CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204042Orig1s027

Trade Name: **INVOKANA**

Generic Name: Canagliflozin

Sponsor: Janssen Pharmaceuticals, Inc.

Approval Date: 10/29/2018

Indications: INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:
• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
• to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204042/S-027

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Janssen Pharmaceuticals, Inc.
Attention: Sukhdev K. Saran
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Saran:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 29, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokana (canagliflozin) tablets.

We acknowledge receipt of your major amendment dated June 28, 2018, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for a new indication "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 (CVD)" for Invokana based on the results of studies 28431754DIA3008, entitled, "A Randomized, Multicenter, Double- Blind, Parallel, Placebo- Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS) and 28431754DIA4003, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS-R).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

The pagination has been revised so that the Medication Guide's page numbers begin with page number 1.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. This was determined because atherosclerosis complications of diabetes mellitus require years to develop, and they are very rare in pediatric patients with diabetes mellitus. For a meaningful study to be conducted, the population would require a diagnosis of type 2 diabetes mellitus AND high cardiovascular risk. The number of pediatric patients fitting these criteria is small, and the required length of follow-up would likely result in patients exceeding the pediatric age range. A clinical trial for the new proposed indication is therefore not feasible.

FULFILLMENT OF POSTMARKETING REQUIREMENT

This supplement contained the final report for the following postmarketing requirement listed in the March 29, 2013, approval letter for NDA 204042.

2027-5 A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the March 29, 2013, approval, and December 4, 2015, postapproval postmarketing requirement letter that are still open.

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate canagliflozin in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: renal cell carcinoma.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Liz Godwin, Regulatory Project Manager, at 240-402-3438.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
10/29/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

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204042Orig1s027

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INVOKANA® safely and effectively. See full prescribing information for INVOKANA.

INVOKANA (canagliflozin) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: LOWER LIMB AMPUTATION
See full prescribing information for complete boxed warning.

- **In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg. (5.1)**
- **Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	10/2018
Warnings and Precautions (5.1, 5.7)	10/2018
Warnings and Precautions (5.5, 5.12)	Removal 10/2018

----------INDICATIONS AND USAGE----------

INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1)

Limitations of Use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose is 100 mg once daily, taken before the first meal of the day (2.2)
- Dose can be increased to 300 mg once daily in patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control (2.2)
- Assess renal function before initiating and periodically thereafter (2.1)
- Limit the dose of INVOKANA to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73 m^2 (2.3)
- Initiation or use of INVOKANA is not recommended if eGFR is below 45 mL/min/1.73 m^2 (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg, 300 mg (3)

----------CONTRAINDICATIONS----------

- Serious hypersensitivity reaction to INVOKANA (4, 5.9)
- Severe renal impairment, ESRD, or on dialysis (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypotension: Before initiating INVOKANA, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or if on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy (5.2)
- Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue INVOKANA, evaluate and treat promptly. Before initiating INVOKANA, consider risk factors for ketoacidosis. Patients on INVOKANA may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis (5.3)
- Acute kidney injury: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy (5.4)
- Urosepsis and pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.5)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKANA (5.6)
- Necrotizing fasciitis of the perineum (Fournier's gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment (5.7)
- Genital mycotic infections: Monitor and treat if indicated (5.8)
- Hypersensitivity reactions: Discontinue INVOKANA and monitor until signs and symptoms resolve (5.9)
- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKANA (5.10)
- Increased LDL-C: Monitor LDL-C and treat if appropriate (5.11)

----------ADVERSE REACTIONS----------

- Most common adverse reactions associated with INVOKANA (5% or greater incidence): female genital mycotic infections, urinary tract infection, and increased urination (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Consider increasing dose from 100 mg to 300 mg (2.4, 7.1)
- Digoxin: Monitor digoxin levels (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- Lactation: Not recommended when breastfeeding (8.2)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (5.2, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.3, 5.4, 8.6)
- Hepatic impairment: Not recommended with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LOWER LIMB AMPUTATION

- **An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
- **Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

INVOKANA® (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- 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 (CVD).

Limitations of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of INVOKANA

Assess renal function before initiating INVOKANA and periodically thereafter *[see Warnings and Precautions (5.4)]*.

In patients with volume depletion not previously treated with canagliflozin, normalize volume status before initiating INVOKANA *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage

The recommended starting dose of INVOKANA (canagliflozin) is 100 mg once daily, taken before the first meal of the day. In patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

2.3 Patients with Renal Impairment

The dose of INVOKANA is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m^2.

Initiation of INVOKANA is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2.

Use of INVOKANA is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

INVOKANA is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (4)]*.

2.4 Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, consider increasing the dosage to 300 mg once daily in patients currently tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control *[see Drug Interactions (7.1)]*.

Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.

3 DOSAGE FORMS AND STRENGTHS

- INVOKANA 100 mg tablets are yellow, capsule-shaped, tablets with “CFZ” on one side and “100” on the other side.
- INVOKANA 300 mg tablets are white, capsule-shaped, tablets with “CFZ” on one side and “300” on the other side.

4 CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions (5.9) and Adverse Reactions (6.1, 6.2)]*.

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease (ESRD), or patients on dialysis *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Adverse Reactions (6.1)]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

5.2 Hypotension

INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions (6.1)]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with

low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with INVOKANA consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.4 Acute Kidney Injury

INVOKANA causes intravascular volume contraction *[see Warnings and Precautions (5.2)]* and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury,

some requiring hospitalization and dialysis, in patients receiving INVOKANA; some reports involved patients younger than 65 years of age.

Before initiating INVOKANA, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing INVOKANA in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue INVOKANA promptly and institute treatment.

Initiation of INVOKANA may increase serum creatinine and decrease eGFR. Patients with hypovolemia may be more susceptible to these changes *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of INVOKANA and monitored periodically thereafter. Dosage adjustment and more frequent renal function monitoring are recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of INVOKANA is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Contraindications (4) and Use in Specific Populations (8.6)]*.

5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.6 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

5.7 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with INVOKANA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.8 Genital Mycotic Infections

INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1)]*. Monitor and treat appropriately.

5.9 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications (4) and Adverse Reactions (6.1, 6.2)]*.

5.10 Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.2)]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions (6.1)]*.

5.11 Increases in Low-Density Lipoprotein (LDL-C)

Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions (6.1)]*. Monitor LDL-C and treat if appropriate after initiating INVOKANA.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lower Limb Amputation *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Ketoacidosis *[see Warnings and Precautions (5.3)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.4)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.5)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.6)]*

- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions (5.7)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.8)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.9)]*
- Bone Fracture *[see Warnings and Precautions (5.10)]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions (5.11)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials

The data in Table 1 is derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26−Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections[‡]	3.8%	5.9%	4.4%
Increased urination[§]	0.7%	5.1%	4.6%
Thirst[#]	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections[†]	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections[¶]	0.7%	4.2%	3.8%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 patients to INVOKANA) were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.2)]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Warnings and Precautions (5.1)]*.

Table 2: CANVAS Amputations

	Placebo N=1441	**INVOKANA 100 mg N=1445**	**INVOKANA 300 mg N=1441**	**INVOKANA (Pooled) N=2886**
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

	Placebo N=2903	**INVOKANA 100 mg (with up-titration to 300 mg) N=2904**
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59

Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma

In the CANVAS trial (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.2)]*, the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and INVOKANA, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions

INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 4) *[see Dosage and Administration (2.3), Warnings and Precautions (5.2), and Use in Specific Populations (8.5 and 8.6)]*.

Table 4: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	**Comparator Group* %**	**INVOKANA 100 mg %**	**INVOKANA 300 mg %**
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls

In a pool of nine clinical trials with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Impairment in Renal Function

Initiation of INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 5) *[see Warnings and Precautions (5.4)]*. The effect on eGFR was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

Table 5: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	**INVOKANA 100 mg N=833**	**INVOKANA 300 mg N=834**
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

* Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

Patients with moderate renal impairment at baseline experience larger mean changes in eGFR relative to patients with normal or mildly impaired renal function. In a trial in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.1)]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9%, 18%, and 22.5% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. At the end of treatment, 4.6%, 3.4%, and 2.2% of patients

treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had a significant renal function decline.

Genital Mycotic Infections

In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively *[see Warnings and Precautions (5.8)]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions (5.8)]*.

Hypoglycemia

In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14.1)]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 6) *[see Warnings and Precautions (5.6)]*.

Table 6: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture

In the CANVAS trial *[see Clinical Studies (14.2)]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures

were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities *[see Warnings and Precautions (5.10)]*.

Laboratory and Imaging Tests

Increases in Serum Potassium

In a pooled population of patients (N=723) with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

Increases in Serum Magnesium

Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean percent change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.1)]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate

Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean percent change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.1)]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C)

In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo

were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions (5.11)]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin

In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1)]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of INVOKANA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ketoacidosis

Acute Kidney Injury

Anaphylaxis, Angioedema

Urosepsis and Pyelonephritis

Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

7 DRUG INTERACTIONS

7.1 UGT Enzyme Inducers

Rifampin: 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%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

7.2 Digoxin

There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3)]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

7.3 Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

7.4 Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA is not recommended while breastfeeding.

Data

Animal Data

Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4 Pediatric Use

Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1)]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

8.6 Renal Impairment

The efficacy and safety of INVOKANA were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.1)]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2). Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in this trial. Increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively *[see Dosage and Administration (2.3), Warnings and Precautions (5.2, 5.4), and Adverse Reactions (6.1)]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3)]*.

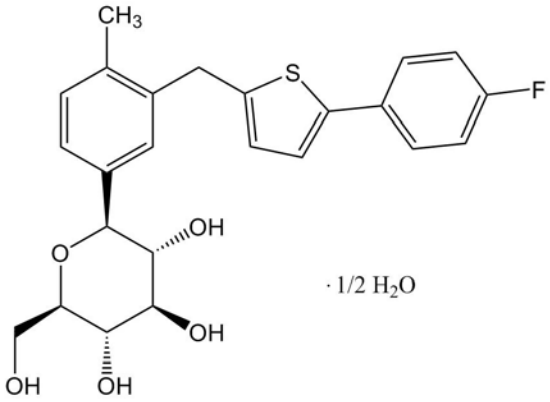
10 OVERDOSAGE

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

11 DESCRIPTION

INVOKANA (canagliflozin) contains canagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin, the active ingredient of INVOKANA, is chemically known as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol

hemihydrate and its molecular formula and weight are $C_{24}H_{25}FO_5S \bullet 1/2\ H_2O$ and 453.53, respectively. The structural formula for canagliflozin is:



Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9.

INVOKANA is supplied as film-coated tablets for oral administration, containing 102 and 306 mg of canagliflozin in each tablet strength, corresponding to 100 mg and 300 mg of canagliflozin (anhydrous), respectively.

Inactive ingredients of the core tablet are croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following excipients: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, macrogol/PEG, talc, and iron oxide yellow, E172 (100 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE).

12.2 Pharmacodynamics

Following single and multiple oral doses of canagliflozin in patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RT_G) and increases in urinary glucose excretion were observed. From a starting RT_G value of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RT_G throughout the 24-hour period. Maximal suppression of mean RT_G over the 24-hour period was seen with the 300 mg daily dose to

approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 trials. The reductions in RT_G led to increases in mean UGE of approximately 100 g/day in subjects with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin. In patients with type 2 diabetes given 100 to 300 mg once daily over a 16-day dosing period, reductions in RT_G and increases in urinary glucose excretion were observed over the dosing period. In this trial, plasma glucose declined in a dose-dependent fashion within the first day of dosing. In single-dose trials in healthy and type 2 diabetic subjects, treatment with canagliflozin 300 mg before a mixed-meal delayed intestinal glucose absorption and reduced postprandial glucose.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, active-comparator, 4-way crossover trial, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1,200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QTc interval were observed with either the recommended dose of 300 mg or the 1,200 mg dose.

12.3 Pharmacokinetics

The pharmacokinetics of canagliflozin is similar in healthy subjects and patients with type 2 diabetes. Following single-dose oral administration of 100 mg and 300 mg of INVOKANA, peak plasma concentrations (median T_{max}) of canagliflozin occurs within 1 to 2 hours post-dose. Plasma C_{max} and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life ($t_{1/2}$) was 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg. Canagliflozin does not exhibit time-dependent pharmacokinetics and accumulated in plasma up to 36% following multiple doses of 100 mg and 300 mg.

Absorption

The mean absolute oral bioavailability of canagliflozin is approximately 65%. Co-administration of a high-fat meal with canagliflozin had no effect on the pharmacokinetics of canagliflozin; therefore, INVOKANA may be taken with or without food. However, based on the potential to reduce postprandial plasma glucose excursions due to delayed intestinal glucose absorption, it is recommended that INVOKANA be taken before the first meal of the day *[see Dosage and Administration (2.2)]*.

Distribution

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is

independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites.

CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

Excretion

Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an *O*-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible.

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as *O*-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min.

Mean systemic clearance of canagliflozin was approximately 192 mL/min in healthy subjects following intravenous administration.

Specific Populations

Renal Impairment

A single-dose, open-label trial evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects.

Renal impairment did not affect the C_{max} of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 53% in subjects with mild (N=10), moderate (N=9), and severe (N=10) renal impairment, respectively, (eGFR 60 to less than 90, 30 to less than 60, and 15 to less than 30 mL/min/1.73 m^2, respectively), but was similar for ESRD (N=8) subjects and healthy subjects.

Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

Canagliflozin was negligibly removed by hemodialysis.

Hepatic Impairment

Relative to subjects with normal hepatic function, the geometric mean ratios for C_{max} and AUC_{∞} of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate hepatic impairment) following administration of a single 300 mg dose of canagliflozin.

These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Pharmacokinetic Effects of Age, Body Mass Index (BMI)/Weight, Gender and Race

Based on the population PK analysis with data collected from 1526 subjects, age, body mass index (BMI)/weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of canagliflozin *[see Use in Specific Populations (8.5)]*.

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Canagliflozin did not induce CYP450 enzyme expression (3A4, 2C9, 2C19, 2B6, and 1A2) in cultured human hepatocytes. Canagliflozin did not inhibit the CYP450 isoenzymes (1A2, 2A6, 2C19, 2D6, or 2E1) and weakly inhibited CYP2B6, CYP2C8, CYP2C9, and CYP3A4 based on *in vitro* studies with human hepatic microsomes. Canagliflozin is a weak inhibitor of P-gp.

Canagliflozin is also a substrate of drug transporters P-glycoprotein (P-gp) and MRP2.

In Vivo Assessment of Drug Interactions

Table 7: Effect of Co−Administered Drugs on Systemic Exposures of Canagliflozin

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0**	
			AUC† (90% CI)	**C_{max} (90% CI)**
See *Drug Interactions (7.1)* for the clinical relevance of the following:				
Rifampin	600 mg QD for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)
No dose adjustments of INVOKANA required for the following:				
Cyclosporine	400 mg	300 mg QD for	1.23	1.01

		8 days	(1.19; 1.27)	(0.91; 1.11)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin	2,000 mg	300 mg QD for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid	500 mg BID for 3 days	300 mg QD for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)

* Single dose unless otherwise noted
† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
QD = once daily; BID = twice daily

Table 8: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0**		
				AUC† (90% CI)	**C_{max} (90% CI)**
See *Drug Interactions (7.2)* for the clinical relevance of the following:					
Digoxin	0.5 mg QD first day followed by 0.25 mg QD for 6 days	300 mg QD for 7 days	Digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
No dose adjustments of co-administered drug required for the following:					
Acetaminophen	1,000 mg	300 mg BID for 25 days	Acetaminophen	1.06‡ (0.98; 1.14)	1.00 (0.92; 1.09)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)
			Levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)
Glyburide	1.25 mg	200 mg QD for 6 days	Glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	Hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg QD for 8 days	Metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Simvastatin	40 mg	300 mg QD for 7 days	Simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			simvastatin acid	1.18	1.26

				(1.03; 1.35)	(1.10; 1.45)
Warfarin	30 mg	300 mg QD for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (0.98; 1.03)	1.05 (0.99; 1.12)

* Single dose unless otherwise noted
† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
‡ AUC_{0-12h}
QD = once daily; BID = twice daily; INR = International Normalized Ratio

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Sprague-Dawley rats. Canagliflozin did not increase the incidence of tumors in mice dosed at 10, 30, or 100 mg/kg (less than or equal to 14 times exposure from a 300 mg clinical dose).

Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone (LH), increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg). In a 12-week clinical trial, LH 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. Also, 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 have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the recommended clinical dose of 300 mg.

Mutagenesis

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the *in vitro* mouse lymphoma assay with but not without metabolic activation. Canagliflozin was not mutagenic or clastogenic in an *in vivo* oral micronucleus assay in rats and an *in vivo* oral Comet assay in rats.

Impairment of Fertility

Canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (approximately 14 times and 18 times the 300 mg clinical dose in males and females, respectively), although there were minor alterations in a number of reproductive

parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered.

14 CLINICAL STUDIES

INVOKANA (canagliflozin) has been studied as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and sitagliptin, metformin and a thiazolidinedione (i.e., pioglitazone), and in combination with insulin (with or without other anti-hyperglycemic agents). The efficacy of INVOKANA was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin), both as add-on combination therapy with metformin and sulfonylurea, and a sulfonylurea (glimepiride), both as add-on combination therapy with metformin. INVOKANA was also evaluated in adults 55 to 80 years of age and patients with moderate renal impairment.

