single-blind placebo run-in period provide investigators with the opportunity to evaluate and optimize the subject's glycemic, lipid and blood pressure controls, as well as the management of renal or CV risk factors prior to randomization as required (refer to Section 6.2.1, Management of Glycemic Control and Section 6.2.2, Management of Renal or CV Risk Factors), and provide subjects with counseling regarding diet and exercise consistent with applicable local guidelines.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Eligible subjects (ie, those who have taken ≥80% of the scheduled single-blind placebo capsules during the single-blind placebo run-in period) will return for the Day 1 (baseline) visit, at which time they will be stratified according to their pretreatment eGFR value most proximate to the baseline visit (eg, screening, unscheduled, or Week -2) and will be randomized within the following 3 strata: 1) ≥30 to <45 mL/min/1.73m^2, 2) ≥45 to <60 mL/min/1.73m^2, 3) ≥60 to <90 mL/min/1.73m^2. They will be randomly assigned in a 1:1 ratio to once daily treatment with canagliflozin 100 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, Subject Completion, Premature Discontinuation of Treatment, or Withdrawal From the Study).

At the randomization visit, in some countries or regions (at the option of local sponsor representatives), subjects will be given information for glucose, lipid and BP management. A glucose meter and materials for SMBG measurements and instructions on the performance of SMBG measurement will also be provided to all subjects.

Visits Following Randomization

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

Subjects who experience doubling of serum creatinine from their baseline average values or nonfatal CV events (ie, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, or hospitalized unstable angina) during the double-blind treatment phase will remain in the study and should continue to receive double-blind study drug and complete all assessments at all scheduled visits, as appropriate.

Note: Throughout the double-blind treatment phase, ACEi or ARB therapy should remain stable, unless changes are medically indicated.

Note: Subjects who are undergoing chronic dialysis or have had renal transplant will discontinue the study drug treatment.

9.1.4. Post-Treatment Follow-up

All subjects should have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) approximately 30 days after the last dose of study drug and prior to the GTED.

All subjects who discontinue study medication prematurely should continue to attend all subsequent study visits in the same way as the subjects who are still on the study drug treatment, and be followed to the GTED, unless the subject has elected to withdraw his/her consent from the study and is not agreeable to follow-up.

Subjects withdrawn early from the study for any reason (except for "withdrawal of consent, not agreeable to follow-up") will be contacted by telephone with the goal of collecting any events that are considered as renal or CV endpoint events (ie, ESKD, doubling of serum creatinine, renal or CV death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, or hospitalized unstable angina), and all-cause death (refer to footnote "h" in the Time and Events Schedule for details).

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

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

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

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

If all means of follow-up fail, at a minimum, the study site must attempt to collect vital status data, as noted in Section 10.4, Circumstances for Reduced Follow-up, by consulting family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law.

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

9.2. Reporting/Adjudication of Events in the Primary and Secondary Composite Endpoints and Other Events for Adjudication

Investigators will be counseled to report any event that they assess as potentially being a component in the primary and secondary composite endpoints (ESKD, doubling of serum creatinine, renal death, CV death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, hospitalized unstable angina and all-cause death). All components in the primary and secondary composite endpoints will be submitted for adjudication. Medical monitors will also have study-wide responsibility to assess adverse events for potential adjudication. For all endpoints, investigators will be alerted if the sponsor identifies a potential event based on eCRF

entries that had not been specifically identified by the investigator as a potential event on the eCRF.

For serum creatinine values indicative of a sustained ≥100% increase (ie, doubling) from baseline average that are identified by the study site or the sponsor, the result should be confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days after the index event. The investigator should make every effort to collect local laboratory data that may facilitate identification of events of sustained doubling of serum creatinine. Such situations would include recording/reporting in the eCRF the local laboratory values as part of routine patient care. Additionally, central or local laboratory values on serum creatinine should be collected following a hospitalization in which an acute renal event emerges and is unresolved prior to discharge, or when a suspected decline in renal function is anticipated (eg, symptomatic uremia). Telephone contacts scheduled between 26-week in-clinic visits will help in determining if additional testing has been conducted outside of the study site, or may trigger a serum creatinine laboratory measurement if clinically warranted.

The sponsor will review the clinical database, the central laboratory database, and the Global Medical Safety (GMS) database (which contains hospitalization data) on an ongoing basis to identify potential endpoint events.

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

More detailed information related to study endpoint events reporting and adverse events reporting can be found in Section 12, Adverse Event Reporting.

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 overseeing the CREDENCE trial is the George Institute for Global Health.

9.3.2. Steering Committee

The Steering Committee is made up of external scientific experts who 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, reviewing study results and for their publication. Details of the composition, roles, and responsibilities of the committee are documented in the Steering Committee 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 1 statistician. The MSRC will include members from the sponsor and may also involve

ARO representatives. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to an 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 have responsibility for safety review during the study, including serious adverse events, events resulting in study drug discontinuation, as well as renal and CV adverse events.

