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APPLICATION NUMBER:

204042Orig1s032

INTEGRATED REVIEW

Executive Summary
Interdisciplinary Assessment
Appendices

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number	NDA 204042 S.032 INVOKANA® (Canagliflozin)
Priority or standard	Priority
Submit date	3/27/2019
Received date	3/27/2019
PDUFA goal date	9/27/2019
Division/Office	Division of Cardiovascular and Renal Products (DCaRP)
Review completion date	See DARRTS electronic signature date
Established name	Canagliflozin (JNJ-28431754)
Trade name	INVOKANA
Pharmacologic class	SGLT2 inhibitor
Code name	JNJ-28431754
Applicant	Janssen Pharmaceuticals, Inc.
Dose form/formulation	100 mg and 300 mg oral tablet

Category	Application Information
Dosing regimen	(b) (4) [redacted]
Applicant proposed indication(s)/population(s)	(b) (4) [redacted]
Proposed SNOMED indication	Chronic kidney disease due to type 2 diabetes mellitus (disorder)
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	To reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day
Approved SNOMED indication	Chronic kidney disease due to type 2 diabetes mellitus (disorder)

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Glossary

AE	adverse event
ACEi	angiotensin-converting enzyme inhibitor
AKI	acute kidney injury
ARB	angiotensin receptor blocker
BNP	B-type natriuretic peptide
CANVAS	Canagliflozin Cardiovascular Assessment Study
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CSR	clinical study report
CV	cardiovascular
DKA	diabetic ketoacidosis
DMEP	Division of Metabolism and Endocrinology Products
EAC	Endpoint Adjudication Committee
ECG	electrocardiogram
EOT	end of treatment
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
eGFR	estimated glomerular filtration rate
FMQ	FDA MedDRA Query
GCP	good clinical practice
HbA_{1c}	hemoglobin A_{1c}
HF	heart failure
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
IND	investigational new drug
IRD	incidence rate difference
ITT	intent-to-treat
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NT-pro-BNP	N-terminal prohormone BNP
OSI	Office of Scientific Investigation
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplemental new drug application
SC	Steering Committee
SGLT2	sodium-glucose cotransporter 2
T2DM	type 2 diabetes mellitus
UACR	urine albumin-to-creatinine ratio

I. Executive Summary

1. Summary of Regulatory Action

The review team agrees that the application provides substantial evidence of canagliflozin's effectiveness in reducing the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day. The application will be approved for this new indication.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Diabetes affects an estimated 23 million adults in the United States with over 1.4 million new cases diagnosed annually. Approximately 95% of these individuals have type 2 diabetes mellitus (T2DM). • Approximately 30 to 40% of patients with diabetes will develop chronic kidney disease related to their diabetes, known as diabetic nephropathy. Approximately 20% of these patients will progress to end stage kidney disease (ESKD) over 20 years. T2DM is the most common cause of ESKD. • Patients with T2DM and diabetic nephropathy are at high risk for cardiovascular (CV) events, including myocardial infarction, stroke, and heart failure, and death.	Diabetic nephropathy is common in the United States and is a serious disease associated with significant morbidity and mortality.
Current treatment options	• The renin-angiotensin system inhibitors irbesartan and losartan are approved for the treatment of diabetic nephropathy in T2DM, whereas captopril is approved for the treatment of diabetic nephropathy in type 1 diabetes, though the beneficial effects are generally considered to be a class effect that applies to other angiotensin converting enzyme inhibitors and angiotensin receptor blockers. • Other interventions believed to delay the progression of diabetic nephropathy include blood pressure and glucose control.	There is unmet medical need for drugs to reduce morbidity and mortality in patients with T2DM and diabetic nephropathy.
Benefit	• Canagliflozin was effective in slowing the loss of kidney function and delaying progression to ESKD and in reducing the risk of cardiovascular death in patients with T2DM and diabetic nephropathy with reduced kidney function and albuminuria > 300 mg/day in the CREDENCE trial, a randomized, double-blind, parallel-group, event-driven trial comparing canagliflozin 100 mg once daily with placebo. – Although the findings in the U.S. population did not favor canagliflozin, analyses of pharmacodynamic data from CREDENCE and data on cardiovascular and renal events from the U.S. population enrolled in the Canagliflozin	The submitted data provide substantial evidence of canagliflozin's effectiveness in in reducing the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria > 300 mg/day.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Cardiovascular Assessment Study (CANVAS) program suggest this was most likely a chance finding. Other subgroup analyses based on age, race/ethnicity, past medical history, blood pressure or glycemic control, and baseline renal function did not suggest any obvious differences in efficacy among the subgroups. Only ~ 5% of the trial population was categorized as Black/African American, likely reflecting where the trial was conducted and the fact that only ~16% of the trial population was enrolled at sites in the US. • Canagliflozin also significantly reduced the risk of the following secondary endpoints: composite endpoint of CV death and hospitalization for heart failure [HR: 0.69; 95% CI: 0.57 to 0.83; p=0.0001], MACE (Major Adverse Cardiovascular Events comprised of non-fatal MI, non fatal stroke and CV death) [HR: 0.80; 95% CI: 0.67 to 0.95; p=0.012], hospitalization for heart failure [HR: 0.61; 95% CI: 0.47 to 0.80; p=0.0003], and a renal composite endpoint (comprised of ESKD, doubling of serum creatinine, and renal death) [HR: 0.66; 95% CI: 0.53 to 0.81; p<0.0001].	
Risk and risk management	• Canagliflozin is currently approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with T2DM and established cardiovascular disease. The approved canagliflozin label contains: – a Boxed Warning for lower limb amputation – Warnings and Precautions for hypotension, diabetic ketoacidosis (DKA), acute kidney injury, urosepsis and pyelonepritis, hyoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, bone fracture, and increased low-density lipoprotein (LDL) cholesterol.	Potential risks of canagliflozin as seen in the CREDENCE trial, were, for the most part, consistent with the findings in trials conducted to assess effects on glycemic control and effects on cardiovascular outcomes in patients at high cardiovascular risk. Labeling is considered sufficient to ensure that the benefits of canagliflozin in the target population outweigh the risks. The risk of acute kidney injury was not greater in the canagliflozin as compared to the placebo arm in CREDENCE; labeling should reflect this finding.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Female genital mycotic infection, urinary tract infection, and increased urination are also listed as common adverse events and the label describes increases in serum potassium, magnesium, phosphate, and hemoglobin and decreases in bone mineral density. • As relates to previously idenified risks, the rate of lower limb amputations in the canagliflozin and placebo arms of CREDENCE was 12.3 vs 11.2 events per 1000 patient years, respectively and rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 and 0.03 per 100 patient-years of follow-up, respectively. The incidence of hypotension was 2.8% and 1.5% on canagliflozin and placebo, respectively. • Although the label carries a Warning and Precaution for acute kidney injury, the incidence of acute kidney injury was not greater in the canagliflozin arm as compared to the placebo arm in CREDENCE (3.9% versus 4.5% of subjects or 17/1,000 patient-years versus 20/1,000 patient-years, canagliflozin versus placebo, respectively). There was also no difference between treatment arms in bone fractures (3.1% of patients in each arm). One renal cell carcinoma event (in the placebo arm) was reported in the trial. • Consistent with findings in other trials, a small mean increase in hemoglobin, magnesium, and phosphate was observed following initiation of canagliflozin therapy. The difference between arms persisted for the treatment duration for hemoglobin and magnesium but not for serum phosphate. There were no obvious differences between arms in changes in potassium or LDL over time. As seen in other trials, initiation of therapy was associated with a small mean increase in creatinine attributed to a hemodynamic effect on renal function.	

Conclusions Regarding Benefit-Risk

Canagliflozin is an oral inhibitor of sodium-glucose cotransporter 2 (SGLT2) that was approved on March 29, 2013 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) and on October 29, 2018 to reduce the

risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with T2DM and established cardiovascular disease. On March 27, 2019, Janssen Pharmaceuticals, Inc. submitted an efficacy supplement for canagliflozin for the following proposed indication: (b) (4)

In support of the proposed indication, the application conducted a randomized, double-blind, event-driven, international trial comparing canagliflozin 100 mg once daily with placebo in ~ 4,400 adults with T2DM, an eGFR $\geq$ 30 to < 90 mL/min/1.73 m^2 and albuminuria (urine albumin/creatinine > 300 to $\leq$ 5000 mg/g) who were receiving standard of care including a maximum-tolerated, labelled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

The trial demonstrated a statistically significant effect on its primary endpoint, the time to first occurrence of end stage kidney disease (ESKD, defined as an eGFR < 15 mL/min/1.73 m^2, initiation of chronic dialysis or renal transplant), doubling of serum creatinine, and renal or CV death [p<0.0001; HR: 0.70; 95% CI: 0.59, 0.82]. The treatment effect reflected a reduction in progression to ESKD, doubling of serum creatinine and cardiovascular death; there were few renal deaths during the trial. The trial also demonstrated a highly statistically persuasive treatment effect on the risk of hospitalization for heart failure [HR: 0.61; 95% CI: 0.47 to 0.80; p=0.0003], a prespecified secondary endpoint that was tested within a pre-specified plan to control the overall type 1 error rate.

Key Review Issue: Efficacy findings in the United States (U.S.)
In contrast to the findings in the overall trial, the point estimate for the HR for the primary composite endpoint did not favor canagliflozin in the U.S. subset (consisting of ~700 patients or ~16% of the trial population), although the confidence interval around the point estimate was wide (HR: 1.05; 95% CI: 0.71, 1.57). Additional analyses were conducted to explore this finding, including analyses to assess whether the expected pharmacodynamic effects of treatment were observed in the U.S. subset in CREDENCE, and analyses of cardiovascular and renal outcomes in the U.S. subset of the CANVAS trials. The CANVAS trials randomized over 10,000 patients with T2DM who were at high cardiovascular risk to canagliflozin or placebo and followed patients for CV outcomes for an average of ~188 weeks. As discussed in the body of this review, effects on albuminuria, eGFR, systolic blood pressure, and weight over time in the U.S. subgroup were largely consistent with effects seen in the overall trial population in CREDENCE. Post-hoc analyses also suggested favorable treatment effects on a renal composite, consisting of renal death/renal replacement therapy and a doubling of serum creatinine, and CV death in the U.S. subset of the CANVAS trials. These analyses, as well as analyses assessing for possible mediation, provided reassurance that the findings in the U.S. likely reflected a chance finding in a small, underpowered subgroup.

Key Safety Findings in the Target Population
Potential risks of canagliflozin as seen in the CREDENCE trial were largely consistent with those seen in trials conducted to assess the product's effect on glycemic control in patients with T2DM and cardiovascular outcomes in patients with T2DM at high cardiovascular

risk. As relates to previously identified risks, rates of genital mycotic infections, urinary tract infections, hypotension and lower limb amputations were greater in the canagliflozin as compared to the placebo arm. Incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were low in both arms, but higher in the canagliflozin as compared to the placebo arm (0.2 and 0.03 per 100 patient-years of follow-up with canagliflozin and placebo, respectively). Of note, the risk of acute kidney injury was not greater in the canagliflozin as compared to placebo arm- an important safety finding since patients with chronic kidney disease are at increased underlying risk of acute kidney injury relative to patients without chronic kidney disease. This information will be included in labeling.

Conclusions Regarding Risk-Benefit

The submitted data provide substantial evidence of canagliflozin's effectiveness in improving renal and cardiovascular outcomes in patients with T2DM and diabetic nephropathy, as well as compelling evidence of clinical benefits that outweigh the products risk. Hence, the review team and I recommend approval of the efficacy supplement.

II. Interdisciplinary Assessment

3. Introduction

The Applicant has submitted a supplemental new drug application (sNDA) for INVOKANA (canagliflozin) (b) (4)

Diabetes affects an estimated 23 million adults in the United States with over 1.4 million new cases diagnosed annually. Approximately 95% of these individuals have T2DM. Despite current therapies, the morbidity and mortality of diabetes remains high. Approximately 30 to 40% of patients with diabetes will develop chronic kidney disease (CKD) related to their diabetes, often referred to as diabetic nephropathy. These patients are also at high risk for cardiovascular events, including myocardial infarction, stroke, and heart failure.

The renin-angiotensin system inhibitors captopril, irbesartan, and losartan have been approved for the treatment of diabetic nephropathy in patients with either type 1 diabetes mellitus (T1DM) or T2DM (Table 3), although the beneficial effects are generally considered to be a class effect that applies to other angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Other interventions believed to delay the progression of diabetic nephropathy include blood pressure and glucose control. Despite these efforts, approximately 20% of patients with T2DM and diabetic nephropathy will progress to ESKD over 20 years. T2DM is the most common cause of ESKD in the United States and worldwide. There remains significant unmet medical need for better treatments.

Table 3. Drugs Approved for the Treatment of Diabetic Nephropathy

Drug	Indication
Angiotensin Converting Enzyme Inhibitors	
Captopril	For the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy. Captopril tablets decrease the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis).
Angiotensin Receptor Blockers	
Irbesartan	For the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension, an elevated serum creatinine, and proteinuria (>300 mg/day). In this population, irbesartan tablets reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).
Losartan	For the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, Losartan potassium tablet reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation).

Canagliflozin is an oral inhibitor of sodium-glucose cotransporter 2 (SGLT2). SGLT2 transporters in the proximal tubule of the kidney reabsorb most of the glucose filtered by the glomerulus. Inhibition of SGLT2 increases urinary glucose excretion and delivery of glucose and sodium to the distal tubules of the kidney. In addition to lowering serum glucose, these changes are believed to activate the macula densa and increase tubuloglomerular feedback, which leads to vasoconstriction of the afferent arteriole of the glomerulus, reduced intraglomerular pressure, and decreased hyperfiltration.

Canagliflozin was approved on March 29, 2013, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and on October 29, 2018 to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. A canagliflozin/metformin immediate release formulation was approved on August 8, 2014, and an extended-release formulation on September 20, 2016. The combination products are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.

The Applicant submitted an original investigational new drug (IND) application in 2013 to investigate canagliflozin for the treatment of renal disease in adult patients with type 2 diabetes mellitus, reduced eGFR, and albuminuria. In support of the proposed indication, the Applicant conducted a single phase 3 trial (28431754DNE3001) titled “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).”

3.1. Approach to the Review

This was a joint review. Kimberly Smith and Fanhui Kong focused on the data supporting efficacy, and Nhi Beasley focused on the data supporting safety. Lisa Yanoff, Patrick Archdeacon, and Michelle Carey with the Division of Metabolism and Endocrinology Products focused on safety-related revisions to labeling related to the broader safety experience with canagliflozin and participated in labeling discussions regarding the dosage regimen for canagliflozin by indication.

4. Patient Experience Data

No patient experience data were collected during the CREDENCE trial.

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The Applicant did not conduct additional clinical pharmacology studies to support the proposed indication.

5.1. Nonclinical Assessment of Potential Effectiveness

The Applicant did not conduct additional nonclinical studies to support the proposed indication.

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

The CREDENCE trial evaluated a dose of 100 mg daily based on preliminary efficacy and safety findings from patients with reduced kidney function enrolled in studies conducted to support the diabetes indication.

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Overview of Study

In support of the proposed indication, the Applicant conducted a single phase 3 trial (28431754DNE3001) titled "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)." The trial was conducted at 690 sites in 34 countries worldwide with 198 centers in North America, 113 centers in Central/South America, 187 centers in Europe, and 192 centers in other regions.

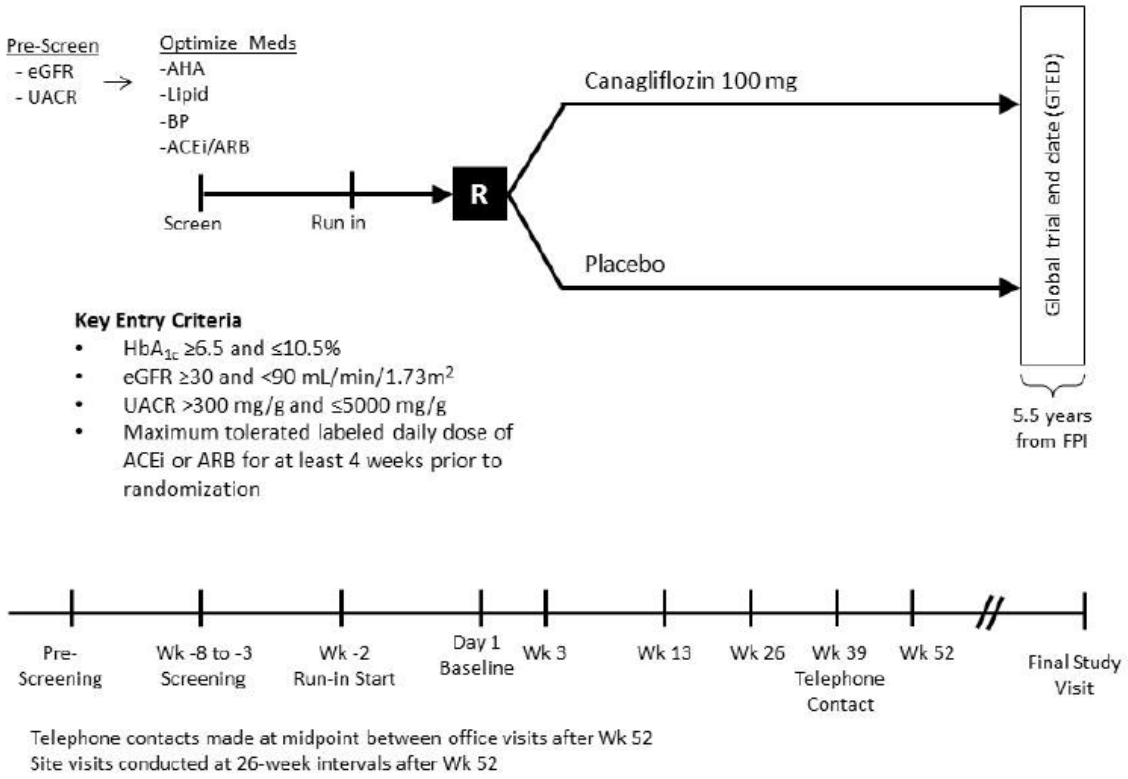
6.2.2. Initial Protocol and Amendments

The original protocol was issued on December 10, 2013, and was amended six times. The overview provided in this section is based on the original protocol with amendments noted.

6.2.3. Study Design

CREDENCE was a randomized, double-blind, parallel-group, event-driven trial comparing canagliflozin 100 mg once daily with placebo. The trial enrolled adults ≥30 years of age with type 2 diabetes mellitus, an eGFR ≥30 to <90 mL/min/1.73 m^2 and albuminuria > 300 to ≤5000 mg/day who were receiving a maximum-tolerated, labeled daily dose of an ACE inhibitor or ARB. Notable exclusions included patients with T1DM, a medical history or clinical evidence suggesting nondiabetic renal disease, renal disease that required treatment with immunosuppressive therapy, a history of chronic dialysis or renal transplant, and New York Heart Association Class IV heart failure. The initial target enrollment was 3700 patients, which was increased to 4200 with protocol amendment INT-4. An overview of the study design is shown in Figure 1.

Figure 1. CREDENCE Study Design



Source: Applicant, CREDENCE Protocol.
Abbreviations: ACEi, angiotensin -converting enzyme inh bitor; AHA, anti-hyperglycemic; ARB, angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; FPI, first ptient in; HBA1c, hemoglobin A1c; R, randomization; UACR, urine albumin-to-creatinine ratio; Wk, week

6.2.4. Study Objectives

The primary objective was 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 were to assess the efficacy of canagliflozin relative to placebo in reducing:

- CV death and hospitalized congestive heart failure (CHF)
- CV death, nonfatal myocardial infarction (MI), and nonfatal stroke
- Hospitalized CHF
- Renal composite of ESKD, doubling of serum creatinine, and renal death
- CV death
- All-cause death
- CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized CHF, and hospitalized unstable angina

Reviewer's comment: Above is the final list of secondary objectives. See the endpoints section below for a summary of changes that were made to the secondary objectives/endpoints during the trial.

6.2.5. Endpoints

Primary Endpoint

The primary endpoint was a composite of the first occurrence of ESKD, doubling of serum creatinine, and renal or CV death defined as follows:

- ESKD: Initiation of maintenance dialysis for at least 1 month, or renal transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2 (by Chronic Kidney Disease Epidemiology Collaboration formula and confirmed by repeat central laboratory measure).
- Doubling of serum creatinine: assessed compared with baseline and sustained and confirmed by a repeat central laboratory measure after ≥30 days and preferably within 60 days from the index measure. Protocol amendment INT-1 clarified that the date of the event was the date the event was first detected by local or central laboratory measurement and could be triggered by either source. The amendment also defined baseline as the average of two pretreatment measures up to 4 weeks apart.
- Renal death: death attributable to kidney failure where dialysis or transplantation might have been applied but was not chosen or not available (protocol amendment INT-1 clarified that this only included subjects who reached ESKD, died without initiating RRT, and had no other cause of death identified during adjudication).
- CV death: death due to myocardial infarction (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 (e.g., aneurysm, peripheral vascular disease, etc.).

Secondary Endpoints

The original protocol specified the following secondary endpoints to be tested in a hierarchical order:

- CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina
- Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- All-cause death

Protocol amendment INT-4 added two secondary endpoints and reordered them to the following:

- CV death and hospitalized CHF
- CV death
- All-cause death
- Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized CHF, and hospitalized unstable angina

Reviewer's comment: As shown in Table 4, amendment INT-4 followed discussion of the results of the EMPA-REG Outcome trial. At the time of the amendment, only 36 of 432 (8%) CV death and hospitalized CHF events and 15 of 250 (6%) of CV death events had accrued (based on the Response to the Food and Drug Administration's (FDA's) Clinical Request for Information #6 dated May 29, 2019).

Protocol amendment INT-6 again added two secondary endpoints and reordered them to the following:

- CV death and hospitalized CHF
- CV death, nonfatal myocardial infarction, and nonfatal stroke
- Hospitalized CHF
- Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- CV death
- All-cause death
- CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized CHF, and hospitalized unstable angina

Reviewer's comment: Amendment INT-6 was issued relatively late in the trial and, at the time, the Applicant asked whether the revised endpoints could be included in the label. As noted in Written Responses dated November 11, 2017, the Agency advised that "What the label says about the proposed secondary endpoints will depend on the results of the trial, including what components are driving the results of a composite endpoint. It will also depend on whether there is concern that knowledge of study findings led to changes in the analytic plan."

As shown in Table 4, in the time leading up to amendment INT-6, the CREDENCE Independent Data Monitoring Committee (IDMC) requested and reviewed analyses of efficacy data, including time to event analyses of primary and secondary composite endpoints and the individual components. The analyses appeared to extend beyond what might be considered necessary to monitor trial conduct and ensure subject safety and therefore raised concerns that knowledge of the trial's findings may have informed the late changes to the secondary endpoints. We raised this concern with the Applicant during a teleconference on July 2, 2019, and requested that they provide a timeline of events leading up to the amendment. In addition, the Applicant offered to have us speak with Dr. Darren McGuire, who initially was an IDMC member and later assumed the role of IDMC chair.

Based on our review of the timeline of events and discussion with Dr. McGuire, we concluded that it was unlikely that knowledge of the trial's findings informed changes to the secondary endpoints. Amendment INT-6 was issued between the closed IDMC sessions held on March 28, 2017, and October 3, 2017. Few events had accrued by March, and, although substantially more events had accrued by October (~40 to 65% depending on the endpoint), this is an overestimate of the data available to the IDMC at that time given delays in adjudication. In addition, the closed report for

the October meeting would not have been available until after amendment INT-6 was issued in early September.

When asked why the IDMC believed it was necessary to review such efficacy analyses, Dr. McGuire clarified that the committee was reviewing emerging data from trials of canagliflozin and other agents in the class, and they were anticipating that it would be necessary to stop the trial early. In that case, they wanted to understand whether efficacy was likely to be driven by more clinically meaningful events. Dr. McGuire confirmed that all changes to secondary endpoints were driven entirely by the Steering Committee (SC) and that the IDMC did not provide input.

Table 4. Summary of Steering Committee and Independent Data Monitoring Committee Discussions Relative to Changes to Study

Source	Date	Primary Events*	Issue/Discussion
IDMC	9/3/2015	1	Discussed results of EMPA-REG Outcome trial; interim Analysis SAP distributed to IDMC before meeting and IDMC approved of suggested stopping criteria; requested that future closed reports include Kaplan-Meier figures of primary composite endpoint as more efficacy data becomes available
SC	9/29/2015		Discussed results of EMPA-REG Outcome trial
SC	12/7/2015		Based on results of EMPA-REG Outcome trial, increased sample size to 4200 and removed cap on patients with an eGFR of 60 to 90 mL/min/1.73 m^2 to accelerate study completion because of concern for drop-in to active SGLT2 inhibitor treatment; agreed to add secondary endpoints 1) CV death or hospitalization for CHF and 2) CV death and to reorder secondary endpoints
SC	1/11/2016		Based on further discussion of EMPA-REG Outcome trial, delayed interim analysis to 540 primary events to ensure longer exposure (>2 years) and more time for renal endpoints to accrue
IND	1/20/2016		Protocol amendment INT-4 submitted to IND with changes to secondary endpoints and interim analysis plan noted above
IDMC	3/15/2016	5	Closed report first included number of EAC-confirmed primary and secondary composite endpoint events, components, and different permutations of components by treatment group with HR and 95% CI and Kaplan-Meier figures
IDMC	9/29/2016	21	Discussed HF hospitalization data and requested additional analyses with future reports
IDMC	3/28/2017	70	Requested additional analyses of HF hospitalization and HF hospitalization/CV death data including frequencies, HR, and Kaplan-Meier figures. No difference in number of MACE events (63 vs. 63), HHF numerically favored canagliflozin (36 vs. 15)
IDMC	5/31/2017		Ad hoc open session for the CANVAS[1] SC to share findings from the CANVAS program (no closed session)

[1] The CANVAS and CANVAS-R trials ("CANVAS program") were randomized, double-blind, placebo-controlled trials in adults with T2DM with inadequate glycemic control (HbA_{1c} 7-10.5%, inclusive) with either known CV disease or two or more CV risk factors and an eGFR ≥ 30 mL/min/1.73 m^2. In CANVAS, 4330 patients were randomized 1:1:1 to canagliflozin 100 mg daily, canagliflozin 300 mg daily, or placebo. In CANVAS-R, 5812 patients were randomized 1:1 to canagliflozin 100 mg daily or placebo. In the canagliflozin arm of CANVAS-R, the dose c ould be increased to 300 mg daily after Week 13 based on tolerability and glycemic needs.

Source	Date	Primary Events*	Issue/Discussion
SC	6/22/2017		Based on results of CANVAS program, discussed changing timing of interim analysis based on potential for greater magnitude of benefit than anticipated, risk of SGLT2 drop-ins or study drop-outs, and desire to characterize safety and efficacy in this population quickly; discussed adding two secondary endpoints high in testing hierarchy: MACE because could support MACE indication if not granted based on CANVAS data and HF hospitalization with goal of including in clinical trial section of label ("not indication seeking")
SC	7/20/2017		Ad hoc follow-up meeting to discuss resignation of IDMC chair because of conflict of interest and changes to interim analysis and secondary endpoints discussed at previous meeting
IDMC	7/24/2017		Ad hoc teleconference for CREDENCE SC and Janssen to discuss CREDENCE IDMC composition; announced resignation of IDMC chair and discussed updates to charter addressing conflicts of interest (e.g., leadership roles in another renal outcome trial for a competing SGLT2 inhibitor). After meeting, two additional IDMC members resigned because of conflicts of interest
IDMC	9/5/2017	170	Three new members of IDMC confirmed and provided introduction to CREDENCE; discussed changes to Interim Analysis Plan targeted for submission to FDA by September 8, 2017, specifically, conduct of analysis at 405 adjudicated events and mean exposure >2 years and addition of composite of CV death, renal death, and ESKD <0.025 to conditions for early termination for efficacy
IND	9/7/2017		Protocol amendment INT-6 submitted to IND with changes to secondary endpoints and interim analysis plan noted above
	9/13/2017		Original Interim Analysis SAP and SAP amendment 1 issued to align analytic plan with protocol amendment INT-6 (neither were submitted to IND)
IDMC	10/3/2017	177	Discussed differences between treatment groups for time to fatal and nonfatal CHF and CV death and requested additional efficacy analyses of CHF by eGFR stratum and of change in eGFR over time; MACE and HHF numerically favored canagliflozin (125 vs. 102 and 51 vs. 27, respectively)
IND	6/1/2018		SAP amendment 2 submitted to IND to change alpha for testing of secondary endpoints from 0.05 to 0.038 following discussions with Agency regarding inflation of type 1 error
IDMC	7/9/2018		Reviewed interim analysis based on data extract through June 9, 2018, with 413 confirmed primary composite endpoint events; IDMC recommended early termination of trial for efficacy

* Endpoint Adjudication Committee positively adjudicated events included in IDMC closed meeting materials.
Abbreviations: CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; EAC, Endpoint Adjudication Committee; IND, Investigational New Drug; MACE, major adverse cardiovascular event; SAP, statistical analysis plan; SGLT2, sodium-glucose cotransporter 2

6.2.6. Protocol Amendments

An overview of the six amendments to the protocol is shown in Table 5.