In patients with type 2 diabetes, treatment with INVOKANA produced clinically and statistically significant improvements in HbA_{1C} compared to placebo. Reductions in HbA_{1C} were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

Monotherapy

A total of 584 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a 26-week double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA. The mean age was 55 years, 44% of patients were men, and the mean baseline eGFR was 87 mL/min/1.73 m^2. Patients taking other antihyperglycemic agents (N=281) discontinued the agent and underwent an 8-week washout followed by a 2-week, single-blind, placebo run-in period. Patients not taking oral antihyperglycemic agents (N=303) entered the 2-week, single-blind, placebo run-in period directly. After the placebo run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily for 26 weeks.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo (see Table 9). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -3.7 mmHg and -5.4 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 9: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA as Monotherapy*

Efficacy Parameter	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
HbA_{1C} (%)			
Baseline (mean)	7.97	8.06	8.01
Change from baseline (adjusted mean)	0.14	-0.77	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.91‡ (-1.09; -0.73)	-1.16‡ (-1.34; -0.99)
Percent of Patients Achieving HbA_{1C} < 7%	21	45‡	62‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	166	172	173
Change from baseline (adjusted mean)	8	-27	-35
Difference from placebo (adjusted mean) (95% CI)†		-36‡ (-42; -29)	-43‡ (-50; -37)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	229	250	254
Change from baseline (adjusted mean)	5	-43	-59
Difference from placebo (adjusted mean) (95% CI)†		-48‡ (-59.1; -37.0)	-64‡ (-75.0; -52.9)
Body Weight			
Baseline (mean) in kg	87.5	85.9	86.9
% change from baseline (adjusted mean)	-0.6	-2.8	-3.9
Difference from placebo (adjusted mean) (95% CI)†		-2.2‡ (-2.9; -1.6)	-3.3‡ (-4.0; -2.6)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

Add-on Combination Therapy with Metformin

A total of 1,284 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day if higher dose not tolerated) participated in a 26-week, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with metformin. The mean age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin dose (N=1009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin dose or patients on metformin in combination with another antihyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind, placebo run-in. After the placebo run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to

metformin. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 10). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -5.4 mmHg and -6.6 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 10: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin*

Efficacy Parameter	Placebo + Metformin (N=183)	INVOKANA 100 mg + Metformin (N=368)	INVOKANA 300 mg + Metformin (N=367)
HbA_{1C} (%)			
Baseline (mean)	7.96	7.94	7.95
Change from baseline (adjusted mean)	-0.17	-0.79	-0.94
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.76; -0.48)	-0.77‡ (-0.91; -0.64)
Percent of patients achieving HbA_{1C} < 7%	30	46‡	58‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	173
Change from baseline (adjusted mean)	2	-27	-38
Difference from placebo (adjusted mean) (95% CI)†		-30‡ (-36; -24)	-40‡ (-46; -34)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	249	258	262
Change from baseline (adjusted mean)	-10	-48	-57
Difference from placebo (adjusted mean) (95% CI)†		-38‡ (-49; -27)	-47‡ (-58; -36)
Body Weight			
Baseline (mean) in kg	86.7	88.7	85.4
% change from baseline (adjusted mean)	-1.2	-3.7	-4.2
Difference from placebo (adjusted mean) (95% CI)†		-2.5‡ (-3.1; -1.9)	-2.9‡ (-3.5; -2.3)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

Initial Combination Therapy with Metformin

A total of 1,186 patients with type 2 diabetes inadequately controlled with diet and exercise participated in a 26-week double-blind, active-controlled, parallel-group, 5-arm, multicenter trial to evaluate the efficacy and safety of initial therapy with INVOKANA in combination with metformin XR. The median age was 56 years, 48% of patients were men, and the mean baseline eGFR was 87.6 mL/min/1.73 m^2. The median duration of diabetes was 1.6 years, and 72% of patients were treatment naïve. After completing a 2-week single-blind placebo run-in period, patients were randomly assigned for a double-blind treatment period of 26 weeks to 1 of

5 treatment groups (Table 11). The metformin XR dose was initiated at 500 mg/day for the first week of treatment and then increased to 1000 mg/day. Metformin XR or matching placebo was up-titrated every 2-3 weeks during the next 8 weeks of treatment to a maximum daily dose of 1500 to 2000 mg/day, as tolerated; about 90% of patients reached 2000 mg/day.

At the end of treatment, INVOKANA 100 mg and INVOKANA 300 mg in combination with metformin XR resulted in a statistically significant greater improvement in HbA_{1C} compared to their respective INVOKANA doses (100 mg and 300 mg) alone or metformin XR alone.

Table 11: Results from 26-Week Active-Controlled Clinical Study of INVOKANA Alone or INVOKANA as Initial Combination Therapy with Metformin*

Efficacy Parameter	**Metformin XR (N=237)**	**INVOKANA 100 mg (N=237)**	**INVOKANA 300 mg (N=238)**	**INVOKANA 100 mg + Metformin XR (N=237)**	**INVOKANA 300 mg + Metformin XR (N=237)**
HbA_{1C} (%)					
Baseline (mean)	8.81	8.78	8.77	8.83	8.90
Change from baseline (adjusted mean)¶	-1.30	-1.37	-1.42	-1.77	-1.78
Difference from canagliflozin 100 mg (adjusted mean) (95% CI)†				-0.40‡ (-0.59, -0.21)	
Difference from canagliflozin 300 mg (adjusted mean) (95% CI)†					-0.36‡ (-0.56, -0.17)
Difference from metformin XR (adjusted mean) (95% CI)†		-0.06‡‡ (-0.26, 0.13)	-0.11‡‡ (-0.31, 0.08)	-0.46‡ (-0.66, -0.27)	-0.48‡ (-0.67, -0.28)
Percent of patients achieving HbA_{1C} < 7%	38	34	39	47§§	51§§

* Intent-to-treat population
† Least squares mean adjusted for covariates including baseline value and stratification factor
‡ Adjusted p=0.001 for superiority
‡‡ Adjusted p=0.001 for non-inferiority
§§ Adjusted p<0.05
¶ There were 121 patients without week 26 efficacy data. Analyses addressing missing data gave consistent results with the results provided in this table.

INVOKANA Compared to Glimepiride, Both as Add-on Combination With Metformin

A total of 1,450 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day if higher dose not tolerated) participated in a 52-week, double-blind, active-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with metformin.

The mean age was 56 years, 52% of patients were men, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients tolerating maximally required metformin dose (N=928) were randomized after completing a 2-week, single-blind, placebo run-in period. Other patients (N=522) were switched to metformin monotherapy (at doses described above) for at least 10 weeks, then completed a 2-week single-blind run-in period. After the 2-week run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or glimepiride (titration allowed throughout the 52-week trial to 6 or 8 mg), administered once daily as add-on therapy to metformin.

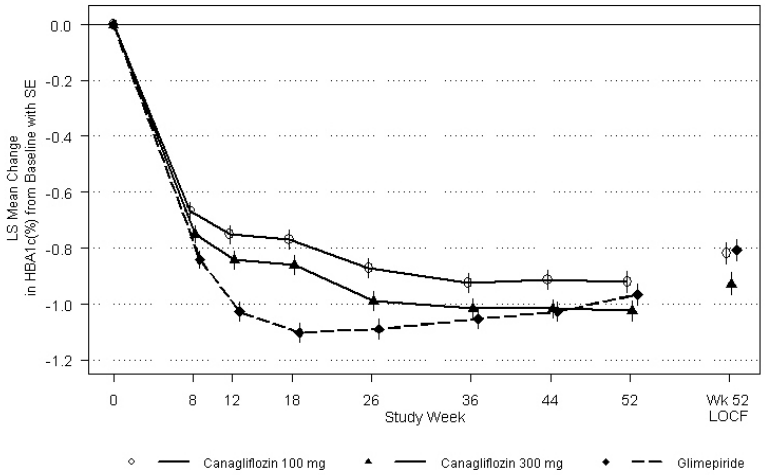
As shown in Table 12 and Figure 1, at the end of treatment, INVOKANA 100 mg provided similar reductions in HbA_{1C} from baseline compared to glimepiride when added to metformin therapy. INVOKANA 300 mg provided a greater reduction from baseline in HbA_{1C} compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: −0.22; −0.02). As shown in Table 12, treatment with INVOKANA 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 12: Results from 52−Week Clinical Study Comparing INVOKANA to Glimepiride in Combination with Metformin*

Efficacy Parameter	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**	**Glimepiride (titrated) + Metformin (N=482)**
HbA_{1C} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)†	-0.01‡ (-0.11; 0.09)	-0.12‡ (-0.22; -0.02)	
Percent of patients achieving HbA_{1C} < 7%	54	60	56
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	165	164	166
Change from baseline (adjusted mean)	-24	-28	-18
Difference from glimepiride (adjusted mean) (95% CI)†	-6 (-10; -2)	-9 (-13; -5)	
Body Weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI)†	-5.2§ (-5.7; -4.7)	-5.7§ (-6.2; -5.1)	

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ INVOKANA + metformin is considered non-inferior to glimepiride + metformin because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.
§ p<0.001

Figure 1: Mean HbA_{1C} Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



Add-on Combination Therapy With Sulfonylurea

A total of 127 patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy participated in an 18-week, double-blind, placebo-controlled sub-study to evaluate the efficacy and safety of INVOKANA in combination with sulfonylurea. The mean age was 65 years, 57% of patients were men, and the mean baseline eGFR was 69 mL/min/1.73 m^2. Patients treated with sulfonylurea monotherapy on a stable protocol-specified dose (greater than or equal to 50% maximal dose) for at least 10 weeks completed a 2-week, single-blind, placebo run-in period. After the run-in period, patients with inadequate glycemic control were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to sulfonylurea.

As shown in Table 13, at the end of treatment, INVOKANA 100 mg and 300 mg daily provided statistically significant ($p<0.001$ for both doses) improvements in HbA_{1C} relative to placebo when added to sulfonylurea. INVOKANA 300 mg once daily compared to placebo resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, (33% vs 5%), greater reductions in fasting plasma glucose (-36 mg/dL vs +12 mg/dL), and greater percent body weight reduction (-2.0% vs -0.2%).

Table 13: Results from 18-Week Placebo−Controlled Clinical Study of INVOKANA in Combination with Sulfonylurea*

Efficacy Parameter	Placebo + Sulfonylurea (N=45)	INVOKANA 100 mg + Sulfonylurea (N=42)	INVOKANA 300 mg + Sulfonylurea (N=40)
HbA_{1C} (%)			
Baseline (mean)	8.49	8.29	8.28
Change from baseline (adjusted mean)	0.04	-0.70	-0.79

Difference from placebo (adjusted mean) (95% CI)[†]		-0.74[‡] (-1.15; -0.33)	-0.83[‡] (-1.24; -0.41)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value
‡ p<0.001

Add-on Combination Therapy With Metformin and Sulfonylurea

A total of 469 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximal or near-maximal effective dose) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with metformin and sulfonylurea. The mean age was 57 years, 51% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the protocol-specified doses of metformin and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to metformin and sulfonylurea.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo when added to metformin and sulfonylurea. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in a significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and sulfonylurea (see Table 14).

Table 14: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	**Placebo + Metformin and Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin and Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin and Sulfonylurea (N=156)**
HbA_{1C} (%)			
Baseline (mean)	8.12	8.13	8.13
Change from baseline (adjusted mean)	-0.13	-0.85	-1.06
Difference from placebo (adjusted mean) (95% CI)[†]		-0.71[‡] (-0.90; -0.52)	-0.92[‡] (-1.11; -0.73)
Percent of patients achieving A_{1C} < 7%	18	43[‡]	57[‡]
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI)[†]		-22[‡] (-31; -13)	-35[‡] (-44; -25)

Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI)[†]		-1.4[‡] (-2.1; -0.7)	-2.0[‡] (-2.7; -1.3)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

Add-on Combination Therapy With Metformin and Sitagliptin

A total of 217 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 1,500 mg/day) and sitagliptin 100 mg/day (or equivalent fixed-dose combination) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with metformin and sitagliptin. The mean age was 57 years, 58% of patients were men, 73% of patients were Caucasian, 15% were Asian, and 12% were Black or African-American. The mean baseline eGFR was 90 mL/min/1.73 m^2 and the mean baseline BMI was 32 kg/m^2. The mean duration of diabetes was 10 years. Eligible patients entered a 2-week, single-blind, placebo run-in period and were subsequently randomized to INVOKANA 100 mg or placebo, administered once daily as add-on to metformin and sitagliptin. Patients with a baseline eGFR of 70 mL/min/1.73 m^2 or greater who were tolerating INVOKANA 100 mg and who required additional glycemic control (fasting finger stick 100 mg/dL or greater at least twice within 2 weeks) were up-titrated to INVOKANA 300 mg. While up-titration occurred as early as Week 4, most (90%) patients randomized to INVOKANA were up-titrated to INVOKANA 300 mg by 6 to 8 weeks.

At the end of 26 weeks, INVOKANA resulted in a statistically significant improvement in HbA_{1C} (p<0.001) compared to placebo when added to metformin and sitagliptin.

Table 15: Results from 26−Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Sitagliptin

Efficacy Parameter	**Placebo + Metformin and Sitagliptin (N=108*)**	**INVOKANA + Metformin and Sitagliptin (N=109*)**
HbA_{1C} (%)		
Baseline (mean)	8.40	8.50
Change from baseline (adjusted mean)	-0.03	-0.83
Difference from placebo (adjusted mean) (95% CI)[†§]		-0.81[#] (-1.11; -0.51)
Percent of patients achieving HbA_{1C} < 7%[‡]	9	28
Fasting Plasma Glucose (mg/dL)[¶]		
Baseline (mean)	180	185
Change from baseline (adjusted mean)	-3	-28
Difference from placebo (adjusted mean) (95% CI)		-25[#]

		(-39; -11)

***** To preserve the integrity of randomization, all randomized patients were included in the analysis. The patient who was randomized once to each arm was analyzed on INVOKANA.

† Early treatment discontinuation before week 26, occurred in 11.0% and 24.1% of INVOKANA and placebo patients, respectively.

‡ Patients without week 26 efficacy data were considered as non-responders when estimating the proportion achieving $HbA_{1c} < 7\%$.

§ Estimated using a multiple imputation method modeling a "wash-out" of the treatment effect for patients having missing data who discontinued treatment. Missing data was imputed only at week 26 and analyzed using ANCOVA.

¶ Estimated using a multiple imputation method modeling a "wash-out" of the treatment effect for patients having missing data who discontinued treatment. A mixed model for repeated measures was used to analyze the imputed data.

# $p<0.001$

INVOKANA Compared to Sitagliptin, Both as Add-on Combination Therapy With Metformin and Sulfonylurea

A total of 755 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (near-maximal or maximal effective dose) participated in a 52-week, double-blind, active-controlled trial to compare the efficacy and safety of INVOKANA 300 mg versus sitagliptin 100 mg in combination with metformin and sulfonylurea. The mean age was 57 years, 56% of patients were men, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and sulfonylurea (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to INVOKANA 300 mg or sitagliptin 100 mg as add-on to metformin and sulfonylurea.

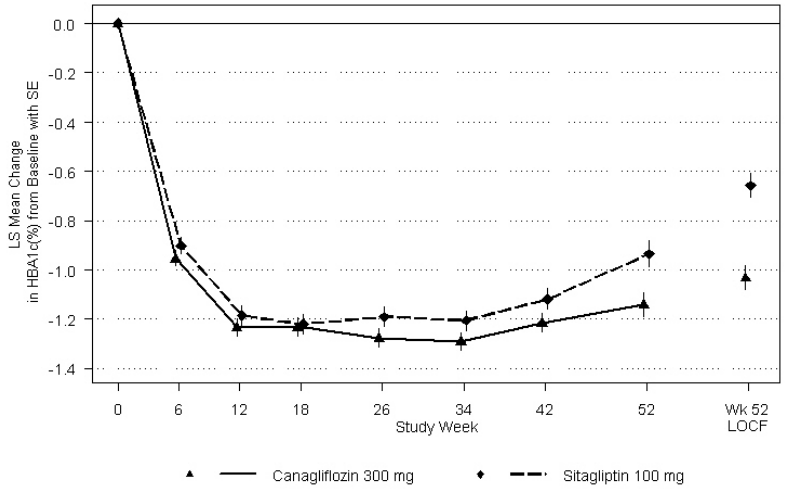
As shown in Table 16 and Figure 2, at the end of treatment, INVOKANA 300 mg provided greater HbA_{1C} reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea ($p<0.05$). INVOKANA 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg. A mean change in systolic blood pressure from baseline of -5.06 mmHg was observed with INVOKANA 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

Table 16: Results from 52-Week Clinical Study Comparing INVOKANA to Sitagliptin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	INVOKANA 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
HbA_{1C} (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)†	-0.37‡ (-0.50; -0.25)	
Percent of patients achieving HbA_{1C} < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI)†	-24 (-30; -18)	
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI)†	-2.8§ (-3.3; -2.2)	

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ INVOKANA + metformin + sulfonylurea is considered non-inferior to sitagliptin + metformin + sulfonylurea because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.
§ p<0.001

Figure 2: Mean HbA_{1C} Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



Add-on Combination Therapy With Metformin and Pioglitazone

A total of 342 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with metformin and pioglitazone. The mean age was 57 years, 63% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and pioglitazone (N=163) entered a 2-week, single-blind, placebo run-in period. Other patients (N=181) were required to be on stable protocol-specified doses of metformin and pioglitazone for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to metformin and pioglitazone.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to metformin and pioglitazone. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG) and in percent body weight reduction compared to placebo when added to metformin and pioglitazone (see Table 17). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 17: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Pioglitazone*