An interim analysis will be conducted when the primary efficacy events have been observed in approximately 405 subjects. If the conditional power (based on the assumption that the hazard ratio in the remaining study is 0.80) is 10% or lower, the study may be stopped for futility. The alpha spending function will be used and the alpha spent in the interim analysis is 0.01 (see Section 11.3.5, Interim Analysis). Detailed stopping guidelines will be specified in the IDMC charter.

9.3.5. Independent Endpoint Adjudication Committee

The IEAC will be responsible for adjudicating all renal and CV events that are components in the primary and secondary composite endpoints in this study. The IEAC is composed of external specialists, blinded to treatment assignment. The operations, processes, and endpoint definitions to be employed by the committee are defined in its charter.

9.4. Efficacy Evaluations and Outcomes

9.4.1. Measures of Efficacy

The key measure of the efficacy is the reduction in the primary composite endpoint of ESKD, doubling of serum creatinine, renal or CV death. The secondary measures of efficacy are the reduction in the composite endpoint of CV death and hospitalized congestive heart failure; the composite endpoint of CV death, non-fatal MI, and non-fatal stroke (ie, 3-point MACE); hospitalized congestive heart failure; the renal composite endpoint of ESKD, doubling of serum creatinine, and renal death; CV death; all-cause death; and the CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina.

Additional exploratory measures of efficacy include reduction in a composite endpoint of ESKD and renal or CV death and reductions in each individual component of the composite endpoints including ESKD, doubling of serum creatinine, renal death, CV death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, hospitalized unstable angina, as well as the changes in eGFR and albuminuria over time.

9.4.2. Efficacy Outcomes

Primary Efficacy Outcome

The primary efficacy outcome is a composite endpoint of the first occurrence of ESKD, doubling of serum creatinine, renal or CV death.

The definitions for each individual component in the primary composite endpoint are:

- ESKD: Initiation of maintenance dialysis for at least 1 month, or renal transplantation, or a sustained eGFR of <15 mL/min/1.73m^2 (by CKD-EPI formula and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days).
- Doubling of serum creatinine: from the baseline average determination (sustained and confirmed by repeat central laboratory measure ≥30 days and preferably within 60 days).
- Renal death: death in subjects who have reached ESKD, die without initiating renal replacement therapy, and no other cause of death is determined via adjudication.
- CV death: death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed above (eg, aneurysm, peripheral vascular disease [PVD]). Detailed information can be found in the IEAC charter.

Confirmatory data for all potential study endpoints will be collected from study investigators and will be adjudicated in a blinded fashion by the IEAC.

Secondary Efficacy Outcomes

The secondary efficacy outcomes are reduction in the composite endpoint of CV death and hospitalized congestive heart failure, the composite endpoint of CV death, non-fatal MI, and non-fatal stroke (ie, 3-point MACE); hospitalized congestive heart failure; the renal composite endpoint of ESKD, doubling of serum creatinine, and renal death; CV death; all-cause death; and the CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina.

The definitions for each component of the secondary outcomes where not listed above are defined in the IEAC charter.

Confirmatory data for the CV composite endpoint will be collected from study investigators and will be adjudicated in a blinded fashion by the IEAC.

Exploratory Efficacy Outcomes

The exploratory efficacy outcomes are reduction in the composite endpoint of ESKD and renal or CV death, and reductions in the individual components of the renal and cardiovascular composite endpoints (ie, ESKD, doubling of serum creatinine, renal death, CV death, fatal or non-fatal MI, fatal or non-fatal stroke, hospitalized congestive heart failure, hospitalized unstable angina), as well as changes in eGFR and albuminuria over time.

9.5. Safety Evaluations and Outcomes

9.5.1. Safety Evaluation

Safety and tolerability evaluations, according to the time points provided in the Time and Events Schedule, will include the collection of adverse events, safety laboratory tests (including chemistry, hematology, and urinalysis), vital signs (pulse, blood pressure), physical examination, and body weight.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study, beginning from when informed consent is provided. Information about all adverse events (serious or not) should be recorded in source documents (eg, progress notes) according to Good Clinical Practice (GCP), and retained at the study sites. All adverse events will be recorded on an eCRF.

Note: For purposes of reporting serious adverse events in this study, non-fatal endpoint events that are adjudicated to be components of the primary or secondary endpoint will not be a subject to immediate or expedited serious adverse experience reporting requirements (refer to Section 12, Adverse Event Reporting).

Adverse Events of Interest and Collection of Additional Information for Adverse Events of Interest

For adverse events of interest (see Section 12, Adverse Event Reporting), investigators will be asked to provide additional information and documentation to support a detailed assessment. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Section 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee).