Table 5. Overview of Protocol Amendments

Amendment # and Date	Summary of Significant Changes
#INT-1 6/12/2014	In response to recommendations from the Agency, added text related to the management and monitoring of glycemic, blood pressure, and lipid control during the study and clarified endpoint definitions (see endpoint section)
#INT-2 2/3/2015	To address recruitment challenges, broadened eligibility criteria and revised prescreening assessment procedures (see study design and eligibility criteria sections)
#INT-3 9/29/2015	Added information and requirements related to diabetic ketoacidosis
#INT-4 1/19/2016	Expanded sample size to 4200 and removed cap on patients with higher eGFRs to maintain study timeline given slower than expected recruitment early in study and potential implications of reporting of EMPA-REG Outcome Trial results; increased the number of events required for the interim analysis from 420 to 540 to allow time for more renal endpoint events to accrue; added and reordered secondary endpoints (see endpoints section); allowed patients to start mineralocorticoid antagonists, if considered medically necessary, and continue study drug
#INT-5 5/5/2016	Added information and requirements related to lower extremity amputations
#INT-6 9/6/2017	Decreased the number of events required for the interim analysis from 540 to 405; added and reordered secondary endpoints (see endpoints section); added information and requirements related to pancreatitis

Abbreviations: eGFR, estimated glomerular filtration rate

Reviewer's comment:

(1) As previously noted, based on review of the SC minutes, amendment INT-4 was based on review of the EMPA-REG Outcome trial results. The increase in sample size and removal of the cap on patients with an eGFR of 60 to 90 mL/min/1.73 m^2 were intended to accelerate study completion because of concerns for drop-in to active SGLT2 inhibitor treatment. The increase in the number of events required for the interim analysis was intended to ensure longer exposure and more time for renal events to accrue.

Similarly, amendment INT-6 was based on review of the CANVAS program results. The decrease in the number of events required for the interim analysis was based on a greater than anticipated benefit observed in CANVAS raising concerns that conduct of the CREDENCE trial would be compromised by SGLT2 drop-ins or study drop-outs. Changes to the IDMC instructions regarding criteria for early termination of the trial was based on the SC's desire to more clearly communicate what findings they would find sufficiently compelling to warrant early termination of the trial.

(2) See the endpoints section above for a discussion of the basis for changes to the secondary endpoints.

6.2.7. Statistical Analysis Plan

The original statistical analysis plan (SAP) was issued on May 30, 2014 (16 patients randomized). SAP Amendment 1 and the original Interim Analysis SAP were issued on September 13, 2017, after the study was fully enrolled and 288 (49%) of total confirmed primary endpoint events had accrued (neither were submitted to the IND). SAP Amendment 2 was issued on June 1, 2018, after

496 (85%) of total confirmed primary endpoint events had accrued. A supplement to the SAP was issued on November 13, 2018. The overview provided in this section is based on the original SAP with amendments as noted.

Datasets

The SAP defined the following key datasets:

- *Intent-to-treat (ITT) analysis set:* all subjects randomly assigned to a treatment group according to randomized assignment regardless of actual treatment received.
- *Safety analysis set:* all randomized patients who received at least one dose of double-blind study medication according to the predominant treatment received (the treatment to which the subject was exposed for the greatest duration).

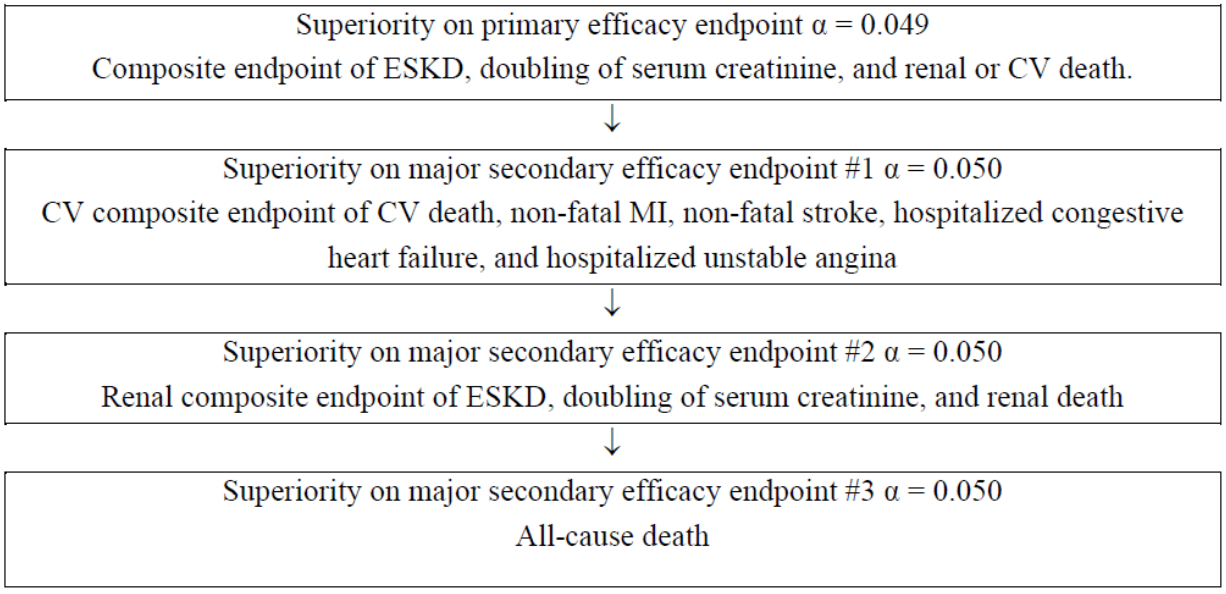
Efficacy Analyses

Primary and secondary efficacy analyses were based on the ITT dataset and included all positively adjudicated events occurring between randomization and the global trial end date. The data were analyzed using Cox proportional hazards models with terms for treatment and screening eGFR category (<45, ≥45 to <60, and ≥60 mL/min/1.73 m^2).

Adjustment for Multiplicity

A closed testing procedure was used to control the family-wise Type I error rate at an unadjusted two-sided alpha of 0.05. According to the original protocol, primary and secondary endpoints were to be tested hierarchically as shown in Figure 2. If an individual test during any step was not statistically significant, later tests would not be declared statistically significant.

Figure 2. Original Testing Hierarchy for Primary and Secondary Endpoints



Abbreviations: CV, cardiovascular; ESKD, end-stage kidney disease; MI, myocardial infarction

The number and ordering of secondary endpoints were modified with protocol amendments INT-4 and INT-6 (see Section 6.2.5).

In an Advice Letter issued March 14, 2016, the Agency advised the Applicant to prespecify "how the secondary endpoints will be tested if the primary endpoint is rejected at the interim analysis" to control the family-wise Type 1 error rate. The Applicant requested a Type C meeting to discuss this issue. In a Written Response dated November 20, 2017, the Agency clarified that the proposed analytic plan could cause inflation of the Type I error rate for testing the secondary endpoints and that the extent of inflation depends on the correlation between the decision-driven primary endpoint and the secondary endpoints and the effect sizes for endpoints preceding any tested endpoint (Hung et al. 2007). The Agency encouraged the Applicant to conduct simulations to assess the extent of inflation.

The Applicant provided the results of these simulations in a letter dated May 17, 2018, and subsequently revised the SAP on June 1, 2018. The results indicated that inflation of the Type I error rate was observed only when correlations between the primary and secondary endpoints were above 0.9 and when the true hazard ratio (HR) of the primary endpoint ranged from 0.87 to 0.93. As a result, the Applicant proposed to allocate a one-sided alpha of 0.019 to testing the secondary endpoints. If the assumptions of the simulations held, this approach was expected to control the overall Type I error rate at the 5% level across the primary and major secondary endpoints. Amendment 2 to the SAP stated that secondary endpoints would be tested using data accrued through the final clinic visit (regardless of whether the study stopped at the interim analysis or proceeded to planned completion) using a two-sided alpha of 0.038.

Reviewer's comment: The Applicant confirmed that the assumptions used for the simulations held (see Response to FDA's Statistical Request for Information #1 dated July 17, 2019). The observed correlations between the primary and the secondary endpoints were all below 0.90 except for the correlation between the primary endpoint and the renal composite, which was 0.92.

Subgroup Analyses

The prespecified efficacy subgroups were age (<65 and ≥65 years), gender, race (white, black, Asian, other), ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported/unknown), region (North America, Central/South America, Europe, rest of world), duration of diabetes at baseline (< median or ≥ median years), CV history at baseline (yes/no), baseline body mass index (<30 or ≥30 kg/m^2), baseline hemoglobin A_{1c} (HbA_{1c}) (<8 or ≥8%), baseline eGFR (<45, ≥45 to <60, ≥60 mL/min/1.73 m^2), baseline urine albumin-to-creatinine ratio (UACR; ≤1000 or >1000 µg/mg), baseline systolic blood pressure (≤ median or > median), and history of amputation (yes/no).

Missing Data

Subjects without documentation of an eligible event were censored at the global trial end date or, if earlier, the last trial contact date defined as the latest of:

- The date of last visit (scheduled or unscheduled visit; office or phone visit), or
- The latest known date of adverse event or the study endpoint event status, concomitant medication, vital sign measures or lab results as reported on their respective electronic case report from page, or
- The date of alternate contact made (e.g., family members, relatives, friends, health care providers) confirming patient was alive at time of the global trial end date announcement.

Amendment 1 to the SAP changed this to state that subjects not experiencing an event would be censored at the earlier of their last trial contact day or "end of the respective data period, if not otherwise specified."

Interim Analyses

According to the original SAP, a single interim analysis was to be conducted after primary efficacy events had been adjudicated in approximately 420 subjects. A Lan-DeMets alpha spending function, which approximates an O'Brien-Fleming stopping boundary, was to be used to control the overall Type I error rate at 0.05 with a two-sided alpha of 0.003 spent at the interim analysis. The IDMC could recommend early termination of the trial for efficacy if canagliflozin was superior to placebo in reducing the rate of occurrence of the primary composite endpoint at a two-sided alpha of 0.003 and the totality of data (including ESKD) was consistent with a benefit of canagliflozin over placebo. If the conditional power was 10% or lower, the study could also be stopped for futility.

SAP Amendment 1 changed the timing of the interim analysis to occur when the mean follow-up duration was at least 2 years and primary efficacy events had been adjudicated in approximately 405 subjects (before SAP Amendment 1, protocol amendments INT-4 and INT-6 had changed the events required for the interim analysis to 540 and 405, respectively). The alpha spent at the interim analysis was also changed to a two-sided alpha of 0.01 based on an alpha spending function taking the form of $\alpha\tau_{\varphi}$ with τ as the information fraction and φ =2.19. The amendment also specified that the IDMC could recommend early termination for efficacy if 1) the p-value for the primary endpoint was <0.01 and 2) the p-value for the composite of ESKD, renal death, and CV death was <0.025 favoring canagliflozin.

The SAP for the interim analysis noted that, if the trial was terminated early for efficacy, the primary endpoint would be tested using data accrued through the final clinic visit at a significance level determined by the alpha spending function and the number of additional events accrued since the interim analysis. It also noted that secondary endpoints would be tested sequentially at an alpha of 0.05%. As noted above, the Applicant later modified the alpha for testing of secondary endpoints to 0.038 via SAP Amendment 2 after discussions with the Agency regarding the potential for inflation of overall Type 1 error.

The Applicant submitted an Interim Analysis Data Integrity plan to the IND on June 27, 2018, to allow representatives from the Steering Committee and Applicant to meet with the IDMC

chairperson to "engage in a focused, high-level, qualitative review of the data," if the IDMC recommended stopping the trial early for efficacy.

Sample Size Calculations

The trial was designed to have 90% power to detect a 20% relative risk reduction in the primary composite endpoint at a 5%, 2-sided significance level. This assumed a placebo event rate of 6.5% per year, a premature treatment discontinuation rate of 6% per year, 1% lost-to-follow-up, a 24-month enrollment period, and an estimated study duration of 66 months. The projected sample size was 3700 subjects (increased to 4200 with protocol amendment INT-4) to obtain primary efficacy events in 844 unique subjects.

Baseline

Baseline serum creatinine was defined as the average of the last two predose measurements (Day 1 and the value immediately preceding Day 1) or, if all pretreatment values are missing, the screening value.

SAP Amendments

A summary of amendments to the SAP, all of which occurred after the trial was fully enrolled, is shown in Table 6. The Applicant states that no unblinded data or analyses were available during conduct of the study or during the time of any protocol or SAP amendments.

Table 6. Overview of Statistical Analysis Plan Amendments

Amendment # and Date	Summary of Changes
#1 9/13/2017	"Clarification of alpha spending" in the interim and final analysis; decrease in the number of primary composite events required for the interim analysis from 420 to 405; added secondary endpoints (MACE and hospitalized CHF) and reordered
#2 6/1/2018	"Update the alpha level" used for testing the secondary efficacy endpoints based on discussions with FDA
SAP Supplement 11/13/2018	Outlined key sensitivity analyses to assess the robustness of the primary efficacy analysis with respect to missing data

Abbreviations: CHF, congestive heart failure; FDA, Food and Drug Administration; MACE, major adverse cardiovascular event; SAP, statistical analysis plan

6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

6.3.1. Demographics

Baseline demographics were similar in the two treatment arms (Table 7). The mean age was 63 years. Two-thirds of subjects were male. Overall, 67% of subjects were white, 20% Asian, and 5% black or African-American. Sites in the United States represented 16% of subject enrollment.

Table 7. Baseline Demographic Characteristics (Intent-to-Treat Analysis Set)

Subgroup	Cana N=2202 n (%)	Placebo N=2199 n (%)
Sex		
Male	1440 (65.4)	1467 (66.7)
Female	762 (34.6)	732 (33.3)
Age, years		
Mean (SD)	62.8 (9.2)	63.2 (9.2)
Min, max	30, 86	34, 89
Median	63	64
Age group, years, n (%)		
≥17 to <65	1200 (54.5)	1163 (52.9)
≥65 to <75	793 (36.0)	813 (37.0)
≥75	209 (9.5)	223 (10.1)
Race		
White	1487 (67.5)	1444 (65.7)
Asian	425 (19.3)	452 (20.6)
Other	132 (6.0)	127 (5.8)
Black or African-American	112 (5.1)	112 (5.1)
American Indian or Alaska Native	36 (1.6)	42 (1.9)
Native Hawaiian or Other Pacific Islander	9 (0.4)	16 (0.7)
Missing	1 (0.0)	6 (0.3)
Ethnicity		
Hispanic or Latino	717 (32.6)	706 (32.1)
Not Hispanic or Latino	1436 (65.2)	1457 (66.3)
Missing	49 (2.2)	36 (1.6)
Region		
North America	574 (21.6)	465 (21.1)
United States and Canada	423 (19.2)	456 (20.7)
United States	344 (15.6)	363 (16.5)
Central/South America	476 (21.6)	465 (21.1)
Europe	454 (20.6)	410 (18.6)
Eastern Europe	228 (10.4)	215 (9.8)
Western Europe	226 (10.3)	195 (8.9)
Rest of World[1]	698 (31.7)	716 (32.6)

Source: Reviewer's analysis: adsl_dm, dataset: si.adsl_r
[1]The Applicant specified four larger groupings of regions (North America, Central/South America, Europe, and Rest of World). The Applicant's analyses included Ukraine with "Rest of World" rather than Europe. The analyses above include the Ukraine (198 canagliflozin and 173 placebo subjects randomized) with "Rest of World."
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

As shown in Table 8, baseline kidney disease characteristics were well balanced between the treatment arms (randomization was stratified by eGFR category) with representation across the spectrum of eGFR and albuminuria categories. All subjects were reported to have diabetic nephropathy. The mean duration of diabetes was 15.8 years with three-quarters of patients having diabetes for at least 10 years. Over 40% reported a history of retinopathy or neuropathy related to diabetes.

Table 8. Baseline Kidney Disease Characteristics

Subgroup	Cana N=2202 n (%)	Placebo N=2199 n (%)
Screening eGFR[1] (mL/min/1.73 m^2)		
30 to <45	657 (29.8)	656 (29.8)
45 to <60	640 (29.1)	639 (29.1)
60 to <90	905 (41.1)	904 (41.1)
Baseline eGFR[1] (mL/min/1.73 m^2)		
<15	1 (0.0)	1 (0.0)
15 to <30	83 (3.8)	89 (4.0)
30 to <45	594 (27.0)	597 (27.1)
45 to <60	630 (28.6)	636 (28.9)
60 to <90	788 (35.8)	770 (35.0)
≥90	105 (4.8)	106 (4.8)
Missing	1 (0.0)	0 (0.0)
Baseline UACR (mg/g)		
<30	16 (0.7)	15 (0.7)
30 to 300	251 (11.4)	245 (11.1)
>300 to ≤3000	1702 (77.3)	1669 (75.9)
>3000	233 (10.6)	270 (12.3)
Baseline HbA_{1c}		
<8%	1027 (46.6)	1029 (46.8)
≥8%	1174 (53.3)	1169 (53.2)
Missing	1 (0.0)	1 (0.0)
History diabetes ≥10 years	1639 (74.4)	1649 (75.0)
Neuropathy[2]	1077 (48.9)	1070 (48.7)
Diabetic retinopathy	935 (42.5)	947 (43.1)
History amputation	119 (5.4)	115 (5.2)

Source: Reviewer's analysis: adsl_dm, dataset: si.adsl_r
[1] Screening eGFR was the value obtained at screening; baseline eGFR was the average of two pretreatment measures up to 4 weeks apart.
[2] Includes autonomic neuropathy, peripheral diabetic neuropathy, and other diabetic neuropathy
Abbreviations: eGFR, estimated glomerular filtration rate; HBA_{1c}, hemoglobin A1c; N, number of subjects in treatment arm; number of subjects with given characteristic; UACR, urine a bumin-to-creatinine ratio

In both treatment arms, nearly all patients had a history of hypertension, half had a prior history of cardiovascular disease, and 15% were reported to have a history of heart failure (Table 9).

Table 9. Cardiovascular History

	Placebo N=2199	Canagliflozin N=2202
Hypertension	2129 (97)	2131 (97)
Cardiovascular disease	1107 (50)	1113 (51)
Heart failure	323 (15)	329 (15)
Atherosclerotic vascular disease		
Coronary	660 (30)	653 (30)
Cerebrovascular	358 (16)	342 (16)
Peripheral vascular	515 (23)	531 (24)

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given characteristic

Nearly all patients were taking an ACE inhibitor or ARB at randomization, with most taking the maximum labeled dose as reported by the investigator (Table 10). Most patients were on an "antithrombotic," which included aspirin, and over two-thirds were on a statin.

Table 10. Use of ACE Inhibitors, ARBs, and Antithrombotics

	Placebo N=2199	Canagliflozin N=2202
ACEi/ARB use (n [%])		
On maximum labeled dose	1570 (71)	1598 (73)
Not on maximum labeled dose	625 (28)	603 (27)
Not taking	4 (0.2)	1 (<0.1)
Antithrombotics (including aspirin)	2017 (92)	2032 (92)
Statins	1497 (68)	1537 (70)

Abbreviations: ACEi, angiotensin -converting enzyme inh bitor; ARB, angiotensin receptor blocker; N, number of subjects in treatment arm; n, number of subjects in specified population or group

Reviewer's comment: During the April 28, 2015, meeting, the Steering Committee noted that investigators were reporting that their patients were on the maximum-labeled dose of an ACE inhibitor or ARB, but it was not clear that the dose recorded in the electronic case report form was consistent with the maximum dose per product labeling. In an attempt to address this issue during the trial, the Applicant, SC, and the National Lead Investigators "attempted to estimate the maximum labeled dose of each agent available across the 34 countries involved in the study, including considerations for use in subjects with renal impairment per local label." When an investigator reported that a patient was on the maximum labeled dose, but the dose was lower than the estimate, the investigator was queried; however, the final determination was made by the investigator.

Baseline diabetes, blood pressure, and hyperlipidemia management was similar in both treatment arms (Table 11).

Table 11. Baseline Diabetes, Blood Pressure, and Hyperlipidemia Management

	Placebo	Canagliflozin
HbA_{1c} (mean % [SD])	8.3 (1.3)	8.3 (1.3)
Systolic Blood Pressure (mean mm Hg [SD])	140.2 (15.6)	139.8 (15.6)
LDL cholesterol (mean mg/dL [SD])	96 (40)	97 (43)

Source: Applicant, Clinical Study Report, Volume 1, Tables 37, 39; Volume 2, Table TEFOLIPID03A_ABS
Abbreviations: HBA1c, hemoglobin A1c; LDL, low-density lipoprotein; SD, standard deviation

6.3.2. Disposition

Screening Period

A total of 12,900 patients were prescreened; of these, 3,968 failed to meet eGFR or albuminuria criteria. Of the 8,932 who were screened, 4,531 were not eligible to enroll. The most common reason for screening failure was failure to meet eGFR and albuminuria criteria via central laboratory measurement.

Randomized Period

A total of 4,401 patients were randomized, 2,199 to placebo and 2,202 to canagliflozin. Four randomized patients (two in each treatment group) did not receive study drug: one refused because they found the single-blind drug difficult to swallow, one experienced a serious adverse event (SAE) at the site before taking study drug, and two refused for personal reasons. All four were included in the ITT analysis set.

As shown in Table 12, 25 (1.1%) placebo subjects and 15 (0.7%) canagliflozin subjects did not complete study follow-up (defined as being followed until a time after the global trial end date or death) because of site closure (2 subjects), withdrawal of consent (16 subjects), or being lost to follow-up (22 subjects). Eight of these subjects had already experienced a primary endpoint event by the time follow-up ended. Vital status was known for all but six subjects.

Table 12. Study Completion and Vital Status (Intent-to-Treat Analysis Set)

Disposition	Canagliflozin N=2202	Placebo N=2199
Randomized	2202 (100.0)	2199 (100.0)
Completed	2022 (91.8)	1977 (89.9)
Died	165 (7.5)	197 (9.0)
Lost to follow-up	9 (0.4)	13 (0.6)
Alive	6 (0.3)	9 (0.4)
Died	2 (0.1)	4 (0.2)
Unknown	1 (0.0)	0
Consent withdrawal	5 (0.2)	11 (0.5)
Alive	2 (0.1)	9 (0.4)
Died	1 (0.0)	1 (0.0)
Unknown	2 (0.1)	1 (0.0)
Closed site	1 (0.0)	1 (0.0)

Source: Reviewer's analysis: disp\adds, dataset: adds
Abbreviations: N, number of subjects in treatment arm; n, number of subjects in specified population or group

The rate of study drug discontinuation was higher in the placebo group (11.0 per 100 subject-years) relative to the canagliflozin group (9.1 per 100 subject-years). As shown in Table 13, the most common reasons for premature discontinuation of study drug in both treatment groups were adverse events (12.5%) and personal reasons (8.3%). Among personal reasons for study drug discontinuation, approximately 32% were due to lack of interest with unspecified reasons and approximately 20% were related to subjects relocating away from the site.

Table 13. Reasons for Study Medication Discontinuation (Safety Population)

	Canagliflozin N=2200	Placebo N=2197
Discontinued study medication prior to GTED	524 (23.8)	630 (28.7)
Adverse event	263 (12.0)	285 (13.0)
Subject discontinued for personal reasons	164 (7.5)	199 (9.1)
Other	60 (2.7)	86 (3.9)
Poor compliance	16 (0.7)	18 (0.8)
Safety or tolerability reasons	13 (0.6)	19 (0.9)
Protocol violation	3 (0.1)	3 (0.1)
Site closure	3 (0.1)	3 (0.1)
Subject started disallowed therapy	2 (0.1)	17 (0.8)
No data	1 (0.0)	0

Source: Reviewer's analysis, adds.sas, where dscat = disposition event and dsscat = end of treatment
Dataset: adsl, adds, adae; Filter: Safety Population Flag (SAFFL): 'Y'. Global trial end date: October 30, 2018
Numbers shown in this table differ slightly from the numbers shown in Section 7.6.4, Dropouts and/or Discontinuations Due to Adverse Events because different case report form data were used to generate the two tables. Note that subjects who died or had dialysis or renal transplant are not counted as discontinued from study medication.
Abbreviations: GTED, global trial end date; N, number of subjects treated

6.3.3. Analysis of Primary Endpoint

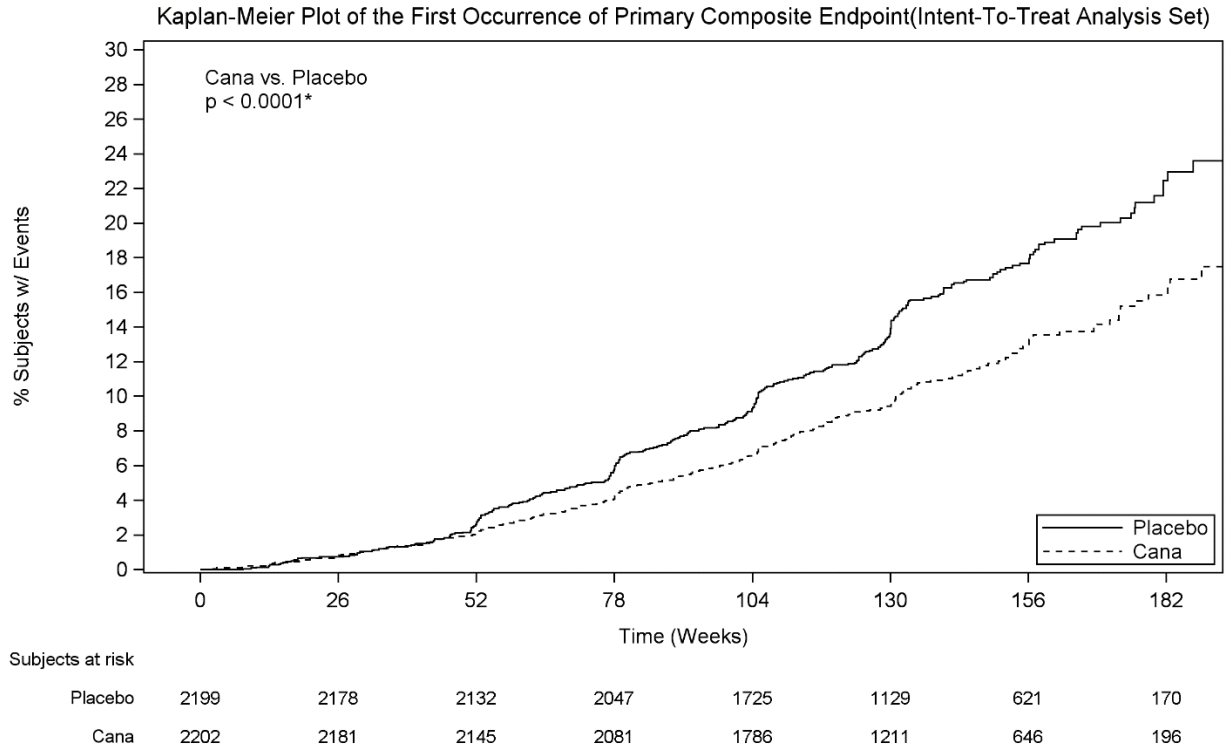
The primary endpoint was a composite of doubling of serum creatinine, ESKD, and renal or CV death. Subjects in the canagliflozin arm experienced fewer primary endpoint events [HR: 0.70; 95% confidence interval (CI): 0.59 to 0.82; p<0.0001] with all components of the composite favoring canagliflozin, although there were few renal deaths (Table 14). The Kaplan-Meier curves for the composite primary endpoint separated around Week 52 and continued to diverge during the treatment period (Figure 3; see Appendix Section III.17.1for Kaplan-Meier plots for ESKD, doubling of serum creatinine and CV death).

Table 14. Primary Efficacy Analysis (Intent-to-Treat Analysis Set)

	Placebo N=2199		Canagliflozin N=2202		
Endpoint	n (%)	Event Rate†	n (%)	Event Rate†	HR (95% CI; P-Value)
Primary composite endpoint	340 (15.5)	6.1	245 (11.1)	4.3	0.70 (0.59, 0.82; <0.0001)
ESKD	41 (1.8)		42 (1.9)		
Doubling of serum creatinine	182 (8.3)		111 (5.0)		
Renal death	1 (0.0)		0 (0.0)		
CV death	116 (5.3)		92 (4.2)		
Individual components (all events)					
ESKD	165 (7.5)		116 (5.3)		0.68 (0.54, 0.86)
Doubling of serum creatinine	188 (8.5)		118 (5.4)		0.60 (0.48, 0.76)
Renal death	5 (0.2)		2 (0.1)		--
CV death	140 (6.4)		110 (5.0)		0.78 (0.61, 1.00)

Source: Applicant, CREDENCE CSR Table 18. Analysis confirmed by FDA statistical reviewer. Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity
† Per 100 patient-years
Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HR, hazard ratio; N, number of subjects treated; n, number of subjects in specified population or group; p-value, probability value

Figure 3. Kaplan-Meier Plot for First Primary Endpoint Event (Intent-to-Treat Analysis Set)



Source: Applicant, CREDENCE CSR Figure 5. Analysis confirmed by FDA statistical reviewer.
* p-value of stratified log rank.