Efficacy Parameter	**Placebo + Metformin and Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin and Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin and Pioglitazone (N=114)**
HbA_{1C} (%)			
Baseline (mean)	8.00	7.99	7.84
Change from baseline (adjusted mean)	-0.26	-0.89	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.81; -0.44)	-0.76‡ (-0.95; -0.58)
Percent of patients achieving HbA_{1C} < 7%	33	47‡	64‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	164
Change from baseline (adjusted mean)	3	-27	-33
Difference from placebo (adjusted mean) (95% CI)†		-29‡ (-37; -22)	-36‡ (-43; -28)
Body Weight			
Baseline (mean) in kg	94.0	94.2	94.4
% change from baseline (adjusted mean)	-0.1	-2.8	-3.8
Difference from placebo (adjusted mean) (95% CI)†		-2.7‡ (-3.6; -1.8)	-3.7‡ (-4.6; -2.8)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

Add-On Combination Therapy With Insulin (With or Without Other Antihyperglycemic Agents)

A total of 1,718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular trial to evaluate the efficacy and safety of INVOKANA in combination with insulin. The mean age was 63 years, 66% of patients were men, and the mean baseline eGFR was 75 mL/min/1.73 m^2. Patients on basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 70% of patients were on a background basal/bolus insulin regimen. After the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to insulin. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo when added to insulin. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reductions in fasting plasma glucose (FPG), and in percent body weight reductions compared to placebo (see Table 18). Statistically significant (p<0.001 for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -2.6 mmHg and -4.4 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 18: Results from 18-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Insulin ≥ 30 Units/Day (With or Without Other Oral Antihyperglycemic Agents)*

Efficacy Parameter	Placebo + Insulin (N=565)	INVOKANA 100 mg + Insulin (N=566)	INVOKANA 300 mg + Insulin (N=587)
HbA_{1C} (%)			
Baseline (mean)	8.20	8.33	8.27
Change from baseline (adjusted mean)	0.01	-0.63	-0.72
Difference from placebo (adjusted mean) (95% CI)†		-0.65‡ (-0.73; -0.56)	-0.73‡ (-0.82; -0.65)
Percent of patients achieving HbA_{1C} < 7%	8	20‡	25‡
Fasting Plasma Glucose (mg/dL)			
Baseline	169	170	168
Change from baseline (adjusted mean)	4	-19	-25
Difference from placebo (adjusted mean) (97.5% CI)†		-23‡ (-29; -16)	-29‡ (-35; -23)

Body Weight			
Baseline (mean) in kg	97.7	96.9	96.7
% change from baseline (adjusted mean)	0.1	-1.8	-2.3
Difference from placebo (adjusted mean) (97.5% CI)[†]		-1.9[‡] (-2.2; -1.6)	-2.4[‡] (-2.7; -2.1)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

Study in Patients Ages 55 to 80

A total of 714 type 2 diabetes patients ages 55 to 80 years and inadequately controlled on current diabetes therapy (either diet and exercise alone or in combination with oral or parenteral agents) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with current diabetes treatment. The mean age was 64 years, 55% of patients were men, and the mean baseline eGFR was 77 mL/min/1.73 m^2. Patients were randomized in a 1:1:1 ratio to the addition of INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily. At the end of treatment, INVOKANA provided statistically significant improvements from baseline relative to placebo in HbA_{1C} ($p<0.001$ for both doses) of -0.57% (95% CI: -0.71%; -0.44%) for INVOKANA 100 mg and -0.70% (95% CI: -0.84%; -0.57%) for INVOKANA 300 mg. *[see Use in Specific Populations (8.5)]*.

Moderate Renal Impairment

A total of 269 patients with type 2 diabetes and a baseline eGFR of 30 mL/min/1.73 m^2 to less than 50 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 26-week, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of INVOKANA in combination with current diabetes treatment (diet or antihyperglycemic agent therapy, with 95% of patients on insulin and/or sulfonylurea). The mean age was 68 years, 61% of patients were men, and the mean baseline eGFR was 39 mL/min/1.73 m^2. Patients were randomized in a 1:1:1 ratio to the addition of INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily.

At the end of treatment, INVOKANA 100 mg and INVOKANA 300 mg daily provided greater reductions in HbA_{1C} relative to placebo (-0.30% [95% CI: -0.53%; -0.07%] and -0.40%, [95% CI: -0.64%; -0.17%], respectively) *[see Warnings and Precautions (5.4), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.

14.2 Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The CANVAS and CANVAS-R trials were multicenter, multi-national, randomized, double-blind parallel group, with similar inclusion and exclusion criteria. Patients eligible for enrollment

in both CANVAS and CANVAS-R trials were: 30 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease (66% of the enrolled population) or were 50 years of age or older and had two or more other specified risk factors for cardiovascular disease (34% of the enrolled population).

The integrated analysis of the CANVAS and CANVAS-R trials compared the risk of Major Adverse Cardiovascular Event (MACE) between canagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

In CANVAS, patients were randomly assigned 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. In CANVAS-R, patients were randomly assigned 1:1 to canagliflozin 100 mg or matching placebo, and titration to 300 mg was permitted at the investigator's discretion (based on tolerability and glycemic needs) after Week 13. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) and exposed for a mean of 149 weeks (exposed for a mean of 223 weeks [4.3 years] in CANVAS and 94 weeks [1.8 years] in CANVAS-R). Approximately 78% of the trial population was Caucasian, 13% was Asian, and 3% was Black. The mean age was 63 years and approximately 64% were male.

The mean HbA_{1C} at baseline was 8.2% and mean duration of diabetes was 13.5 years with 70% of patients having had diabetes for 10 years or more. Approximately 31%, 21% and 17% reported a past history of neuropathy, retinopathy and nephropathy, respectively, and the mean eGFR 76 mL/min/1.73 m^2. At baseline, patients were treated with one (19%) or more (80%) antidiabetic medications including metformin (77%), insulin (50%), and sulfonylurea (43%).

At baseline, the mean systolic blood pressure was 137 mmHg, the mean diastolic blood pressure was 78 mmHg, the mean LDL was 89 mg/dL, the mean HDL was 46 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 115 mg/g. At baseline, approximately 80% of patients were treated with renin angiotensin system inhibitors, 53% with beta-blockers, 13% with loop diuretics, 36% with non-loop diuretics, 75% with statins, and 74% with antiplatelet agents (mostly aspirin). During the trial, investigators could modify anti-diabetic and cardiovascular therapies to achieve local standard of care treatment targets with respect to blood glucose, lipid,

and blood pressure. More patients receiving canagliflozin compared to placebo initiated anti-thrombotics (5.2% vs 4.2%) and statins (5.8% vs 4.8%) during the trial.

For the primary analysis, a stratified Cox proportional hazards model was used to test for non-inferiority against a pre-specified risk margin of 1.3 for the hazard ratio of MACE.

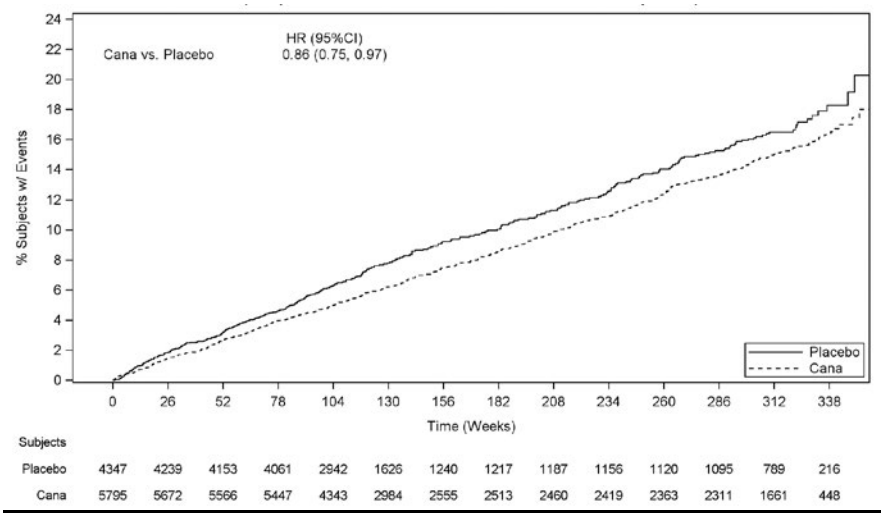
In the integrated analysis of CANVAS and CANVAS-R trials, canagliflozin reduced the risk of first occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.86 (0.75, 0.97). Refer to Table 19. Vital status was obtained for 99.6% of patients across the trials. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 3.

Table 19: Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the Integrated Analysis of CANVAS and CANVAS-R studies[*]

	Placebo N=4347	**Canagliflozin N=5795**	**Hazard ratio (95% C.I.)[¶]**
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[†, ‡, §,]	426 (10.4)	585 (9.2)	0.86 (0.75, 0.97)
Non-fatal myocardial infarction[‡, §]	159 (3.9)	215 (3.4)	0.85 (0.69, 1.05)
Non-fatal Stroke[‡, §]	116 (2.8)	158 (2.5)	0.90 (0.71, 1.15)
Cardiovascular Death[‡, §]	185 (4.6)	268 (4.1)	0.87 (0.72, 1.06)

[*] Intent-To-Treat Analysis Set
[†] P-value for superiority (2-sided) = 0.0158
[‡] Number and percentage of first events
[§] Due to pooling of unequal randomization ratios, Cochran-Mantel-Haenszel weights were applied to calculate percentages
[¶] Stratified Cox-proportional hazards model with treatment as a factor and stratified by study and by prior CV disease

Figure 3: Time to First Occurrence of MACE



16 HOW SUPPLIED/STORAGE AND HANDLING

INVOKANA (canagliflozin) tablets are available in the strengths and packages listed below:

100 mg tablets are yellow, capsule-shaped, film-coated tablets with "CFZ" on one side and "100" on the other side.

NDC 50458-140-30	Bottle of 30
NDC 50458-140-90	Bottle of 90
NDC 50458-140-50	Bottle of 500
NDC 50458-140-10	Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

300 mg tablets are white, capsule-shaped, film-coated tablets with "CFZ" on one side and "300" on the other side.

NDC 50458-141-30	Bottle of 30
NDC 50458-141-90	Bottle of 90
NDC 50458-141-50	Bottle of 500
NDC 50458-141-10	Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Lower Limb Amputation

Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Hypotension

Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.2)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of INVOKANA. Instruct patients to check ketones (when

possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical advice immediately *[see Warnings and Precautions (5.3)]*.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of INVOKANA. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOKANA use in those settings *[see Warnings and Precautions (5.4)]*.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.5)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKANA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.7)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.8)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.8)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions (5.9)]*.

Bone Fracture

Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions (5.10)]*.

Pregnancy

Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation

Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions (7.3)]*.

Missed Dose

If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Active ingredient made in Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Finished product manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778

Or

Janssen Cilag SpA
Latina, Italy

Licensed from Mitsubishi Tanabe Pharma Corporation

Medication Guide
INVOKANA® (in-vo-KAHN-uh)
(canagliflozin)
Tablets

What is the most important information I should know about INVOKANA?

INVOKANA can cause important side effects, including:

- **Amputations. INVOKANA may increase your risk of lower limb amputations. Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.**
  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have heart disease or are at risk for heart disease
  - have had blocked or narrowed blood vessels, usually in your leg
  - have damage to the nerves (neuropathy) in your leg
  - have had diabetic foot ulcers or sores

Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Your doctor may decide to stop your INVOKANA for a while if you have any of these signs or symptoms.

Talk to your doctor about proper foot care.

- **Dehydration. INVOKANA can cause some people to become dehydrated (the loss of too much body water). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).**
  You may be at higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including diuretics (water pill)
  - are on a low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older

Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

- **Vaginal yeast infection.** Women who take INVOKANA may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKANA may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

What is INVOKANA?

- INVOKANA is a prescription medicine used:
  - along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes.
  - to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes who have known cardiovascular disease.
- INVOKANA is not for people with type 1 diabetes.
- INVOKANA is not for people with diabetic ketoacidosis (increased ketones in blood or urine).
- It is not known if INVOKANA is safe and effective in children under 18 years of age.

Who should not take INVOKANA?

Do not take INVOKANA if you:

- are allergic to canagliflozin or any of the ingredients in INVOKANA. See the end of this Medication Guide for a list of ingredients in INVOKANA. Symptoms of allergic reaction to INVOKANA may include:
  - rash

- raised red patches on your skin (hives)
- swelling of the face, lips, mouth, tongue, and throat that may cause difficulty in breathing or swallowing

- have severe kidney problems or are on dialysis.

What should I tell my doctor before taking INVOKANA?

Before you take INVOKANA, tell your doctor if you:

- have a history of amputation.
- have heart disease or are at risk for heart disease.
- have had blocked or narrowed blood vessels, usually in your leg.
- have damage to the nerves (neuropathy) in your leg.
- have had diabetic foot ulcers or sores.
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your doctor may change your diet or your dose of INVOKANA.
- are going to have surgery.
- are eating less due to illness, surgery, or a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short-term ("binge" drinking).
- have ever had an allergic reaction to INVOKANA.
- have other medical conditions.
- are pregnant or plan to become pregnant. INVOKANA may harm your unborn baby. If you become pregnant while taking INVOKANA, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. INVOKANA may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking INVOKANA. Do not breastfeed while taking INVOKANA.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

INVOKANA may affect the way other medicines work, and other medicines may affect how INVOKANA works. Especially tell your doctor if you take:

- diuretics (water pills)
- phenytoin or phenobarbital (used to control seizures)
- digoxin (Lanoxin®)* (used to treat heart problems)
- rifampin (used to treat or prevent tuberculosis)
- ritonavir (Norvir®, Kaletra®)* (used to treat HIV infection)

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take INVOKANA?

- Take INVOKANA by mouth 1 time each day exactly as your doctor tells you to take it.
- Your doctor will tell you how much INVOKANA to take and when to take it. Your doctor may change your dose if needed.
- It is best to take INVOKANA before the first meal of the day.
- Your doctor may tell you to take INVOKANA along with other diabetes medicines. Low blood sugar can happen more often when INVOKANA is taken with certain other diabetes medicines. See "**What are the possible side effects of INVOKANA?**"
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take two doses of INVOKANA at the same time. Talk to your doctor if you have questions about a missed dose.
- If you take too much INVOKANA, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Stay on your prescribed diet and exercise program while taking INVOKANA.
- Check your blood sugar as your doctor tells you to.
- INVOKANA will cause your urine to test positive for glucose.

- Your doctor may do certain blood tests before you start INVOKANA and during treatment as needed. Your doctor may change your dose of INVOKANA based on the results of your blood tests.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A_{1C}.

What are the possible side effects of INVOKANA?

INVOKANA may cause serious side effects including:

See "**What is the most important information I should know about INVOKANA?**"

- **ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes**, during treatment with INVOKANA. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with INVOKANA even if your blood sugar is less than 250 mg/dL. Stop taking INVOKANA and call your doctor right away if you get any of the following symptoms**:
  - o nausea
  - o vomiting
  - o stomach area (abdominal) pain
  - o tiredness
  - o trouble breathing

  If you get any of these symptoms during treatment with INVOKANA, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- **kidney problems.** Sudden kidney injury has happened to people taking INVOKANA. Talk to your doctor right away if you:
  - o reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - o you start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long
- **serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking INVOKANA. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people may also have a fever, back pain, nausea, or vomiting.
- **low blood sugar (hypoglycemia).** If you take INVOKANA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take INVOKANA.

  Signs and symptoms of low blood sugar may include:
  - o headache
  - o drowsiness
  - o weakness
  - o confusion
  - o dizziness
  - o irritability
  - o hunger
  - o fast heartbeat
  - o sweating
  - o shaking or feeling jittery
- **a rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take INVOKANA. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around your anus and genitals:**
  - o pain or tenderness
  - o swelling
  - o redness of the skin (erythema)
- **serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKANA and call your doctor right away or go to the nearest hospital emergency room. See "**Who should not take INVOKANA?**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **broken bones (fractures).** Bone fractures have been seen in patients taking INVOKANA. Talk to your doctor about factors that may increase your risk of bone fracture.

The most common side effects of INVOKANA include:

- vaginal yeast infections and yeast infections of the penis (See "**What is the most important information I should know about INVOKANA?**")
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of INVOKANA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Pharmaceuticals, Inc. at 1-800-526-7736.

How should I store INVOKANA?

- Store INVOKANA at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep INVOKANA and all medicines out of the reach of children.**

General information about the safe and effective use of INVOKANA.

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use INVOKANA for a condition for which it was not prescribed. Do not give INVOKANA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about INVOKANA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about INVOKANA that is written for healthcare professionals.

For more information about INVOKANA, call 1-800-526-7736 or visit our website at www.invokana.com.

What are the ingredients of INVOKANA?

Active ingredient: canagliflozin

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. In addition, the tablet coating contains iron oxide yellow E172 (100 mg tablet only), macrogol/PEG, polyvinyl alcohol, talc, and titanium dioxide.

*The brands listed are trademarks of their respective owners and are not trademarks of Janssen Pharmaceuticals, Inc.

Active ingredient made in Belgium. Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560. Manufactured by: Janssen Ortho LLC, Gurabo, PR 00778 or Janssen Cilag SpA, Latina, Italy. Licensed from Mitsubishi Tanabe Pharma Corporation.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 10/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	29 Oct 2018
From	Lisa Yanoff, M.D. Acting Division Director Division of Metabolism and Endocrinology Products
NDA/BLA #	204-042 Supplement 027 204-353 Supplement 025 205-879 Supplement 007
Applicant	Janssen Research and Development, LLC
Date of Submission	29 Sep 2017
PDUFA Goal Date	29 Oct 2018 (3-month extension)
Proprietary Name / Established (USAN) names	Invokana (canagliflozin) Invokamet (canagliflozin/metformin HCl) Invokamet XR (canagliflozin/metformin XR)
Proposed Indication	To reduce the risk of major adverse cardiovascular events (b) (4) in adults with type 2 diabetes mellitus who have established cardiovascular disease (b) (4)
Approved Indication(s)	**N204-042:** An adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus **N204-353** / **N205-879:** An adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus who are not adequately controlled on metformin or canaglifozin alone or in patients already treated with the combination of canaglifozin and metformin
Regulatory Action	**Approval** with changes to the proposed indication and labeling

1. Introduction

The current supplemental New Drug Applications (sNDA) seek to add information to the Prescribing Information for Invokana (canagliflozin), Invokamet (canagliflozin + metformin), and Invokamet XR (canagliflozin + metformin XR) based on the results of the CANVAS Program: Study DIA3008 (**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy, or CANVAS) and Study DIA4003 (**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy-**R**enal, CANVAS-R) which are both CV outcome studies conducted in patients with type 2 diabetes who had or who were at high risk for CV disease.