Information pertaining to adverse events of interest will be recorded on supplemental case report forms.

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time treatment is discontinued (either prematurely or at completion of the study) will be followed by the investigator until resolution or until a clinically stable endpoint is reached, or until further follow up is no longer considered by the investigator to provide clinically meaningful information. (See Section 9.1.4, Post-Treatment Follow-up, for details of follow-up required).

Clinical Safety Laboratory Tests

Subjects will be monitored with safety laboratory measurements as described in Attachment 1.

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

General standards for management of hyperkalemia should be applied in case of an elevation in serum potassium.

Vital Signs (pulse, blood pressure)

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

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

Guidance for the management of subjects who experience a volume depletion adverse event (eg, hypotension, hypovolemia) or a meaningful change in eGFR will be provided in a separate document (see Section 15, Study Specific Materials).

Body Weight

Body weight will be measured using a consistent scale at each visit. Scale calibration is not required for this trial, but if the institution has a scale calibration policy, compliance with this policy is expected. As far as possible, subjects should be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes.

Note: If disrobing for weighing is logistically impossible, the subject should be dressed as lightly as possible, with consistency from visit to visit; subjects will be asked to urinate before being weighed.

Physical Examination

Full physical examination will be performed at the run-in Week -2 visit, and 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, rectal and prostate or gynecologic examinations) should be performed if considered clinically appropriate by the investigator.

Focused physical examination will be performed at the follow-up visits occurring at Week 52, and every 52-weeks thereafter, and will include targeted examinations based on the subject's specific complaints, signs or symptoms of a disease.

Urine Pregnancy Testing

Urine pregnancy testing will be performed on all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. A urine pregnancy test will be performed at the baseline visit unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations (if a serum pregnancy test is required, it will be performed at the screening visit). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to Section 12.3.3, Pregnancy, for instructions in cases of a positive pregnancy test).

9.5.2. Safety Outcomes

The safety outcomes include the overall safety and tolerability of canagliflozin.

Modified Rankin Scale

For subjects who experience a stroke, the modified Rankin Scale assessment will be conducted through a structured interview during an in-clinic visit approximately 3 months after the event. For events occurring at the end of the study (GTED) this evaluation should occur at least 1 month after the onset of the stroke. In a situation when a subject with a recent stroke would not be able to attend an in-clinic visit, the structured interview may be conducted over the phone with either the subject or a caregiver. A pre-stroke modified Rankin Score will be retrospectively assessed and captured in the eCRF to assist with determining a pre-existing degree of impairment associated with a prior stroke or other disability. The modified Rankin Scale assessment form is provided in Attachment 6.

9.6. Pharmacogenomic Evaluations

DNA samples will be analyzed if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to diabetes or diabetic nephropathy. They may also be used to develop tests/assays related to canagliflozin and diabetic nephropathy. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to canagliflozin or diabetic nephropathy clinical endpoints.

This pharmacogenomic evaluation is optional and will only be performed in subjects who give informed consent for this specific component of the study and where local regulations permit.

9.7. Exploratory Biomarker 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, diabetic nephropathy, 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.

10. SUBJECT COMPLETION, PREMATURE DISCONTINUATION OF TREATMENTINTERVENTION, OR WITHDRAWAL FROM THE STUDY

10.1. Subject Completion

A subject will be considered as having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until after the sponsor announces the projected GTED and when the GTED actually occurs. Subjects who continue on the study treatment up to the projected GTED notification date will continue administering the study drug until the final on-site visit (ie, the end of treatment visit/end of study visit). It will be important for sites to schedule the last on-treatment visit as soon as possible after being notified of the projected GTED. The post-treatment follow up telephone contact should occur approximately 30 days after the final on-site visit and must occur prior to the GTED. Subjects who discontinue study drug treatment early will also have a final on-site visit as soon as possible after announcement of the projected GTED and preferable 30 days before the GTED. Subjects who die prior to the GTED are followed until the time of death. The occurrence of a non-fatal renal or CV endpoint, or any other safety or efficacy outcome does not comprise study completion and is not a criterion for subject withdrawal from the study.

10.2. Study Drug Treatment Premature Discontinuation and Reinstitution

10.2.1. Study Drug Treatment Premature Discontinuation

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

- The investigator believes that for safety or tolerability reasons it is essential for the subject to stop treatment
- The investigator formally unblinds the subject's treatment allocation
- The subject becomes pregnant (study therapy should be immediately interrupted based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β-hCG test)
- The subject initiates chronic dialysis or renal transplantation

Note: The requirement for chronic dialysis or renal transplantation are the only endpoints for which treatment with double-blind study drug should be discontinued.

- The subject is currently using disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)
- The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA.