6.3.4. Analyses of Secondary Endpoints

Since the primary endpoint was successful, the secondary endpoints were tested hierarchically at a two-sided alpha of 0.038 in the following order:

- CV death and hospitalized CHF
- CV death, nonfatal myocardial infarction, and nonfatal stroke (MACE)
- Hospitalized CHF
- Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death
- CV death
- All-cause death
- CV composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalized CHF, and hospitalized unstable angina

As shown in the table below, canagliflozin 100 mg reduced the risk of the following four secondary endpoints: composite endpoint of CV death and hospitalized heart failure [HR: 0.69; 95% CI: 0.57 to 0.83; p=0.0001], MACE [HR: 0.80; 95% CI: 0.67 to 0.95; p=0.0121], hospitalized heart failure [HR: 0.61; 95% CI: 0.47 to 0.80; p=0.0003], and renal composite endpoint [HR: 0.66; 95% CI: 0.53 to 0.81; p<0.0001]. The hierarchical testing stopped at the CV death endpoint because the p-value did not reach the prespecified level of significance. See Appendix Section III.16.2 for Kaplan-Meier plots for the first four secondary endpoints.

Table 15. Secondary Endpoint Analyses (Intent-to-Treat Analysis Set)

Endpoint	Placebo N=2199 n (%)	Canagliflozin N=2202 n (%)	HR (95% CI; P-Value)
CV death/HHF	253 (11.5)	179 (8.1)	0.69 (0.57, 0.83; 0.0001)
CV death	112	90	
HHF	141	89	
MACE	269 (12.2)	217 (9.9)	0.80 (0.67, 0.95; 0.0121)
CV death	120	98	
Nonfatal MI	84	68	
Nonfatal stroke	65	51	
HHF	141 (6.4)	89 (4.0)	0.61 (0.47, 0.80; 0.0003)
Renal composite	224 (10.2)	153 (6.9)	0.66 (0.53, 0.81; <0.0001)
ESKD	41	42	
Doubling of serum creatinine	182	111	
Renal death	1	0	
CV death	140 (6.4)	110 (5.0)	0.78 (0.61, 1.00; 0.0502)
All-cause death	201 (9.1)	168 (7.6)	0.83 (0.68, 1.02; 0.0727)
CV composite	361 (16.4)	273 (12.4)	0.74 (0.63, 0.86; 0.0001)

Source: Applicant, CREDENCE CSR Volume 1 Tables 18, 23, 24, 26, and 29 and Volume 2, Table TEFCV01_ADJDIE. Analyses confirmed by statistical reviewer. For components, table shows first event of composite. Abbreviations: CV, cardiovascular; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; N, number of subjects in treatment arm; n, number of subjects in specified population or group; p-value, probability value

Table 15 shows only first events for individual components of composite endpoints. See Table 14 and Table 16 for all events.

Table 16: Analysis of all myocardial infarction and stroke events (Intent-to-Treat Analysis Set)

Endpoint	Placebo N=2199 n (%)	Canagliflozin N=2202 n (%)	HR (95% CI)
Nonfatal myocardial infarction	87 (4.0)	71 (3.2)	0.81 (0.59, 1.10)
Nonfatal stroke	66 (3.0)	53 (2.4)	0.80 (0.56, 1.15)

Source: Applicant, CREDENCE CSR Volume 1 Table 24. Analyses confirmed by statistical reviewer.

Reviewer's comment: We reviewed a random sample of cases adjudicated as hospitalized heart failure, nonfatal myocardial infarction, and nonfatal stroke. The adjudication of these cases was consistent with the specified event definitions.

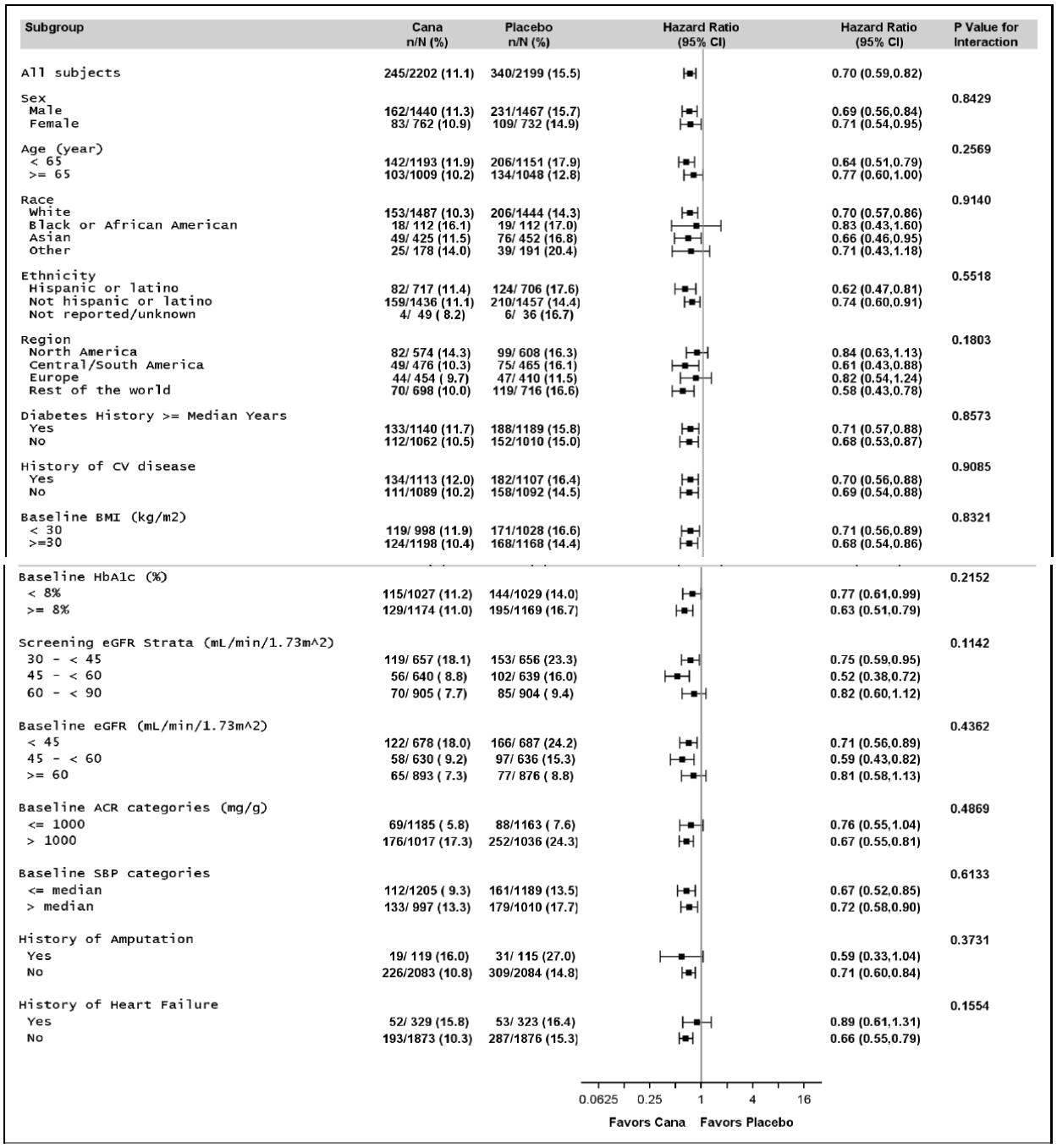
6.3.5. Subgroup Analyses

Primary Endpoint

Exploratory statistical testing of the primary endpoint for an interaction did not suggest large differences in treatment effect across the prespecified subgroups[2] (Figure 4). History of heart failure and screening eGFR strata were not prespecified subgroups, but the results were generally consistent in those groups as well.

[2] Age (<65 and ≥65 years), gender, race (white, black, Asian, other), ethnicity (Hispanic/Latino, not Hispanic/Latino, not reported/unknown), region (North America, Central/South America, Europe, rest of world), duration of diabetes at baseline (<median or ≥ median years), CV history at baseline (yes/no), baseline body mass index (<30 or ≥30 kg/m^2), baseline HbA_{1c} (<8 or ≥8%), baseline eGFR (<45, ≥45 to <60, ≥60 mL/min/1.73 m^2), baseline urine albumin-to-creatinine ratio (UACR; ≤1000 or >1000 µg/mg), baseline systolic blood pressure (≤ median or > median), and history of amputation (yes/no).

Figure 4. Primary Efficacy Endpoint by Subgroup



Source: Applicant, CREDENCE CSR Figure 6. Statistical reviewer confirmed findings for a subset of the subgroups (sex, age, race, and region).
Abbreviations: ACR, albumin-to-creatinine ratio; CANA, canagliflozin; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HBA1c, hemoglobin A1c; N, number of subjects in treatment arm; p-value, probability value; SBP, systolic blood pressure

The Applicant did not prespecify which countries would be included in each region, and the Applicant's analyses included Ukraine with "rest of world" instead of Europe. We separated Europe into Eastern and Western Europe and reclassified the 198 canagliflozin and 173 placebo

subjects enrolled in Ukraine with Eastern Europe (see table below). The treatment effect was consistent with that of the overall trial population.

Table 17. Primary Efficacy Endpoint for Subjects Enrolled in Europe (Intent-to-Treat Analysis Set)

Subgroup	Canagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)
Eastern Europe	47/426 (11.0)	59/388 (15.2)	0.69 (0.47, 1.01)
Western Europe	15/226 (6.6)	17/195 (8.3)	0.73 (0.36, 1.47)

Source: Statistical reviewer's analyses.
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of subjects in treatment arm; n, number of subjects in specified population or group

Concomitant metformin use was common in the trial population with approximately 58% of subjects on metformin at baseline (based on the Response to FDA's Clinical Request for Information #2 dated May 21, 2019). The treatment effect on key efficacy endpoints in this subgroup was consistent with that of the overall population (Table 18).

Table 18. Key Efficacy Analyses in Patients on Metformin at Baseline (Intent-to-Treat Analysis Set)

Endpoint	Placebo N=1269 n (%)	Canagliflozin N=1276 n (%)	HR (95% CI)
Primary composite endpoint	157 (48.3)	107 (32.4)	0.68 (0.53, 0.86)
CV death/HHF	126 (38.8)	93 (28.2)	0.73 (0.56, 0.95)
MACE	131 (40.5)	115 (35.4)	0.87 (0.68, 1.12)
HHF	69 (12.3)	44 (13.3)	0.63 (0.43, 0.92)
Renal Composite	102 (31.4)	58 (17.6)	0.57 (0.41, 0.78)

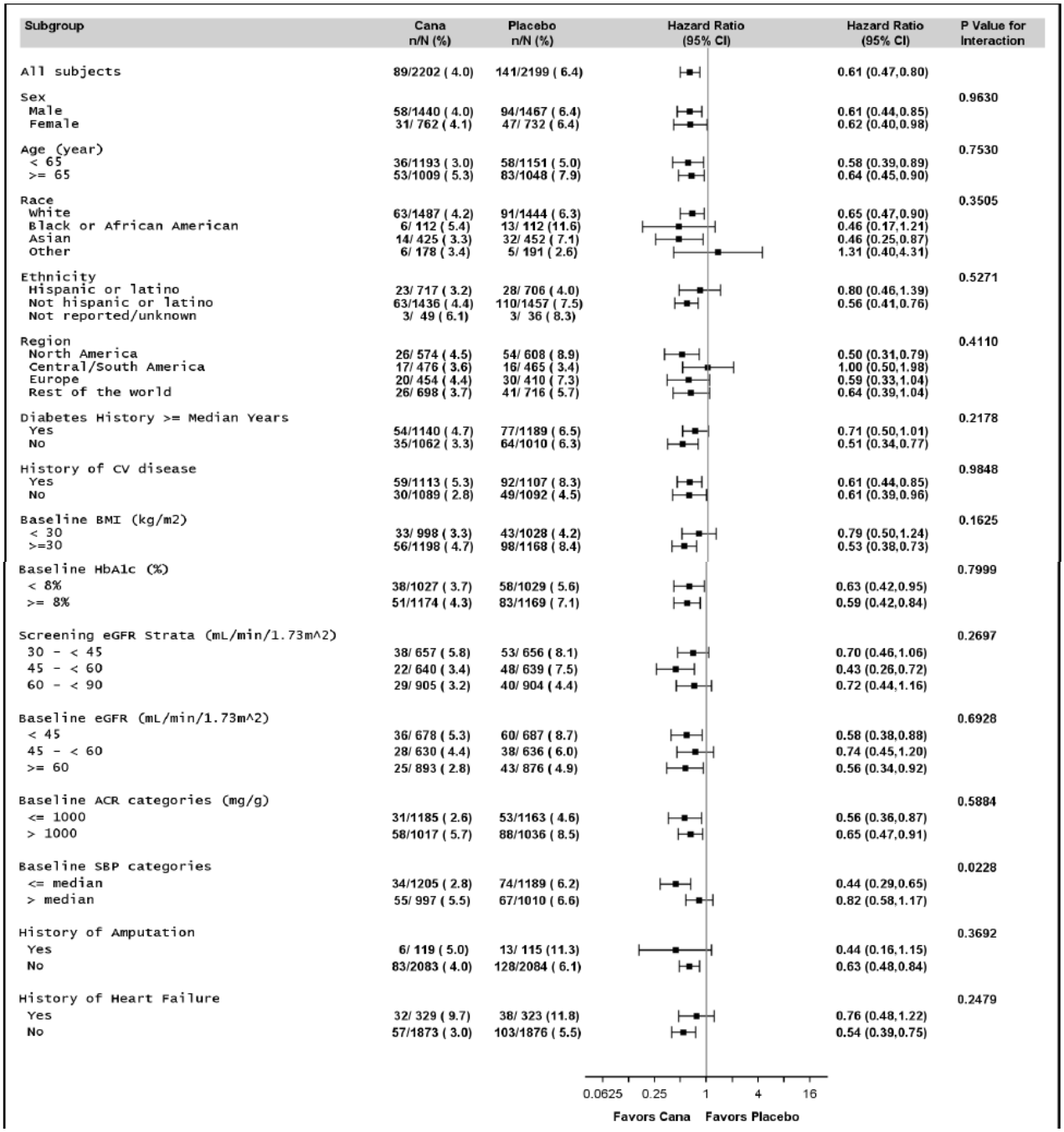
Source: Applicant, Response to FDA's Clinical Request for Information #2 dated May 21, 2019.
Abbreviations: CI, confidence interval; HHF, ; HR, hazard ratio; MACE, major adverse cardiovascular event; N, number of subjects in treatment arm; n, number of subjects in specified population or group

See Section 6.4.1 for further discussion of the findings in the U.S. population and Section 6.4.2 for further discussion of the findings in the black/African-American population.

Secondary Endpoint: Hospitalization for Heart Failure.

Exploratory statistical testing of the secondary endpoint Hospitalization for Heart Failure for an interaction did not suggest large differences in treatment effect across the same subgroups as were tested for the primary endpoint (Figure 5).

Figure 5: Hospitalization for Heart Failure Secondary Efficacy Endpoint by Subgroup



Source: Applicant, CREDENCE CSR Figure 16. Statistical reviewer confirmed findings for a subset of the subgroups (sex, age, race, ethnicity, and region).
Abbreviations: ACR, albumin-to-creatinine ratio; CANA, canagliflozin; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HBA1c, hemoglobin A1c; N, number of subjects in treatment arm; p-value, probability value; SBP, systolic blood pressure

6.4. Review Issues Relevant to the Evaluation of Benefit

Review issues relevant to the evaluation of benefit included data supporting efficacy in the U.S. and the black/African-American populations and the management of cardiovascular and renal risk factors, which are discussed below. An additional review issue related to late changes to secondary endpoints and the hierarchical testing strategy, which is discussed in Section 6.2.

6.4.1. U.S. Population

In the Applicant's analysis by region, the United States, Canada, and Mexico were grouped into "North America." The primary efficacy analysis this subgroup was consistent with the overall trial population; however, for patients enrolled in the United States, the point estimate for the HR did not favor canagliflozin, although the confidence interval was wide (Table 19).

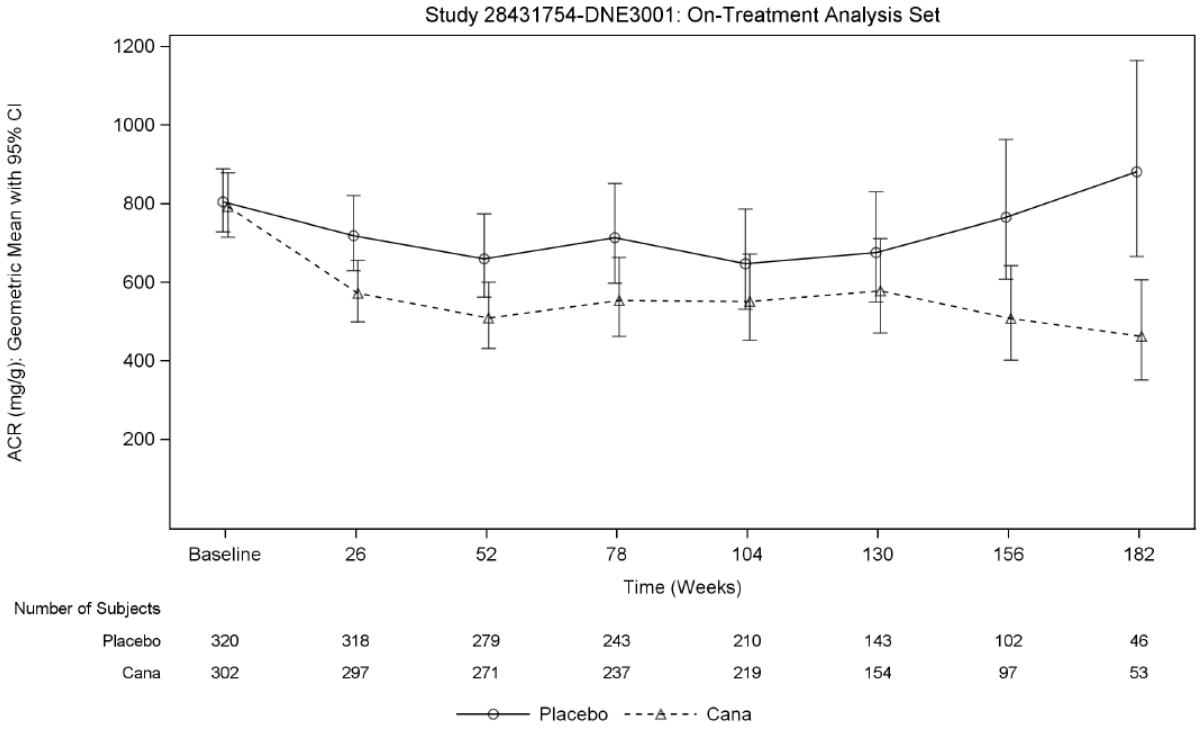
Table 19. Primary Efficacy Endpoint for Subjects Enrolled in U.S. and Non-U.S. (Intent-to-Treat Analysis Set)

Subgroup	Canagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)
U.S.	49/344 (14.2)	48/363 (13.2)	1.05 (0.71, 1.57)
Non-U.S.	196/1858 (10.5)	292/1836 (15.9)	0.64 (0.53, 0.76)

Source: Statistical reviewer's analyses.
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of subjects in treatment arm; n, number of subjects in specified population or group; U.S., United States

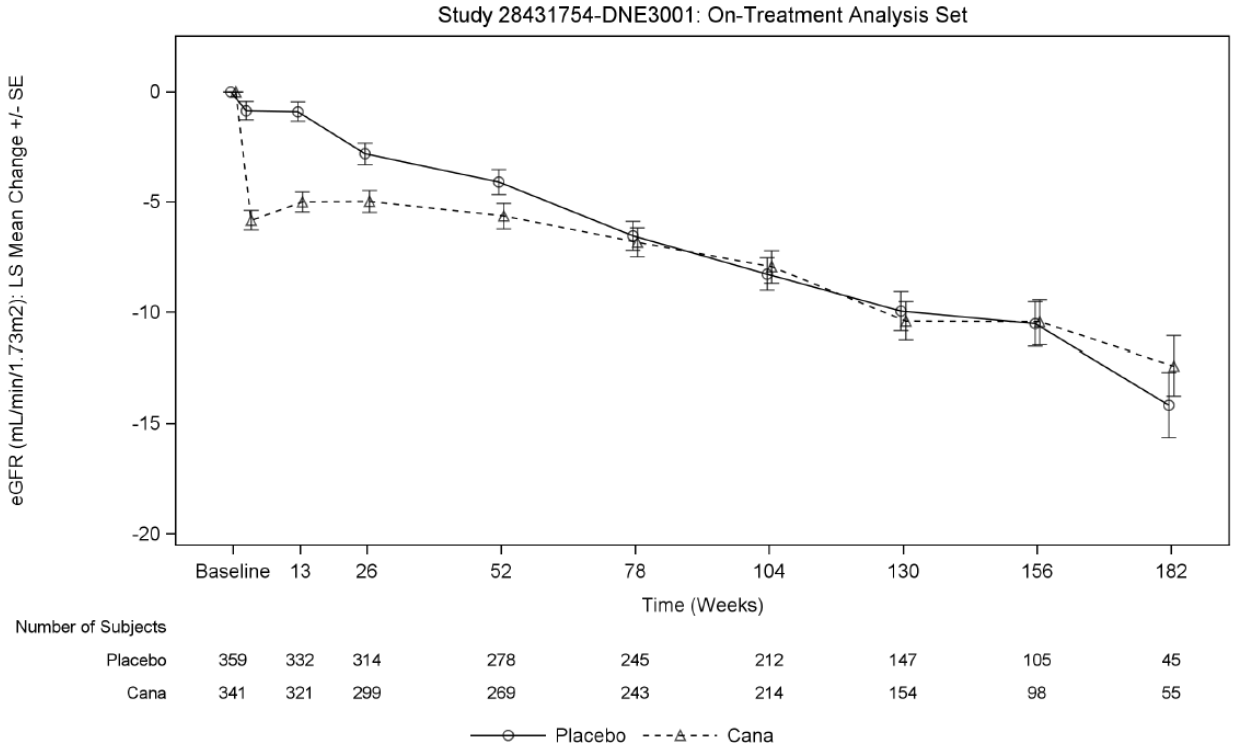
In response to an information request, the Applicant provided analyses of albuminuria, eGFR, systolic blood pressure, and weight over time in the U.S. subgroup (Figure 6 to Figure 9). These analyses suggest that canagliflozin had the expected acute pharmacodynamic effect in the U.S. population. In addition, the Applicant provided analyses of key cardiovascular and renal outcomes for U.S. patients enrolled in the CANVAS program (Table 20 and Table 21). In the CANVAS trials, the findings in the U.S. subgroup were consistent with those in the overall trial population. Finally, analyses to assess mediation did not indicate that the treatment effect was diminished in those on the maximal labeled dose of an ACE inhibitor or ARB as determined by the investigator, providing further reassurance that the trial's findings are likely applicable to the U.S. population receiving recommended background therapy. Collectively, these analyses provide reassurance that the result in the U.S. population in CREDENCE likely represents a chance finding.

Figure 6. Change in Albuminuria Over Time in U.S. Subgroup



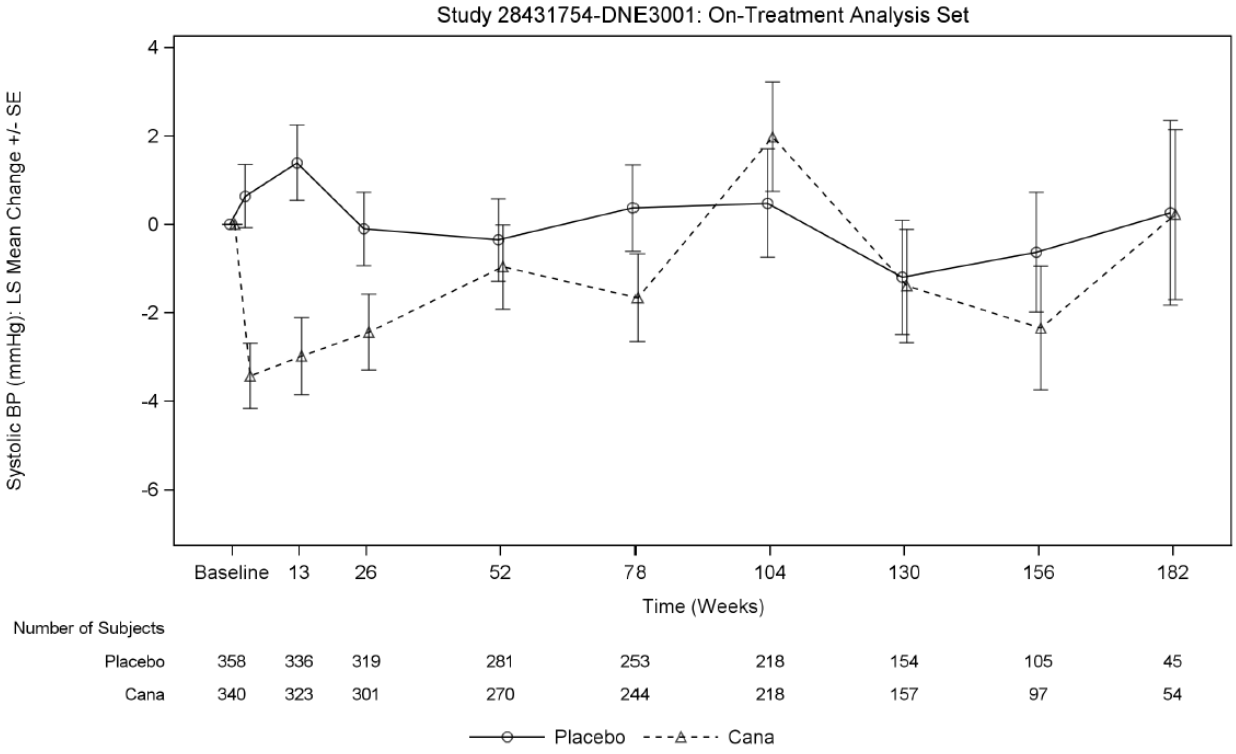
Abbreviations: ACR, albumin-to-creatinine ratio; CANA, canagliflozin; CI, confidence interval

Figure 7. Change in eGFR Over Time in U.S. Subgroup



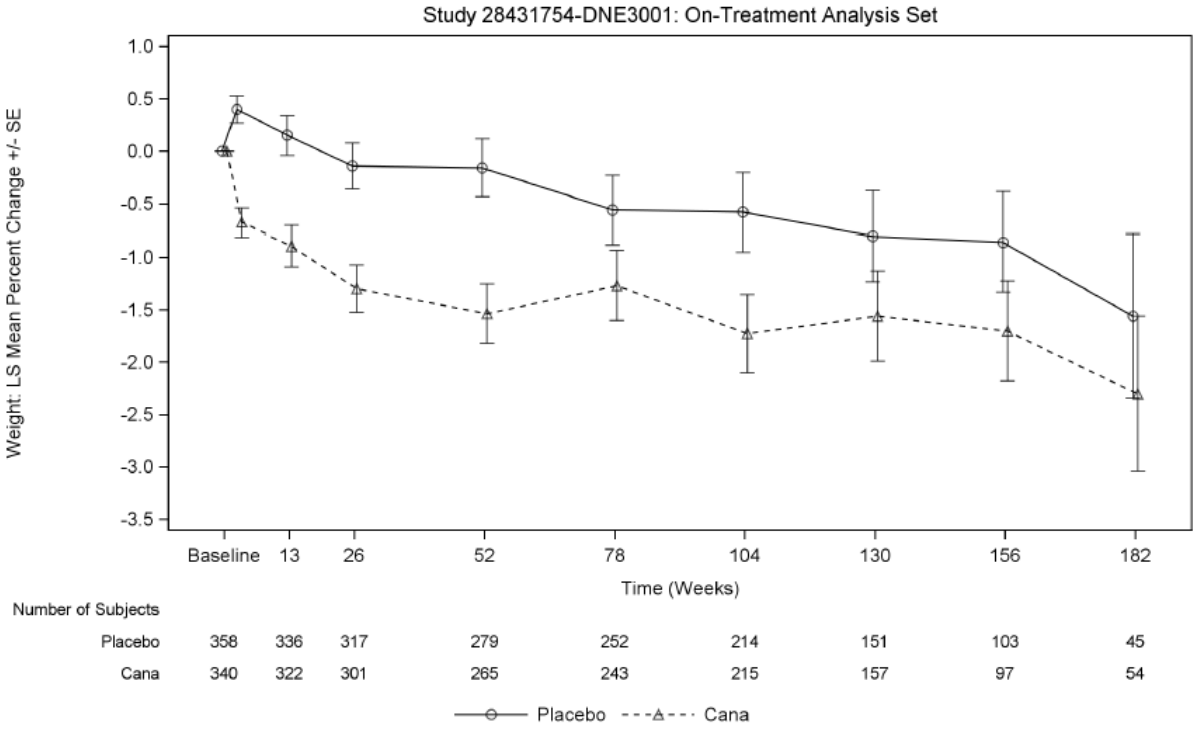
Abbreviations: CANA, canagliflozin; eGFR, estimated glomerular filtration rate; LS Mean, least square mean; SE, standard error

Figure 8. Change in Systolic Blood Pressure Over Time in U.S. Subgroup



Abbreviations: BP, blood pressure; CANA, canagliflozin; LS Mean, least square mean; SE, standard error

Figure 9. Change in Weight Over Time in U.S. Subgroup



Source: Applicant, Response to Information Request dated July 10, 2019.
Abbreviations: CANA, canagliflozin; LS Mean, least square mean; SE, standard error

Table 20. Primary and Supportive Cardiovascular Endpoints, U.S. Subjects Enrolled in CANVAS Program

Analysis Set	---------- Placebo ----------		---------- Cana ----------				Log-Rank[c]
Endpoint	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	HR[b] (95% CI)	P-value[b]	P-value
ITT							
MACE	65/ 577 (11.3)	37.03	94/ 823 (11.4)	30.02	0.76 (0.55, 1.05)	0.0951	0.0942
CV Death	29/ 577 (5.0)	13.72	44/ 823 (5.3)	12.17	0.81 (0.51, 1.30)	0.3831	0.3823
Non-Fatal MI	26/ 577 (4.5)	14.67	33/ 823 (4.0)	10.36	0.67 (0.40, 1.12)	0.1291	0.1267
Non-Fatal Stroke	15/ 577 (2.6)	8.30	23/ 823 (2.8)	7.18	0.92 (0.47, 1.78)	0.8039	0.8038
MI (Fatal/Non-Fatal)	29/ 577 (5.0)	16.36	38/ 823 (4.6)	11.93	0.68 (0.41, 1.10)	0.1158	0.1137
Stroke (Fatal/Non-Fatal)	16/ 577 (2.8)	8.85	24/ 823 (2.9)	7.49	0.89 (0.47, 1.69)	0.7144	0.7142
Composite CV Death/HHF	43/ 577 (7.5)	23.55	61/ 823 (7.4)	18.79	0.72 (0.49, 1.07)	0.1076	0.1062
All-Cause Mortality	45/ 577 (7.8)	21.29	72/ 823 (8.7)	19.92	0.87 (0.60, 1.27)	0.4682	0.4680
All-Cause Hospitalization	220/ 577 (38.1)	165.82	336/ 823 (40.8)	143.99	0.87 (0.73, 1.04)	0.1200	0.1198
HHF	16/ 577 (2.8)	8.84	22/ 823 (2.7)	6.80	0.73 (0.38, 1.41)	0.3493	0.3475
On-Treatment							
MACE	38/ 577 (6.6)	29.74	66/ 821 (8.0)	27.61	0.93 (0.62, 1.40)	0.7433	0.7432
On-Study[d]							
MACE	65/ 577 (11.3)	37.03	94/ 821 (11.4)	30.04	0.76 (0.55, 1.05)	0.0961	0.0952

Note: [a] Event rate per 1000 patient-years.
Note: [b] Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazard model including treatment as the explanatory variable, and stratified by study and prior CV disease subgroup.
Note: [c] Stratified by study and prior CV disease subgroup.
Note: [d] The on-study analysis set is identical to the ITT analysis set, except it is restricted to subjects who received at least one dose of study medication.