This document contains the acting Deputy Director's discussion of the summary basis for regulatory action (approval) for the sNDAs which was based on the primary and secondary reviews tabulated below.

Subject	DARRTS Author	Date in DARRTS
Clinical efficacy and safety review	Dr. Hyon Kwon	26 Oct 2018
Statistical review efficacy (DBII) and safety (DBVII)	Dr. Roberto Crackel	25 Jun 2018
Office of Clinical Pharmacology memo	Dr. Sury Sista	21 May 2018
Nonclinical supervisory review	Dr. Todd Bourcier	11 Oct 2018
Nonclinical review(s)	Dr. Fred Alavi	18 Sep 2018
Enhanced pharmacovigilance interim report review	Dr. Christine Chamberlain	12 Sep 2018
Division of Oncology Products consult memo	Dr. Sundeep Agrawal	8 Aug 2018
Division of Epidemiology consult memo	Dr. Christian Hampp	10 Aug 2018
Sentinel ARIA sufficiency memo	Dr. Christian Hampp	15 Oct 2018

2. Background

Canagliflozin is an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and increases urinary glucose excretion, thereby lowering plasma glucose levels in patients with T2DM. Canagliflozin was approved with the trade name Invokana for the treatment of type 2 diabetes mellitus (T2DM) in the US on March 29, 2013 (NDA 204-042).

Metformin is an oral biguanide, which decreases production of hepatic glucose, intestinal glucose absorption and improves insulin sensitivity. It was approved for the treatment of T2DM in US with the trade name Glucophage (NDA 020-357) on March 3, 1995. Metformin is generally recommended as first line pharmacologic treatment for T2DM.

Invokamet and Invokamet XR are a fixed-combination drug product that containing the two anti-diabetic medications described above: canagliflozin and metformin and the data submitted to support the Invokana NDA is applicable to Invokamet and Invokamet XR.

Canagliflozin-containing products were approved with the postmarketing requirement 2027-5: A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

Cardiovascular Assessment

As a new therapy for type 2 diabetes mellitus, Invokana was subject to the December 2008 guidance for industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. This meant that at the time of approval the development program for canagliflozin should demonstrate that canagliflozin was not associated with an unacceptable increase in cardiovascular risk. The initial marketing application of Invokana included an interim analysis (also pooled with phase 2/3 data) of the cardiovascular outcomes trial (CVOT): CANagliflozin cardioVascular Assessment Study (CANVAS, also referred to as DIA 3008) to meet the 1.8 CV risk goalpost as described in the CV guidance. Invokana was approved with a postmarketing requirement to rule out the 1.3 CV risk margin (2027-5 described above). To accomplish this goal the sponsor initiated a second CVOT: CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R, also referred to as DIA 4003) to obtain further data that was intended to be pooled with data from CANVAS. To facilitate the pooling of data from CANVAS and CANVAS-R, design characteristics such as inclusion/exclusion criteria and event definitions were identical. The integrated studies were called the 'CANVAS Program'. Please see Dr. Roberto Crackel's statistical review and Dr. Kwon's clinical review for details of the regulatory history of the CANVAS Program.

This submission, intended to support a new claim of a reduction in the risk of major adverse cardiovascular events (MACE), in addition to being intended to fulfill the postmarketing requirement, provides the pre-planned integrated analysis of CANVAS and CANVAS-R.

Lower limb amputation

The issue of a risk for atraumatic lower limb amputation was identified prior to the submission of the supplemental NDAs that are the subject of this memo, and the regulatory history of the issue is briefly described here. The reader should refer to the primary reviews by Drs. Crackel and Kwon for details. In diabetes patients, atraumatic lower limb amputation is a known complication due to diabetic neuropathy and/or peripheral vascular disease sometimes resulting in gangrene and the need for amputation of the affected limb(s). The sponsor received an initial notification on 2/18/2016 from the Independent Data Monitoring Committee (IDMC) following a regularly scheduled IDMC meeting held on 1/11/2016 regarding an observed increase in the rate of lower extremity amputations in subjects randomized to canagliflozin compared to placebo in CANVAS (ongoing with a mean on-trial follow-up time of approximately 4.5 years). The annualized incidence reported by the IDMC was 3.0, 7.3, and 5.4 events per 1000 subject-years in the placebo, canagliflozin 100mg, and canagliflozin 300 mg treatment groups respectively. CANVAS-R had a mean follow up of less than a year at that time, but a signal seemed to also be apparent in that trial (a total of 28 subjects had experienced an event, with a corresponding annualized incidence rate of 5.3 and 7.0 per 1000 subject-years in the placebo group and the pooled canagliflozin group respectively). FDA was subsequently notified by the sponsor and on 5/18/2016 the FDA issued a Drug Safety Communication (DSC) to notify the public of this risk. On 5/16/2017 the FDA added a Boxed Warning to the product label for canagliflozin-containing products.

Renal Cell Carcinoma

See separate memo in DARRTS dated 29 Oct 2018 that discusses the background of the renal cell carcinoma safety signal with canagliflozin.

3. CMC/Device

This submission does not contain any new chemistry/manufacturing/controls (CMC) data.

4. Nonclinical Pharmacology/Toxicology

This submission does not contain any new pharmacology/toxicology data. No changes were proposed to the nonclinical sections of labeling. Dr. Alavi recommends approval of these supplements. Dr. Bourcier provided and supervisory nonclinical pharmacology/toxicology memo pertaining to the subject of the safety signal for renal cell carcinoma (see DARRTS, 11 Oct 2018)

5. Clinical Pharmacology/Biopharmaceutics

There are no new Clinical Pharmacology studies included in this sNDA. No changes were proposed to clinical pharmacology sections of labeling. Dr. Sista recommends approval of these supplements.

6. Clinical Microbiology

Not applicable to this NDA

7. Clinical/Statistical- Efficacy

Dr. Kwon from the Division of Metabolism and Endocrinology Products (DMEP) and Dr. Roberto Crackel from the Office of Biostatistics reviewed the efficacy data submitted to support the proposed new indication from the clinical and statistical perspectives, respectively. Both recommended approval of these supplements.

CANVAS and CANVAS-R were event driven, multinational, randomized, double-blind, placebo-control, add-on to standard of care, cardiovascular outcomes trials. As noted above the CANVAS Program was intended to fulfill the CV guidance recommendations, and as such, the number of MACE events from the two trials combined that was pre-specified for the trials to be terminated was 688 and the sponsor estimated that this would provide approximately 90% power to rule out the 1.3 post-marketing margin for CV risk. In addition, the last subject

randomized was to have approximately 78 weeks of follow-up. Testing for MACE superiority was not pre-specified.

The trials were enriched with those at risk for MACE events to facilitate accrual of events and ensure the trial had adequate statistical power in a reasonable timeframe. Eligibility criteria included two groups of patients with 'inadequate glycemic control' i.e. Hba1c from 7.0% to 10.5%, those with a history of documented CV disease and at least 30 years of age (target 70% of the trial population), and those with 2 or more CV risk factors and at least 50 years of age (target 30% of the trial population). Patients could be on no background glycemic lowering therapy, monotherapy, or combination therapy with any approved agent.

For the CANVAS study, patients were enrolled in a 1:1:1 fashion to placebo, canagliflozin 100mg, or canagliflozin 300mg. For the CANVAS-R study, patients were randomized in a 1:1 fashion to either placebo or canagliflozin 100mg. The canagliflozin/placebo dosage were up-titrated from 100mg to 300mg only if better glycemic control was necessary.

The primary endpoint was time to first occurrence of MACE, which is a 3-point composite of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction. The primary analysis model was a Cox proportional hazards model which included treatment as the explanatory variable, and study (CANVAS or CANVAS-R), and prior CV disease subgroup (secondary or primary prevention) as stratification factors. The first step in the testing hierarchy was to demonstrate non-inferiority. All canagliflozin patients were pooled and tested against placebo.

Type 1 error was to be avoided using a hierarchical testing procedure. The sequence was first: non-inferiority of canagliflozin for MACE with a 1.3 margin, followed by superiority of canagliflozin for all-cause mortality, and superiority of canagliflozin for CV death. The rationale for the hypothesis tests apparently had to do with the sponsor knowing the results of the EMPA-REG OUTCOMES study (CVOT with empagliflozin, another member of the SGLT2i class) which demonstrated a reduction in CV death vs. placebo. The testing sequence was still prespecified prior to trial completion and unblinding, however. Note that although superiority in MACE was not part of the pre-specified testing strategy, the sponsor is seeking a superiority claim for canagliflozin in the reduction of MACE risk.

In total, 10,142 patients were randomized in CANVAS and CANVAS-R.

	Placebo (N=4348*) n (%)	Cana (N=5795) n (%)	Total (N=10143*) n (%)
Study in ITT analysis set	4347 (>99.9)	5795 (100)	10142 (>99.9)
Completed Study	4163 (95.7)	5571 (96.1)	9734 (96.0)
Final vital status known	4327 (99.5)	5773 (99.6)	10100 (99.6)
Alive	4046 (93.1)	5371 (92.7)	9417 (92.8)
Died	281 (6.5)	402 (6.9)	683 (6.7)
Final vital status Unknown	20 (0.5)	22 (0.4)	42 (0.4)

[Source: Integrated Summary of Efficacy Page 28]

***: One subject was randomized at 2 different sites and only the first randomization was included in the ITT**

The median and maximum follow-up times for the CANVAS study were approximately 6 and 7 years, respectively while the median and maximum follow-up times for the CANVAS-R study were approximately 2 and 3 years, respectively. For baseline demographic and disease characteristics at baseline please see the FDA statistical review. Characteristics were balanced between treatment groups. As per the protocol-stated goals, 66% had established cardiovascular disease at baseline while 34% had 2 or more risk factors.

The table below shows the primary efficacy results for the CANVAS and CANVAS-R integrated analysis. The hazard ratio for time to first occurrence of MACE is 0.86 with a 95% C.I. of (0.75, 0.97) p=0.0158. Since the upper bound is less than 1, the evidence supports the claim that canagliflozin is superior to placebo in reducing CV risk. Sensitivity analyses conducted by the FDA statistician found the results to be nearly identical to the primary analysis and concluded that the impact of missing data is negligible. None of the individual components were statistically significant but the point estimates and trends are generally consistent with the composite MACE endpoint. The event rates and hazard ratio for all-cause mortality using the intention-to-treat population in the pooled CANVAS and CANVAS-R studies were 281/4347 (6.5) for placebo, 402/5795 (6.9) for canagliflozin, and 0.87 (0.75, 1.02) which trends similarly to the MACE composite results but is not in and of itself statistically significant because the upper bound of the 95% CI includes 1.0. Recall that superiority on all-cause mortality was the second hypothesis to be tested in the hierarchy. Since the testing scheme was sequential, all of alpha is spent and subsequent endpoints were not tested.

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo	
Endpoint			**HR (95% C.I.)**	**P-value**
MACE	426/4347 (9.8)	585/5795 (10.1)	0.86 (0.75, 0.97)	0.0158
CV Death	185/4347 (4.3)	268/5795 (4.6)	0.87 (0.72, 1.06)	0.1658
Non-Fatal MI	159/4347 (3.7)	215/5795 (3.7)	0.85 (0.69, 1.05)	0.1257
Non-Fatal Stroke	116/4347 (2.7)	158/5795 (2.7)	0.90 (0.71, 1.15)	0.3967
All MI	173/4347 (4.0)	248/5795 (4.3)	0.89 (0.73, 1.09)	0.2588
All Stroke	133/4347 (3.1)	176/5795 (3.0)	0.87 (0.69, 1.09)	0.2343

[Source: Integrated Summary of Efficacy Page 44, 93 and Statistical Reviewer's Analysis]

*Note that the percentages of some of the endpoints are lower in the placebo group. For example, for MACE 9.8% in the placebo arm and 10.1% in the canagliflozin arm. This phenomenon is known as Simpson's paradox and occurs when studies with unequal randomization rates are pooled. Please see the FDA statistical review for details. The hazard ratios in this table, however, take into account the different randomization ratios by including study as a stratification factor.

Subgroup analyses for time to first occurrence of MACE were performed by the sponsor and there were no other significant interactions among the reported subgroups. However, there

were significant interactions among baseline use of beta blockers and baseline use of diuretics. Of interest, the interaction term for region: North America, Central/South America, Europe, and Rest of World was 0.89. For history of CV disease, the data were as follows:

Group	Category	Placebo: n/N (%)	Cana: n/N (%)	HR (95% C.I.)	Interaction P-value
History of CV disease	Yes	346/2900 (11.9)	450/3756 (12.0)	0.82 (0.72, 0.95)	0.1803
	No	80/1447 (5.5)	135/2039 (6.6)	0.98 (0.74, 1.30)	

Note that there is no statistical evidence for a history of CV disease-treatment interaction, but the percentage of patients with events was relatively lower in the subgroup of patients with no history of CV disease, and the point estimate of the HR for MACE is numerically close to 1.0 for this subgroup. (b) (4)

8. Safety

Dr. Kwon completed a comprehensive safety review of the data in the sNDA. The data generally supported the known safety profile of canagliflozin (and canagliflozin plus metformin). Further, as noted above the CANVAS Program was successful in excluding the 1.3 MACE risk margin to fulfill PMR regarding cardiovascular risk.

Two major non-cardiovascular safety issues identified in the review of the CANVAS were lower limb amputation and a signal for renal cell carcinoma. Lower limb amputation is discussed here, and renal cell carcinoma is discussed in an addendum to this memo (see DARRTS dated 29 Oct 2018)

Atraumatic lower limb amputation

Please see Background section above for a discussion of the regulatory history of the safety issue of atraumatic lower limb amputation. This section describes the final review of the data related to this issue based on the completed CANVAS and CANVAS-R studies. The analysis was conducted by the FDA statistical reviewers, and details can be found in Dr. Crackel's review including methods of event ascertainment and event analysis. An integrated time-to-event analysis showed that canagliflozin was associated with an approximately 2-fold increase in the risk of amputation compared to placebo, with a hazard ratio (HR) estimate of 1.97 and a 95% confidence interval (CI) [1.41, 2.75]. The exposure-adjusted annualized incidence rates for canagliflozin and placebo were 6.30 and 3.37, respectively, based on the two trials, CANVAS and CANVAS-R. Most of the follow-up time were accrued in the CANVAS study as is evident in the tables below created by the FDA statistical reviewer. Sensitivity analysis

was consistent with the primary analysis, and additional analysis conducted did not suggest that the hazard ratio estimates were statistically different between the CANVAS and CANVAS-R studies. The reason for the apparent slightly higher risk for canagliflozin 100 mg vs. canagliflozin 300 mg is unclear but likely due to chance as the two doses of canagliflozin are known to have similar pharmacodynamic effect (see original canagliflozin reviews for details); the estimated hazard ratio of amputations was consistent in the two canagliflozin dose groups in CANVAS relative to placebo; with an estimated HR and 95% CI of 2.239 (0.356, 3.697) for canagliflozin 100 mg, and 2.006 (1.205, 3.340) for canagliflozin 300 mg (see FDA statistical review). Also of interest, the subgroup of subjects age 65 or older had a numerically higher HR estimate than the subgroup of age younger than 65, with HR estimates and 95% CIs being 2.48 [1.39, 4.43] and 1.74 [1.24, 2.53], respectively. Subjects with no peripheral vascular disease (PVD) history had a numerically higher HR estimate associated with canagliflozin (2.44 [1.38, 4.32]) than those with PVD history (1.67 [1.10, 2.54]). No clear difference in risk was observed in subgroups defined by trial or amputation history.

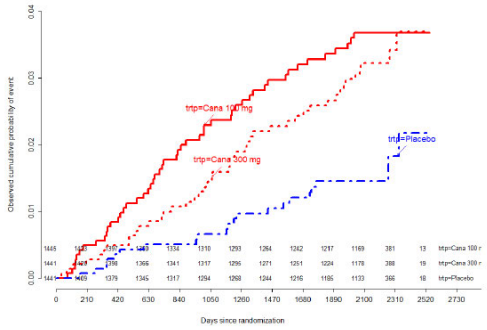
	Placebo (N=1441)	Canagliflozin 100 mg (N=1445)	Canagliflozin 300 mg (N=1441)
CANVAS			
Mean on-study follow-up (years)	5.53	5.61	5.64
Mean on-treatment time (years)	4.07	4.40	4.39
Subjects with an event (%) (on-study)	22 (1.5%)	50 (3.5%)	45 (3.1%)
IR per 1000 PY (on-study)	2.76	6.17	5.54

Note: Exposure time was calculated up to first amputation event.