Premature discontinuation of study treatment does not comprise study completion and is not a criterion for withdrawal from the study.

All subjects who prematurely discontinue study treatment should continue subsequent study visits and post treatment follow-up evaluations (see Section 9.1.4, Post-Treatment Follow-up, and the Time and Events Schedule). Treatment should be recommenced wherever possible and routinely considered at every visit following discontinuation (see Section 10.2.2, Reinstitution of Treatment With Study Drug That Has Been Interrupted).

Note: Double-blind study drug should be permanently discontinued for any subject who experiences a serious adverse event of biochemically-confirmed DKA, has his/her treatment allocation formally unblinded by the investigator, or undergoes a renal transplant or initiates maintenance dialysis.

Subjects who decide to discontinue double-blind study drug must be interviewed by the investigator so as to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the contribution of possible adverse events to their decision to discontinue study drug, and investigators should confirm that any adverse event information elicited has been documented. If a subject elects to discontinue study drug due to an adverse event, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the adverse event would not require study drug discontinuation. The reason for study drug discontinuation is to be documented in the eCRF and in the source documentation. Study drug assigned to the discontinued subject may not be assigned to another subject. Subjects who discontinue study drug treatment will not be replaced.

10.2.2. Reinstitution of Treatment With Study Drug That Has Been Interrupted

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

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

10.3. Withdrawal From the Study

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

- Death
- Lost to follow-up
- Withdrawal of consent

For subjects withdrawing from the study before study completion, an early withdrawal evaluation should be performed as soon as possible after stopping the study drug. Refer to the Time and Events Schedule for procedures to be conducted at the end-of-treatment/early withdrawal evaluation.

10.3.1. Lost to Follow-up

If a subject is lost to follow-up, **all reasonable efforts must be made by the study site personnel to contact the subject and to determine endpoint status and the reason for discontinuation/withdrawal.** This should include repeated telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers), as well as other contact information (eg, email addresses) from subjects before randomization. In addition, the study site should emphasize the importance of follow-up information to the subject before randomization. The measures taken to obtain follow-up information must be documented.

10.3.2. Withdrawal of Consent

Withdrawal of consent should be a very unusual occurrence in a clinical trial. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence. Unless consent is specifically withdrawn, subjects are expected to be followed up through one of the alternative follow-up mechanisms discussed in Section 10.4, Circumstances for Reduced Follow-up.

Subjects who wish to withdraw from the study should be asked if they are agreeable to be contacted to obtain post-study drug follow-up information. Subjects who are not agreeable to follow-up contact will be withdrawn from the study as “withdrawal of consent, not agreeable to follow-up” on the End of Study eCRF. Subjects who no longer wish to take study drug but agree to provide follow-up information will be noted as “Subject discontinued for personal reasons” on the End of Treatment eCRF (refer to Section 10.2.1, Study Drug Treatment Premature Discontinuation for details). The recording of withdrawal of consent in the eCRF for this trial should only occur after a discussion between the investigator and the appropriate sponsor representative has taken place.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

If a subject had previously withdrawn consent but decides to retract that withdrawal, the subject will be reconsented. The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

A subject who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed and no further testing will take place. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study; no further testing will take place. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

10.4. Circumstances for Reduced Follow-up

There may be circumstances in which a reduced follow-up schedule is required and the options for this are described in Section 9.1.5, Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits. If one of these regimens is not possible it will be necessary for the study site investigator to contact the sponsor representative to indicate the reasons why no further follow-up is necessary. It is important to note that a subject declining further follow-up does not constitute withdrawal of consent and the alternate follow-up mechanisms that the participant agreed to when signing the consent form will still apply (eg, searches of databases, use of locator agencies at study completion) as permitted by local regulations.

In this regard, the subject will be asked as a condition of entry into the study to agree to grant permission for the investigator to consult family members, the subject’s physicians and medical

records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's status with respect to the renal and CV safety composite endpoint, in the event the subject is not reachable by conventional means (eg, office visit, telephone, e-mail, or certified mail). The subject is also to be advised that if the study 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 study 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, and also by the ARO. 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 Statistical Analysis Plan (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 and secondary objectives will be based upon this analysis set.

The safety analysis set includes all randomized subjects who receive at least one dose of double-blind study medication. The safety analysis will be based on this analysis set.

11.2. Sample Size Determination

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

The above sample size calculation is estimated based on the following additional assumptions (ADVANCE 2008; Class 2011; Packham 2012; Amin 2013):

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

11.3. Efficacy Analyses

11.3.1. Primary Efficacy Analysis

The primary efficacy measure will be the time from randomization to the first occurrence of composite endpoint events of ESKD, doubling of serum creatinine, and renal or CV death. The date of onset for events of doubling of serum creatinine that are confirmed by the central laboratory ≥30 days (and preferably within 60 days) will be the date that the first doubling from baseline average determination is detected from local or central laboratory determinations. The baseline value will be determined using the average of 2 pretreatment measures preferably no more than 4 weeks apart.