Source: Applicant, Response to Information Request dated July 31, 2019.
Abbreviations: CANA, canagliflozin; CI, confidence interval; CV, cardiovascular; EVRT, event rate; HHF, hospitalization for heart failure; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event; MI, myocardial infarction; N, number of subjects treated; p-value, probability value

Table 21. Analysis of Renal Endpoints, U.S. Subjects Enrolled in CANVAS Program

Analysis Set	---------- Placebo ---------		---------- Cana ----------		Cana vs. Placebo
Endpoint	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	HR[b] (95% CI)
ITT					
Progression of Albuminuria[c]	139/ 486 (28.6)	133.61	183/ 719 (25.5)	89.44	0.72 (0.57, 0.90)
Regression of Albuminuria[d]	45/ 156 (28.8)	176.30	114/ 207 (55.1)	333.72	2.12 (1.48, 3.03)
Renal Composite					
40% eGFR dcr/renal death/renal replacement	24/ 577 (4.2)	13.35	16/ 823 (1.9)	4.93	0.36 (0.19, 0.69)
40% eGFR dcr/renal death/renal replacement/CV death	53/ 577 (9.2)	29.21	57/ 823 (6.9)	17.49	0.56 (0.38, 0.82)
40% eGFR dcr/macroalbuminuria/renal death/renal replacement	65/ 577 (11.3)	37.83	58/ 823 (7.0)	18.41	0.49 (0.34, 0.70)
2X SCr/renal death/renal replacement	10/ 577 (1.7)	5.48	6/ 823 (0.7)	1.84	0.33 (0.12, 0.92)
2X SCr/renal death/renal replacement/CV death	39/ 577 (6.8)	21.17	49/ 823 (6.0)	14.97	0.65 (0.42, 0.99)
2X SCr/macroalbuminuria/renal death/renal replacement	52/ 577 (9.0)	29.79	49/ 823 (6.0)	15.49	0.52 (0.35, 0.78)
On-Treatment					
Progression of Albuminuria[c]	130/ 486 (26.7)	133.00	160/ 719 (22.3)	81.76	0.66 (0.52, 0.84)
Regression of Albuminuria[d]	43/ 156 (27.6)	174.88	111/ 207 (53.6)	347.04	2.16 (1.50, 3.11)

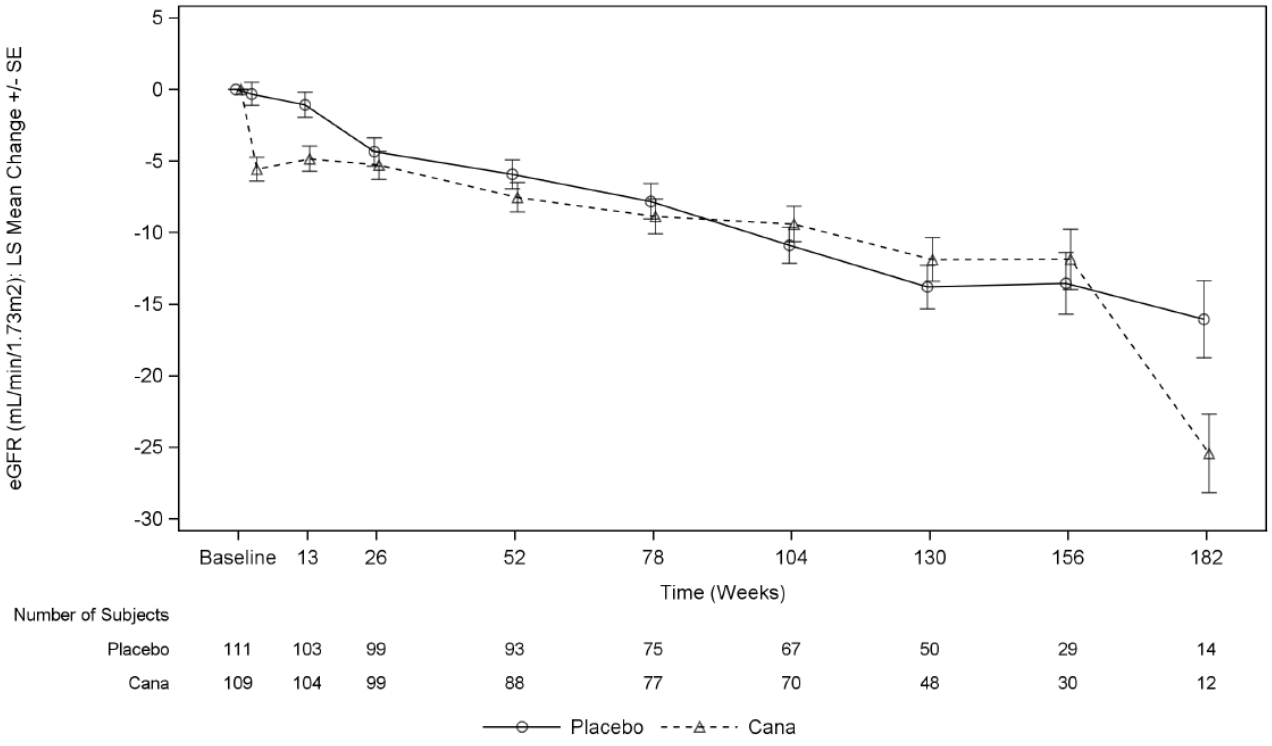
Note: dcr = decrease, 2X SCr = doubling of SCr, renal replacement = requirement for renal replacement therapy, macroalbuminuria = conversion to macro.
Note: [a] Event rate per 1000 patient-years.
Note: [b] Hazard ratio (all canagliflozin compared to placebo) and its 95% CI are estimated using a stratified Cox proportional hazard model including treatment as the explanatory variable, covariates (baseline albuminuria status for the progression and regression endpoints; stage of baseline chronic kidney disease for renal composite endpoints) and stratified by study.
Note: [c] Progression from baseline normo- to micro-/macroalbuminuria or from baseline micro- to macroalbuminuria with an ACR increase ≥ 30% from baseline. Subjects with macroalbuminuria at baseline (ACR>300 mg/g) are excluded from the analysis.
Note: [d] Regression from baseline macro- to normo-/microalbuminuria or from baseline micro- to normoalbuminuria with an ACR decrease ≥ 30% from baseline Subjects with normoalbuminuria at baseline (ACR<30 mg/g) are excluded from the analysis.

Source: Applicant, Response to Information Request dated July 31, 2019.
Abbreviations: ACR, ; CANA, canagliflozin; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EVRT, event rate; ITT, intention to treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group; SCr, serum creatinine

6.4.2. Black / African-American Subgroup

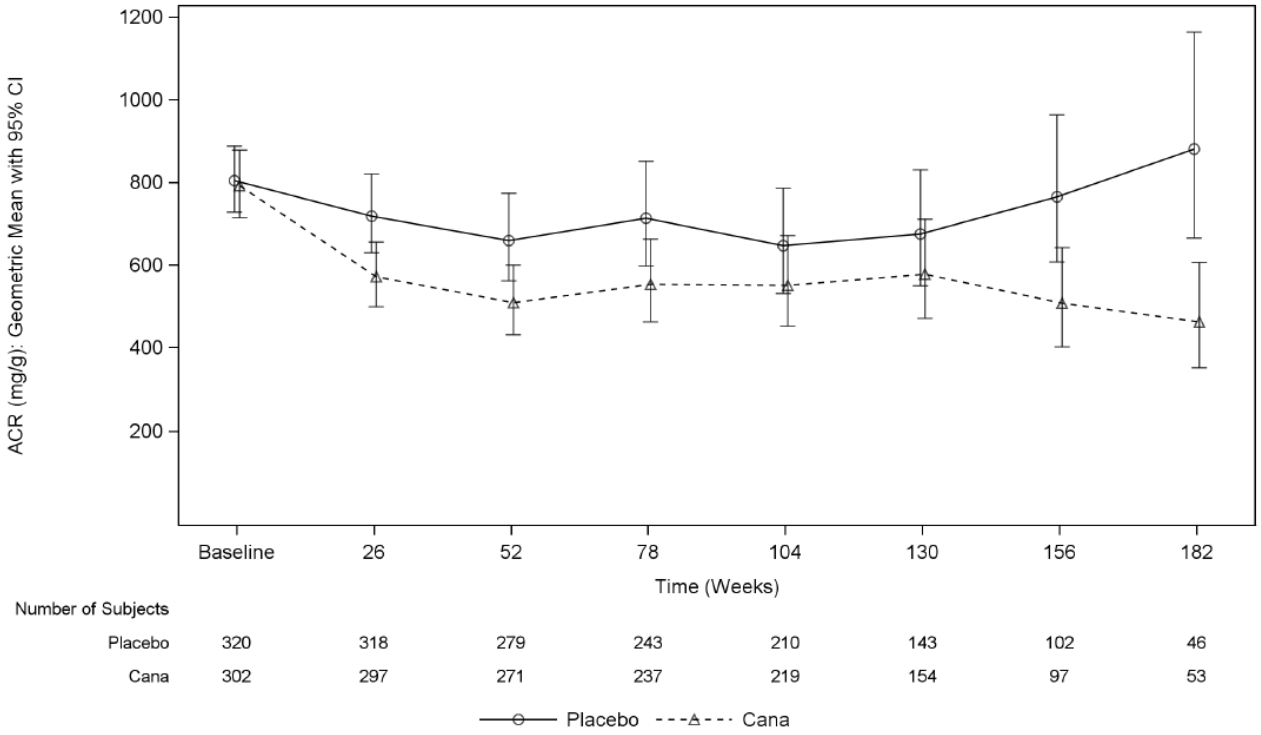
Only 224 patients in CREDENCE identified as black or African-American, and few experienced primary endpoint events, making it challenging to draw inferences about efficacy in the black/African-American subgroup. To address whether canagliflozin had the expected pharmacodynamic effect in this population, the Applicant provided analyses of eGFR, albuminuria, and systolic blood pressure over time (Figure 10 to Figure 12). The findings were consistent with the expected acute, pharmacodynamic effects of the drug.

Figure 10. LS Mean Change From Baseline in eGFR Over Time, Black or African-American Subgroup (on-Treatment Analysis Set)



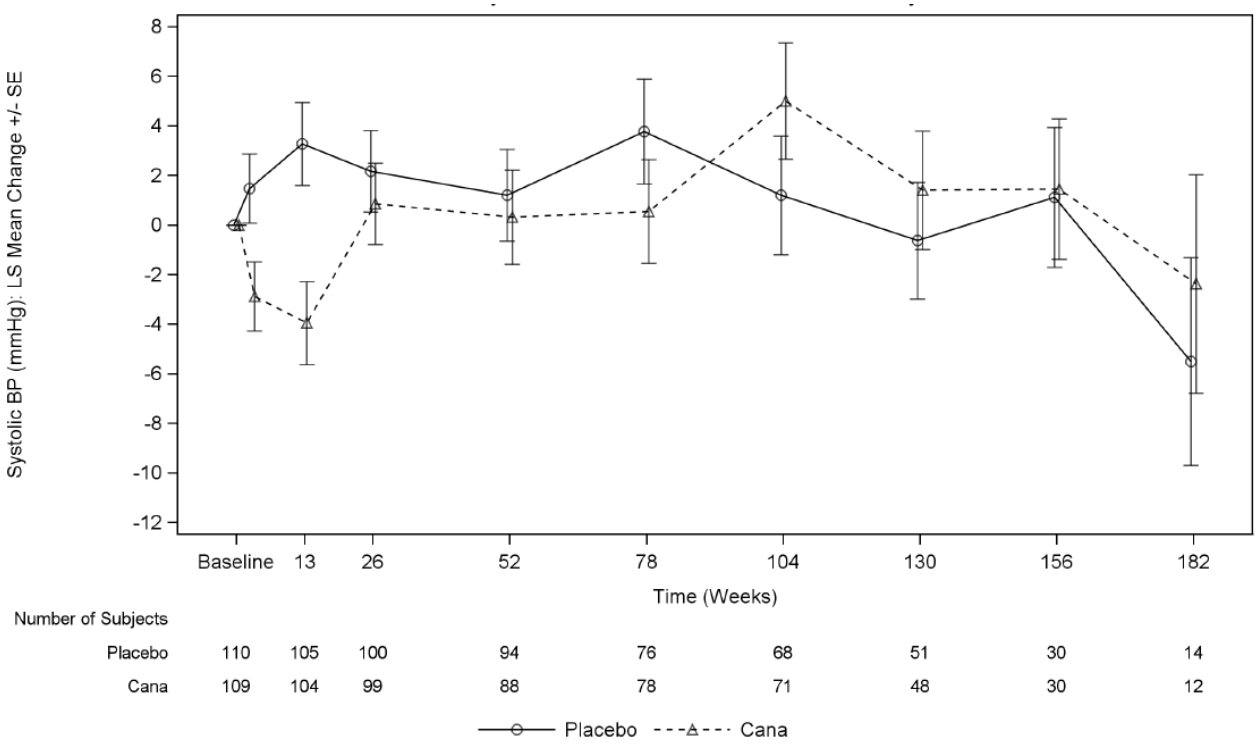
Source: Applicant, Response to the Food and Drug Administration's Clinical Request for Information #9 Dated July 2, 2019, Figure 8.
Abbreviations: CANA, canagliflozin; eGFR, estimated glomerular filtration rate; LS Mean, least square mean; SE, standard error

Figure 11. Change in Albuminuria Over Time, Black or African-American Subgroup (on-Treatment Analysis Set)



Source: Applicant, Response to the Food and Drug Administration's Clinical Request for Information #9 Dated July 2, 2019, Figure 2.
Abbreviations: ACR, albumin-to-creatinine ratio; CANA, canagliflozin; CI, confidence interval; eGFR, estimated glomerular filtration rate

Figure 12. LS Mean Change From Baseline in Systolic Blood Pressure Over Time, Black or African-American Subgroup (on-Treatment Analysis Set)



Source: Applicant, Response to the Food and Drug Administration's Clinical Request for Information #9 Dated July 2, 2019, Figure 14.
Abbreviations: BP, blood pressure; CANA, canagliflozin; LS Mean, least square mean; SE, standard error

6.4.3. Concomitant Management of Cardiovascular and Renal Risk Factors

Diabetes and blood pressure management and weight were similar at both baseline and end of treatment (Table 11). Review of the IDMC minutes indicated that the committee monitored diabetes and blood pressure parameters during the study and provided feedback to the Steering Committee as needed.

Table 22. Diabetes, Blood Pressure, and Weight at Baseline and End of Treatment

	Placebo	Canagliflozin
HbA_{1c} (mean % [SD])		
Baseline	8.3 (1.3)	8.3 (1.3)
End of treatment	8.0 (1.6)	7.9 (1.4)
Systolic Blood Pressure (mean mm Hg [SD])		
Baseline	140.2 (15.6)	139.8 (15.6)
End of treatment	140.1 (17.7)	137.1 (17.1)
Weight (mean kg [SD])		
Baseline	86.9 (20.7)	87.3 (20.7)
End of treatment	86.8 (20.8)	85.7 (20.7)

Source: Applicant, Clinical Study Report, Volume 1, Tables 37, 38, and 39.
Abbreviations: HBA1c, hemoglobin A1c; SD, standard deviation

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No additional nonclinical studies were conducted to support the proposed indication. According to the canagliflozin label:

- Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone, increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg, corresponding to less than or equal to 14 times exposure from a 300 mg clinical dose). In a 12-week clinical trial, luteinizing hormone did not increase in males treated with canagliflozin.
- Renal tubular adenoma and carcinoma increased significantly in male and female rats dosed at 100 mg/kg, or approximately 12-times exposure from a 300 mg clinical dose. Adrenal pheochromocytoma increased significantly in males and numerically in females dosed at 100 mg/kg. Carbohydrate malabsorption associated with high doses of canagliflozin was considered a necessary proximal event in the emergence of renal and adrenal tumors in rats. Clinical trials did not demonstrate carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the recommended clinical dose of 300 mg.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Warnings and Precautions for approved members of the pharmacologic class (SGLT2 inhibitors) include:

- Hypotension (intravascular volume contraction)
- Ketoacidosis (including fatal cases)
- Acute kidney injury (AKI) (including hospitalization and dialysis) and renal impairment
- Urosepsis and pyelonephritis requiring hospitalizations
- Necrotizing fasciitis of the perineum (Fournier's gangrene) including hospitalizations, multiple surgeries and death
- Hypoglycemia with concomitant insulin and insulin secretagogues
- Genital mycotic infections
- Increase in LDL cholesterol

Warnings and Precautions for specific SGLT2 inhibitors include:

- Lower limb amputations (canagliflozin)
- Bone fracture risk (canagliflozin)
- Hypersensitivity (canagliflozin and empagliflozin; also described in Section 6.1 of labeling for dapagliflozin)
- Malignancy: Possible increased risk of bladder cancer risk (dapagliflozin).

7.3. Potential Safety Concerns Identified Through Postmarket Experience

See Section 7.2.

7.4. FDA Approach to the Safety Review

The safety review of CREDENCE focused on previously identified risks and included a review of data quality and integrity,[3] adverse event, and laboratory datasets. Adverse events were analyzed by MedDRA preferred term (similar to the Applicant's analyses) and by pooling similar adverse events (referred to as the FDA Medical Dictionary for Regulatory Activities [MedDRA] Query [FMQ]). The FMQ analysis is similar to a customized MedDRA query. Adverse events of interest in CREDENCE included all malignancies, fatal and hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, lower extremity events and amputation, and pregnancy. For adverse events (AEs) of interest, the Applicant grouped preferred terms, similar to a customized MedDRA query. In addition to the CREDENCE clinical study report (CSR), the documents shown in the table below were reviewed.

Table 23. Documents Reviewed

Document	Period Covered or Submission Date	Report Date
FDA DMEP Clinical review of efficacy supplement 27 – canagliflozin for patients with established cardiovascular disease (cardiovascular outcome trials, CANVAS and CANVAS-R)	Submission date 9/29/2017	10/25/2018
Applicant Periodic Safety Update Report (PSUR)	3/29/2017 to 9/28/2017	12/8/2018
Applicant Periodic Benefit Risk Evaluation Report (PBRER)	3/29/2018 to 3/28/2019	5/20/2019
Applicant 4-month safety update	Clinical trial cutoff date 3/28/2019	7/22/2019

Abbreviations: DMEP, Division of Metabolism and Endocrinology Products; FDA, Food and Drug Administration

[3] Data integrity was examined using Cluepoints, the Office of Computational Science Core Data Fitness, SAS and JMP Clinical.

Except where noted, safety analyses used the treated population (received at least one dose of study drug) and the on-treatment data period. Definitions and data periods for analyses are shown in the table below.

Table 24. Definitions and Data Periods for Safety Analyses

Analysis Set	Analysis Population	Canagliflozin Subjects	Placebo Subjects	Data Period
On-treatment	Treated subjects	2200	2197	D1 to the earlier of the last dose plus X days or last study contact date
On-study	Treated subjects	2200	2197	D1 to last study contact up the GTED
ITT	Randomized subjects	2202	2199	D1 to last study contact up the GTED

Source: CREDENCE CSR, Table 1
D1 was first day of treatment. If missing, then D1 was the randomization date.
X =2 days for laboratory and vital sign measurements, and 30 days for adverse events, cardiovascular, renal, and mortality endpoints.
Abbreviations: GTED, global trial end date: October 30, 2018; ITT, intention to treat

SAS version 9.4 was used for most analyses; MedDRA Adverse Event Diagnosis, JMP Clinical, JMP, and the Office of Computational Science table builder tool were also used. Results are presented as percent of subjects (%), rate per 1,000 patient years, and the incidence rate difference (IRD) with 95% CI. The IRD was calculated as the canagliflozin rate/1,000 patient-years minus the placebo rate/1000 patient-years.

7.5. Adequacy of the Clinical Safety Database

The mean duration of canagliflozin exposure in CREDENCE was 26.8 months (or 2.2 years). This exposure, in combination with the extensive prior clinical experience, is considered adequate to characterize safety.[4] See the table below for additional information on duration of treatment in CREDENCE.

Table 25. Duration of Exposure, Safety Population, CREDENCE

Parameter	Canagliflozin N=2200		Placebo N=2197	
Duration of treatment (days)				
Mean (SD)	816	(326)	788	(326)
Median (min, max)	846	(6, 1592)	817	(3, 1581)

[4] As of March 28, 2019, in both completed and ongoing studies, the estimated cumulative number of subjects exposed to canagliflozin in clinical trials is 19,198. The safety database includes cardiovascular outcome trials, CANVAS and CANVAS-R, conducted to assess cardiovascular safety. In the CANVAS program, 10,134 patients were randomized to placebo or canagliflozin with mean canagliflozin exposure of 4.3 years and 1.8 years in CANVAS and CANVAS-R, respectively.

Parameter	Canagliflozin N=2200		Placebo N=2197	
Patients treated, by duration, n (%)				
Any duration (at least 1 dose)	2200	(100)	2197	(100)
<1 month	30	(1.4)	19	(0.9)
≥1 month	2170	(98.6)	2178	(99.1)
≥3 months	2129	(96.8)	2141	(97.5)
≥6 months	2067	(94.0)	2051	(93.4)
≥12 months	1944	(88.4)	1914	(87.1)
≥24 months	1403	(63.8)	1326	(60.4)
≥36 months	438	(19.9)	399	(18.2)

Source: Reviewer's analysis: ex.sas, dataset ades
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety evaluation of canagliflozin in CREDENCE was adequate and acceptable for the proposed indication. There was generally a greater incidence of adverse events in the placebo arm compared to the canagliflozin arm, including deaths, SAEs, AEs, and study drug discontinuation due to AEs. There were no SAEs that occurred at a significantly higher rate in the canagliflozin arm compared to the placebo arm. Between 13 to 14% of subjects in each arm discontinued medication due to an AE. The most common reasons for medication discontinuation were infection (2.4% of subjects) and blood creatinine increase (<1% of subjects); the rates were similar between treatment arms. Hypotension and fungal infection occurred more frequently with canagliflozin than placebo. The rate of lower limb amputations was greater in the canagliflozin as compared to placebo arm in CREDENCE (12.3 vs 11.2 events per 1000 patient years, respectively); the difference between the treatment arms was not as great as was observed in the CANVAS program, likely reflecting strategies that were implemented in CREDENCE to mitigate this risk.

Consistent with findings in other trials, small mean increases in hemoglobin, magnesium, and phosphate were observed following initiation of canagliflozin. The difference between arms persisted for the treatment duration for hemoglobin and magnesium but not phosphate. There were no obvious differences between treatment arms in changes in potassium or LDL over time. As seen in other trials, initiation of therapy was associated with a small mean increase in creatinine attributed to a hemodynamic effect on renal function. The incidence of acute kidney injury was not greater in the canagliflozin as compared to the placebo arm in CREDENCE (3.9% versus 4.5% of subjects or 17/1,000 patient-years versus 20/1,000 patient-years, canagliflozin versus placebo, respectively). There was no difference between treatment arms in bone fractures (3.1% of patients in each arm). One renal cell carcinoma event (in the placebo arm) was reported in the trial.

7.6.1. Overall Adverse Event Summary

The overall incidence and rate of adverse events were lower in the canagliflozin arm as compared to the placebo arm. As shown in the table below, most adverse events were reported to be mild in intensity.

Table 26. Overview of Adverse Events,[1] CREDENCE, Safety Population, on-Treatment

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
Event	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference	95% CI
Any adverse event	1784	(81.1)	351.4	1860	(84.7)	379.3	-27.9	(-51.6, -4.2)
Mild	1466	(66.6)	288.8	1558	(70.9)	317.7	-28.9	(-50.5, -7.3)
Moderate	1095	(49.8)	215.7	1209	(55.0)	246.5	-30.8	(-49.7, -11.9)
Severe	522	(23.7)	102.8	586	(26.7)	119.5	-16.7	(-29.8, -3.6)
Serious	737	(33.5)	145.2	806	(36.7)	164.4	-19.2	(-34.7, -3.7)
Serious w/fatal outcome	109	(5.0)	21.5	122	(5.6)	24.9	-3.4	(-9.4, 2.6)
AE leading to study drug withdrawn[2]	267	(12.1)	52.6	286	(13.0)	58.3	-5.7	(-15.0, 3.6)
AE leading to study drug interrupted[2]	356	(16.2)	70.1	400	(18.2)	81.6	-11.5	(-22.3, -0.7)

Source: Reviewer's analysis: adae.sas, dataset: adae, si\adsl_r
[1] Includes treatment-emergent AE defined as on-treatment (last dose +30 days for adverse events)
[2] "AE leading to study drug withdrawal" and "drug interrupted" reflect data from the ADAE dataset as collected.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with at least one event; pt-yrs, patient years; SAE, serious adverse event

7.6.2. Deaths

As discussed under efficacy, all-cause mortality was lower in the canagliflozin as compared to the placebo arm. AEs that led to death based on the AE case report form are shown in the next table and Table 12, study completion and vital status.[5] Based on the AE case report form, the total number of subjects with AEs that were fatal in CREDENCE were 168 (29.1/1,000 patient-years) and 202 (35.3/1000 patient-years) in the canagliflozin and placebo arms, respectively; the incidence was generally higher in the placebo arm compared to the canagliflozin arm across AEs.

[5] Deaths were part of the efficacy analysis. All deaths that occurred during the study were sent to the EAC for adjudication; deaths adjudicated as having cardiovascular or renal causes were included in the primary composite endpoint. All-cause mortality was a secondary efficacy endpoint.