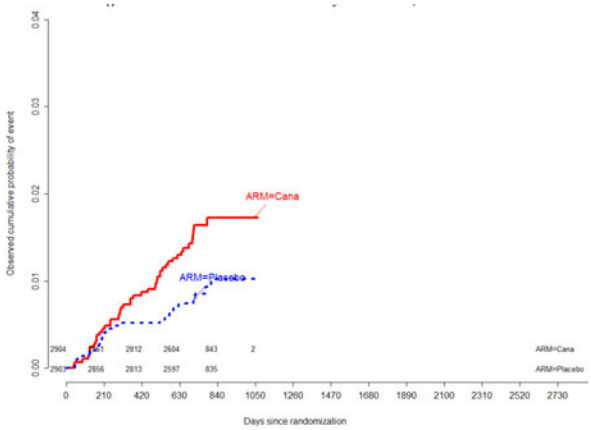
	Placebo (N=2903)	Canagliflozin * (N=2904)
CANVAS-R		
Mean on-study follow-up (years)	2.06	2.06
Mean on-treatment time (years)	1.86	1.89
Subjects with an event (%) (on-study)	25 (0.9)	45 (1.6)
IR per 1000 PY (on-study)	4.18	7.52

Note: Exposure time was calculated up to first amputation event.
*All subjects randomized to canagliflozin in CANVAS-R were initially on 100 mg with possible dose change to 300 mg after 13 weeks. See Section 3.2.1 for more information on trial design.

Cumulative Incidence Plot of Atraumatic Lower Limb Amputation created by FDA statistical reviewer – CANVAS study (left) and CANVAS-R (right)



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The corresponding survival probability plot with confidence bars is available in the Appendix.
Source: Created by FDA statistical reviewer using dataset adtteaep.xpt



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The corresponding survival probability plot with confidence bars is available in the Appendix.
Source: Created by FDA statistical reviewer using dataset adtteaep.xpt

These analyses confirm the safety information that was already added to the product labels for canagliflozin-containing products; no updates to the product labeling are currently warranted.

Renal Cell Carcinoma

See separate memo in DARRTS dated 29 Oct 2018.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this sNDA as there were no issues that rose to the level of needing advisory input.

10. Pediatrics

These sNDAs trigger the Pediatric Research Equity Act (PREA) because of the new indication. However, the Sponsor will be granted a full waiver because necessary studies are impossible or highly impracticable. This was determined because atherosclerosis complications of diabetes mellitus require years to develop, and they are very rare in pediatric patients with diabetes mellitus. For a meaningful study to be conducted, the population would require a diagnosis of type 2 diabetes mellitus AND high cardiovascular risk. The number of pediatric patients fitting these criteria is small, and the required length of follow-up would likely result in patients exceeding the pediatric age range. A clinical trial for the new proposed indication is therefore not feasible.

11. Other Relevant Regulatory Issues

For a discussion of submission quality, compliance with good clinical practices, and financial disclosures, please see Dr. Kwon's review. No concerns were identified regarding these issues.

12. Labeling

Some labeling issues are discussed elsewhere (refer to this memo and to the addendum to this memo regarding renal cell cancer). With respect to the sponsor's proposed indication, (b) (4) The components of the 3-point MACE endpoint were generally consistent with the composite, so it is acceptable to include specific data for the components (b) (4) . (b) (4)

In these sNDAs we are also approving several other labeling changes most notably combining Invokamet and Invokamet XR into a single PI and removing the Warning and Precaution for Hyperkalemia from the PI. The CANVAS Program did not show clinically significant changes in potassium levels and 'hyperkalemia' events (based on MedDRA terms) were infrequent and did not lead to serious sequelae in patients for whom the drug is indicated. Notable elevations of serum potassium appear to occur in the subset of patients with Stage 3b chronic kidney disease, on certain anti-hypertensive mediations, and only with the higher 300 mg dose of canagliflozin. However, canagliflozin 300 mg is not recommended in patients with Stage 3b chronic kidney disease. Monitoring of serum potassium levels in the patient population for whom canaglifozin is indicated are not warranted. Of note, no other product in the SGLT2i class contains a Warning and Precaution for hyperkalemia. 'Increases in serum potassium' should remain in Adverse Reactions, section 6.1.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The favorable risk benefit profile of canagliflozin was determined at the time of its original NDA approval. For this submission, there are three major issues that require consideration.

Cardiovascular Assessment

I conclude that the CANVAS Program provides adequate evidence of superiority of canagliflozin vs. placebo on 3-point composite MACE for patients with established cardiovascular disease.

The following indication will be approved: to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease

The rationale is based on the following:

- Statistical significance of the primary endpoint: The primary endpoint was time to first occurrence of MACE, a 3-component composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction and nonfatal stroke. Results from the integrated analysis showed that the hazard ratio and 95% confidence interval (CI) for time to first occurrence of MACE are 0.86 and (0.77, 0.97). Since the upper bound of the confidence interval is less than 1, superiority in 3-point MACE of canagliflozin to placebo was demonstrated.

- Confidence that results are likely to be true (despite the lack of pre-specification of the 3-point MACE superiority test): The p value for superiority was slightly above 0.01. Confidence in the result is increased because of the similar (although not identical) findings in the EMPA-REG OUTCOMES trial for empagliflozin. In addition, there is regulatory precedent in the CVOT for liraglutide (LEADER) which was also granted a superiority indication with a similar p value, i.e. similar strength of evidence.

- Similar trends in MACE risk reduction for the two studies, CANVAS and CANVAS-R, separately were found: the results for each study were similar while not statistically significant on their own. It is reasonable to believe that the risk reduction in MACE observed in each trial independently is similar to the integrated analysis, but that statistical significance was not reached because the confidence intervals were wider (lack of statistical power).

- Consistency of the components of MACE with the overall composite within each study: the 3 components of MACE, CV death, nonfatal MI, and nonfatal stroke, all trended favorably with point estimates similar to the composite. Lack of statistical superiority is likely due to lack of power.

- General consistency within subgroups except for a lack of robust data supporting efficacy of canagliflozin in reducing the risk of MACE in patients without established CV disease.

- Clinically relevant and believable reduction in MACE: a 0.86 point estimate for the Hazard Ratio translates into a 14% risk reduction of MACE (as defined in the CANVAS Program – nonfatal myocardial infarction, nonfatal stroke and cardiovascular death) vs. placebo on a background of standard of care. While the mechanism of action of the risk reduction remains unclear it is notable that the relative risk reduction is similar to composite MACE findings from the cardiovascular outcomes trial for another antidiabetic drug (liraglutide).

- Appropriate design of CANVAS and CANVAS-R such that the integrated analysis is valid: Both studies were similar in design, eligibility criteria, study population, and MACE event collection and other aspects of trial conduct.

- Adequate trial conduct and integrity: Trial integrity appears to have been maintained, and concerns related to unblinding of data at the time of an interim analysis were adequately addressed in the pre-specified statistical analysis plan. Dr. Crackel confirmed that there did not appear to be any meaningful bias in the statistical results due to the interim unblinding. Both studies were overseen by a single Steering Committee and Independent Data Monitoring Committee (IDMC) and cardiovascular endpoints were adjudicated by a single Endpoint Adjudication Committee (EAC).

- Excellent patient retention, follow-up and ascertainment of vital status at the end of the studies: Through public records searches, the final vital status of 99.6% of patients were captured. The rate of missing MACE data was low (4%) and sensitivity analyses that addressed missing data were almost identical to the primary analysis.

- Regulatory precedent of relying on one study's worth of evidence (in this case an integrated analysis of 2 trials) to support a claim for a clinically meaningful endpoint such as composite MACE for which a second confirmatory trial would either be infeasible or unethical: (see the Division director memos for the EMPA-REG OUTCOMES [see NDA 20462] trial review and the LEADER trial review [NDA 022341]). FDA has previously relied on a single, well conducted and controlled study in circumstances where a single trial has provided "highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds." See Guidance for Industry: Providing clinical evidence of effectiveness for human drug and biological products, May 1998.

Lower Limb Amputation

No further labeling changes are warranted based on these sNDAs. A safety signal for atraumatic lower extremity amputation associated with canagliflozin was identified in the CANVAS program. As discussed above, this safety issue was previously labeled (boxed warning) in canagliflozin-containing products.

Renal Cell Carcinoma

Please refer to the addendum to the Division Director memo on this topic (in DARRTS dated 29 Oct 2018). In brief, longer follow up and more information is needed to make a more informed decision on whether canagliflozin is truly contributing to or causing an increased incidence of RCC compared to placebo. At this time, the most reasonable action is to place the known information in section 6.1 of the PI (Adverse Reactions) with a statement acknowledging that causality cannot be confirmed. An observational study will be conducted by FDA at which time there is sufficient follow up to allow for a valid analysis.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None. Based on the ARIA assessment no postmarketing required studies for renal cell carcinoma will be issued with the action on these supplements. As noted above, there will be no PREA-related postmarketing requirements.

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate canagliflozin in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: renal cell carcinoma.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website.

These supplemental NDAs **fulfill** the postmarketing requirement 2027-5: A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

- Recommended Comments to Applicant

None. All comments to the Applicant have been conveyed at the time of the completion of this review.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
10/29/2018

Addendum to Clinical Review and Division Director Memo

Efficacy Supplements: NDA 204042, S-27; NDA 204353, S-25; NDA 205879, S-07

Products: Invokana (canagliflozin), Invokamet (canagliflozin and metformin HCl immediate release), Invokamet XR (canagliflozin and metformin extended release)

Applicant: Janssen Pharmaceuticals, Inc.

Subject: Renal Cell Carcinoma

Reviewer: Hyon Kwon

Table of Contents

1. Background:

In the original NDA for canagliflozin, renal cell carcinoma was an adverse event of interest based on the nonclinical program, where a 2-year rat study showed increased renal tubule adenoma/carcinoma in both male and female rats at the highest dose studied (100 mg/kg, about 12x clinical exposure for 300 mg dose). In addition, 4 of 5 SGLT2 inhibitors under development reported neoplasms of the renal tubules in nonclinical studies. Therefore, the Applicant was required to continue to follow the incidence of renal malignancies with post-marketing surveillance and in other clinical studies with canagliflozin under PMR 2027-3.

Findings in CANVAS Program:

In this efficacy supplement, the Applicant submitted results of meta-analysis of cardiovascular (CV) outcomes from two CV outcome studies, DIA3008 (also called CANVAS) and DIA4003 (also called CANVAS-R), to assess canagliflozin's cardiovascular risk as part of post-marketing requirement (PMR 2027-5). CANVAS and CANVAS-R studies together are also called the CANVAS Program. DIA3008 was initiated (initial protocol issued August 2009) before marketing approval of canagliflozin in the U.S. (March 29, 2013), whereas DIA4003 was initiated (initial protocol issued September 2013) after US approval with the intent to combine its results with DIA3008 for CV assessment of canagliflozin. Please refer to the Clinical Review for these supplemental NDAs for details of the CANVAS program.

During the safety review of pooled DIA3008 and DIA4003 data, an imbalance in renal cell cancer (RCC) not favoring canagliflozin was observed. In the pooled data, the incidence of RCC in the canagliflozin arm was 0.62 per 1000 person-years (14 subjects [0.2%]) compared to 0.21 per 1000 person-years in the placebo arm (3 subjects [0.1%]), with incidence rate difference of 0.41 per 1000 person-years (95% CI: -0.04, 0.86). See 'Renal Cancer' in Section 7.3.5.1 of the Clinical Review for discussion of initial finding and narratives of these cases. The Applicant did not address this imbalance in the supplement submission or provide interpretation of this data.

Due to the need for Applicant clarification to assess this safety signal, an information request (IR) was sent to the Applicant. The response from the Applicant included new analyses; this triggered a PDUFA clock extension of 3 months. Additional IRs were subsequently sent to the Applicant and are discussed in more detail below.

We also consulted our Oncology colleagues and Division of Epidemiology; their consults are summarized in respective sections in Section 3 and Section 4. Dr. Todd Bourcier, supervisory nonclinical reviewer also re-reviewed nonclinical data for canagliflozin in the context of more recent data with other SGLT1/SGLT2 inhibitors to re-assess the clinical relevance of rat carcinogenicity study conducted for initial approval in light of new clinical data from subsequent canagliflozin studies and new nonclinical data from other SGLT development programs; his review is summarized in Section 6.

2. Response to Information Request (IR) #1 Received on June 28, 2018:

The first IR was sent to the Applicant on June 21, 2018 and the response was received on June 28, 2018. The PDUFA goal date extension for this efficacy supplement was based on the Applicant's response, because this was considered to be a major amendment.

The Applicant's responses to our questions are summarized here (the Applicant also provided narratives for all the cases, along with CIOMS; renal cases have already been discussed in the Clinical Review for the supplement):

Question: We note a numerical imbalance in cases of renal cell carcinoma not favoring canagliflozin in the integrated CANVAS analysis. We are concerned about this numerical imbalance in light of findings from the nonclinical program for canagliflozin, which showed an increased incidence of renal tubule adenoma and carcinoma with canagliflozin.

Although Section 2.1.4.1.2.2.3 in the Integrated Summary of Safety reports the numerical data regarding renal cell carcinoma, it does not include clinical interpretation of this imbalance (e.g., comparative analyses, causality assessment). We request that you submit additional analyses and/or additional information including your interpretation of finding(s).

Applicant's response (summarized):

Canagliflozin is not genotoxic, and an increased incidence of renal tubular tumors (RTT) was seen in Sprague-Dawley rats but not in CD-1 mice. The exposure at the highest approved clinical dose, 300 mg daily, is 5 to 7-fold lower than the lowest exposure that caused tumors in rats.

Results from mechanistic studies in rats were consistent with canagliflozin-induced glucose/galactose malabsorption due to intestinal SGLT1 inhibition leading to RTT formation in rats. Fructose diet that was glucose/galactose free prevented canagliflozin-induced glucose/galactose malabsorption and renal tubule cell proliferation that preceded tumor formation; glucose/galactose malabsorption led to increased intestinal calcium absorption, increased urinary calcium excretion, decreases in parathyroid hormone and 1,25 hydroxyvitamin D, and hyperostosis. The tumor findings in rats are not considered to be relevant to humans since canagliflozin do not appear to induce glucose/galactose malabsorption (i.e., no increase in urinary calcium or decreases in 1, 25 dihydroxy-vitamin D or parathyroid hormone).

The incidence rate for renal cell carcinoma in the canagliflozin group was 0.62 per 1000 person-years (14 subjects) and 0.21 per 1000 person-years (3 subjects) in the placebo group, with the incidence rate difference of 0.41 (0.95% CI: -0.04, 0.86). For interpretation of these numbers, the Surveillance, Epidemiology, and End Results (SEER) database was used to estimate the expected numbers of cases for each treatment group and a standardized incidence ratio (SIR) with 95% CI (Table 1).

Table 1: Standardized Incidence Ratio (SIR) Compared with SEER for Renal Cancer

Treatment	Observed	Expected*	SIR (95% CI)**	p-value**
Cana	14	14.24	0.983 (0.54-1.65)	0.91
Placebo	3	8.84	0.339 (0.070-0.99)	0.0475
All	17	23.08	0.737 (0.43-1.18)	0.239

*Estimated based on SEER incidence rate, prevalence of diabetes in general US population, and relative risk of renal cancer comparing type 2 diabetes vs non-diabetes (Larsson et al., 2011).

**Two-sided p-values and 95% CI from exact test based on Poisson distribution (Rosner 2000) and Fisher's exact test (Rothman and Boice 1979).

Source: NDA 204042, IR response received June 28, 2018; Table 1.

While expected number of cases were seen in the canagliflozin group, a significantly lower number of cases was seen in the non-canagliflozin group, despite balanced baseline characteristics between treatment groups in the CANVAS Program in BMI, hypertension, duration of diabetes, and smoking history. The Applicant also stated that most renal cell cancers were found incidentally, with about one-third of subjects having symptoms leading to their diagnostic evaluation (5 of 14 subjects receiving canagliflozin and 1 of 3 subjects receiving placebo).

Reviewer's comment: We consulted Division of Epidemiology (DEPI) to confirm the Applicant's SEER data analysis as well as to comment on this analysis. See discussion of DEPI's consult in Section 4.

A Table summarizing cases of renal cancer in the CANVAS Program (Table 2) was provided. All 17 subjects had at least one risk factor, and most had 2 or 3 risk factors including tobacco use, hypertension, obesity, being male, and all subjects had T2DM. All subjects except for one were Caucasian, and the mean age was calculated as 66.2 years. Similar subjects developed renal cancer in 100 mg and 300 mg canagliflozin groups.

Table 2: Subjects with Renal Carcinoma in the CANVAS Program

Subject	Treatment	Age at dx	Sex	Race	Country	BMI	Risk factors	Day of Dx	Exposure at Dx	Largest dimension of tumor	Relationship	Other notes
(b) (6)	Cana	59	F	W	DEU	38.2	HTN, Tobacco use, Obesity	40	40	4.5 cm	Not related	Onset < 180 days
	Cana 100 mg	63	M	W	USA	36.1	HTN, Tobacco use, Obesity	1254	664	Not indicated	Doubtful	History of bilateral renal cancer
	Cana 100 mg	75	M	W	NLD	29.6	HTN	705	705	12 cm	Not related	
	Cana 300 mg	65	M	W	NLD	31.3	HTN, Obesity	1356	1356	25 cm	Possible	
	Cana 100 mg	70	F	W	DEU	43.9	HTN, Obesity	1614	1614	Not indicated	Doubtful	History of renal cyst in same kidney
	Cana 100 mg	72	M	W	NLD	31.1	HTN, Tobacco use, Obesity	1099	77	6 cm	Doubtful	Exposure < 180 days
	Cana 300 mg	60	M	W	UKR	41.5	HTN, Obesity	32	32	4.7 cm	Not related	Onset < 180 days
	Cana 300 mg	87	M	W	AUS	26.1	HTN	722	722	3.2 cm	Doubtful	Reported 2 simultaneous primary tumors
	Cana 300 mg	50	M	W	AUS	36	HTN, Obesity	1806	1806	3 cm	Not related	
	Cana 100 mg	62	M	W	AUS	33.1	Obesity	849	849	10 cm	Possible	
	Cana 100 mg	69	M	W	RUS	30.3	HTN, Tobacco use, Obesity	451	451	2 cm	Not related	
	Cana 300 mg	66	F	W	EST	37.5	HTN, Obesity	1767	1767	7 cm	Not related	
	Cana 300 mg	55	M	AA/AI	USA	40	HTN, Tobacco use, Obesity	1808	1808	4.9 cm	Not related	
	Cana 100 mg	78	M	W	ISR	35.2	HTN, Tobacco use, Obesity	1767	1767	Not indicated	Doubtful	
	Placebo	60	M	W	RUS	29.1	HTN, Tobacco use	710	710	8.2 cm	Doubtful	
	Placebo	63	M	W	RUS	30.1	HTN, Tobacco use, Obesity	1343	1343	4 cm	Not related	
	Placebo	71	F	W	ARG	28.9	HTN	241	42	6.4 cm	Doubtful	Exposure < 180 days

Source: NDA 204042, IR Response received June 28, 2018; Table 2

The Applicant pointed out that in 3 cases in the canagliflozin group, "the biologic plausibility of a relationship was doubtful due to limited exposure to canagliflozin; in Subjects (b) (6) and (b) (6) the diagnosed occurred within 180 days of study participation, and exposure to canagliflozin was 77 days in Subject (b) (6) One placebo case (Subject (b) (6) also received the study drug for less than 180 days".