The comparison of the treatment groups will be assessed by means of a stratified Cox proportional hazard model with terms of treatment and strata defined by pretreatment eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73m^2). The primary analysis will be based on the ITT analysis set up to the GTED. Subjects will be analyzed according to the treatment group that they are randomized, regardless of actual treatment received.

Estimates of RRR, hazard ratio and the corresponding 95% CI will be derived from the model. Kaplan-Meier estimates for the event curve will be provided for the 2 treatment groups.

In addition, ratios of cause-specific hazards between the treatment groups will be obtained for each component of the primary efficacy composite endpoint (ESKD, doubling of serum creatinine, renal death, or CV death), with stratification of the baseline hazard by pretreatment eGFR group as in the analysis of the primary efficacy composite endpoint. Sensitivity analysis using a stratified log-rank test will be conducted to assess the robustness of the primary efficacy analysis.

Extensive efforts will be made to collect complete data for all subjects randomized in this study. Subjects will be followed up to the end of the study and will complete all required data collection, regardless of their compliance with study drug or visits. For subjects who are lost to follow up or withdraw consent, efforts will be made to obtain their vital status at the end of study from permitted sources.

Efforts will be made to clean up the missing or partially missing event date for primary and secondary efficacy endpoints, as well as key safety endpoints, before database lock. Imputation rules for the missing or partially missing date will be specified in the SAP.

11.3.2. Secondary Efficacy Analyses

The time from randomization to the first occurrence of the secondary endpoint events will be analyzed separately in a similar fashion as the primary analysis. If superiority of canagliflozin 100 mg over placebo in reducing the risk of the primary efficacy endpoint is established, the treatment effects in secondary endpoints will be tested subsequently in the following hierarchical order:

- The composite endpoint of CV death and hospitalized congestive heart failure

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

Statistical significance is required before testing the next hypothesis in the hierarchical test procedure.

11.3.3. Exploratory Efficacy Analyses

The time from randomization to the first occurrence of composite endpoint events of ESKD and CV death or renal death will be analyzed by a method similar to that used for the primary efficacy analysis.

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

Similar modeling analysis will be performed for UACR. Since the distribution of UACR value is highly skewed, log transformation of UACR values will be made prior to the modeling.

When the trial is fully recruited, the baseline characteristics of the subjects will be examined. Additional covariates can be considered in exploratory analyses. A more detailed description of the analyses for all outcomes will be pre-specified in the SAP for this study.

11.3.4. Multiplicity Adjustment

A closed testing procedure will be implemented to control the overall type I error at 5% for primary and secondary endpoints as described in Section 11.3.2, Secondary Efficacy Analyses.

11.3.5. Interim Analysis

An interim analysis will be conducted when the primary efficacy (adjudicated) events have been observed in approximately 405 subjects. The analysis method for primary efficacy endpoint described in Section 11.3.1, Primary Efficacy Analysis, will be used for the interim analysis. In addition, if the conditional power (based on the assumption that the hazard ratio in the remaining study is 0.80) is 10% or lower, the study may be stopped for futility. The alpha spending function will be used and the alpha spent in the interim analysis is 0.01. Detailed stopping guideline will be specified in the Interim Analysis Plan.

11.4. Safety Analyses

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

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

Adverse Events of Interest

For adverse events of interest (see Section 9.5.1, Safety Evaluation), treatment differences in incidence rates and corresponding 95% CI will be provided, and the Kaplan-Meier plots for the event curve by treatment group will also be generated.

Adverse Events

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

Further analyses will be described in the SAP for this study, including analyses of prespecified adverse events for which additional information is collected from the investigators (see Section 9.5.1, Safety Evaluations).

Clinical Laboratory Tests

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

Vital Signs, Weight

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

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by

regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse Events of Interest

For adverse events of interest, investigators will be asked to provide additional information. Adverse events of interest include all malignancies, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, lower extremity events, and pregnancy.

Adverse Events and Procedures Requiring Reporting Within 24 Hours

Ketone-related events (eg, DKA, ketoacidosis, metabolic acidosis, or acidosis) and pancreatitis events have been designated an adverse event of special interest and need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. Events with characteristics suggestive of DKA or pancreatitis will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition within the adjudication committee charters. These adverse events must be recorded on the supplemental Diabetic Ketoacidosis and Ketone-related Events or Pancreatitis eCRF to complement standard information collected on the eCRF AE/SAE page.