Table 27. Deaths in Safety Population, CREDENCE, on-Study Period, FDA MedDRA Query

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference*	95% CI
Total AE with fatal outcome**	**168**	**(7.6)**	**29.1**	**202**	**(9.2)**	**35.3**	**-6.2**	**(-12.8, 0.4)**
Treatment-emergent† deaths**	109	(5.0)	18.9	122	(5.6)	21.3	-2.4	(-7.6, 2.8)
Infections[1]	20	(0.9)	3.5	29	(1.3)	5.1		
Myocardial infarction	16	(0.7)	2.8	20	(0.9)	3.5		
Cardiac arrest, sudden cardiac death, asystole, electrical mechanical dissociation	16	(0.7)	2.8	19	(0.9)	3.3		
Solid neoplasia	11	(0.5)	1.9	11	(0.5)	1.9		
Congestive heart failure[2]	8	(0.4)	1.4	17	(0.8)	3.0		
Respiratory failure[3]	7	(0.3)	1.2	5	(0.2)	0.9		
Stroke[4,5]	7	(0.3)	1.2	11	(0.5)	1.9		
Bleeding[5]	7	(0.3)	1.2	5	(0.2)	0.9		
Renal injury[6]	5	(0.2)	0.9	6	(0.3)	1.0		
Nontreatment-emergent deaths**	59	(2.7)	10.2	80	(3.6)	14.0	-3.8	(-7.9, 0.3)

Source: Reviewer's analysis: deaths.sas, AE death table, datasets: ODE1 coding, adsl, adae
[1] Infections included pneumonia, septic shock, UTI, cellulitis, gangrene (2, both in placebo arm), bacterial meningitis, erysipelas
[2] Congestive heart failure includes cardiac failure, cardiogenic shock, acute pulmonary edema, pulmonary edema, right ventricular failure
[3] Respiratory failure also include acute respiratory distress syndrome
[4] Stroke includes hemorrhagic, ischemic, cerebrovascular and cerebellar
[5] Bleeding includes intracranial hemorrhage, cerebral hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke, subdural hematoma. Note that 2 hemorrhagic strokes are counted in both "Bleeding" and "Strokes" (1 in each arm)
[6] Renal injury includes acute kidney injury, renal failure, anuria, and renal impairment
* Rates calculated using on-study duration data
** Subjects counted once
Subjects could be counted in more than one FDA query leading to death. Only FDA queries occurring in at least 5 subjects are shown in the table.
† treatment-emergent defined as last dose +30 days
Abbreviations: AE, adverse event; CI, confidence interval; FDA, Food and Drug Administration; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of deaths; pt-yrs, patient years

7.6.3. Serious Adverse Events

The overall rate of SAEs was higher in the placebo arm. There were no SAEs that occurred at a significantly higher rate in the canagliflozin arm compared to the placebo arm. Notable SAEs that were numerically higher in the canagliflozin arm included fracture and diabetic gangrene. Notable SAEs that were numerically higher in the placebo arm included CHF and AKI. Results of the MedDRA Preferred Term Analysis and FDA MedDRA Query (FMQ) Analysis, in which terms capturing similar concepts are grouped, are shown discussed in greater detail below.

MedDRA Preferred Term Analysis

There were no preferred terms that occurred with a frequency of at least 2% greater in the canagliflozin arm compared to the placebo arm. The following table summarizes actions taken as a

result of SAEs and shows preferred term SAEs occurring in at least 2% of subjects. The incidence rate of SAEs was generally lower in subjects treated with canagliflozin than placebo; analyses pooling preferred terms that capture a similar medical concept (e.g., cardiac failure and cardiac failure congestive) are discussed in the next section.

Table 28. SAE Summary and MedDRA Preferred Term Analysis, CREDENCE

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference	95% CI
Serious	737	(33.5)	145.2	806	(36.7)	164.4	-19.2	(-34.7, -3.7)
Study drug withdrawn	134	(6.1)	26.4	159	(7.2)	32.4	-6.0	(-12.8, 0.8)
Study drug interrupted	238	(10.8)	46.9	276	(12.6)	56.3	-9.4	(-18.3, -0.5)
SAE Preferred term in at least 2% of subjects								
Pneumonia	63	(2.9)	12.4	86	(3.9)	17.5	-5.1	(-9.9, -0.3)
Acute kidney injury	41	(1.9)	8.1	50	(2.3)	10.2	-2.1	(-5.9, 1.7)
Cardiac failure	34	(1.5)	6.7	50	(2.3)	10.2	-3.5	(-7.2, 0.2)
Cardiac failure congestive	24	(1.1)	4.7	48	(2.2)	9.8	-5.1	(-8.5, -1.7)

Source: Reviewer's analysis: adsae, saetable, dataset adae, adsl
Abbreviations: CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years; SAE, serious adverse event

FDA MedDRA Query (FMQ) Analysis

Similar to the MedDRA preferred term analysis, SAEs were generally higher in the placebo arm than in the canagliflozin arm (as indicated by the negative risk difference in the table below). There were three FMQs (bolded in table) with a higher incidence in the canagliflozin arm compared to placebo. Urosepsis is a labeled risk of SGLT2 inhibitors and lower limb amputations are a labeled risk of canagliflozin, and are discussed further in the section on previously identified risks (see Section 7.2). Analyses of AE data on cancer did not suggest an obvious signal for a particular malignancy (see Section III.17.1).

Table 29. SAE FDA MedDRA Query in at Least 2% of Subjects

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference*	95% CI
Infection, all**	219	(10.0)	43.1	270	(12.3)	55.1	-12.0	(-20.7, -3.3)
Pneumonia	66	(3.0)	13.0	91	(4.1)	18.6	-5.6	(-10.6, -0.6)
Urinary tract infection	**37**	**(1.7)**	**7.3**	**33**	**(1.5)**	**6.7**	**0.6**	**(-2.7, 3.9)**
Gangrene	24	(1.1)	4.7	25	(1.1)	5.1	-0.4	(-3.2, 2.4)
Sepsis	23	(1.0)	4.5	31	(1.4)	6.3	-1.8	(-4.7, 1.1)

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference*	95% CI
CAD, myocardial ischemia, ACS[1]	103	(4.7)	20.3	126	(5.7)	25.7	-5.4	(-11.4, 0.6)
ACS, AMI and unstable angina[2]	85	(3.9)	16.7	96	(4.4)	19.6	-2.9	(-8.2, 2.4)
AMI and MI	60	(2.7)	11.8	63	(2.9)	12.8	-1.0	(-5.4, 3.4)
CHF or pulmonary edema	71	(3.2)	14.0	128	(5.8)	26.1	-12.1	(-17.7, -6.5)
Solid neoplasia, all (benign, malignant, unknown)	**66**	**(3.0)**	**13.0**	**50**	**(2.3)**	**10.2**	**2.8**	**(-1.5, 7.1)**
Cerebral ischemia (includes stroke and TIA)	65	(3.0)	12.8	76	(3.5)	15.5	-2.7	(-7.4, 2.0)
Stroke (includes ischemic and hemorrhagic)	57	(2.6)	11.2	71	(3.2)	14.5	-3.3	(-7.8, 1.2)
Renal injury[3]	55	(2.5)	10.8	66	(3.0)	13.5	-2.7	(-7.1, 1.7)
Acute kidney injury	41	(1.9)	8.1	50	(2.3)	10.2	-2.1	(-5.9, 1.7)
Arteriosclerosis, vascular disease, PVD[4]	**43**	**(2.0)**	**8.5**	**34**	**(1.5)**	**6.9**	**1.6**	**(-1.9, 5.1)**
Angina	33	(1.5)	6.5	43	(2.0)	8.8	-2.3	(-5.8, 1.2)

Source: Reviewer's analysis: ODE1\adsae, SAE ode1 table, dataset adae, adsl
** FMQ occurring in at least 1% of canagliflozin subjects are listed under the primary FMQ
[1] Includes acute MI, angina unstable, coronary artery disease, arteriosclerosis coronary artery, acute coronary syndrome, coronary artery stenosis, myocardial infarction, and myocardial ischaemia
[2] Includes acute coronary syndrome, angina unstable, acute MI and myocardial infarction
[3] Renal injury includes acute kidney injury, anuria, renal failure, renal impairment, and cardiorenal syndrome.
[4] The preferred terms occurring in at least 5 canagliflozin subjects include peripheral arterial occlusive disease, diabetic gangrene, and peripheral vascular disease.
Abbreviations: AMI, acute myocardial infarction; ACS, acute coronary syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; FDA, Food and Drug Administration; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years; PVD, peripheral vascular disease; SAE, serious adverse event; TIA, transient ischemic attack

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Approximately 13% of subjects in the canagliflozin arm and 14% of subjects in the placebo arm discontinued medication due to an AE. The most common reasons for medication discontinuation in both arms were infection and blood creatinine increase; the percentage of subjects with discontinuations for such events was similar in the two arms. Results from the MedDRA Preferred Term Analysis and FDA MedDRA Query (FMQ) Analysis, discussed below, were generally consistent.

MedDRA Preferred Term Analysis

There were no preferred terms (PTs) that had an incidence of at least 1%, and there were no PTs with an IRD at least 2. The PTs acute myocardial infarction, chronic kidney disease, and diabetic

ketoacidosis had an IRD of at least 1. The incidence rates of those AEs were all <0.5%. The most common reason for study drug withdrawal was blood creatinine increase (0.9% versus 0.7%, canagliflozin versus placebo, respectively).

FDA MedDRA Query (FMQ) Analysis

The most common AE resulting in medication discontinuation was infection (2.4% of subjects in each arm). Blood creatinine increased was the next most common reason. There were no FDA MedDRA queries that had an IRD of 1 or greater in the canagliflozin arm compared to placebo.

The largest IRD [-4.9, 95% CI: -7.4 to -2.4] for discontinuation due to an AE in the placebo arm was for the FDA MedDRA query of heart failure or pulmonary edema (0.3% of subjects versus 1.4% of subjects in canagliflozin versus placebo arms, respectively).

The table below shows the two FMQs that occurred in at least 2% of canagliflozin treated subjects. It also shows preferred terms in the FMQ occurring in at least two subjects.

Table 30. FDA MedDRA Queries Leading to Discontinuation, Safety Population, CREDENCE

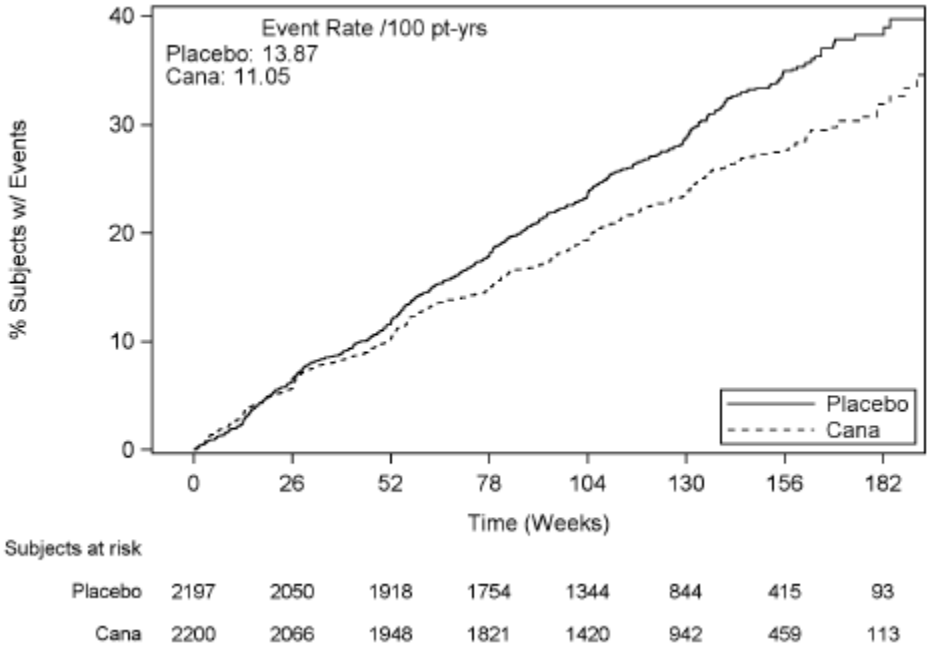
FDA MedDRA Query (FMQ) Preferred Terms[1]	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference	95% CI
AE leading to study drug withdrawal[2]	267	(12.1)	52.6	286	(13.0)	58.3	-5.7	(-15.0, 3.6)
AE leading to study drug withdrawal or interrupted and not restarted[3]	293	(13.3)	57.7	313	(14.2)	63.8	-6.1	(-15.8, 3.6)
Infection FMQ	53	(2.4)	10.4	52	(2.4)	10.6	-0.2	(-4.3, 3.9)
Urinary tract infection	9	(0.4)	1.8	8	(0.4)	1.6	0.2	(-1.5, 1.9)
Pneumonia	8	(0.4)	1.6	9	(0.4)	1.8	0.2	(1.9, 1.5)
Localised infection	4	(0.2)	0.8	3	(0.1)	0.6	0.2	(-1.0, 1.4)
Cellulitis	3	(0.1)	0.6	2	(0.1)	0.4	0.2	(-0.9, 1.3)
Diabetic gangrene	3	(0.1)	0.6	1	(0.0)	0.2	0.4	(-0.6, 1.4)
Cholecystitis	2	(0.1)	0.4	.		.	.	
Gangrene	2	(0.1)	0.4	8	(0.4)	1.6	-1.2	(-2.6, 0.2)
Necrotising fasciitis	2	(0.1)	0.4	.		.	.	
Osteomyelitis	2	(0.1)	0.4	2	(0.1)	0.4	0.0	(-1.1, 1.1)
Sepsis	2	(0.1)	0.4	1	(0.0)	0.2	0.2	(-0.8, 1.2)
Wound infection	2	(0.1)	0.4	.		.	.	

FDA MedDRA Query (FMQ) Preferred Terms[1]	Canagliflozin N=2200 n	(%)	Rate/1000 Pt-Yrs	Placebo N=2197 n	(%)	Rate/1000 Pt-Yrs	Canagliflozin - Placebo Rate Difference	95% CI
AEs suggestive of renal-related injury	42	(1.9)	8.3	49	(2.2)	10.0	-1.7	(-5.5, 2.1)
Blood creatinine increased	20	(0.9)	3.9	16	(0.7)	3.3	0.6	(-1.8, 3.0)
Glomerular filtration rate decreased	10	(0.5)	2.0	10	(0.5)	2.0	0.0	(-1.9, 1.9)
Acute kidney injury	7	(0.3)	1.4	8	(0.4)	1.6	-0.2	(-1.8, 1.4)
Renal impairment	6	(0.3)	1.2	12	(0.5)	2.4	-1.2	(-3.0, 0.6)
Blood urea increased	4	(0.2)	0.8	.		.	.	
Renal failure	3	(0.1)	0.6	3	(0.1)	0.6	0.0	(-1.2, 1.2)

Source: Reviewer's analysis med dc ODE1, datasets: adae adsl
[1] Data shown if FMQ occurs in at least 2% canagliflozin treated subjects; select PTs shown.
[2] "AE leading to study drug withdrawal" is when the action taken due to an AE was study drug withdrawal.
[3] "interrupted and not restarted" includes subjects who had AEs marked as "study drug interrupted" and where the treatment end date is the same as the AE start date.
Abbreviations: AE, adverse event; CI, confidence interval; FDA, Food and Drug Administration; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years

Figure 13 shows the time to medication discontinuation in CREDENCE with the two curves starting to separate after 26 weeks. Subjects in the placebo arm had a higher rate of medication discontinuation.

Figure 13. Time to Medication Discontinuation, on-Treatment, CREDENCE



Source: Applicant CREDENCE CSR, Figure 4. Gsiexp01.sas
Abbreviation: CANA, canagliflozin

7.6.5. Treatment-Emergent Adverse Events

Results from the MedDRA Preferred Term Analysis and FDA MedDRA Query (FMQ) Analysis, discussed below, were generally consistent. Both hypotension and fungal infection occurred more frequently with canagliflozin than placebo (Table 31), both of which are described in current labeling.

Canagliflozin causes osmotic diuresis, which may lead to reductions in intravascular volume. The rate of hypotension was 12.6/1,000 patient-years versus 6.7/1,000 patient-years on canagliflozin versus placebo, respectively, similar to the rates seen in trials of glycemic control and the CANVAS program. Subjects with lower eGFRs appear to be at increased risk for hypotension (Table 33). While the current Warning and Precaution for hypotension in the canagliflozin label indicates that the elderly, baseline diuretic use, and low systolic blood pressure are risk factors for hypotension, these factors did not appear to increase risk in CREDENCE.

The rate of fungal infections was 24.8/1,000 patient-years versus 20.0/1,000 patient-years on canagliflozin versus placebo, respectively. The PTs that drove the difference in fungal infections were onychomycosis, vulvovaginal mycotic infection, balanitis candida, and vulvovaginal candidiasis.

Table 31. Adverse Events[1] Occurring at Incidence Rate Difference ≥2, Phase 3 Safety Population, CREDENCE

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
Preferred Term	**n**	**(%)**	**Rate/1000 Pt-Yrs**	**n**	**(%)**	**Rate/1000 Pt-Yrs**	**Rate Difference**	**95% CI**
Hypotension	**61**	**(2.8)**	**12.0**	**33**	**(1.5)**	**6.7**	**5.3**	**(1.48, 9.12)**
Skin ulcer	99	(4.5)	19.5	77	(3.5)	15.7	3.8	(-1.43, 9.03)
Diabetic foot	**43**	**(2.0)**	**8.5**	**24**	**(1.1)**	**4.9**	**3.6**	**(0.34, 6.86)**
Urinary tract infection	219	(10.0)	43.1	199	(9.1)	40.6	2.5	(-5.54, 10.54)
Onychomycosis	45	(2.0)	8.9	33	(1.5)	6.7	2.2	(-1.31, 5.71)
Diabetic retinopathy	70	(3.2)	13.8	59	(2.7)	12.0	1.8	(-2.69, 6.29)

Source: Reviewer's analysis adae PT, dataset adae, adsl
[1] AE in at least 2% of canagliflozin treated subjects
[2] Coded as MedDRA preferred terms
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; pt-yrs, patient years

Table 32. FDA MedDRA Queries[1] Occurring at Higher Frequency in Treatment Arm Than Comparator Arm, Phase 3 Safety Population

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
FDA MedDRA Query[2] Preferred Term	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference	95% CI
Hypotension	64	(2.9)	12.6	33	(1.5)	6.7	5.9	(2.02, 9.78)
Hypotension	61	(2.8)	12.0	33	(1.5)	6.7	5.3	(1.48, 9.12)
Blood pressure decreased	3	(0.1)	0.6	.		.	.	
Infection, fungal	126	(5.7)	24.8	98	(4.5)	20.0	4.8	(-1.09, 10.69)
Onychomycosis	45	(2.0)	8.9	33	(1.5)	6.7	2.2	(-1.31, 5.71)
Fungal skin infection	20	(0.9)	3.9	18	(0.8)	3.7	0.2	(-2.28, 2.68)
Tinea pedis	13	(0.6)	2.6	15	(0.7)	3.1	-0.5	(-2.69, 1.69)
Vulvovaginal mycotic infection	9	(0.4)	1.8	3	(0.1)	0.6	1.2	(-0.30, 2.70)
Fungal infection	8	(0.4)	1.6	7	(0.3)	1.4	0.2	(-1.43, 1.83)
Balanitis candida	7	(0.3)	1.4	1	(0.0)	0.2	1.2	(-0.05, 2.45)
Vulvovaginal candidiasis	7	(0.3)	1.4	4	(0.2)	0.8	0.6	(-0.84, 2.04)

Source: Reviewer's analysis TEAE ODE1, datasets: Adsl adae
At least 2% of canagliflozin subjects and IRD of 2
Preferred terms shown if in at least 5 canagliflozin subjects
[1] Treatment-emergent adverse event defined as [definition]
[2] Coded as MedDRA preferred terms
Abbreviations: CI, confidence interval; IRD, incidence rate difference; N, number of subjects in treatment arm; n, number of subjects with adverse event; pt-yrs, patient years

Table 33. Subgroup Analysis of Hypotension FMQ

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo
Subgroup	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference
Hypotension FMQ[1]	64	(2.9)	12.6	33	(1.5)	6.7	5.9
Subgroup							
Baseline eGFR (mL/min/1,73 m^2)							
<45	32	(1.5)	6.3	13	(0.6)	2.7	3.7
45 to <60	19	(0.9)	3.7	11	(0.5)	2.2	1.5
≥60	13	(0.6)	2.6	9	(0.4)	1.8	0.7
Age							
<55	10	(0.5)	2.0	3	(0.1)	0.6	1.4
55 to <65	21	(1.0)	4.1	11	(0.5)	2.2	1.9
65 to <75	21	(1.0)	4.1	13	(0.6)	2.7	1.5
≥75	12	(0.5)	2.4	6	(0.3)	1.2	1.1
Baseline diuretics							
Y	33	(1.5)	6.5	20	(0.9)	4.1	2.4
N	31	(1.4)	6.1	13	(0.6)	2.7	3.5
Baseline SBP ≤120 mmHg	13	(0.6)	2.6	4	(0.2)	0.8	1.7
Baseline SBP >120 mmHg	51	(2.3)	10.0	28	(1.3)	5.7	4.3

Source: Reviewer's analysis: adae_PT_hypotension, dataset: adae, adsl
[1] Hypotension FMQ includes the PTs "hypotension" and "blood pressure decreased"
Abbreviations: eGFR, estimated glomerular filtration rate; FMQ, FDA MedDRA Query; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years, Y=yes, N=no

Table 34 shows the incidence of mycotic genital infections by gender. The percentage of females with mycotic genital infections was higher than males, but the incidence overall was lower than in the glycemic control trials and the CANVAS program. The median duration of infection was shorter in females (14 days in the canagliflozin arm) compared to males (42 days in the canagliflozin arm; based on the Applicant's CSR.).

Table 34. Mycotic Genital Infections, On-Treatment, CREDENCE

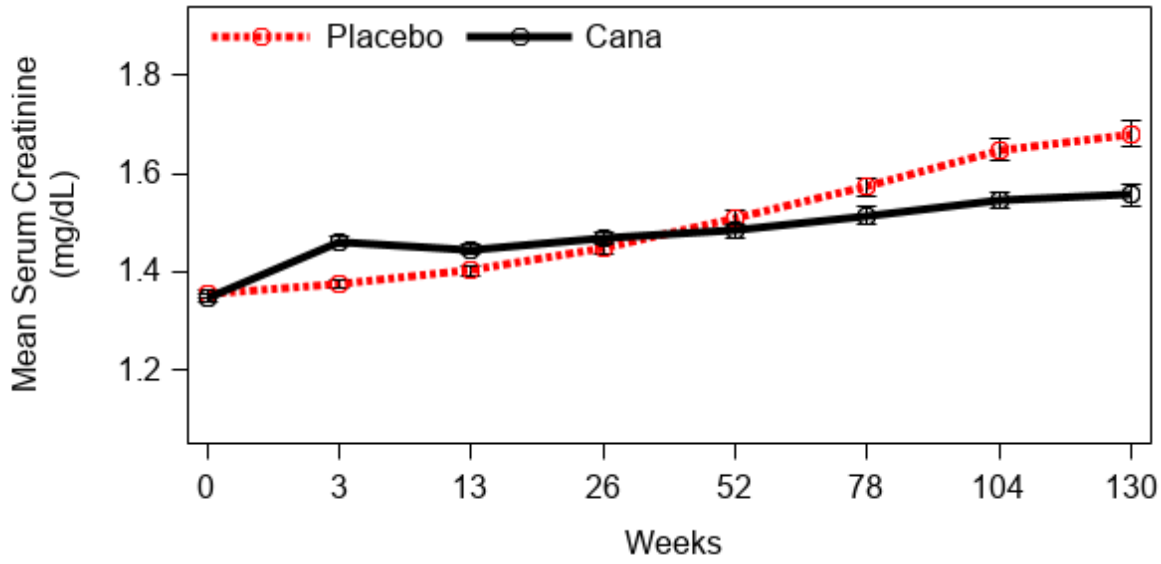
	Canagliflozin N=1439			Placebo N=1466		
Preferred Term	**n**	**(%)**	**Rate/1000 Pt-Yrs**	**n**	**(%)**	**Rate/1000 Pt-Yrs**
Leading to d/c in males	5	(0.3)		0		
Total Males	**28**	(1.9)	**8.4**	**3**	(0.2)	**0.9**
Balanoposthitis	15	(1.0)		2	(0.1)	
Balanitis candida	7	(0.5)		1	(0.1)	
Genital candidiasis	2	(0.1)		0		
Genital infection	1	(0.1)		0		
Genital infection fungal	3	(0.2)		0		
Penile infection	1	(0.1)		0		
	Canagliflozin N=761			**Placebo N=731**		
Leading to d/c in females	2	(0.3)		0		
Total Females	**22**	**(2.9)**	**12.6**	**10**	**(1.4)**	**6.1**
Vulvovaginal mycotic infection	9	(1.2)		2	(0.3)	
Vulvovaginal candidiasis	7	(0.9)		4	(0.5)	
Vaginal infection	4	(0.5)		2	(0.3)	
Vulvovaginitis	3	(0.4)		3	(0.4)	
Vulvitis	1	(0.1)		0		
Genital infection fungal	1	(0.1)		0		

Source: reviewer's analysis: adae PT, dataset adae adsl
Abbreviations: d/c, discontinuation; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years

7.6.6. Laboratory Findings

Section 6.1 Clinical Studies Experience of the current label describes increases in serum potassium, magnesium, phosphate, LDL, and hemoglobin, and decreases in bone mineral density. In CREDENCE, small mean increases in hemoglobin, magnesium, and phosphate were observed following initiation of canagliflozin. The difference between arms persisted for the treatment duration for hemoglobin and magnesium but not phosphate. There were no obvious differences between treatment arms in changes in potassium or LDL over time (See Appendix III.17 for tables of summary laboratory information and figures of changes over time). In CREDENCE, the mean baseline serum creatinine was similar between arms (1.4±0.4 mg/dL in both arms). At the end of treatment, the mean serum creatinine was 1.7±1.1 mg/dL and 1.8±1.1 mg/dL in the canagliflozin and placebo arms, respectively. There was an initial small rise in serum creatinine by week 3 in the canagliflozin arm compared to placebo (Figure 14).

Figure 14. Serum Creatinine Over Time



Source: Reviewer's analysis, lab\scre\lab_scr, dataset: adlbcmReview Issues Relevant to the Evaluation of Risk
Abbreviation: CANA, canagliflozin

7.6.7. Previously Identified Risks

Overview

The safety review focused on previously identified risks of SGLT2 inhibitors and canagliflozin (see Section 7.2). Canagliflozin's label contains a Boxed Warning for lower limb amputations based on the CANVAS program.[6] As compared to the CANVAS trials, the rate/1,000 patient years of lower limb amputations was higher in both arms in CREDENCE (see table below). The rate and incidence of such events was slightly numerically greater in the canagliflozin as compared to the placebo arm, resulting in a HR greater than 1 with wide confidence intervals (on-study HR (95% CI) of 1.1 (0.8 to 1.6); on-treatment HR (95% CI) of 1.2 (0.8 to 1.8).

Table 35. Summary of Atraumatic Lower Extremity Amputations, Safety Population

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
Location	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference	95% CI
All on-study analysis	70	(3.2)	12.3	63	(2.9)	11.2	1.2	(-2.87, 5.18)
All on-treatment	55	(2.5)	10.8	45	(2.0)	9.3	1.6	(-2.40, 5.60)

Source: Reviewer's analysis: amputation, dataset: ampu.
Subject-years calculated as time from first dose to first amputation. 5030 patient-years for canagliflozin, 4862 patient-years for placebo
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years

[6] The incidence rate of lower limb amputation in CANVAS was 5.9 vs 2.8 events per 1000 patient-years and in CANVAS-R was 7.5 vs 4.2 events per 1000 patient-years, canagliflozin versus placebo, respectively. The HR (95% CI) in CANVAS was 2.12 (1.34 to 3.38) and in CANVAS-R was 1.80 (1.10 to 2.93).

As shown in Table 36, the incidence of acute kidney injury in CREDENCE was not greater in the canagliflozin as compared to the placebo arm (3.9% versus 4.5% of subjects or 17/1,000 patient-years versus 20/1,000 patient-years, canagliflozin versus placebo, respectively). There was no difference between treatment arms in bone fractures (3.1% of patients in each arm). Hyperkalemia was more common in the placebo arm than in the canagliflozin arm.

Table 36. FDA MedDRA Analyses of Select TEAEs

	Canagliflozin N=2200			Placebo N=2197			Canagliflozin - Placebo	
TEAE	n	(%)	Rate/1000 Pt-Yrs	n	(%)	Rate/1000 Pt-Yrs	Rate Difference*	95% CI
Fracture	69	(3.1)	13.6	68	(3.1)	13.9	-0.3	(-4.94, 4.34)
Fracture (SAE)	25	(1.1)	4.9	22	(1.0)	4.5	0.4	(-2.35, 3.15)
Renal injury[1]	140	(6.4)	27.6	184	(8.4)	37.5	-9.9	(-17.01, -2.79)
Acute kidney injury (PT)	86	(3.9)	16.9	98	(4.5)	20.0	-3.1	(-8.46, 2.26)
Renal injury (SAE)	55	(2.5)	10.8	66	(3.0)	13.5	-2.7	(-7.07, 1.67)
Acute kidney injury (PT)	41	(1.9)	8.1	50	(2.3)	10.2	-2.1	(-5.90, 1.70)
Diabetic ketoacidosis (PT)	11	(0.5)	2.2	2	(0.1)	0.4	1.8	(0.23, 3.37)
Hyperkalemia FMQ[2]	151	(6.9)	29.7	181	(8.2)	36.9	-7.2	(-14.39, -0.01)
Hyperkalemia (PT)	135	(6.1)	26.6	159	(7.2)	32.4	-5.8	(-12.57, 0.97)
Renal cell carcinoma[3]	1	(0.0)	0.2	2	(0.1)	0.4	-0.2	(-1.16, 0.76)

Source: Reviewer's analysis: ode1, teae dataset: adae

[1] Renal injury FMQ includes the PTs acute kidney injury, renal failure, cardiorenal syndrome, anuria, nephropathy toxic, postrenal failure, renal impairment, urine output decreased

[2] Hyperkalemia FMQ includes hyperkalemia and blood potassium increased

[3] Renal cell carcinoma includes the PTs metastatic renal cell carcinoma, renal cell carcinoma, renal cell carcinoma stage I

Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects in specified population or group; PT, preferred term; pt-yrs, patient years; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Diabetic Ketoacidosis

A Diabetic Ketoacidosis Adjudication Committee provided an independent assessment of ketone-related events to determine whether or not the events met criteria for a clinical diagnosis of diabetic ketoacidosis (DKA) using criteria specified in a committee charter. Potential DKA events were 1) reported by investigators on a supplemental data collection form or 2) identified by the Applicant based on a list of preferred terms. For nonserious AEs, only those with signs/symptoms suggestive of DKA or requiring medical intervention were adjudicated. Each case was assigned one of the following categories related to the likelihood of the case being a DKA event: confirmed, probable, possible, doubtful, confirmed as not, or unable to determine. If the event was not adjudicated as DKA, the committee was to assess whether there was an alternative diagnosis such as lactic acidosis.