The Applicant also pointed out that 2 cases were confounded by the subjects' prior history. Subject (b) (6) had a prior history of bilateral renal cancer, and Subject (b) (6) had a history of renal cyst in the same kidney where renal cancer was diagnosed during CANVAS study. Both subjects received canagliflozin.

Reviewer's comment: I agree that the reported renal cancer is unlikely to be related to the study drug in 4 cases (3 with canagliflozin and 1 placebo) where either the patient received <90 days of study drug or RCC diagnosis occurred within 180 days of initiating the study drug, given the long latency associated with drug-related malignancies.

In addition, I agree that 2 additional cases were confounded by past medical history of renal cancer and renal cyst. It is difficult to determine whether the reported renal cancer was a recurrence for Subject (b) (6) or was related to underlying renal cyst in Subject (b) (6) as renal cancer occurred in the same left kidney. Both subjects received canagliflozin.

The narratives of all 17 reported RCC cases are summarized and discussed in Section 7.3.5.1 of Clinical Review for this efficacy supplement.

The Applicant discussed presumed growth rates of the observed tumors and pointed to publications where a mean growth rate of renal malignancies averaged a rate of 0.5 cm per year, acknowledging that "these estimates of tumor growth rates are based on subjects who were observed with existing tumors and did not take into account the time the malignancy was clinically undetected". The Applicant pointed out that 3 subjects (b) (6) reported metastatic tumors sized 10 cm or more with exposures ranging from 1.9 to 3.7 years and suggested that tumors were present before study entry based on this rate of growth.

Reviewer's comment: We asked our Oncology colleague to provide their assessment as to whether the reported renal cancer in these subjects may have been present and undetected before their entry into the study based on the reported tumor size. Dr. Agrawal addressed this in his review and stated that the actual rate of renal tumors is highly variable[1]; see summary of his review in Section 3. Therefore, it appears that we cannot reliably estimate how long the renal tumors may have been growing undetected based on the size of the tumor. Also, it is theoretically possible that if there is a causal relationship between canagliflozin and RCC, exposure to canagliflozin may have accelerated the growth of tumors.

[1] Chawla SN, Crispen PL, Hanlon AL, et al. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. Journal of Urology, 175(2):425-31, February 2006.

3. Division of Oncology Product 1 (DOP1) Consult by Dr. Sundeep Agrawal:

We asked DOP1 to provide input regarding the increased incidence of RCC seen in DIA3008 and DIA4003. Our consult questions and Dr. Sundeep Agrawal's responses are presented here; see his review dated August 8, 2018 for full details.

Of note, in his summary and review of cases, Dr. Agrawal summarized method of diagnosis for all cases (Table 3). Dr. Agrawal did not believe that Subject (b) (6) had RCC because urothelial cancer does not typically metastasize to the kidney.

Table 3: Per Case Evaluation of Method of Diagnosis of RCC by Dr. Agrawal

Patient ID	Treatment Arm	Notes
(b) (6)	Cana	Histology confirmed
	Cana	Reported at RCC but no diagnostic testing or histology available
	Cana	No biopsy performed but clinical scenario highly suggestive of RCC, large mass, with metastatic lesions
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	No histology confirms RCC, but patient did have papillary urothelial carcinoma with renal lesion; *not necessarily RCC* (urothelial cancer does not typically metastasize to the kidney)
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Placebo	No biopsy but large renal mass and metastatic lesions, likely RCC
	Placebo	Histology confirmed
	Placebo	Histology confirmed

Source: Dr. Agrawal's memo dated August 8, 2018, Table 3

Consult Questions: DMEP is requesting your interpretation of the imbalance in cases of RCC including your opinion on issues such as (but not limited to):

1) Causality (drug-relatedness assessment:

DOP1 Answer: Surveillance studies of enhancing renal masses have reported mean tumor growth rates of 0.3 cm to 0.5 cm per year, but the populations studied vary and the actual rate of growth of

renal tumors is heterogenous and highly variable. The 3 cases of renal tumors in the Cana arm that were diagnosed in patients with less than 180 days of exposure to study therapy are highly unlikely to be related to study treatment. These tumors, as well as the one case in the placebo arm with <180 days of exposure, were very likely present prior to the patient receiving study drug, but were only identified after they had enrolled onto the trial. In the other 10 cases reviewed, when taking into account the timing of diagnosis in relation to Cana exposure and size of the tumors, Cana contributing to the development of these tumors cannot be excluded.

2) *Whether the event rates of RCC observed in the trial are generally what you would expect in this patient population (i.e. older diabetes patients). Alternatively, is the placebo group rate unusually low?*

DOP1 Answer: The event rates in the placebo group do appear to be low. This may be explained by the following: Patients receiving placebo were less likely to have adverse events caused by the active drug. Patients on the active drug likely developed more adverse events related to its use, which in turn prompted more diagnostic evaluations, resulting in more diagnoses of RCC. Upon review of the case narratives, some of these tumors were found incidentally when evaluating another adverse event. It is possible that the actual incidence of RCC is higher in the placebo group, and are yet to be diagnosed due to lack of symptoms prompting further evaluation.

Event rates in this specific patient population are not well elucidated, but DOP1 conducted a literature search and case narrative review and wanted to provide supplemental information based on this search.

A.) Approximately 1.7% of men and women will be diagnosed with kidney and renal pelvis cancer at some point during their lifetime, and the median age of diagnosis is 64 years, based on 2013-2015 data from the SEER database.

B.) The incidence of renal cell carcinoma in diabetic patients is not well elucidated, but two large prospective cohort studies have examined type 2 diabetes in relation to the risk of RCC among men and women. Following women from the Nurses' Health Study (NHS) with over 28 years of follow up, women with type 2 diabetes had a significantly increased risk of RCC compared with women without type 2 diabetes (multivariable HR 1.53; 95% CI: 1.14-2.04). Among men followed in the Health Professionals Follow-up Study (HPFS) for up to 38 years, type 2 diabetes was not associated with total RCC (HR 0.89; 95% CI 0.56-1.41). It is important to note that many of the same risk factors for diabetes (poor diet, sedentary lifestyle, etc.) are also risk factors for development of malignancy, and as such, identifying a causal relationship between the two is difficult.

C.) Upon review of cases in CANVAS and CANVAS-R, one patient on study was 50 years old when diagnosed with RCC, and another was 45 years old. Both had extended exposure >1700 days, and were much younger than the expected age of diagnosis. Other than these 2 patients, the other 12 patients were in the expected age range of patients diagnosed with RCC.

3) *Data quality issues/reliability of MedDRA searches for malignancy signal detection (i.e. no pathology confirmation available for all patients)*

DOP1 Answer: Histologic confirmation was not available for all patients, as noted in Table 3. Overall, only 3 patients on Cana diagnosed with RCC did not have histologic confirmation. It is unclear if Patient (b) (6) had true RCC. The other 2 cases (Patients (b) (6)) had narratives that were highly suggestive of RCC in the absence of histologic confirmation. Overall, 13 out of 14 cases were either histologically confirmed or highly suggestive of the RCC diagnosis so the reliability of the diagnoses appears adequate. Of note, it may be of value to confirm with the sponsor that other terms such as neoplasm, carcinoma, and cancer were searched along with the term "kidney," in addition to "renal," to evaluate for other cases noted but not reported by the sponsor.

4) *Clinical implications of the various reported pathological diagnoses, i.e. renal cell carcinoma vs clear cell and how this may impact data interpretation or labeling language if the RCC risk were to be added to the product's prescribing information.*

DOP1 Answer: The current WHO classification has many RCC histologic subtypes with diverse tumor biology, and many different terms may be used to describe a malignancy originating in the kidney and renal collecting system. All the terms included in the 14 cases provided appear consistent with renal cell carcinoma. Given the lack of histologic confirmation in some of these cases and the lack of information regarding pathologic features of each case, using a histologic descriptor may not be ideal for labeling language. Instead, a broader term such as kidney cancer may be more appropriate to consider.

5) *Except for 3 subjects, the size of tumor was available in case narratives; please provide your assessment as to whether the reported renal cancer in these subjects may have been present and undetected before their entry into the study, based on the reported tumor size when the renal cancer was detected during their participation in the study.*

DOP1 Answer: Please see answer to Question 1.

Summary of DOP1 Impression: The statistical analysis comparing Cana vs. placebo has confidence intervals that include 1, therefore insufficient evidence exists to conclude that the groups are statistically significantly different. There are also a number of confounding factors when interpreting this data, including lack of histology in some cases, and variability in imaging or screening procedures that led to diagnosis between patients and arms of the study that could introduce bias, including lead-time bias. Longer follow up and more information is needed to make a more informed decision on whether Cana is truly contributing to or causing an increased incidence of RCC compared to placebo.

The incidence of renal cancer with canagliflozin on the CANVAS trial should be compared to both the incidence in the general population and to the placebo arm. While patients entering the CANVAS trial were not screened, they did undergo a general medical examination that may have detected gross abnormalities. The incidence on the placebo arm may, therefore, be a better comparator to the

incidence with canagliflozin. However, as noted above, the incidence of renal cancers with canagliflozin could have been influenced by evaluation of adverse events on canagliflozin with an increase in adverse events on canagliflozin versus placebo.

Reviewer's comment: In summary, Dr. Agrawal acknowledged that data is insufficient to establish causality, there are several confounding factors (such as risk factors and past medical history), and discussed that theoretically there may have been bias that may have led to differences in diagnostic evaluations between treatment arms (such as patients on active drug developing more adverse events leading to more diagnostic evaluations).

However, he concluded that excluding cases that were diagnosed in patients with less than 180 days of exposure to study drug treatment, contribution of canagliflozin to the development of RCC cannot be excluded in the remaining cases.

He suggested confirming with the Applicant that other terms such as neoplasm, carcinoma, and cancer were searched along with the term "kidney", in addition to "renal". Information request to confirm this was sent to the Applicant on August 21, 2008 and received on August 28, 2018 (see IR #3 discussion in Section 5).

4. Division of Epidemiology (DEPI-1) Consult by Dr. Christian Hampp and Response to IR #2 Received on July 16, 2018:

As discussed, in the Applicant's response to IR #1, SEER database was used to calculate the expected number of cases and SIR. We consulted DEPI-1 on July 3, 2018 to confirm and evaluate the Applicant's SEER database calculations, as well as to comment on this comparison. On July 6, 2018, based on DEPI-1's request, another IR (IR #2) was sent for the Applicant to provide detailed description of methods that were used in SIR calculation. The Applicant provided response on July 16, 2018, which also included a refined analysis (Table 4).

In the original analysis submitted on June 28, 2018 (Table 1), cancers of the "kidney and renal pelvis" seen in the canagliflozin arm of the CANVAS Program were observed to be close to expected based on SEER database (SIR 0.98; 95% CI, 0.54-1.65; Table 1), and rates seen in the placebo arm was lower than expected based on the SEER database (SIR 0.34; 95% CI, 0.07-0.99; Table 2). Dr. Hampp pointed out that "the point estimate of the SIR for canagliflozin is close to the upper bound of the 95% CI of the SIR for the placebo arm, but because it falls inside the latter 95% CI, it can be inferred that the two SIRs are not statistically significantly different".

In the refined analysis submitted on July 16, 2018 in response to IR #2, the Applicant used SEER data for RCC rather than cancer of "kidney and renal pelvis", and since RCC is a subset of "kidney and renal pelvis", expected events were fewer than original analysis (Table 4). In this analysis, the Applicant also conducted this refined analysis in the newly available SEER database collected in November 2017 that

was released in April 2018, which included new data from 2000 through 2015, as well as previously used 2016 SEER database (data from 2000 through 2014), and the results are very similar in both data collections. Similar to the original analysis, both 95% CIs cover SIR estimate of the other arm, again indicating that the two SIRs are not statistically different.

Table 4: Standardized Incidence Ratio of Renal Cell Carcinoma in the CANVAS Program Compared with the SEER Database Using Relative Risk for Renal Cell Carcinoma

Treatment	Observed	SEER Nov 2017 data collection†			SEER Nov 2016 data collection††		
		Expected* RCC	SIR (95% CI) **	P-value**	Expected* RCC	SIR (95% CI) **	P-value**
Cana	14	11.51	1.216 (0.67-2.04)	0.54	11.41	1.227 (0.67-2.06)	0.52
Placebo	3	7.12	0.421 (0.087-1.23)	0.15	7.06	0.425 (0.088-1.24)	0.16
All	17	18.63	0.913 (0.53-1.46)	0.82	18.47	0.920 (0.54-1.47)	0.85

RCC in SEER was identified by using ICD-O-3 primary site code C64.9 in combination with histology codes 8010-8051 and 8131-8719.
95% CI = 95% confidence interval
† Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015)
†† Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (2000-2014)
* Estimated based on SEER incidence rate, prevalence of diabetes in general US population, and relative risk of RCC comparing diabetes vs. non-diabetes (Larsson et al. 2011)
** Two-sided p-values and 95 % CI from exact test based on Poisson distribution (Rosner 2000) and Fisher's exact test (Rothman and Boice 1979) http://www.openepi.com/PDFDocs/SMRDoc.pdf accessed 7/12/2018

Source: NDA 204042, IR response received July 16, 2018; Table 1

The Applicant also discussed that relative to the overall population in the CANVAS Program, subjects with RCC were more likely to have risk factors for RCC such as being male, Caucasian, hypertensive, and obese (Table 5). The characteristics of subjects with RCC in the CANVAS Program is what would be expected for RCC occurring in the general population.

Table 5: Selected Baseline Characteristics in the Overall CANVAS Population and Subjects Diagnosed with Renal Cell Carcinoma

	Mean age at Rand (years)	Mean age at RCC dx (years)	% Male	% White	% African-American	Mean BMI (kg/m^2)	% BMI ≥ 30 kg/m^2	% HTN	% Current Tobacco use
Overall population (n=10142)	63.3	--	64.2	78.3	3.3	32	59.3	90	17.8*
Subjects w/ RCC (n=17)	63	66.2	70.6	94.1	5.9	34	76.5	94.1	17.6#
Subjects on Cana w/ RCC (n=14)	63.1	66.5	78.5	92.9	7.1	35	85.7	92.9	7.1#

* Only current daily cigarette smoking was captured in the eCRF at baseline
# Based on information from the eCRF and reported in CIOMS, 47.1% and 42.9% of subjects with RCC, and subjects receiving canagliflozin with RCC were current or former tobacco users, respectively

Source: NDA 204042, IR response received July 16, 2018; Table 3

In addition, the Applicant provided the incidence rate for blinded cases from the ongoing CREDENCE Study (DNE3001), which is a multi-center, multi-national, randomized, double-blind, placebo-controlled, Phase 3 study designed to assess whether canagliflozin has a renal and cardiovascular protective effect in reducing the progression of renal impairment compared to placebo in subjects with type 2 diabetes mellitus. A total of 4,398 subjects were randomized and treated, with 10,203 subject-year follow-up as of July 13, 2018. So far 3 RCC cases have been reported, and 2 of 3 reported cases in the CREDENCE occurred within the first 6 months of the study (Days 2 and 32), and the third case was reported on Day 603. Histology was available in 2 cases, and queries for details about the histology for the third case are currently ongoing.

Table 6: Post-Randomization Renal Cell Carcinoma by Preferred Term (Study DNE3001: On-Study Analysis Set)

Dictionary-Derived Term	Total Group (N=4398) n (%)
Total no. subjects with the AEs	3 (0.07)
Incidence rate per 1000 person-years	0.29
Renal cancer	1 (0.02)
Renal cell carcinoma	1 (0.02)
Renal cell carcinoma stage I	1 (0.02)

Note: Percentages calculated with the number of subjects in total group as the denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Source: NDA 204042, IR Response received July 16, 2018; Attachment 4

Dr. Christian Hampp reviewed the Applicant's analysis and confirmed the Applicant's estimates provided in the original response to IR #1 and in the refined analysis submitted to IR #2. He agreed that using SEER database, the RCC rate in the canagliflozin arm of the CANVAS Program was similar to what may be

expected, whereas the rate seen in the placebo arm was lower than expected, although not statistically significantly different. However, Dr. Hampp outlined multiple limitations in comparing observed rates seen in clinical trials to observed rates calculated based on an external population. He therefore agreed with the Applicant's conclusion that this analysis was not appropriate to exclude a causal role of canagliflozin for RCC. Please see Dr. Hampp's review dated August 10, 2018 for full details.