In addition, all lower-extremity amputation procedures are considered adverse events of special interest and need to be reported to Janssen within 24 hours of becoming aware of the procedure. The underlying condition leading to the lower-extremity amputation must be recorded on the supplemental Lower-Extremity Event eCRF to complement standard information collected on the AE/SAE eCRF, and the details relating to the amputation procedure must be recorded on the Lower-Extremity Amputation eCRF.

Additional information and documentation will be requested from investigators to support a detailed assessment of all deaths. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC. 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. Some events will be subject to adjudication by an ad hoc adjudication committee to standardize the diagnosis.

12.1. Adverse Events as Study Efficacy Endpoints

All deaths and events that are assessed by the investigator as being one of the components of the primary or secondary composite endpoints (ie, ESKD, doubling of serum creatinine, renal death, or CV death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, hospitalized unstable angina, all-cause death) should be handled as follows:

Investigator Responsibilities:

All deaths, renal and CV endpoint events must be reported to the sponsor within 24 hours of knowledge of the event. Investigators are also required to submit a specific package of information on all such possible events for adjudication; details on assembly and submission of adjudication packages will be provided in an Adjudication Manual.

Sponsor Responsibilities:

All study endpoint events (ie, ESKD, doubling of serum creatinine, renal death, CV death, non-fatal stroke, non-fatal myocardial infarction, hospitalized unstable angina, hospitalized congestive heart failure, or all-cause death) will be submitted blinded to the IEAC for adjudication. To protect the integrity of the trial, these events that are adjudicated to be components of the primary or secondary endpoints will **not** be unblinded or reported to either Health Authorities (HAs) or investigators as safety reports unless otherwise requested by HAs or Ethics Committees. After study completion, these events will be included in the final analysis which will be unblinded and submitted to HAs with the study report.

Serious non-fatal events that are adjudicated as **not** being components of the primary or secondary endpoints and are considered possibly, probably, or definitely related to study drug by the investigator, will be subject to reporting requirements to HAs, and will be unblinded where required by local regulations. Such events will be reported blinded to the investigator when and where possible. The reporting timeline starts when the IEAC notifies the sponsor of the decision. Detailed information for standard reporting of serious adverse events can be found in Section 12.3.1, All Adverse Events, and Section 12.3.2, Serious Adverse Events.

Table 1 summarizes the reporting process for serious unexpected and related events.

Table 1: Reporting of Serious Unexpected and Related Events (Unless Otherwise Requested by Health Authorities or Ethics Committees)

Event Type	Expedited Report to Health Authorities and Investigators	Unblinding to Health Authorities	Unblinding to Investigators
Study endpoint event	N	N	N
Non-endpoint event	Y	Y	N

12.2. Definitions

12.2.1. Adverse Event Definitions and Classifications

Adverse Event

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

related to that medicinal (investigational or non-investigational) product (definition per International Conference on Harmonization [ICH]).

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

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use 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
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that 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. These should usually be considered serious.

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 canagliflozin, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event 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 12.2.2, Attribution Definitions.

12.2.2. 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).

12.2.3. 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).

12.3. Procedures

12.3.1. All Adverse Events

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the study, ie, GTED (including subjects who discontinue study drug treatment).

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

All deaths will also be recorded.

For adverse events of interest (see Section 9.5.1, Safety Evaluation), a supplemental reporting form will be used to collect additional information. Investigators may be asked to provide additional information on adverse events, based upon review by the MSRC or the IDMC.

Serious adverse events, including those spontaneously reported to the investigator within 30 days 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 study-site personnel, 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.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, 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 the sponsor's instructions.

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

Consistent with standard diabetes treatment guidelines, all study subjects 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 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 subjects, 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. However, consider withdrawal of other antihypertensive agents prior to adjusting dose of ACE inhibitors or ARBs.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The reporting process for adverse events as study efficacy endpoints is described in Section 12.1, Adverse Events as Study Efficacy Endpoints. The reporting process for other serious adverse events that are unlisted (unexpected) and associated with the use of the drug is described in Section 12.3.2, Serious Adverse Events. 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 IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

12.3.2. Serious Adverse Events

Reporting process for all deaths and serious adverse events that are assessed by the investigator as being one of the components of the primary or secondary composite endpoints can be found in Section 12.1, Adverse Events as Study Efficacy Endpoints.

Reporting process for serious adverse events occurring during the study that are assessed by investigator as **not** a primary or secondary efficacy endpoint, or serious adverse events that are adjudicated as **not** meeting charter-specified event definitions by the IEAC is outlined below.

These serious adverse events must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding these serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the study-site personnel, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

Events that are adjudicated as **not** meeting with charter-specified event definitions by the IEAC will be subject to standard reporting requirements, but the reporting time limit will start when the sponsor learns that the event is not a renal or CV component event for the composite efficacy outcomes as per the IEAC.