DKA events were uncommon overall, occurring in fewer than 1% of study subjects, but were more common in the canagliflozin arm (12 confirmed, probable, or possible DKA events in 11 subjects) compared with placebo (one event). Nine of the events in the canagliflozin arm were serious, and

six led to discontinuation of study drug. None were fatal. All events in the canagliflozin arm occurred in patients on background insulin. Two of the subjects were diagnosed with T1DM by antibody testing after the event, and a third was diagnosed with latent autoimmune diabetes of adults. The DKA event generally occurred in the setting of recent or concurrent illness or a reduction in insulin dose.

Necrotizing Fasciitis

There were two cases of necrotizing fasciitis, and both occurred in the canagliflozin arm in the setting of operations for unrelated conditions (penile carcinoma and plantar wart):

Subject (b) (6): 49-year-old man with a history of T2DM for 18 years complicated by retinopathy, neuropathy, and nephropathy with a baseline eGFR of 51 mL/min/1.73 m^2, hyperlipidemia, hypertension, hyperuricemia, and peripheral vascular disease complicated by left above knee and right toe amputations. On an unknown date, the subject developed a foreskin mass. On Day 62, he was diagnosed with phimosis and underwent circumcision. Histology of the foreskin identified an invasive keratotic squamous epithelial carcinoma. Two days later, on Day 64, the subject developed swelling of the scrotum and inflammation of the perineum and was diagnosed with necrotizing fasciitis (reported term Fournier gangrene on scrotum and penis) and sepsis. Canagliflozin was discontinued, he was started on broad spectrum antibiotics, and he underwent amputation of the penis. The sepsis resolved on Day 68, and the necrotizing fasciitis resolved on Day 91.

Subject (b) (6): 60-year-old white male with a history of T2DM for 13 years complicated by neuropathy and nephropathy with a baseline eGFR of 80 mL/min/1.73 m^2, hyperlipidemia, and hypertension. On Day 552, he had a plantar wart removed from his right foot and was treated with sulfadiazine silver. On Day 555, he went to the podiatrist with a wound infection at the base of the fourth and fifth toe and cellulitis extending to the midcalf. He was treated with cephalexin and wound care. Canagliflozin was discontinued on Day 560. He was admitted to the hospital on Day 561 with necrotizing fasciitis of the right foot requiring a right below knee amputation. The necrotizing fasciitis was considered doubtfully related to canagliflozin.

7.6.8. Concomitant Metformin Use

As previously noted, concomitant metformin use was common in the trial population. Key safety findings in this subgroup were consistent with those of the overall trial population (Table 37 and Table 38).

Table 37. Summary of Adverse Events for Subjects With Baseline Metformin Use

	------- Placebo ------- ------- (N=1268) ------		--------- Cana -------- ------- (N=1275) ------	
	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**
Any Adverse Events	1068 (84.2)	366.55	1013 (79.5)	336.73
Adverse Events Leading to Discontinuation	136 (10.7)	46.68	127 (10.0)	42.22
Adverse Events Related to Study Drug*	204 (16.1)	70.01	252 (19.8)	83.77
Adverse Events Related to Study Drug* and Leading to Discontinuation	25 (2.0)	8.58	34 (2.7)	11.30
Serious Adverse Events	417 (32.9)	143.12	390 (30.6)	129.64
Serious Adverse Events Leading to Discontinuation	75 (5.9)	25.74	66 (5.2)	21.94
Serious Adverse Events Related to Study Drug*	21 (1.7)	7.21	32 (2.5)	10.64
Serious Adverse Events Related to Study Drug* and Leading to Discontinuation	7 (0.6)	2.40	7 (0.5)	2.33
Death	63 (5.0)	21.62	64 (5.0)	21.27

Note: Percentages calculated with the number of subjects in each group as the denominator.
Note: *Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
Note: **The Denominator is the total of each subject's exposure of the study medication plus 30 days.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Death is based on the number of subjects who have AE with fatal outcome.
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Source: Applicant, Response to FDA's Clinical Request for Information dated May 21, 2019.
Abbreviations: CANA, canagliflozin; N, number of subjects in treatment arm; n, number of subjects in specified population or group; pt-yrs, patient years

Table 38. Selected Adverse Events of Interest for Subjects With Baseline Metformin Use

	----- Placebo (N=1268) -----		------- Cana (N=1275) ------		------- Cana vs. Placebo -------	
	n(%)	Rate(/1000 subject-years)	n(%)	Rate(/1000 subject-years)	IRD(/1000 subject-years)	95% CI
Osmotic Diuresis	20 (1.6)	6.86	26 (2.0)	8.64	1.78	(-2.80, 6.36)
Volume Depletion	64 (5.0)	21.97	80 (6.3)	26.59	4.63	(-3.36, 12.62)
Hypoglycemia	108 (8.5)	37.07	113 (8.9)	37.56	0.50	(-9.39, 10.38)
UTI	114 (9.0)	39.13	137 (10.7)	45.54	6.41	(-4.10, 16.93)
Female GMI	8 (1.8)	7.85	16 (3.5)	15.08	7.23	(-2.37, 16.82)
Hypersensitivity/Cutaneous Reactions	16 (1.3)	5.49	11 (0.9)	3.66	-1.83	(-5.42, 1.75)
Hepatic Injury	17 (1.3)	5.83	17 (1.3)	5.65	-0.18	(-4.16, 3.80)
Renal related AEs (including AKI)	188 (14.8)	64.52	139 (10.9)	46.20	-18.32	(-30.36, -6.28)
Male GMI	3 (0.4)	1.58	20 (2.4)	10.27	8.69	(3.57, 13.80)
Photosensitivity	1 (0.1)	0.34	1 (0.1)	0.33	-0.01	(-1.34, 1.31)
VTE	7 (0.6)	2.40	12 (0.9)	3.99	1.59	(-1.46, 4.63)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: 95% CI is based on the Normal approximation for the incidence rate difference (IRD).
Note: Denominators are restricted to the respective gender for female and male GMI.
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Source: Applicant, Response to FDA's Clinical Request for Information dated May 21, 2019.
Abbreviations: AE, adverse event; AKI, acute kidney injury; CANA, canagliflozin; GMI, genital mycotic infection; N, number of subjects in treatment arm; n, number of subjects in specified population or group; UTI, urinary tract infection; VTE, venous thromboembolism

Lactic acidosis is a known risk of metformin use in patients with lower levels of kidney function. In CREDENCE, lactic acidosis events were reported by investigators as adverse events but were not adjudicated. Six events, two of them serious, were reported in patients randomized to canagliflozin, and three nonserious events were reported in patients randomized to placebo. Half of the events in the canagliflozin arm occurred in the setting of metformin use within 45 days of the event. One led to withdrawal of study drug. Two occurred in the setting of acute illness (heart failure and diarrhea secondary to *Campylobacter jejuni* in subjects (b) (6) and (b) (6), respectively). One occurred 301 days after discontinuation of canagliflozin (Subject (b) (6)), and one occurred 47 days after discontinuation of canagliflozin (Subject (b) (6)). Two were incidental laboratory findings with no clinical sequelae that were identified at a site in Spain that appeared to be screening for DKA in asymptomatic individuals (Subjects (b) (6) and (b) (6)).

8. Therapeutic Individualization

8.1. Intrinsic Factors

No additional clinical pharmacology studies were submitted as part of the application. CREDENCE was conducted in patients with reduced kidney function. See the label for other intrinsic factors that affect exposures.

8.2. Drug Interactions

No additional drug interaction studies were submitted as part of the application. The Office of Clinical Pharmacology (OCP) reviewed the dosing recommendations for canagliflozin when used concomitantly with UDP-Glucuronosyl Transferase (UGT) enzyme inducers.

In patients with an eGFR of 60 mL/min/1.73 m^2 or greater, the recommended starting dose of canagliflozin is 100 mg once daily, taken before the first meal of the day. In patients tolerating canagliflozin 100 mg once daily who require additional glycemic control, the dose can be increased to 300 mg once daily. Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%.

For patients with an eGFR of 60 mL/min/1.73 m^2 or greater taking a UGT inducer, the applicant proposed to increase the dose of canagliflozin to 300 mg once daily only if they required additional glycemic control; however, the proposed labeling did not address the reduced exposure for patients who do not require additional glycemic control but who might have reduced renal and heart failure benefits. For such patients, OCP recommended doubling the dose of canagliflozin to 200 mg once daily. Patients with an eGFR of 60 mL/min/1.73 m^2 or greater who require additional glycemic control could then titrate the dose to 300 mg once daily, which is supported by the available dose-response data in patients with this level of renal function (Reference: Clinical Pharmacology review NDA204042 dated August 22, 2012).

In patients with an eGFR of 45 to < 60 mL/min/1.73 m^2 and 30 to < 45 mL/min/1.73 m^2 (with albuminuria >300 mg/day) the recommended dose of canagliflozin is 100 mg once daily; patients already initiated on therapy whose eGFR falls below those levels can continue 100 mg once daily. For those taking a concomitant UGT inducer, OCP recommended increasing the dose of canagliflozin to 200 mg once daily. The dose-response data in patients with eGFR less than 60 mL/min/1.73m^2 does not support titration to 300 mg for additional glycemic control; therefore, OCP recommends adding another antihyperglycemic agent for additional glycemic control in these patients.

8.3. Pediatric Labeling/Plans for Pediatric Drug Development

There are no new pediatric data. A full waiver will be issued for pediatric studies under Pediatric Research Equity Act for the treatment of diabetic nephropathy in pediatric patients with T2DM. The condition is rare in pediatric patients and hence the drug is not likely to be used in a substantial number of pediatric patients and necessary studies are impossible or highly impractical.

8.4. Pregnancy and Lactation

There are no new data related to pregnancy and lactation.

9. Product Quality

There are no new product quality data.

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

FDA Inspections: We did not request inspections of clinical investigator sites. This was based on review of financial disclosures and consistency of the primary endpoint findings after excluding individual sites that enrolled over 25 subjects.

Site Audits and Data Quality Assurance: During the course of the trial, the Applicant and Clinical Research Organization monitored the study and conducted investigator site audits to ensure the accuracy and reliability of clinical study data. The study-specific monitoring guidelines are stored in the trial master file.

According to the CSR, written instructions were provided for the collection of source documentation. Source documentation was reviewed for accuracy and completeness by the contract research organization during on-site monitoring visits, and internal data were reviewed throughout the study and at the time of database lock. Discrepancies were resolved with the investigator or designees. Risk-Based Monitoring was employed to further assure data quality. A flexible monitoring strategy was in place which allowed the monitoring frequency to be adjusted based on a site's operational and quality metrics and trends. Ongoing evaluation of data was done both by on-site and in-house remote monitoring.

Financial Disclosures: The Applicant has adequately disclosed financial arrangements with clinical investigators in CREDENCE (see Section 24 for details). None of the investigators were full or part-time employees of Janssen Pharmaceuticals, Inc. Six investigators reported disclosable financial interests: two reported "significant payments of other sorts" and four reported significant equity interest in Johnson and Johnson.

Protocol Deviations: A total of 679 (31%) placebo subjects and 677 (31%) canagliflozin subjects had one or more protocol deviations (Table 39). The most common deviations were classified as "other" (539 [25%] placebo and 557 [25%] canagliflozin subjects) and "entered but did not satisfy criteria" (143 [6.5%] placebo and 147 [6.7%] canagliflozin subjects). The most common deviations listed as "other" were delays in signing updated informed consent documents following randomization. The protocol deviations were balanced between arms.

Table 39. Protocol Deviations in Randomized Subjects

Protocol Deviations	Canagliflozin N=2202 (%)	Placebo N=2199 (%)
Subjects with protocol deviations	677 (30.7)	679 (30.9)
Other	557 (25.3)[1,2]	539 (24.5)
Informed consent	467 (21.2)	461 (21.0)
Late serious adverse event reporting	107 (4.9)	102 (4.6)
Exam, lab, or ECG done at wrong time	12 (0.5)	11 (0.5)
Declined participation, but samples drawn	12 (0.5)[2]	10 (0.5)
Other	3 (0.1)	2 (0.1)
Not a protocol violation	1 (0.0)	0
Entered but did not satisfy criteria	146 (6.6)[2]	143 (6.5)
Compliance missing or <80%	20 (0.9)	21 (1.0)
eGFR or UACR	19 (0.9)	13 (0.6)
Prohibited med (MRA)	19 (0.9)	21 (1.0)
Lab	17 (0.8)	14 (0.6)
Blood pressure	16 (0.7)	22 (1.0)
ACEi or ARB not stable or maxed	12 (0.5)	21 (1.0)
Procedure or cardiovascular history	12 (0.5)	9 (0.4)
Prohibited meds (ACEi and ARB)	11 (0.5)	6 (0.3)
Diabetic medical history	8 (0.4)	4 (0.2)
Other medical history	5 (0.2)	3 (0.1)
Malignancy	4 (0.2)	3 (0.1)
Time in study periods	4 (0.2)	9 (0.4)
HbA_{1c} or glucose	3 (0.1)	4 (0.2)
Participation in another trial (concurrent or too soon)	2 (0.1)	2 (0.1)
Prior canagliflozin	1 (0.0)	0

Protocol Deviations	Canagliflozin N=2202 (%)	Placebo N=2199 (%)
Received a disallowed concomitant treatment during randomization	23 (1.0)	50 (2.3)[3]
Received wrong treatment or incorrect dose	20 (0.9)[2]	23 (1.0)
Developed withdrawal criteria but not withdrawn	2 (0.1)	1 (0.0)

Source: Office of Computational Science Analysis Studio, Custom Table Builder, reviewer's analysis: dev.
Dataset: DV, ADSL;
The reviewer reviewed the protocol deviation descriptions for subjects with reasons categorized as "other" and regrouped them into the subcategories shown under "Other". The sum of the subcategories is greater than the number of subjects categorized in "other" because some subjects had more than one protocol deviation categorized as "other".
Source: Reviewer's analysis differs from the Applicant's. Subject ID 702344 received the wrong dose, but Applicant categorized as "other." Subject ID 700435 declined participation in a substudy, but had lab samples drawn; the Applicant had categorized as "Entered but did not satisfy criteria."
Subject ID 700811 and 707092 started disallowed mineralocorticoid antagonist during screening, so are not counted in "received disallowed concomitant treatment".
Abbreviations: ACEi, angiotensin -converting enzyme inh bitor; ARB, angiotensin II receptor blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid antagonist; N, number of subjects; UACR, urine a bumin-to-creatinine ratio

11. Advisory Committee Summary

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held.

III. Appendices

12. Summary of Regulatory History

Canagliflozin was approved on March 29, 2013, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and on October 29, 2018, to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. The canagliflozin/metformin immediate release formulation was approved on August 8, 2014, and the extended-release formulation on September 20, 2016. The combination products are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.

In 2013, the Applicant submitted an original investigational new drug (IND) application to investigate canagliflozin for the treatment of renal disease in adult patients with type 2 diabetes mellitus, reduced estimated glomerular filtration rate (eGFR), and albuminuria. The IND-opening study was the phase 3 trial (28431754DNE3001) titled "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)."

13. Pharmacology Toxicology Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

No new preclinical studies were conducted to support the proposed indication.

13.2. Individual Reviews of Studies Submitted to the NDA

Not applicable.

14. Clinical Pharmacology Assessment: Additional Information

No new clinical pharmacology studies were conducted to support the proposed indication.

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Not applicable.

15. Trial Design: Additional Information

Important Trial Dates

The first patient visit occurred on February 21, 2014. The database was locked for the interim analysis on June 13, 2018. The Independent Data Monitoring Committee (IDMC) met on July 9, 2018, to evaluate the interim data, and they recommended early termination of the trial for efficacy at that time. The Applicant announced that the trial would be terminated early on July 16, 2018, and the last patient visit occurred on October 30, 2018. The database was locked November 26, 2018.

Trial Administrative Structure

Steering Committee

A Steering Committee (SC) of external scientific experts and representatives of the Applicant and Academic Research Organization provided scientific input on study design, provided academic leadership to study sites, reviewed study progress, and played a lead role in the study analysis and publication of results. Meetings were to be held at least quarterly, and additional ad hoc meetings could be scheduled as deemed necessary by the SC. The Applicant submitted minutes for meetings of the SC.

Independent Data Monitoring Committee

An IDMC monitored study progress and safety and efficacy data on a regular basis. IDMC membership and responsibilities were defined by a written charter. The committee met at least every 6 months or "as considered appropriate by the IDMC Chairperson." Each meeting began with an open session that generally included the SC co-chairs, representative for Janssen, and members of the Statistics Collaborative. This was followed by a closed session that included only individuals from the IDMC and the Statistics Collaborative. Data for the closed session were presented in a semiblinded manner (Group A and B), but the IDMC received the identities of the groups. At the end of each IDMC meeting, a "CREDENCE IDMC Meeting Report" was submitted

to the SC Chairperson providing a high-level recommendation regarding the trial. The objectives of the IDMC were to:

1. Monitor unblinded safety and endpoint data by treatment group, including serious adverse events (SAEs), events resulting in study drug discontinuation, and renal and cardiovascular (CV) adverse events.
2. Review and evaluate unblinded safety and efficacy results from a prespecified interim analysis.

The Applicant submitted minutes for meetings of the IDMC.

Reviewer's comment: Steering Committee and IDMC discussions pertaining to trial design and protocol amendments are discussed in the relevant sections of this review.

Statistics Reporting Group

An independent Statistics Reporting Group performed analyses and generated reports for the IDMC according to a prespecified analysis plan.

Endpoint Adjudication Committee

An Endpoint Adjudication Committee (EAC) adjudicated all renal and cardiovascular events that were components of primary and secondary endpoints. The EAC classified the cause of all deaths and determined whether prespecified endpoint criteria were met for nonfatal events.

Potential endpoint events were each assigned to two reviewers. If a reviewer believed they had been unblinded to treatment, they were required to alert the EAC Coordinator who would redact the relevant information and then assign another adjudicator. Discordant adjudication decisions were either sent to a third adjudicator who was blinded to the initial adjudication result or was discussed at a disagreement meeting. It is not clear how this determination was made. If the third adjudicator supported the decision of one of the initial adjudicators, that was the final decision. Otherwise the event was reviewed in a disagreement meeting by a minimum of three committee members, including the two original adjudicators and a committee chairperson. The final decision was made by consensus. The committee was governed by an EAC Charter issued on June 17, 2014, with revisions issued on October 24, 2016, and September 1, 2017.

Reviewer's comment: The October 2016 revision updated the definition of doubling of serum creatinine events to include events in which a confirmatory creatinine value could not be obtained due to death or dialysis and there was no evidence of acute kidney injury. Both revisions to the charter otherwise included only minor modifications to the process and clarifications to endpoint definitions.

Medical Safety Review Committee

A Medical Safety Review Committee internal to the Applicant was to include at least one medical expert and one statistician. The committee reviewed blinded clinical and laboratory safety data across the canagliflozin clinical development program on a regular basis and could refer potential safety concerns to the IDMC.

Safety Committees

Independent safety committees were responsible for evaluating specific adverse events across the canagliflozin development program:

- A Diabetic Ketoacidosis Adjudication Committee adjudicated "ketone-related events" (e.g., diabetic ketoacidosis [DKA], metabolic acidosis, or acidosis) to determine whether the event met criteria for a clinical diagnosis of DKA.
- A Fracture Adjudication Committee provided independent assessment, verification, and classification of bone fracture events.
- A Pancreatitis Adjudication Committee provided independent assessment and classification of events related to pancreatitis.

Phases of Study

Subjects first entered a pretreatment phase that included prescreening, screening, and run-in periods:

- Prescreening: investigators identified patients with an eGFR of ≥30 to <90 mL/min/1.73 m^2 and a urine albumin-to-creatinine ratio (UACR) >300 mg/g to ≤5000 mg/g within the prior 3 months based on local laboratory measurements and assessed ACE inhibitor and angiotensin receptor blocker (ARB) use. With protocol amendment INT-2, these criteria were broadened to allow patients to meet prescreening criteria based on an albumin excretion rate >300 mg/24 hours, urine protein-to-creatinine ratio >500 mg/g, or protein excretion rate >500 mg/24 hours if UACR was not available; to remove the upper cutoff for UACR to allow a wider range local laboratory values to continue to screening and central laboratory measurement; to extend the time period for local laboratory values from 3 to 6 months before screening; and to allow repeat of local laboratory tests for those failing prescreening.
- Screening (up to 8 weeks): subjects meeting eligibility criteria were to be stabilized on a maximum-tolerated, labeled daily dose of an ACE inhibitor or ARB for at least 4 weeks before randomization. Other antihypertensive, lipid-lowering, and antihyperglycemic therapies were also to be stabilized and eligibility criteria were confirmed by central laboratory measurements.
- Run-in: subjects who continued to meet eligibility criteria entered a 2-week, single-blind, placebo run-in period during which they were to take one capsule daily to assess compliance with study drug. Subjects were also counseled to monitor blood glucose and provided with information on diet/exercise, hypoglycemia recognition and management, and medications for renal and CV risk factors. Subjects who completed the run-in period with ≥80% compliance by pill count and who continued to meet other entry criteria were eligible to be randomized.

Following successful completion of the pretreatment period, eligible subjects were randomized 1:1 to canagliflozin 100 mg daily or matching placebo. Subjects were to continue treatment unless they progressed to chronic dialysis or received a kidney transplant.

Study Assessments

Subjects were to return for visits at Weeks 3, 13, 26, and every 26 weeks thereafter. At Week 39 and the midpoint between office visits after Week 52 (i.e., Weeks 65, 91, 117, 143, 169, 195, 221, 247, and 273) patients were contacted by phone to assess status, diary entries, concomitant medication use, adverse events, and clinical endpoints.

A physical examination was conducted during the run-in phase, yearly, and at end of treatment (EOT). Vital signs and weight alone were measured at intervening visits. Serum chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total bilirubin, alkaline phosphatase, creatine phosphokinase, lactate dehydrogenase, uric acid, calcium, phosphate, albumin, total protein, magnesium) were assessed during prescreening and screening, on Day 1, at Weeks 3, 13, 26, 52 then every 26 weeks, and at EOT. With protocol amendment INT-1, the Applicant added an additional serum creatinine measurement at the run-in visit for subjects with an extended screening period. A hematology panel (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count) and dipstick urinalysis were assessed during screening, on Day 1, at Week 52 then yearly, and at EOT. Microscopic urinalysis was performed if the dipstick was abnormal. A first morning urine was collected for UACR during prescreening, screening, on Day 1, at Week 26 then every 26 weeks, and at EOT. Hemoglobin A_{1c} (HbA_{1c}) was assessed at screening, on Day 1, at Weeks 13, and 26, then every 26 weeks. A fasting lipid profile was assessed at screening, Day 1, yearly, and at EOT.

All protocol-specified testing was conducted by a central laboratory. The protocol noted that local laboratory tests could be performed more frequently, as clinically indicated, and that investigators were to "make every effort to collect all local laboratory data related to serum creatinine and eGFR during the study." Per protocol amendment INT-1, investigators were also instructed to collect the latest three prestudy local laboratory serum creatinine values, if available. Protocol amendment INT-1 also added a modified Rankin Scale assessment for subjects experiencing stroke during the study.

Study Procedures

Randomization

Randomization occurred centrally using an interactive web response system and a computer-generated randomization schedule prepared before the study. Randomization was balanced using randomly permuted blocks stratified by eGFR category (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2). Protocol amendment INT-2 specified that this would be based on the pretreatment eGFR value most proximate to the randomization visit.

Enrollment of subjects with an eGFR ≥60 to <90 mL/min/1.73 m^2 was initially limited to approximately 25% of the overall randomized subjects globally, but this cap was removed with protocol amendment INT-4. At that time, text was added indicating that capping might occur at the regional and/or site level if the ratio of 60:40 chronic kidney disease (CKD) 3: CKD 2 drifted substantially off target.

Blinding

The study was designed to be double-blind. Because canagliflozin causes glycosuria, the protocol noted that, if a urinalysis was performed locally for clinical management (e.g., to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis, if microscopic evaluation would be sufficient. The central laboratory was not to report urine glucose results.

Compliance

Investigators maintained a log of all study drug dispensed and returned, including a capsule count. Subjects who were poorly compliant were to receive counseling.

Concomitant Medications

Prohibited medications included other sodium-glucose cotransporter 2 (SGLT2) inhibitors (including commercially available canagliflozin), other investigational agents, combination use of ACE inhibitors and ARBs, and use of mineralocorticoid receptor antagonists (protocol amendment INT-4 allowed for concomitant use of mineralocorticoid receptor antagonists, if considered medically necessary) or a direct renin inhibitor.

Before randomization and throughout the study, investigators were expected to manage the subject's diet/exercise and medication regimen to achieve treatment goals for CKD and CV risk factors (HbA_{1c}, lipids, blood pressure) based on local guidelines for the care of patients with type 2 diabetes mellitus (T2DM) and CKD. After receiving comments from the Agency, the Applicant provided investigators with American Diabetes Association guidance as a reference for standards of care in the management of glycemic, blood pressure, and lipid control; instituted biannual individualized site metric reports; required IDMC monitoring of these data; and informed investigators that these measures had been instituted. With protocol amendment INT-2, investigators were encouraged to keep concomitant agents stable for ~4 weeks before randomization and to keep medications known to impact serum creatinine levels (e.g., nonsteroidal anti-inflammatory drugs, trimethoprim, cimetidine, probenecid, aminoglycosides, amphotericin, ketoconazole, and clofibrate) stable during screening and for ~2 weeks before any serum chemistry measurement during the study.

Reviewer's comment:

(1) The protocol did not provide specific recommendations regarding the concomitant use of metformin. All sites were provided with the American Diabetes Association Standards of Medical Care in Diabetes as a reference for standard of care, which recommends metformin as first-line treatment.

(2) The closed meeting minutes of the IDMC indicate that the committee was reviewing data on baseline use of antihyperglycemic, antihypertensive, lipid modifying, and antithrombotic agents. Early in the trial, the committee noted lower than expected use and recommended that the Steering Committee encourage investigators to use these agents. The IDMC also monitored the percentage of subjects reaching treatment goals during the study.

(3) The protocol did not require that patients be on background therapy for heart failure. In addition, in part because of concerns for hyperkalemia in a population with reduced kidney

function taking an ACE inhibitor or ARB, the protocol excluded patients on a mineralocorticoid receptor antagonist at baseline and, until protocol amendment INT-4, prohibited their concomitant use during the trial. We believe this approach was generally reasonable given that only ~ 15% of patients in each arm had a history of heart failure, and the appropriate management of heart failure in an advanced CKD population is not well established.

Subjects experiencing a volume depletion event or meaningful change in eGFR were to have concomitant medications reviewed and adjustments made as appropriate. A separate document provided guidance for the management of volume depletion events.

Follow-Up

Subjects who discontinued study medication prematurely were expected to attend all subsequent study visits in the same way as subjects still on study medication until the global trial end date. Subjects unwilling or unable to attend visits were offered a reduced schedule or were encouraged to allow regular contact (e.g., via phone, email, letter, social media, or fax) until study end, either with the subject, a friend, a relative, or their primary care physician, or to allow review of medical records. Vital status was to be collected by phone, in person, or by review of medical or public records for all subjects who permanently discontinued study drug early, withdrew from the study, or were lost to follow-up at the EOT visit.

Identification and Adjudication of Endpoints

Identification of Potential Endpoint Events

Potential endpoint events could be reported by site investigators, identified by medical monitors through review of adverse events, or identified by the Applicant through review of the clinical database, central laboratory database, or Global Medical Safety database (containing hospitalization data).

Reviewer's comment: The Applicant confirmed that they used standardized programmatic and manual searches to detect potential endpoint events and that the approach remained unchanged throughout the study.

Adjudication of Potential Endpoint Events

The EAC adjudicated all suspected endpoint events of end-stage kidney disease (ESKD), doubling of serum creatinine, death, myocardial infarction (MI), stroke, and hospitalized congestive heart failure (CHF). They also adjudicated hospitalized unstable angina. The criteria that needed to be met to qualify as such an event are not discussed below because the Applicant is not seeking a claim related to these events.