Reviewer's comment: Dr. Hampp confirmed the Applicant's analysis of U.S. SEER database in calculating expected rates and SIRs. However, as Dr. Hampp discussed, there are many limitations for comparing observed rates in a study to expected rates of an external data such as U.S. SEER data. Some limitations such as surveillance bias, detection bias, and different event definition and adjudication can lead to higher rates in clinical trials compared to external data, and other limitations such as healthier study population or lower rates in developing countries participating in study can lead to lower rates in clinical trials compared to U.S. SEER data. Therefore, I agree that the U.S. SEER database did not help to explain observed imbalance in the incidence of RCC not favoring canagliflozin arm in the CANVAS Study.

The CREDENCE Study, a dedicated renal outcome study for canagliflozin, has so far identified 3 RCC cases; 2 of these cases occurred during the first 6 months of study. CREDENCE was also stopped early because the study achieved pre-specified efficacy criteria, and the duration of exposure and follow-up may not be as long as the CANVAS study. Thus, because of the very limited number of cases and shorter duration of follow-up, it is unlikely that additional safety information that may be available from CREDENCE would help to provide additional information about possible relationship between RCC and canagliflozin.

5. Response to Information Request (IR) #3 Received on August 28, 2018:

A third IR regarding renal cancer was sent to the Applicant on August 20, 2018 and the Applicant submitted their response on August 28, 2018, which are summarized here. The intent of the IR was to explore the signal for RCC with canagliflozin if a very strict, i.e. specific, case definition of RCC was used, to ensure all relevant cases of kidney cancer were captured, and to explore further ways to assess the safety signal.

Question 1: Calculate the incidence rates of kidney cancer in canagliflozin and placebo groups among subjects followed for >180 days after randomization and who had >90 days of drug exposure (events and follow-up time prior to 180 days of follow-up will be ignored) in CANVAS and CANVAS-R. The following patients only were identified as experiencing a qualifying event: Cana: (b) (6) *These patients are those whose cancer occurred >180 days after randomization, had >90 days of drug exposure, had verified histology or strongly suggestive clinical narrative, and had no history of kidney cancer at the time of enrollment.*

Applicant's response: The incidence rates including only cases with 'qualifying event', 8 cases with canagliflozin and 2 cases with placebo, were 0.18 and 0.42 per 1000 subject-years in the placebo and canagliflozin groups, respectively (Table 7).

Table 7: Risk Difference and 95% CI of Post-Randomization Kidney Cancer (Pooled DIA30008 and DIA4003; On-Study Analysis Set)

	Placebo		Cana		Cana vs. Placebo	
	n(%)	Rate (/1000 subject-years)	n(%)	Rate (/1000 subject-years)	IRD (/1000 subject-years)	95% CI
All Kidney Cancers*	3/4344 (0.1)	0.21	14/5790 (0.2)	0.62	0.41	(-0.04, 0.86)
Qualifying Kidney Cancers**	2/4141 (<0.1)	0.18	8/5534 (0.1)	0.42	0.24	(-0.23, 0.71)

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).
* Kidney Cancer includes MedDRA terms derived from the high-level term of 'Renal Neoplasms Malignant'.
** The subjects with qualifying kidney cancer are those whose cancer occurred >180 days after randomization, had >90 days of drug exposure, had verified histology or strongly suggestive clinical narrative, and had no history of kidney cancer at the time of enrollment. The subjects included are (b) (6) in the canagliflozin group, and (b) (6) in the placebo group.
tsfae00_os_renal_rcc2_fda.rtf generated by tsfae00_os_renal_rcc2_fda.sas, 22AUG2018 21:07

Source: NDA 204042, IR response received August 28, 2018; Table 1

Reviewer's comment: Subjects where RCC was diagnosed with less than 180 days of exposure, had history of renal cancer/renal cyst in same kidney, or unlikely to be RCC based on Dr. Agrawal's review (Subject (b) (6) were excluded from this calculation of incidence rates. Although exclusion of these cases lowered the overall incidence rate as well as incidence rate difference between treatment arms, the relative incidence rate between treatment groups remained about 2-fold higher in the canagliflozin group compared to placebo.

Question 2: Confirm that in the CANVAS program terms such as neoplasm, carcinoma, and cancer were searched along with the term "kidney", in addition to "renal", to evaluate for other cases.

Applicant's response: Possible cases of RCC were searched by using PTs coded to the pre-specified list contained in the high-level term of 'Renal Neoplasms Malignant', and the following additional PTs: benign renal neoplasm, malignant neoplasm of renal pelvis, papillary tumor of renal pelvis, renal adenoma, renal neoplasm, renal oncocytoma, transitional cell cancer of renal pelvis and ureter metastatic, transitional cell cancer of the renal pelvis and ureter, transitional cell cancer of the renal pelvis and ureter localized, transitional cell cancer of the renal pelvis and ureter recurrent, and transitional cell cancer of the renal pelvis and ureter regional.

In response to our request to search for additional PTs including 'neoplasm', the Applicant identified one additional case in the placebo group. Subject (b) (6) who was randomized to placebo reported to have a 'right kidney tumor' on Day 1195 days after randomization. Tumor was found on CT scan, histology was not done, and the patient reportedly received an embolization procedure for treatment.

Reviewer's comment: The provided CIOMS report did not include much additional information about 'renal tumor' for this patient. Given that the event was reported as 'right kidney tumor', histology was

not available, and no metastatic lesions were detected, it is unclear if this case should be considered RCC.

Question 3: In the ongoing CREDENCE trial, capture of kidney cancer events is occurring using the same methodology as was used in the CANVAS program. We recommend that before unblinding you amend the CREDENCE protocol to include blinded independent adjudication of kidney cancer events.

Applicant's response: The Applicant agreed to implement blinded independent adjudication of kidney cancer events before database lock by an independent and blinded reviewer, Dr. Samuel Cohen, Professor of Oncology in the Department of Pathology and Microbiology at the University of Nebraska. Since the CREDENCE protocol already includes provision for *ad hoc* adjudication committees, a protocol amendment to include adjudication of kidney events was not considered necessary.

Question 4: In the CANVAS program, you compared the prevalence of selected baseline covariates between RCC cases and the overall trial population. Imbalances between RCC cases and all patients confirm that the following are risk factors for RCC: male sex, Caucasian race, hypertension, and obesity. Clarify if renal impairment was evaluated a potential risk factor for RCC. Clarify if we might expect a higher incidence of RCC in CREDENCE because of the entry criteria for renal impairment.

Applicant's response: Based on the available literature[2,3,4,5], the Applicant concluded that only more severe renal impairment (i.e., Chronic Kidney Disease Stages [CKD] of 3a or worse kidney disease) was associated with an increased risk of RCC.

In the CANVAS Program, eGFR of <30 mL/min/1.73m^2 (CKD Stage 4 or worse kidney disease) was an exclusion criterion. Subjects with RCC in the CANVAS Program had a mean eGFR of 73 mL/min/1.73m^2, and none of the subjects with RCC in the CANVAS Program were CKD Stage 3b at baseline.

The mean baseline eGFR in CREDENCE was lower (56.2 mL/min/1.73m^2) compared to the CANVAS Program (76.5 mL/min/1.73m^2), and a larger proportion of subjects had CKD Stage 3a and 3b impairment in CREDENCE (28.8% and 27.1% respectively) compared to the CANVAS Program (14.6% and 5.2% respectively). CREDENCE excluded CKD Stage 4 and worse renal impairment.

Reviewer's comment: Renal impairment do not appear to be a risk factor for RCC based on the CANVAS Program, as none of the RCC cases had CKD Stage 3b at baseline. DIA3008 and DIA4003 studies excluded subjects with CKD Stage 4 or worse kidney disease.

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[2] Gigante M, Neuzillet Y, Patard JJ, e t al. Renal cell carcinoma arising in native kidneys of dialyzed and transplant patients: are they different entities? BJU Int 2012;110:E570-573.
[3] Ljungberg B, Campbell SC, Choi HY et al. The epidemiology of renal carcinoma. Eur Urol 2011;60:615-621.
[4] Lowrance WT, Ordonez J, Udaltsova N et al. CKD and the risk of incident cancer. J Am Soc Nephrol 2014;25:2327-2334.
[5] McLaughlin JK, Lipworth L, Tarone RE. Epidemiologic aspects of renal cell carcinoma. Semin Oncol 2006;33:527-533.

Question 5: Comment on the feasibility of safety extension, i.e., extension of follow-up, for CREDENCE, to accrue further events of kidney cancer that would be sufficient to rule out a prespecified risk margin (for example 3-fold) with 80% power.

Applicant's response: CREDENCE was stopped on July 16, 2018 after IDMC recommendation because the study met pre-defined criteria for efficacy. As of August 19, 2018, about 3263 of 4401 subjects in CREDENCE completed their final clinic visit and discontinued study drug if on treatment; remaining subjects are in the process of completing their final clinic visits. It is estimated that the date of final contact for the last subject is on or before October 18, 2018. Based on the status of CREDENCE study, all subjects would be off study drug for a period of time before re-initiating treatment in an extension study.

To rule out 3-fold excess risk with 80% power at one-sided alpha of 0.025, about 26 cases of RCC are needed. Three cases of RCC have been identified in CREDENCE after about 11,000 subject-years of follow-up, and 2 of 3 cases occurred less than 180 days after randomization; this leaves additional 25 cases that would need to be accrued.

About 3000 subjects would be on study drug at completing CREDENCE, and about 75% (~2250 subjects) would be potentially eligible for an extension study. If 66% of these subjects are assumed to agree to a safety extension, about 1485 total subjects (742 per treatment arm) would possibly enter the extension study. Based on the incidence rates of RCC and assuming 1485 subjects would enter the safety extension, it is estimated that CREDENCE extension would need to be followed for 18 years (using annual event rate of CANVAS Program, 0.044%) and 28 years (using annual event rate of CREDENCE, 0.028%) to accrue 23 additional cases in order to exclude a 3-fold risk with 80% power.

Reviewer's comment: We agree that a safety extension of CREDENCE would not be informative based on the current status of study and duration of follow-up needed to accrue additional cases in order to rule out excess risk of RCC.

6. Consideration of Nonclinical Data related to RCC: Summary of Dr. Todd Bourcier's Review and Response to IR #4 Received on September 25, 2018:

Dr. Bourcier assessed possible tumorigenic mode of action (MOA) to address the clinical relevance of the rat study to help interpret the imbalance of RCC seen with canagliflozin.

At the time of canagliflozin approval, carbohydrate malabsorption due to intestinal SGLT1 inhibition was determined as key tumorigenic MOA for renal tumors in rats exposed to canagliflozin, and since clinical studies did not indicate occurrence of carbohydrate malabsorption, it was concluded that the tumor risk in humans was small. However, additional findings from more recent members in the class that have SGLT1/2 mixed inhibitors, particularly in those with greater selectivity for SGLT1 (i.e., sotagliflozin and mizagliflozin) raised some concerns as to whether carbohydrate malabsorption is the correct MOA. Dr. Bourcier observed that there were inconsistent findings of renal tumors in rodents across class members, where it was not seen in 6 of 8 other class members as shown in the Table below.

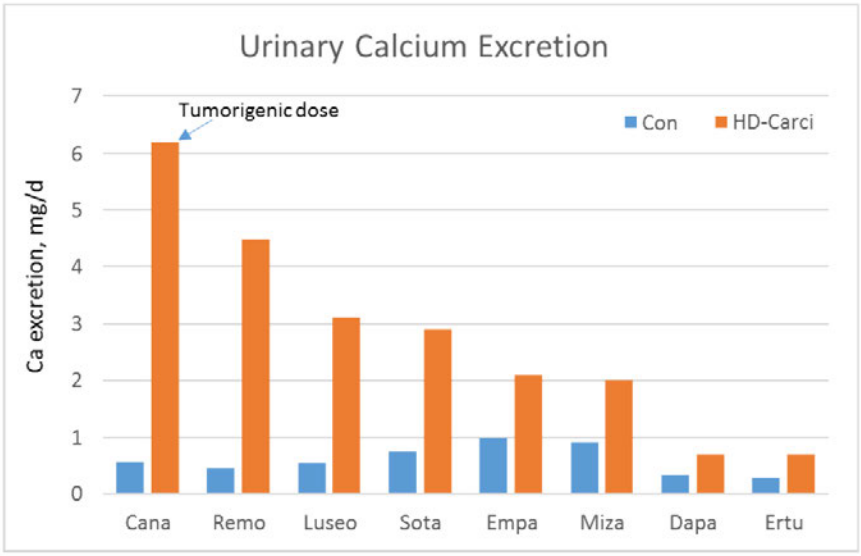
Neoplasms with SGLT2 inhibitors in rodents				
Drug	Renal Tubules	Adrenal PC	Testicular Leydig	Other
Canagliflozin	X	X	X	
Dapagliflozin	atypical hyperplasia	-	-	
Empagliflozin	X (mice)	-	X	hemangioma
Remogliflozin	X (mice)	X (mice & rats)	X	bladder papilloma
Ipragliflozin	atypical hyperplasia	X	-	bladder hyperplasia
Luseogliflozin	-	X	X	
Sotagliflozin	-	-	-	Thyroid FC Bladder hyperplasia
Ertugliflozin	-	X	-	Bladder hyperplasia
Mizagliflozin	-	X	X	

'-' = not observed; 'X' denotes positive finding in rats unless otherwise noted
Source: Dr. Todd Bourcier's review dated October 11, 2018; Appendix 1

To re-evaluate the validity of the carbohydrate malabsorption MOA, Dr. Bourcier selected and compared key events from nonclinical data for canagliflozin and other class members, mainly focusing on biomarkers indicative of calcium disruption in the nonclinical program for canagliflozin and other members in the class. The markers included urinary calcium excretion, parathyroid hormone, and 1,25-dihydroxy vitamin D3.

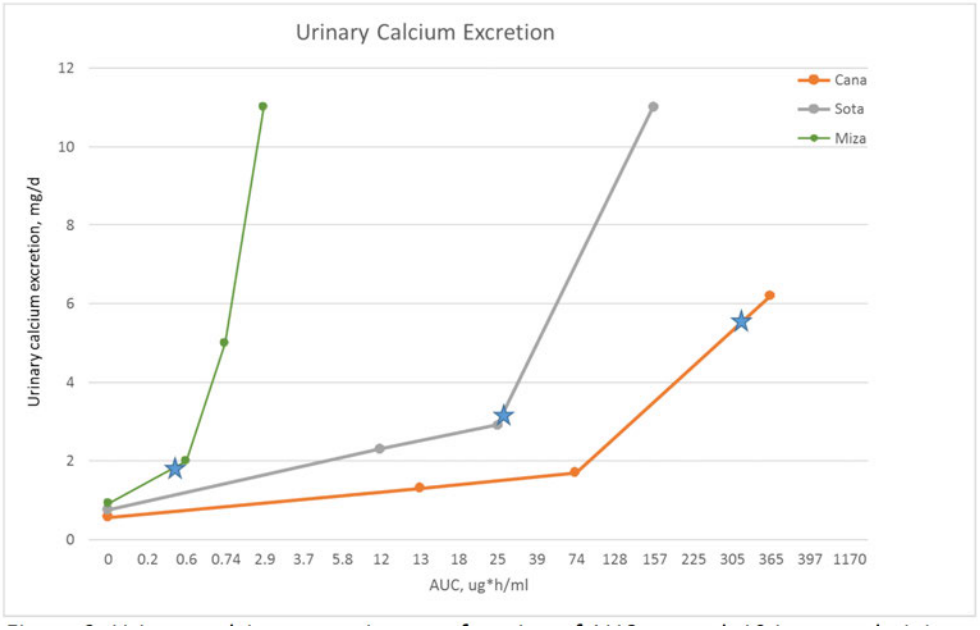
Urinary calcium excretion: Dr. Bourcier's analysis showed that the urinary calcium excretion was greatest for canagliflozin at the highest dose studies in 2-year rat study; only at the high dose 100 mg/kg showed increase in renal tubule adenoma/carcinoma (Figure 1). No renal tumors were seen in rats with other products as shown in the Table above. Figure 1 indicates that discrepancy in tumor outcome may be due to the degree of calcium disruption related to the highest dose evaluated; however, sotagliflozin ('Sota') and mizagliflozin ('Miza') is more selective for SGLT1 and would be expected to be more disruptive in calcium homeostasis that canagliflozin. To assess this, Dr. Bourcier plotted calcium excretion as a function of exposure to Cana, Sota, and Miza at all doses evaluated at Week 13 (Figure 2); this showed that Sota and Miza can lead to more calcium excretion that Cana, but Cana was tested at a higher AUC exposure than other products. This is thought to have led to a higher degree of calcium excretion with canagliflozin for longer duration in the rat carcinogenicity studies.