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available

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

Any event occurring during the study that is assessed by the investigator as **not** a primary or secondary efficacy endpoint, or that is adjudicated as **not** meeting charter-specified event definitions by the IEAC, requiring hospitalization (or prolongation of hospitalization) must be reported as a serious adverse event, except hospitalizations for the following:

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

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, and congenital anomalies, ectopic pregnancy) 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.

12.4. 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 study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, 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 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. A list of excipients can be found in the IB.

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

14.2. Packaging

The study drug will be packaged as individual bottles. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the study 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 Clinphone drug

accountability module in the IWRS system. Subjects, or their legally-acceptable representative where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel 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 study 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 study 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 study-site personnel, 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 study 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
- The IWRS manual and worksheets
- eCRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding renal or CV events, documentation required, and adjudication-related procedures
- Guidance for Management of Volume Depletion Adverse Events or eGFR Changes
- ADA Standards of Medical Care in Diabetes
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution (optional by country/region)
- Materials to promote healthy dietary and exercise habits
- Laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The goal of this study is to assess whether canagliflozin has a renal and vascular protective effect in reducing the progression of renal impairment in subjects with T2DM, Stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care for glycemic control as well as maximum tolerated labeled daily dose of ACEi or ARB.

This double-blind, placebo controlled study does not impose an increased risk of failing to achieve optimal glycemic control, as the study design allows adjustment of background AHA therapy to take place at any time during the course of the study. Before randomization and throughout the study, investigators will be expected to manage all subjects' diet/exercise and background medication regimens so as to achieve goals for controlling Stage 2 or 3 CKD and CV risk factors (eg, HbA_{1c}, lipid levels, blood pressure) based upon standard guidelines for the care of subjects with T2DM and Stage 2 or 3 CKD.

Diabetic kidney disease in all subjects enrolled in this study will be managed based on the standards of care, according to established local and regional guidelines: All subjects will be treated with either ACE inhibitors or ARBs and maintain stable blood pressure, unless there is a clinical indication for adjustment. An IDMC is commissioned for this study to review unblinded safety information on a periodic basis during the study and an interim analysis is planned when the primary efficacy events have been observed in approximately 405 subjects. Significant differences in renal protection effect between canagliflozin and placebo (eg, futility or overwhelming evidence of efficacy) will result in changes in the trial proceedings.

Potential subjects will sign an informed consent form before any study-related procedures are performed. These subjects will be informed of the risks and requirements of the study and, during the study, 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.

The potential risks in the present study include exposure to study drug, with the potential for side effects (Section 1.1.2.5, Safety) and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors. As per Section 9.3.4, Independent Data Monitoring Committee, an IDMC is commissioned for this study to review unblinded safety information on a periodic basis during the study.

Hypoglycemia is a common adverse event in patients with T2DM. Treatment with canagliflozin alone or in combination with other AHAs not associated with hypoglycemia in Phase 2 and Phase 3 studies lead to a low incidence of hypoglycemia with no increase in incidence of severe hypoglycemia. This is likely based upon the observation that the renal threshold for glucose (lowered to approximately 90-100 mg/dL [5.0-5.6 mmol/L] in subjects with T2DM) is not

lowered below the usual hypoglycemia threshold (considered as 70 mg/dL [3.9 mmol/L])—hence even if the steady-state glucose was to decrease to the level of the renal threshold, hypoglycemia would not be expected with canagliflozin alone or in combination with other AHAs not associated with hypoglycemia, such as metformin in this study. Nonetheless, subjects will be routinely monitored with fingerstick glucose levels, and reports of potential episodes of hypoglycemia will be carefully collected and evaluated.

Amputations have been designated as adverse events of special interest and will be managed based on standard diabetes treatment guidelines.

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. They will be measured more frequently at the beginning of the double blind treatment (ie, Day 1, Week 3, Week 13, Week 26) and then every 26 weeks thereafter until the end of the study.

For a subject who completes the study (including all procedures outlined in the pretreatment and double-blind treatment phases over approximately 5 to 5.5 years), the total blood volume to be collected will be approximately 340 mL, with the maximum amount collected in a single visit being approximately 40 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).

This study was designed based on the guidelines for the identification and management of kidney disease (NICE 2008; NKF 2012), in general accordance with the US FDA and EMA guidance on the development of medications and clinical investigations for the treatment and prevention of diabetes mellitus (FDA 2008; EMEA 2012) and in consultation with Health Authorities. This study will be conducted under U.S. FDA IND regulations intended for a new indication of "Treatment of renal disease in adult patients with type 2 diabetes mellitus, reduced eGFR, and albuminuria".

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), 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.