ESKD events were required to meet one of the following criteria:

- Kidney transplantation (death during the transplant surgery were to be considered kidney transplantation)
- Chronic dialysis: dialysis performed for 30 days or more and not subsequently known to recover. The patient was contacted 90 days after the initiation of dialysis to confirm dialysis was continuing. If the patient was taken off dialysis because of enough kidney function to live independently, the diagnosis was rescinded. If the patient was known to have received dialysis for >30 days but <90 days, and was not known to recover, ESKD was confirmed. The reason for unavailability of data was to be documented. If dialysis was not continued for 30 days because of death, futility, or transplant, the patient as considered to have reached ESKD. The reason for discontinuation of dialysis was to be documented.
- Dialysis not administered: in cases where dialysis is not available or not administered due to futility or subject refusal, a sustained eGFR of <15 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology formula and confirmed by repeat central laboratory measure (the first amendment to the EAC charter clarified that the confirmatory central laboratory value was to be assessed ≥30 days after the initial value)

The date of the ESKD event was the date of transplant, initiation of chronic dialysis, or, if dialysis was not administered, when the eGFR fell below 15 mL/min/1.73 m^2.

Doubling of serum creatinine was defined as ≥2-fold increase in serum creatinine from the baseline assessment that persists for 30 days or more and is not thought to be due to a reversible cause. The investigator was to make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. Baseline was defined as the average of the two values closest to randomization. Both central and local laboratory values could be used to calculate the increase in serum creatinine. The first amendment to the EAC charter noted that, if a confirmatory value was not available due to death or dialysis, such events were to be positively adjudicated if there was no evidence of acute kidney injury.

Reviewer's comment: The Applicant confirmed that, to be eligible for adjudication, the initial and confirmatory 2-fold increase from the baseline average in serum creatinine values were to be consecutive. An intervening value of <2-fold increase from the baseline average rendered the event ineligible for adjudication.

The date of the doubling of serum creatinine event was the date on which the creatinine first doubled.

Deaths were adjudicated as CV, non-CV, or undetermined as follows:
CV death included deaths categorized as being due to one of the following:

1. *Acute Myocardial Infarction* – death by any CV mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after an MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia, or resulting from a procedure to treat a MI or to treat a complication resulting from MI. Acute MI was to be verified to the extent possible by the diagnostic criteria

outlined below for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/ operation should be considered as a death due to a CV procedure.

2. *Sudden Cardiac Death* – death occurring unexpectedly, not following an acute myocardial infarction, including the following:
   a. Death witnessed and occurring without new or worsening symptoms
   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
   c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiogram [ECG] recording, witnessed on a monitor, or unwitnessed but found on informed consent document review)
   d. Death after successful resuscitation from cardiac arrest
   e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology
   f. Unwitnessed death in a subject seen alive and clinically stable ≤24 hours before being found dead without any evidence supporting a specific noncardiovascular cause of death

      General considerations: unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤24 hour of being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. *Heart Failure* – death in association with clinically worsening symptoms and/or signs of heart failure regardless of heart failure (HF) etiology. Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.
4. *Stroke* - death occurring up to 30 days after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
5. *Cardiovascular Procedures* – death caused by the immediate complications of a cardiac procedure.
6. *Cardiovascular Hemorrhage* – death related to hemorrhage such as a nonstroke intracranial hemorrhage, nonprocedural or nontraumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
7. *Other Cardiovascular Causes* - CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Noncardiovascular death was defined as any death that is not thought to be due to a CV cause. The following was a suggested list of non-CV causes of death:

- Pulmonary
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Noninfectious (e.g., systemic inflammatory response syndrome)
- Hemorrhage that is neither cardiovascular bleeding or a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Nonprescription drug reaction or overdose
- Prescription drug reaction or overdose
- Neurological (noncardiovascular)
- Malignancy
- Other non-CV

Undetermined Cause of Death was defined as a death not attributable to one of the above categories of CV death or to a non-CV cause.

The date of event for all deaths was the date the subject died.

Nonfatal MI was defined as an event meeting the following definition that does not result in death within 30 days from onset. In general, the diagnosis of MI required 1) evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings) and 2) supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging. The totality of the clinical, electrocardiographic, and cardiac biomarker information was to be considered to determine whether an MI has occurred including timing and trends in cardiac biomarkers and ECG information.

Criteria for Myocardial Infarction:

1. Clinical presentation consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI were considered because several conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information could include myocardial imaging and coronary imaging. The totality of the data was to help differentiate acute MI from the background disease process.
2. Biomarker elevations above 99th percentile of the upper reference limit for local lab or, if unavailable, above the upper reference limit for myocardial necrosis or the MI decision limit for the lab. Troponins were preferred, followed by CK-MB then total CK, depending on availability.

3. ECG changes that could be used to support or confirm a MI:
   - Acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block):
     - ST-elevation
       - New ST-elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women
     - ST depression and T-wave changes
       - New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1.

     In patients with elevations in cardiac biomarkers, lesser ECG abnormalities may represent an ischemic response.
   - Pathological Q-wave:
     - Any Q-wave in leads V2-V3≥0.02 seconds or QS complex in leads V2 and V3
     - Q-wave ≥0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)

       The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.
   - Prior myocardial infarction:
     - Pathological Q-waves, as defined above
     - R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect
   - Prior myocardial infarction (any of below):
     - Pathological Q-waves with or without symptoms in the absence of nonischemic causes
     - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause
     - Pathological findings of a prior MI

The date of the event was determined by the date of the following information, in the specified order: first signs/symptoms, hospitalization date, time when ECG conducted, time when biomarkers were detected as elevated, or time when the percutaneous coronary intervention or coronary artery bypass grafting was conducted.

Stroke

A nonfatal stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or vascular injury due to hemorrhage or infarction.

- Ischemic stroke was defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue, including central retinal artery occlusion. Hemorrhage may be a consequence of ischemic stroke. In this

situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

- Hemorrhagic stroke was defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined stroke was defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by presumed brain, spinal cord, or retinal vascular injury due to hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic stroke.

The date of the event was determined by the date of the following information, in the specified order: first signs/symptoms, date of first medical contact, or date when scan or CT is conducted.

Hospitalized Congestive Heart Failure

Heart failure requiring hospitalization was defined as an event that meets the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF
2. The patient's length-of-stay in hospital extends for at least 24-hours (or a date change if the time of admission/discharge is not available).
3. The patient exhibits documented new or worsening symptoms due to HF on presentation including at least one of the following:
   - Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   - Fatigue
   - Decreased exercise tolerance
   - Other symptoms of worsened end-organ perfusion or volume overload
4. The patient has objective evidence of new or worsening HF including at least two physical examination findings OR one physical examination finding and at least one laboratory criterion, including:
   - Physical examination findings considered to be due to HF, including new or worsened:
     - Peripheral edema
     - Pulmonary rales/crackles/crepitations
     - Increased jugular venous pressure and/or hepatojugular reflux
     - Clinically significant or rapid weight gain thought to be related to fluid retention
     - S3 gallop
     - Increasing abdominal distension or ascites (in the absence of primary hepatic disease)
   - Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
     - Increased B-type natriuretic peptide (BNP)/ N-terminal (NT)-pro hormone BNP (NT-pro-BNP) consistent with decompensation of HF (such as BNP >500 pg/mL or NT-pro-BNP >2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
     - Radiological evidence of pulmonary congestion, including noninvasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15

or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract minute stroke distance (time velocity integral).

OR

- Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure ≥18 mm Hg, central venous pressure ≥12 mm Hg, or a cardiac index <2.2 L/min/m^2

5. The patient receives initiation or intensification of treatment specifically for HF, including at least one of the following:
   - Augmentation of oral diuretic therapy
   - Intravenous diuretic, inotrope, or vasodilator therapy
   - Mechanical or surgical intervention (mechanical circulatory support e.g., intra-aortic balloon pump, ventricular assist device), or mechanical fluid removal (e.g., ultrafiltration, hemofiltration, or dialysis)

The date of the event was the date of presentation.

Eligibility Criteria

Key Inclusion Criteria (Screening)

1. Man or woman ≥30 years of age with a clinical diagnosis of T2DM
2. HbA_{1c} ≥6.5% to ≤10.5% (protocol amendment INT-2 increased upper limit to ≤12%)
3. eGFR ≥30 to <90 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology equation
4. UACR >300 mg/g to ≤5000 mg/g
5. All subjects must be on a maximum tolerated labeled daily dose of ACE inhibitor or ARB for at least 4 weeks prior to randomization ("Stable" was added with protocol amendment INT-2). This was defined as the maximum approved labeled dose for diabetic nephropathy (for agents with an approved indication for diabetic nephropathy in patients with T2DM, i.e., 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 ACE inhibitor or ARB, investigators will be required to document why a higher dose cannot be tolerated.
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 >40 IU/L, or
   - Surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion), or otherwise be incapable of pregnancy, or
   - Heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., 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 (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 (i.e., 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 (a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations).

Inclusion Criterion (Randomization)

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

Key Exclusion Criteria (Screening)

1. History of diabetic ketoacidosis or type 1 diabetes mellitus
2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria
3. Known medical history or clinical evidence suggesting nondiabetic renal disease
4. Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant (Subjects with a history of treated childhood renal disease, without sequelae, may participate)
5. Uncontrolled hypertension (systolic BP ≥180 and/or diastolic BP ≥100 mm Hg)
6. History of hyperkalemia requiring treatment, or blood potassium level >5.5 mmol/L at baseline. (Subjects in whom hyperkalemia was associated with the use of NSAIDs, beta-blockers, or mineralocorticoid receptor antagonists [e.g., 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 (e.g., stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before screening (protocol amendment INT-3 changed to before randomization), or a revascularization procedure is planned during the trial
8. Current or history of New York Heart Association Class IV heart failure
9. ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance)
10. Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis)
11. Alanine aminotransferase >2.0 times upper limit of normal or total bilirubin >1.5 times upper limit of normal, unless in the opinion of the investigator and as agreed upon by the Applicant's medical officer, the findings are consistent with Gilbert's disease
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 Applicant's medical monitor, is considered cured with minimal risk of recurrence)
13. History of HIV antibody positive
14. Major surgery (i.e., requiring general anesthesia) within 12 weeks before screening (protocol amendment INT-3 changed to before randomization), or has not fully recovered from surgery

(subjects with planned surgical procedures to be conducted under local anesthesia may participate)
15. Combination use of ACE inhibitor and ARB
16. Use of mineralocorticoid receptor antagonists or a direct renin inhibitor (amendment INT-2 allowed for discontinuation of these agents during screening at least 8 weeks before enrollment, if deemed clinically appropriate by the investigator)
17. Use of an SGLT2 inhibitor within 3 months prior to screening (protocol amendment INT-3 changed to before randomization)
18. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients
19. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
20. 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 (exclusion added with protocol amendment INT-5)

Investigators were to ensure that all study enrollment criteria were met at screening and that the subject did not have any interval change in clinical status between screening and randomization. Patients who failed screening based on a physical or laboratory measurement such as HbA_{1c}, blood pressure, or potassium could be rescreened after appropriate medical management. More than one rescreening was allowed with concurrence of the medical monitor.

16. Efficacy Assessment Additional Information and Assessment

16.1. Primary Endpoint: Additional Assessment

Kaplan-Meier Plots for Individual Components of Primary Endpoint

Figure 15 to Figure 17 show the corresponding Kaplan-Meier curves.

Figure 15. Kaplan-Meier Plot for ESKD

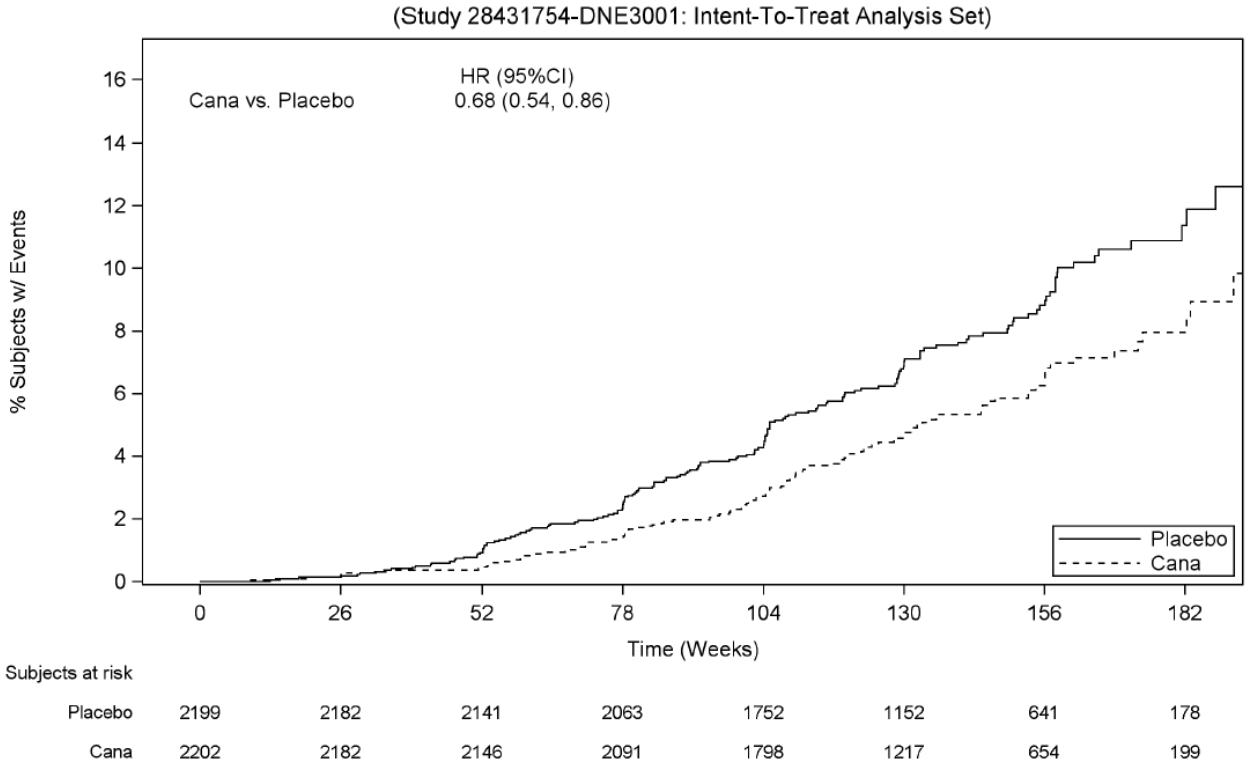


Figure 16. Kaplan-Meier Plot for Doubling of Serum Creatinine

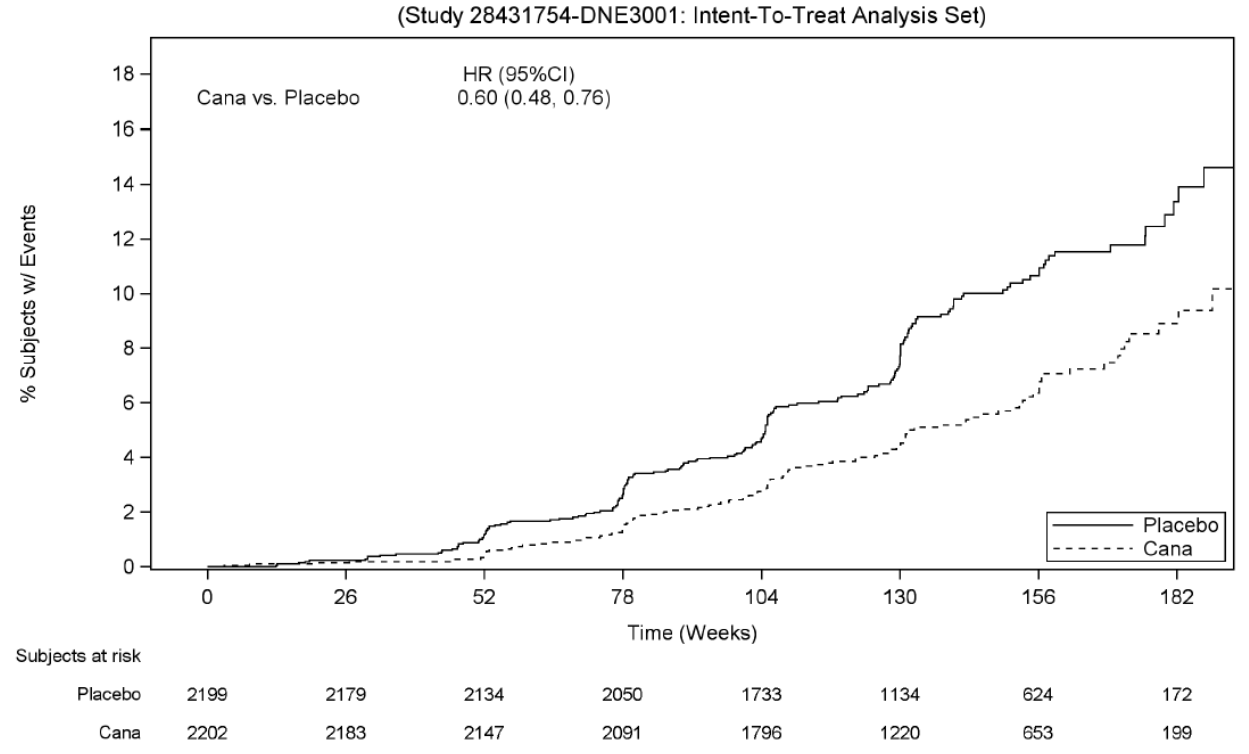
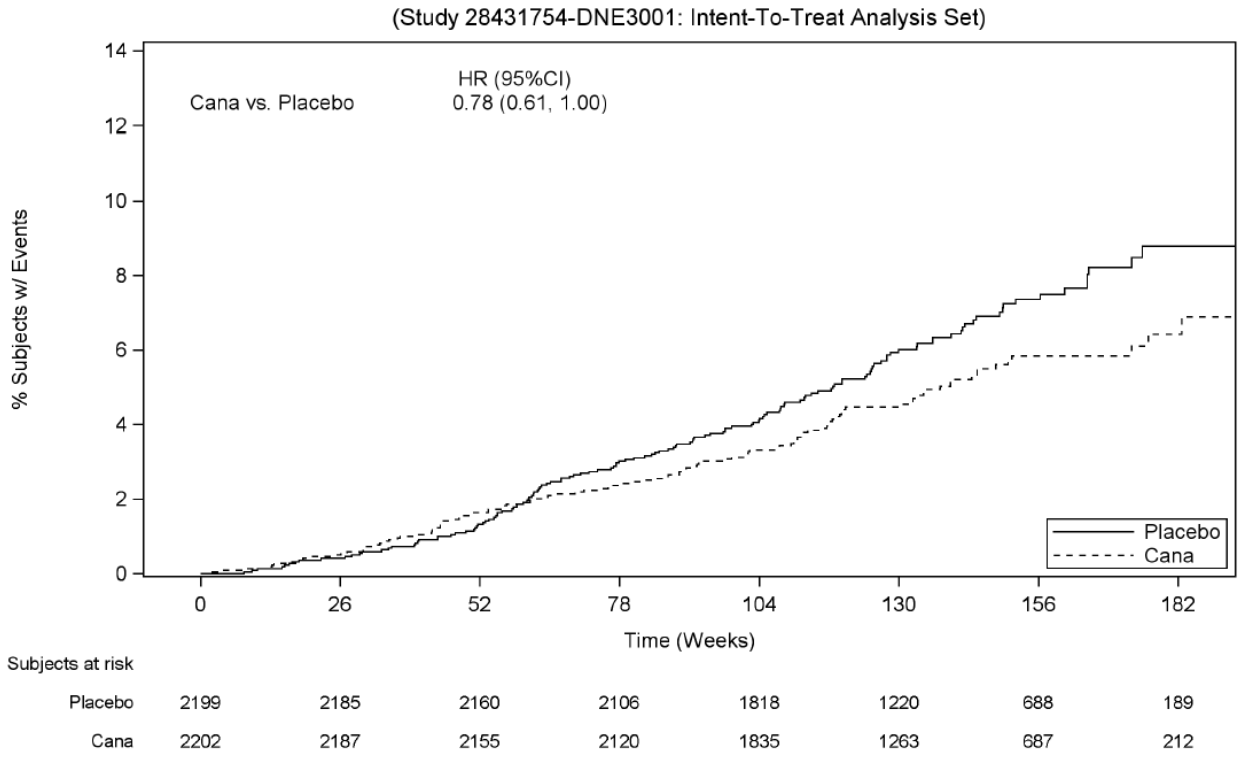


Figure 17. Kaplan-Meier Plot for CV Death



Source: Applicant, CREDENCE CSR Figures 8, 9, and 10.
Abbreviations: CANA, canagliflozin; HR, hazard ratio

Reviewer's comment: The Applicant prespecified CV death as a secondary endpoint but not ESKD or doubling of serum creatinine; however, these analyses help to understand the contribution of the individual components to the composite endpoint result.

Causes of Cardiovascular Death

The CV deaths were primarily sudden cardiac deaths or deaths related to heart failure or cardiogenic shock, stroke, or acute myocardial infarction (Table 40). The cause of death was undetermined for 56 (2.6%) subjects. The protocol specified that these deaths would be classified as CV deaths for the primary efficacy analysis. The Applicant conducted a sensitivity analysis excluding undetermined deaths from the primary composite endpoint analysis, and the result was unchanged (HR 0.69; 95% CI: 0.58 to 0.82; p-value<0.0001).

Table 40. Causes of Cardiovascular Death

Cause	Placebo N=2199 n (%)	Canagliflozin N=2202 n (%)
Sudden cardiac death	51 (2.3)	46 (2.1)
Heart failure or cardiogenic shock	46 (2.1)	29 (1.3)
Stroke	19 (0.9)	16 (0.7)
Acute myocardial infarction	22 (1.0)	19 (0.9)
Other cardiovascular causes	19 (0.9)	15 (0.7)
Undetermined	32 (1.5)	24 (1.1)

Source: Applicant, CREDENCE CSR Table 22.
Abbreviation: n, number of subjects in specified population or group

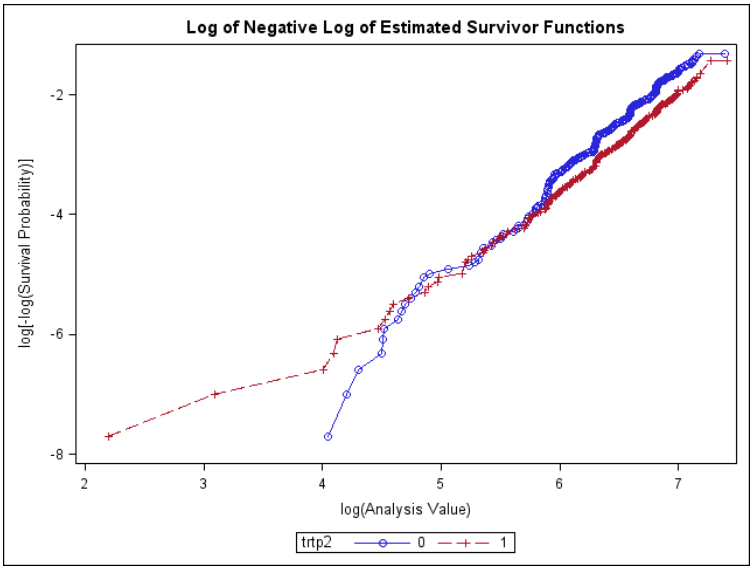
Sensitivity Analysis

The Applicant conducted a multiple imputation analysis to assess the impact of missing follow-up data for clinical outcomes or laboratory assessments. The treatment effect was maintained (HR 0.694; 95% CI: 0.59 to 0.81).

Assessment of Statistical Model

The statistical reviewer plotted the logarithm of the negative logarithm of the estimated survival function versus the logarithm of the survival time to check the proportional hazards assumption for the primary endpoint (Figure 18). The two curves are roughly parallel after substantial number of events are observed, which suggests that the Cox proportional hazards model is reasonable for testing the treatment effect of canagliflozin versus placebo.

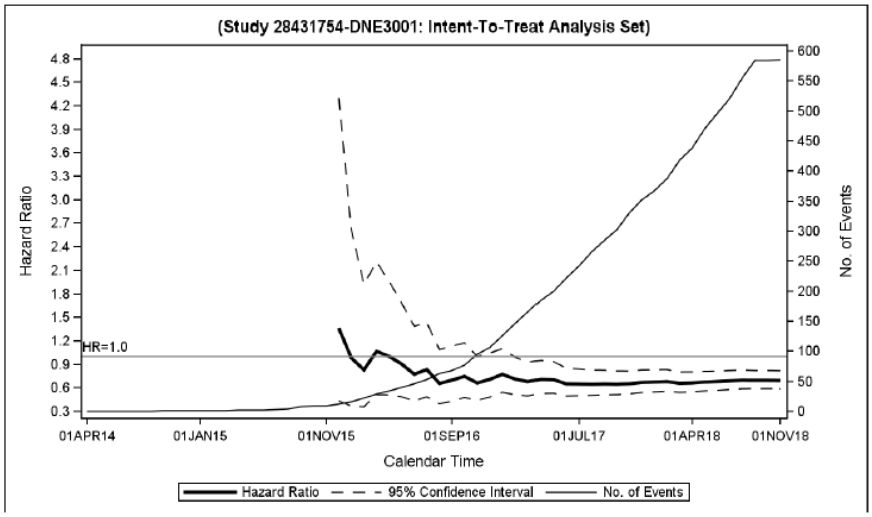
Figure 18. Estimated Log(-Log(Survival)) Versus Log of Survival Time (Intent-to-Treat Analysis Set)



A stratified log-rank test shows a similar p-value as the stratified Cox proportional hazards model analysis. The hazard ratio for the primary efficacy endpoint over calendar time is presented in

Figure 19 and illustrates that the reduction in the HR for the risk of the primary efficacy endpoint became apparent in September 2016 and was approximately constant shortly thereafter.