For participating centers, approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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 study site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. A consent form must be signed before performing any study-related activities. For subjects who require additional local laboratory assessment solely for the purpose of prescreening, either the optional prescreening-specific or full informed consent must be obtained. The prescreening-specific informed consent is an abbreviated form of the full document that focuses on the risks associated with the prescreening-specific laboratory assessments and provides general information about the study without detailing study procedures and the potential benefits/risks associated with participating in the study. If an optional prescreening-specific informed consent is obtained, and the subject is eligible to enter the screening period, the full informed consent must be obtained before screening is initiated. 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 study-site personnel 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–the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

After informed consent for the study is appropriately obtained, subjects will be asked to provide consent for optional samples (blood and urine) for research (where local regulations permit). Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

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

16.2.4. Privacy of Personal Data

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

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

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

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA or biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (according to local regulations) for additional research. Samples may be used to understand effect of canagliflozin on diabetic nephropathy, to understand differential drug responders, and/or to develop tests/assays related to canagliflozin in diabetic nephropathy. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3.2, Withdrawal of Consent).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations) 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 study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

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

In addition, the author of an entry in the source documents should 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 study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

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

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

Designated study-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.

The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the 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 or in the time frame specified in the clinical trial agreement.

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

- Study 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)
- Study site manager can generate a query for resolution by the study-site personnel
- Clinical data manager can generate a query for resolution by the study-site personnel

17.6. Data Quality Assurance/Quality Control

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

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

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy 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 CRO 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 study 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 study-site personnel and are accessible for verification by the sponsor site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

17.9. Study Completion/Termination

17.9.1. Study Completion

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

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-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 a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, 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 study 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 study-site personnel are responsible for being present and available for consultation during routinely scheduled study 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 or exploratory biomarker 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 complete 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 study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker 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 (ICMJE) guidelines, the Steering Committee shall have the right to publish such primary (multicenter) 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, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. 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.

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Attachment 1: Clinical Laboratory Tests

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

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein
  -magnesium

- Follicle-stimulating hormone only for women >45 years of age who have had amenorrhea for at least 6 months and less than 18 months before screening
- Fasting serum lipid profile (triglycerides, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol)*.
- HbA_{1c}
- Fasting plasma glucose*
- Urinalysis

  Dipstick done at central laboratory
  -specific gravity
  -pH
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase
  If dipstick result is abnormal, microscopic examination will be performed.

- Urine pregnancy testing, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations, for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status

*Subjects must be fasting for at least 8 hours before blood sample collections.

- **Estimated Glomerular Filtration Rate (eGFR)**
  - The estimated glomerular filtration rate (eGFR) will be reported according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation** at study visits when serum creatinine is measured. The CKD-EPI equation based on serum creatinine, age, sex, and race for adults age ≥18 years expressed as a single equation is:

    CKD-EPI Formula (for S_{cr} expressed in mg/dL)

    $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

    $\kappa = 0.7$ for females

    $\kappa = 0.9$ for males

    $\alpha = -0.329$ for females

    $\alpha = -0.411$ for males

    min = the minimum of S_{cr}/κ or 1

    max = the maximum of S_{cr}/κ or 1

    CKD-EPI Formula (for S_{cr} expressed in µmol/L)

    $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

    $\kappa = 61.9$ for females

    $\kappa = 79.6$ for males

    $\alpha = -0.329$ for females

    $\alpha = -0.411$ for males

    min = the minimum of S_{cr}/κ or 1

    max = the maximum of S_{cr}/κ or 1

**Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Attachment 2: New York Heart Association Classification of Cardiac Disease

The following table represents the New York Heart Association 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 3: Volume of Blood to be Collected From Each Subject During First Year

(including EOT/EW visit)

Volume of Blood to be Collected From Each Subject During First Year (includes EOT/EW visit)				Number of additional samples every year thereafter
Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]	
Hematology	2	3	6	1
Serum chemistry/(FSH x 1)	2.5	6	15	2
Lipid LDL/VLDL	5	3	15	1
HbA_{1c}	2	5	10	2
Biomarkers (serum archive collection)[b]	8.5	2	17	1
Biomarkers (plasma archive collection)	10	2	20	1
Pharmacogenomic collection[b]	10	1	10	0
Approximate Total[c]			93	

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] A blood sample will be collected only from subjects who have consented to provide an optional samples for DNA and biomarker research.
[c] Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

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 appropriate K_2EDTA-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 2 pre-labeled 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.

Preparation of Exploratory Serum Samples

- Collect one full blood sample into the appropriate plastic collection tube (Serum SST; SST with clot accelerator and gel barrier, also called Red & Black Tiger top) provided (8.5 mL or 5 mL) 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 2 pre-labelled 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: Modified Rankin Scale

MODIFIED RANKIN SCALE (MRS)

Subject ID: _____
Site ID: _____
Rater: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

SCORE (0–6): _____

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): Yshai Yavin, MD

Institution: Janssen Research & Development, LLC

Signature: [redacted] Date: 6 September 2017

(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.