Figure 19. Hazard Ratio Plot of the Primary Composite Over Calendar Time (Intent-to-Treat Analysis Set)

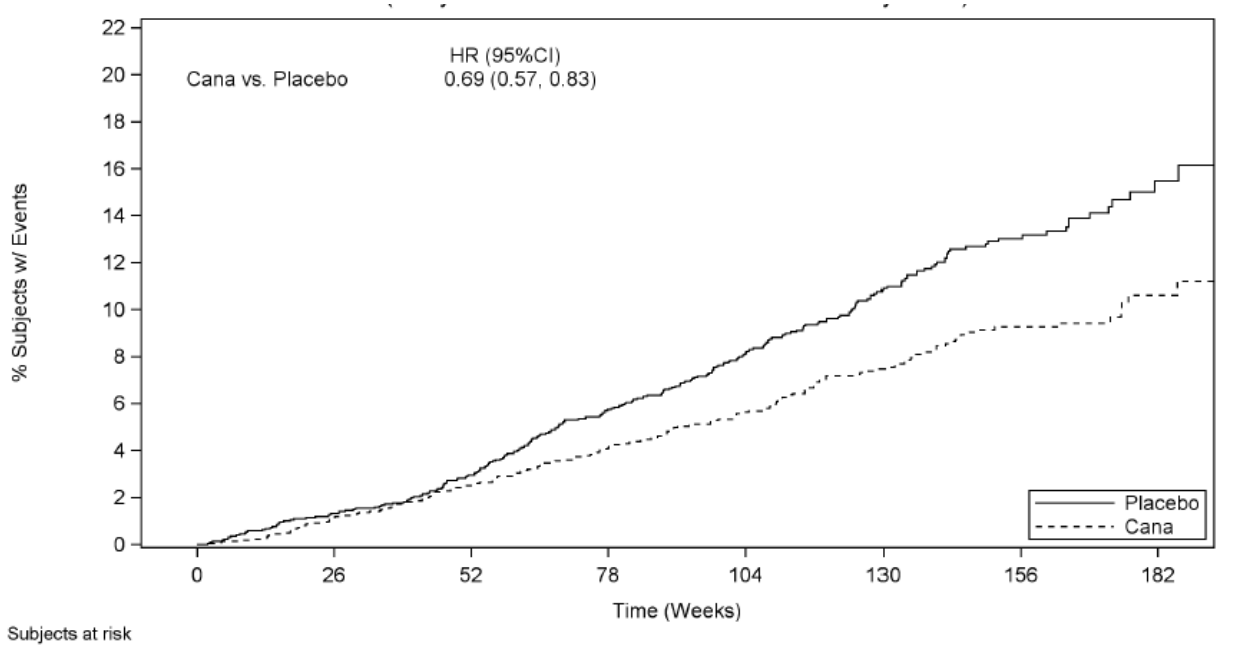


Source: Figure 5 in Clinical Study Report: Study 28431754-DNE3001

16.2. Secondary Endpoints: Additional Assessment

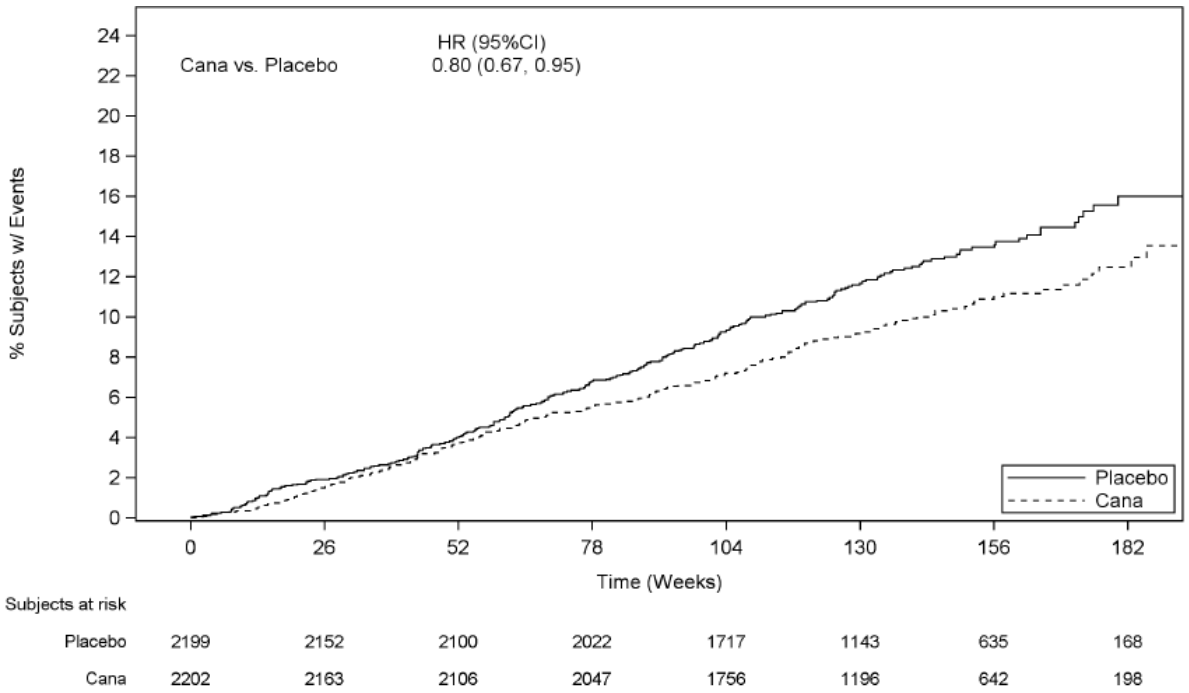
Figure 20 to Figure 23 show the Kaplan-Meier plots for secondary endpoints that reached statistical significance. All of the curves separated early and continued to diverge during the treatment period

Figure 20. Kaplan-Meier Plot for CV Death and HHF (ITT)



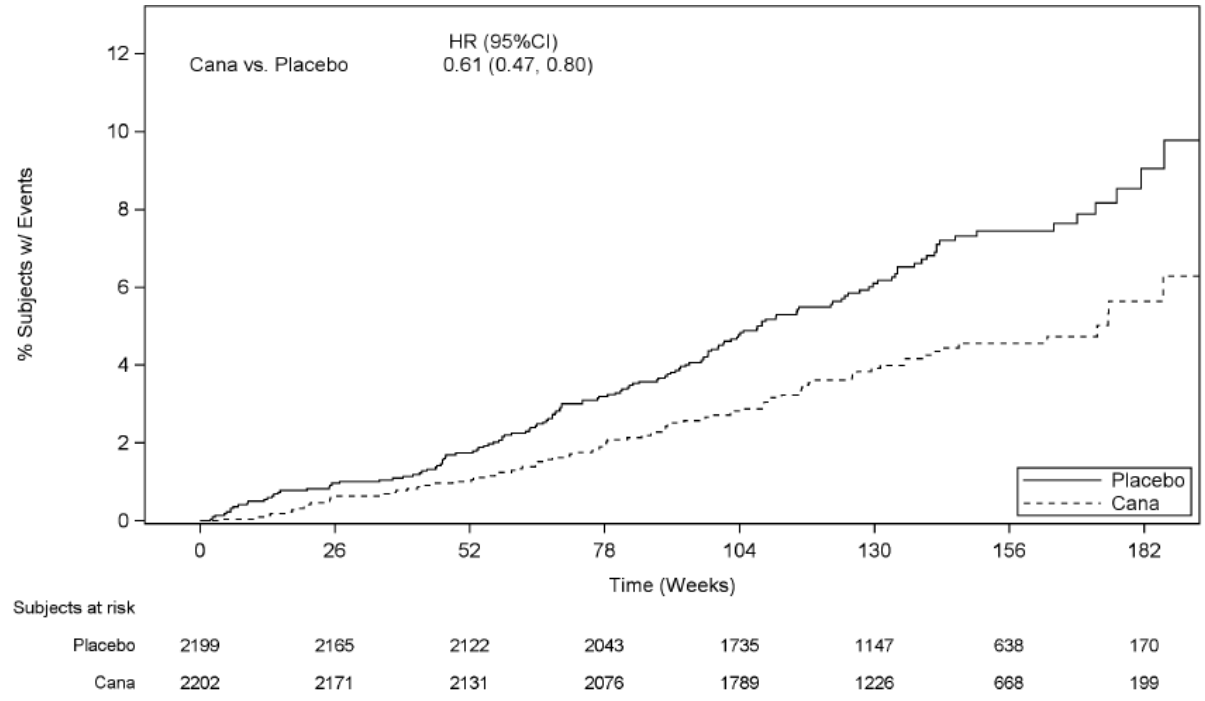
Source: Applicant, CREDENCE CSR Figure 11.
Abbreviations: CANA, canagliflozin; CV, cardiovascular; hhf, hospitalization for heart failure; HR, hazard ratio; ITT, intention to treat

Figure 21. Kaplan-Meier Plot for MACE (ITT)



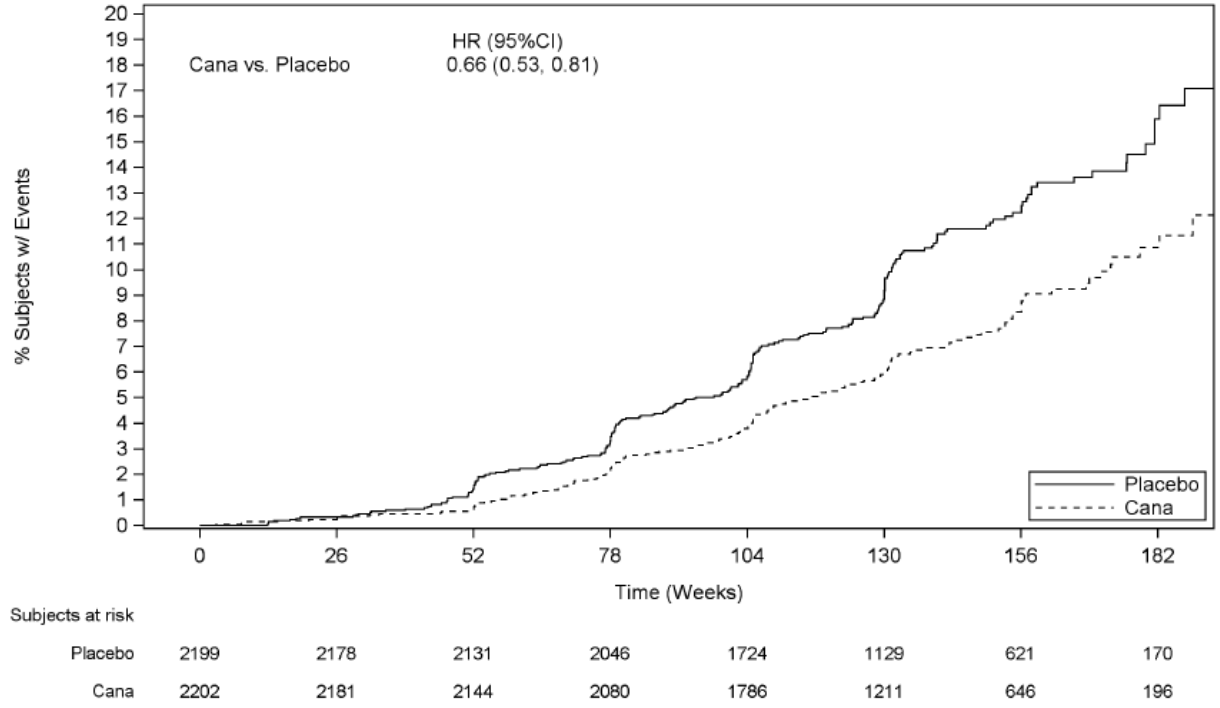
Source: Applicant, CREDENCE CSR Figure 14.
Abbreviations: CANA, canagliflozin; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event

Figure 22. Kaplan-Meier Plot for HHF (ITT)



Source: Applicant, CREDENCE CSR Figure 13.
Abbreviations: CANA, canagliflozin; CI, confidence interval; hhf, hospitalization for heart failure; HR, hazard ratio; ITT, intention to treat

Figure 23. Kaplan-Meier Plot for Renal Composite (ITT)



Source: Applicant, CREDENCE CSR Figure 17.
Abbreviations: CANA, canagliflozin; CI, confidence interval; HR, hazard ratio; ITT, intention to treat

17. Clinical Safety Assessment Additional Information and Assessment

17.1. Other Adverse Event Analyses

The table below shows the High Level neoplasm terms in CREDENCE occurring at a higher incidence in the canagliflozin arm compared to placebo and in at least 3 canagliflozin treated subjects.

Table 41. Neoplasm High Level Terms in CREDENCE

	Canagliflozin N=2200		Placebo N=2197		Canagliflozin - Placebo		
High Level Term (HLT)	n	(%)	n	(%)	Risk Difference	95% CI	
Skin neoplasms malignant and unspecified (excl melanoma)	19	(0.9)	12	(0.6)	0.32	-0.18	0.81
Skin preneoplastic conditions NEC	8	(0.4)	2	(0.1)	0.27	-0.01	0.55
Breast and nipple neoplasms malignant	8	(0.4)	3	(0.1)	0.23	-0.07	0.52
Laryngeal and adjacent sites disorders NEC (excl infections and neoplasms)	5	(0.2)	1	(0.1)	0.18	-0.04	0.4
Colorectal neoplasms malignant	9	(0.4)	5	(0.2)	0.18	-0.15	0.51
Uterine neoplasms	3	(0.1)	0	0.0	0.14	-0.02	0.29
Prostatic neoplasms malignant	10	(0.5)	7	(0.3)	0.14	-0.23	0.5

Source: Reviewer's analysis: ae\maed\cancer dataset: adae
Sorted by risk difference in descending order, minimum of 3 canagliflozin treated subjects

17.2. Laboratory Analyses

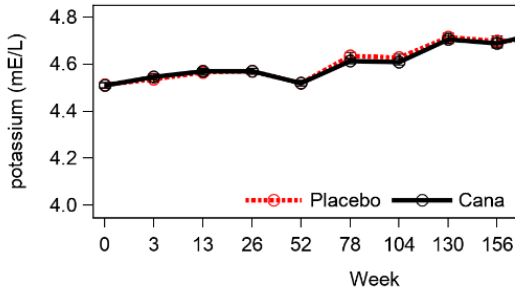
Below are tables and figures relevant to the safety review that were not included in preceding sections. Fewer than 50% of patients had follow-up beyond Week 130 making data at later timepoints difficult to interpret. As such, the figures below are truncated.

Table 42. Change in Potassium From Baseline to End of Treatment

Lab	Summary Type	Canagliflozin N=2177	Placebo N=2176
Potassium	Baseline	4.5±0.5	4.5±0.5
Potassium	End of treatment	4.7±0.6	4.7±0.6
Potassium	Maximum change	0.2±0.6	0.2±0.6
Potassium	Maximum percent change	4.8±13.1	4.7±13.4

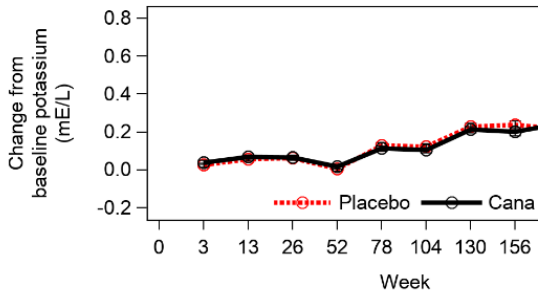
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: N, number of subjects in treatment arm

Figure 24. Potassium Levels Over Time, Weeks 0 to 156



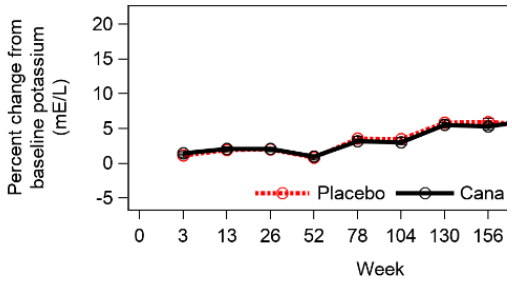
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 25. Potassium Absolute Change From Baseline, Weeks 0 to 156



Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 26. Potassium Percent Change From Baseline, Weeks 0 to 156



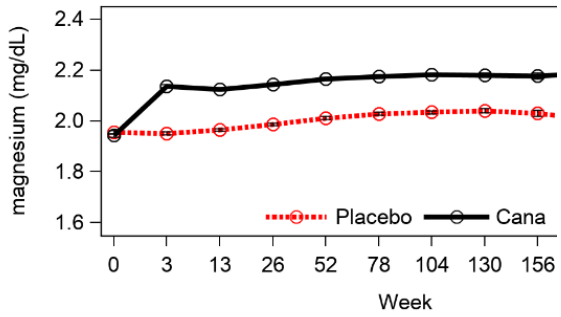
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Table 43. Change in Magnesium From Baseline to End of Treatment

Lab	Summary Type	Canagliflozin N=2179	Placebo N=2178
Magnesium	Baseline	1.9±0.3	2.0±0.3
Magnesium	End of treatment	2.2±0.3	2.0±0.3
Magnesium	Maximum change	0.2±0.3	0.1±0.3
Magnesium	Maximum percent change	13.1±15.3	4.7±13.7

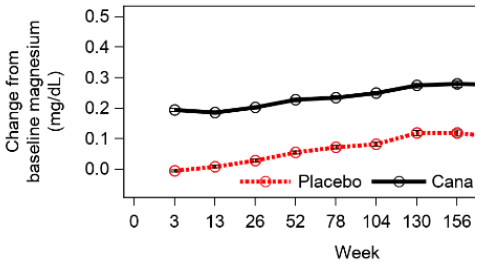
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: N, number of subjects in treatment arm

Figure 27. Magnesium Levels Over Time, Weeks 0 to 156



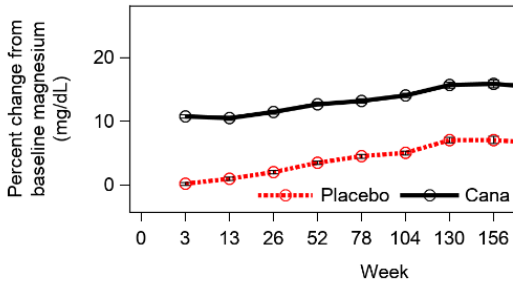
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 28. Magnesium Absolute Change From Baseline, Weeks 0 to 156



Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 29. Magnesium Percent Change From Baseline, Weeks 0 to 156



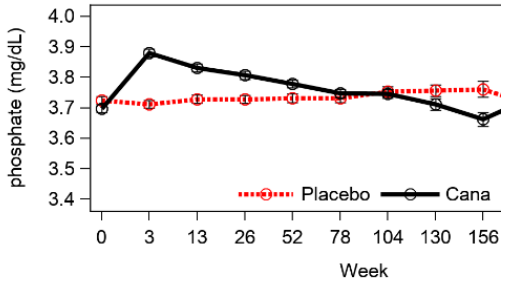
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Table 44. Change in Phosphate From Baseline to End of Treatment

Lab	Summary Type	Canagliflozin N=2177	Placebo N=2177
Phosphate	Baseline	3.7±0.6	3.7±0.6
Phosphate	End of treatment	3.8±0.7	3.8±0.7
Phosphate	Maximum change	0.1±0.7	0.1±0.7
Phosphate	Maximum percent change	4.6±20.3	3.8±19.3

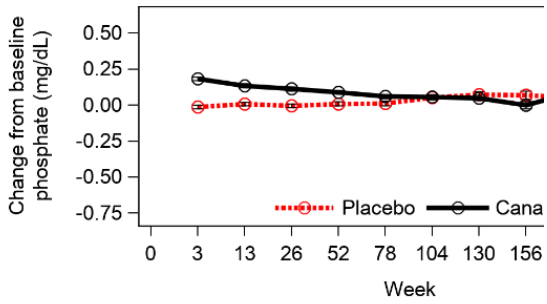
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: N, number of subjects in treatment arm

Figure 30. Phosphate Levels Over Time, Weeks 0 to 156



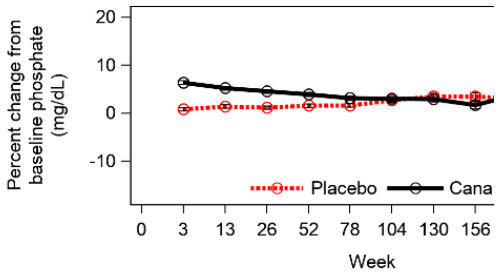
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 31. Phosphate Absolute Change From Baseline, Weeks 0 to 156



Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 32. Phosphate Percent Change From Baseline, Weeks 0 to 156



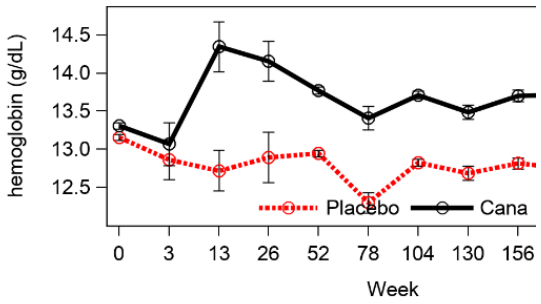
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Table 45. Change in Hemoglobin From Baseline to End of Treatment

Lab	Summary Type	Canagliflozin N=1956	Placebo N=1920
Hemoglobin	Baseline	13.3±1.7	13.2±1.8
Hemoglobin	End of treatment	13.5±2.0	12.6±1.9
Hemoglobin	Maximum change	0.2±1.4	-0.6±1.3
Hemoglobin	Maximum percent change	1.6±10.8	-4.0±10.3

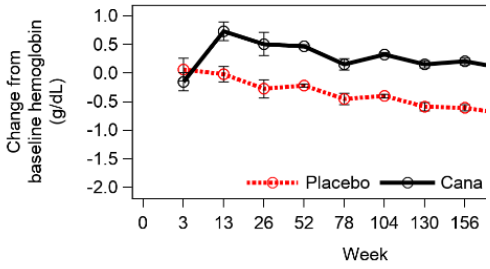
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: N, number of subjects in treatment arm

Figure 33. Hemoglobin Levels Over Time, Weeks 0 to 156



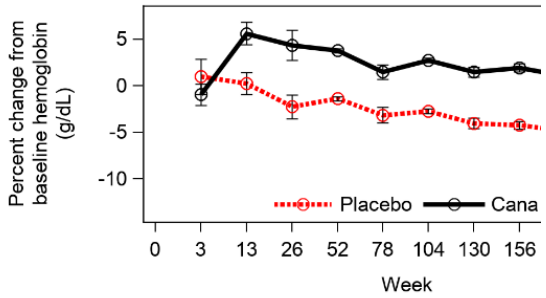
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 34. Hemoglobin Absolute Change From Baseline, Weeks 0 to 156



Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Figure 35. Hemoglobin Percent Change From Baseline, Weeks 0 to 156



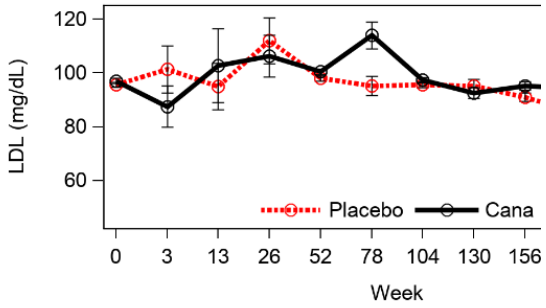
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviation: cana, canagliflozin

Table 46. Change in LDL From Baseline to End of Treatment

Lab	Summary Type	Canagliflozin N=1943	Placebo N=1912
LDL	Baseline	97±42	96±40
LDL	End of treatment	96±43	94±43
LDL	Maximum change	-1.2±40	-1.7±40
LDL	Maximum percent change	8.3±59	5.9±54

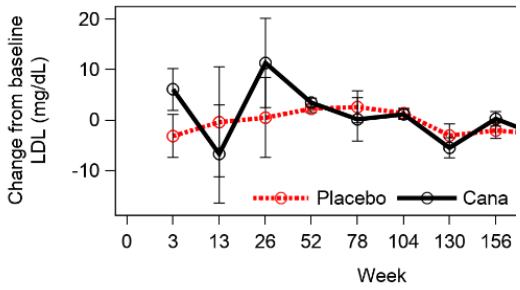
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviations: N, number of subjects in treatment arm; LDL, low-density lipoprotein

Figure 36. LDL Levels Over Time, Weeks 0 to 156



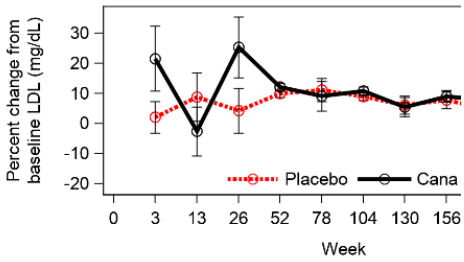
Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviations: CANA, canagliflozin; LDL, low-density lipoprotein

Figure 37. LDL Absolute Change From Baseline, Weeks 0 to 156



Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviations: CANA, canagliflozin; LDL, low-density lipoprotein

Figure 38. LDL Percent Change From Baseline, Weeks 0 to 156



Source: Reviewer's analysis: Lab\lab_1 and lab_sum_time, dataset: adlbcm
Abbreviations: CANA, canagliflozin; LDL, low-density lipoprotein

18. Data Sources and Quality

The Applicant's electronic data sources were stored in the directories of \\CDSESUB1\evsprod\NDA204042\0000 and \\CDSESUB1\evsprod\NDA204042\0278 of the electronic document room (i.e., study reports, raw data sets in Study Data Tabulation Model format, analysis data sets in analysis data model format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature references). The SAS datasets and analysis code are stored in the directory of \\CDSESUB1\evsprod\NDA204042\0000\m5\datasets\.

The Applicant provided high quality datasets and the programs used to produce the analysis datasets and efficacy results, which allowed the statistical reviewer to confirm the efficacy results. The reviewer was also able to verify the randomized treatment assignments by comparing the treatment assignment sheet with the analysis data set.

19. Mechanism of Action / Drug Resistance Additional Information and Assessment

None.

20. Other Drug Development Considerations Additional Information

None.

21. Data Integrity-Related Consults (OSI, Other Inspections)

We did not request inspections for this application. This was based on review of financial disclosures and consistency of the primary endpoint findings after excluding individual sites that enrolled over 25 subjects.

22. Labeling Summary of Considerations and Key Additional Information

Members of the review team worked closely with Mike Monteleone, Associate Director for Labeling, and the Division of Metabolism and Endocrinology Products on revisions to the canagliflozin label. There were extensive discussions around labeling reflecting, in part, different Divisional approaches to labeling and different perspectives on the interpretation of safety findings in CREDENCE and how they should inform existing labeling language on the safety profile of the product. Relevant sections of labeling were also reviewed by clinical pharmacology and pharmacology-toxicology reviewers. Highlights include the following:

- *Indications and Clinical Studies:* The Indications and Clinical Studies sections were updated to include the new indication and a description of the CREDENCE trial.
- *Contraindications and Dosage and Administration:* The Contraindication related to use in patients with an eGFR < 30 was revised and the Dosage and Administration section was updated based on the results and design of the CREDENCE and CANVAS trials (population studied and rules for discontinuation of therapy).
- *Warnings and Precautions:* Increased LDL-C was removed from the Warnings and Precautions section of labeling given the beneficial effects on MACE events observed in the CANVAS program. A description of the finding is retained in the Adverse Reactions section.
- *Adverse Reactions:*
  - The Adverse Reactions Section of the label was updated to include information on key safety findings in CREDENCE and, specifically, important differences and similarities in the adverse reactions profile seen in CREDENCE as compared to trials conducted to support other indications. Similar to the findings in other trials, the incidence of amputations, DKA, and hypotension was greater in the canagliflozin as compared to the placebo arm in CREDENCE; in contrast to the findings in trials conducted to support other indications, the risk of AKI was not greater in the canagliflozin as compared to the placebo arm in CREDENCE. See below for further discussion of labeling related to bone fracture and renal cell carcinoma.
  - Descriptions of acute changes in serum creatinine/eGFR were modified.
  - Labeling related to changes in magnesium and phosphate were removed because it is not believed the level of detail previously provided is necessary for the safe and effective use of the product.
- *Other Safety Related Changes Proposed by the Applicant:* The Division of Metabolism and Endocrinology Products evaluated safety related labeling changes proposed by the

Applicant related to amputations, bone fracture, and renal cell carcinoma. Their recommendations follow:

- **Amputations**: The Applicant proposed presenting amputation incidence rates observed in Canagliflozin Cardiovascular Assessment Study (CANVAS) and Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R), so that absolute risk can be derived easily by prescribers. The Applicant argued that the prior phrasing describing an "approximately 2-fold increased risk" of amputation with use of canagliflozin is nonspecific and confusing to prescribing physicians. DMEP agreed that is reasonable to present amputation data in terms of incidence rates. DMEP did not agree to the Applicant's proposals (b) (4) but did agree with including this information in the Adverse Reactions section of the label. DMEP's rationale was that the CREDENCE population was at high-risk for amputation events and collected a reasonable number of events despite the shorter-than-planned duration of the trial (70 patients had amputations in the canagliflozin arm versus 63 in the placebo arm).
- **Bone Fracture:** The Applicant proposed (b) (4) . DMEP did not agree (b) (4)
- **Renal Cell Carcinoma:** The Applicant proposed relocating the Renal Cell Carcinoma subheading to a lower position in the Adverse Reactions section of the label, and adding a statement (b) (4)

[redacted] (b) (4) DMEP recommended removing this statement and retaining the original placement of the Renal Cell Carcinoma subheading.

- *Drug-Drug Interaction:* Recommendations related to concomitant use of canagliflozin with UGT Enzyme Inducers were revised (Section II.8.214).

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed Invokana Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors, and provided recommendations to improve the clarity of dosing information in Section 2 Dosage and Administration of the PI. They did not identify any areas for improvement for the MG. According to DMEPA, Janssen implemented all of their recommendations for the PI and they have no additional recommendations at this time. The Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) also provided input on the MG (reviewed by DMPP and OPDP) and/or PI (reviewed by OPDP).

23. Postmarketing Requirements and Commitments

None.

24. Financial Disclosure

Table 47. Covered Clinical Studies: CREDENCE

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 690 (one principal investigator at each of 690 sites enrolling at least one subject)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 4 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 48. Disclosable Financial Arrangements

Investigator	Center Number	Location	Number of Subjects	Amount Disclosed	Disclosure
(b) (6)				>25,000	Significant payments of other sorts
				>25,000	Significant payments of other sorts
				>50,000	Significant equity interest in Johnson & Johnson
				>50,000	Significant equity interest in Johnson & Johnson
				>50,000	Significant equity interest in Johnson & Johnson
				>50,000	Significant equity interest in Johnson & Johnson

The Applicant addressed steps taken to minimize the potential for bias resulting from these interests and arrangements including the design of CREDENCE as a randomized, double-blind, placebo-controlled, multicenter trial and each individual site contributing a relatively small proportion of subjects to the overall trial population.

Reviewer's comment: Given the number of subjects enrolled at these sites, it is unlikely that these financial arrangements could have biased the study findings. The statistical reviewer also conducted the primary efficacy analysis excluding individual sites enrolling over 25 subjects, including site (b) (6) *and noted that the findings did not change.*

25. References

Hung, HM, SJ Wang, and R O'Neill, 2007, Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials, J Biopharm Stat, 17(6):1201-1210.

National Kidney Foundation, 2007, KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease, Am J Kidney Dis, 49(2 Suppl 2):S12-154.

National Kidney Foundation, 2012, KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update, Am J Kidney Dis, 60(5):850-886.

26. Review Team Acknowledgements

Table 49. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Anna Park*
Nonclinical Reviewer	William Link*
Nonclinical Team Leader	Jean Wu*
Office of Clinical Pharmacology Reviewer(s)	Snehal Samant*
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan*
Clinical Reviewers	Kimberly Smith, Nhi Beasley
Clinical Team Leader	Aliza Thompson
Statistical Reviewer	Fanhui Kong
Statistical Team Leader	Hsien Ming (James) Hung
Cross-Disciplinary Team Leader	Aliza Thompson
Division Director (DHOT)	N/A
Division Director (OCP)	N/A
Division Director (OB)	Hsien Ming (James) Hung
Division Director (OHOP)	N/A
Office Director (or designated signatory authority)	Aliza Thompson

OB = Office of Biometrics
OHOP = Office of Hematology and Oncology

*Participated in relevant discussions during the review but did not review integrated assessment.

Table 50. Additional Reviewers of Application

Office or Discipline	Name(s)
DMEP	Lisa Yanoff, Patrick Archdeacon, Michelle Carey
OPQ	N/A
Microbiology	N/A
OPDP	Samantha Bryant
OSI	N/A
Patient Labeling	Morgan Walker/ LaShawn Griffiths
OSE/DMEPA	Sarah Thomas/ Alice Tu (TL)

DMEP = Division of Metabolism and Endocrinology Products
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPV = Department of Pharmacovigilance

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/s/

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