Figure 1: Urinary Calcium Excretion in Rats at Week 13 with SGLT Inhibitors



'HD-Carci' represents the highest dose of each compound evaluated in the 2 yr carcinogenicitiy study; 'tumorigenic dose' represents the only compound (cana) and dose associated with an unequivocal increase in RCC.
Source: Dr. Bourcier's review dated October 11, 2018; Figure 1

Figure 2: Urinary Calcium Excretion as a Function of AUC at Week 13 in Rats

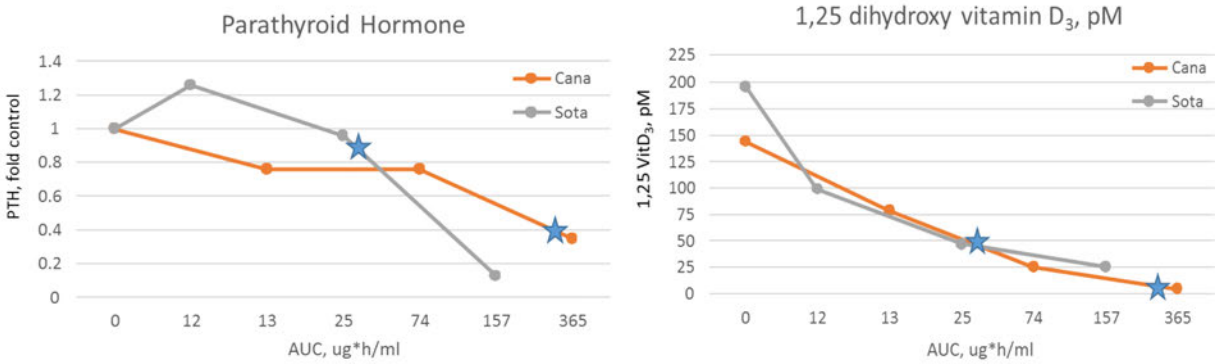


The superimposed starts indicate the highest exposure evaluated in 2-year rat study for each product.
Source: Dr. Bourcier's review dated October 11, 2018; Figure 2

Parathyroid Hormone and 1,25 $(OH)_2$ Vitamin D3: Plasma levels of PTH and 1,25 $(OH)_2$ were only available for Cana and Sota and was derived from Week 13 from either 3-month or 6-month toxicology studies in single-dose rats (Figure 3). The superimposed stars indicate the highest exposure of Cana and Sota tested in 2-year study, and the higher exposure with Cana had bigger reduction in both biomarkers

compared to Sota which appear to have lower exposure. This again supports the conclusion that Cana was associated with greater disruption of calcium balance in the 2-year rat study compared to Sota.

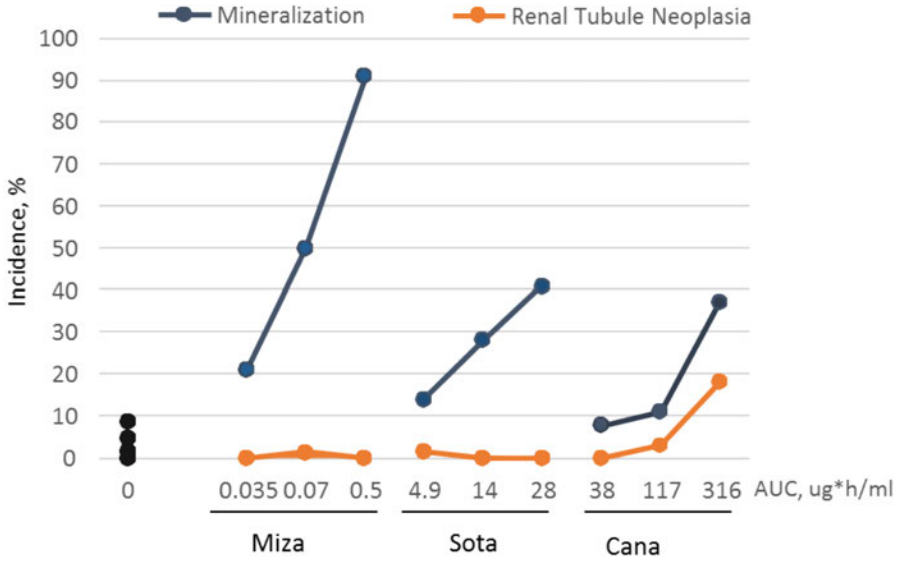
Figure 3: Plasma PTH and 1,25 dihydroxy Vitamin D_3 in Single-Dose Rats at Week 13



The superimposed starts indicate the highest exposure evaluated in 2-year rat study for each product.
Source: Dr. Bourcier's review dated October 11, 2018; Figure 3

Looking at the incidence of renal tubule mineralization against the incidence of renal cell tubule neoplasia in the 2-year rat study for Cana, Sota, and Miza, the incidence of tubule mineralization and neoplasia appear to correspond for Cana, but not for Miza and Sota (Figure 4). This suggested that mineralization alone is insufficient for renal neoplasia.

Figure 4: Incidence of Renal Tubule Mineralization and Renal Tubule Neoplasia in 2-Year Rat Studies for Miza, Sota, and Cana



Source: Dr. Bourcier's review dated October 11, 2018; Figure 4

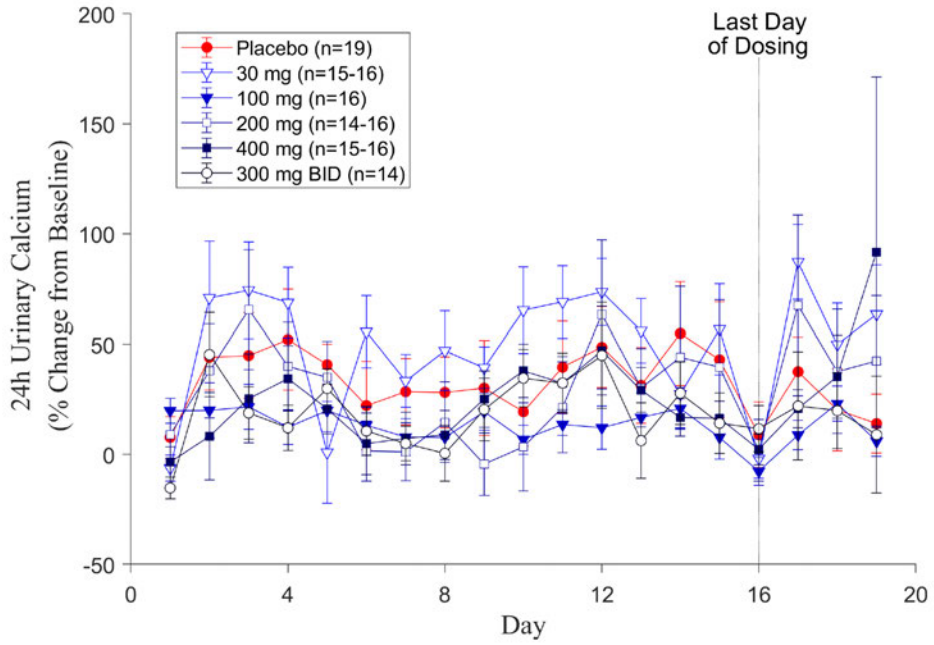
Based on this analysis, Dr. Bourcier concluded that "the higher exposure and greater degree of carbohydrate malabsorption likely achieved by Cana in the 2-year rat study is thus a plausible explanation for an absence of renal tumors in rats administered Sota or Miza".

Information Request (IR) #4:

To review data related to carbohydrate malabsorption in the clinical program for canagliflozin, an IR was sent to the Applicant on September 21, 2018 to ask about any 24 urine samples from clinical trials that tested urinary calcium excretion. The Applicant submitted the summary on September 25, 2018.

Urinary calcium excretion: The Applicant summarized that 24-hour urinary calcium excretion was measured in a single ascending dose study in healthy subjects (NAP1001) and in a multiple ascending dose study in subjects with T2DM treated for 2 weeks with canagliflozin at 30 to 600 mg/day (NAP1002). There was a larger increase in urinary calcium excretion with 30 mg dose in NAP1002, but otherwise no notable increase in % change from baseline in 24-hour urinary calcium excretion with canagliflozin compared to placebo, particularly in the approved dose of 100 mg and 300 mg (Figure 5). It is unclear why 30 mg canagliflozin dose showed difference in urinary calcium excretion compared to higher dose of canagliflozin studied in NAP1002.

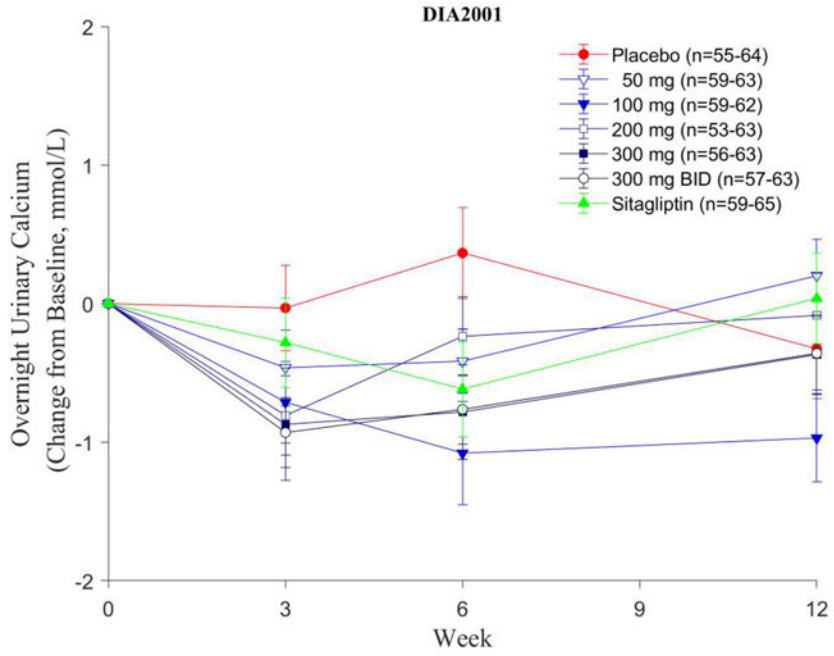
Figure 5: Percent Change from Baseline in 24-Hour Urinary Calcium (Study NAP1002)



Source: NDA 204042, IR response received September 25, 2018; Figure 1

Overnight urinary calcium excretion was measured in a 12-Week Phase 2 studies DIA2001 (in subjects with T2DM) and OBE2001 (in overweight subjects). Although 50 mg of canagliflozin appear to have slight increase in the overnight urinary calcium excretion compared to placebo, this increase was similar with sitagliptin. There was no consistent pattern of increase in the overnight urinary calcium excretion with canagliflozin compared to placebo or sitagliptin, and no notable changes from baseline in overnight urinary calcium (Figure 6).

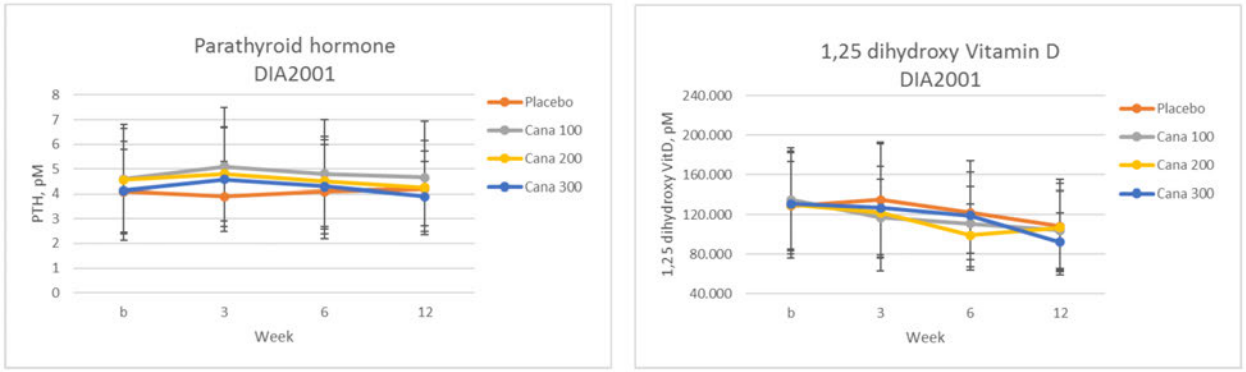
Figure 6: Change from Baseline in Overnight Urinary Calcium (Study DIA2001)



Source: NDA 204042, IR response received September 25, 2018; Figure 2

Parathyroid Hormone and Vitamin D: In DIA2001 study of subjects with T2DM, a small, non-dose dependent increase in parathyroid hormone was seen at Week 3 with canagliflozin versus placebo but returned to baseline by Week 6 through Week 12.

Figure 7: Change in Parathyroid Hormone and 1,25 dihydroxy vitamin D_3 During Study DIA2001 (Mean ±SD)



Source: Dr. Bourcier's review dated October 11, 2018; Figure 8

Hydrogen breath test and intestinal glucose absorption: In DIA1022 in healthy volunteers, canagliflozin 300 mg delayed intestinal glucose absorption without meaningfully reducing overall glucose absorption (see Figure 3 of Applicant's response submitted September 25, 2018; not shown here). Carbohydrate malabsorption was pre-defined as an increase of at least 10 parts per million in breath hydrogen and methane excretion at 2-hours following a 75-gram oral glucose tolerance test. However, this was not

associated with carbohydrate malabsorption when tested by assessing changes in hydrogen breath test values with canagliflozin (100 mg and 300 mg) compared to placebo group after 4 weeks of treatment in clinical study DIA1007 (see Attachment 3 in the Applicant's response; not shown here).

In summary, after reviewing nonclinical data across different SGLT1/SGLT2 inhibitors and clinical data with canagliflozin, Dr. Bourcier concluded that "evaluation of clinical data from phase 1 and 2 studies re-affirmed that canagliflozin did not result in carbohydrate malabsorption to any notable degree in human subjects, which minimizes the clinical relevance of the renal tumor signal in rats. The clinical RCC signal with canagliflozin, therefore, is very unlikely to reflect same renal tumorigenic pathway that occurs in rats." Therefore, additional nonclinical studies will not inform the relationship the imbalance in clinical RCC events not favoring canagliflozin.

Reviewer's comment: Dr. Bourcier identified differences in drug exposure and degree of calcium disruption as a possible explanation for discrepancy in renal tumors seen across the class, and SGLT1-related carbohydrate malabsorption remains as the likely tumorigenic MOA for renal tumors seen with canagliflozin in rats. The possible mechanism for RCC in humans with canagliflozin remains unclear. Dr. Bourcier's review, in addition, does not support a class-labeling approach for the RCC signal.

We considered whether the imbalance seen with canagliflozin was a class effect for SGLT2 inhibitors. Dapagliflozin had no nonclinical findings related to RCC and their CV outcome studies are currently ongoing; in their original submission, there were no imbalance against dapagliflozin (3 cases of renal cancer in the comparator versus none with dapagliflozin). There was a positive nonclinical signal for RCC with empagliflozin (renal tubule adenomas and carcinomas at 45x clinical dose of 25 mg), but imbalance in RCC was not observed in their dedicated CV outcome study EMPA REG; see table below.

EMPA-REG (malignancies of interest after 6 months of exposure); mean exposure was 2.56 years in the pooled empagliflozin group		
	Placebo (N=2333)	Empa (N=4687)
Renal Cancer, N (%)	5 (0.23%)	9 (0.20%)
Clear cell renal cell carcinoma	3 (0.14%)	3 (0.07%)
Renal cancer	0	2 (0.05%)
Renal cancer metastatic	1 (0.02%)	0
Renal cell carcinoma	2 (0.05%)	1 (0.05%)
Renal cell carcinoma stage 1	1 (0.02%)	0
Renal cell carcinoma stage 2	0	1 (0.05%)

Ertugliflozin did not have nonclinical signal related to RCC, and there were no cases of renal cancer at the time of NDA submission; their CV outcome study is currently ongoing. Sotagliflozin also did not show nonclinical signal for RCC, and the NDA for sotagliflozin is currently under DMEP review.

7. Response to Information Request (IR) #5 Received on September 27, 2018:

In exploring whether an observational study may be informative to help elucidate the relationship between canagliflozin and RCC, an IR was sent to the Applicant on September 21, 2018, and the Applicant submitted their response on September 27, 2018. We asked the following question:

> *We are exploring how the potential detection bias may impact the evaluation of renal cell cancer data from clinical investigations of canagliflozin. Please provide the following information for CANVAS and CANVAS-R (safety population) about patients who underwent the procedure below – provide separate tables for CANVAS and CANVAS-R and then another table with both studies pooled. In your response clarify how imaging 'events' were captured in the CANVAS Program.*

Applicant's response: Individual study data were provided for procedures, in Table 8 for DIA3008 and in Table 9 for DIA4003, and pooled data were not provided because some information is available in only one of the studies or because there were differences in collection methodologies, as discussed below.

Imaging studies such as ultrasounds, MRIs, and CT scans were not pre-specified for data collection in either DIA3008 or DIA4003 studies. If an imaging study was done in DIA3008, information related to imaging study were recorded on the Diagnostic and Therapeutics Procedure (DTP) electronic Case Report Form (eCRF) page, and the Applicant conducted a manual review and analysis and provided data below for DIA3008 (Table 8). However, information on imaging studies was not available because DTP was not included in DIA4003 as an eCRF.

In DIA3008, urinalysis was done at Week 18 and Week 52 and every 52 weeks thereafter. In CANVAS-R, urinalysis was not pre-specified for data collection and were done at unscheduled visits as needed by the investigator. Testing for blood was assessed by urine dipstick and reported as 'urine blood' in DIA3008, and blood in the urine was assessed from urine sediment and reported as 'urine occult blood' in DIA4003. See Table 8 for DIA3008 and Table 9 for DIA4003.

Table 8: Summary of Imaging Studies and Urinalysis in DIA3008 (On-Study Analysis Set)

	------- Placebo ------- ------- (N=1441) ------		----- Cana 100 mg ----- ------- (N=1445) ------		----- Cana 300 mg ----- ------- (N=1441) ------		------ Cana Total ----- ------- (N=2886) ------	
	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs
Total No. of subjects with abdominal or pelvic imaging performed	232(16.1)	28.93	228(15.8)	27.58	217(15.1)	26.28	445(15.4)	26.93
Ultrasound	155(10.8)	19.33	159(11.0)	19.23	164(11.4)	19.86	323(11.2)	19.55
CT	88(6.1)	10.98	94(6.5)	11.37	74(5.1)	8.96	168(5.8)	10.17
MRI	14(1.0)	1.75	18(1.2)	2.18	6(0.4)	0.73	24(0.8)	1.45
Imaging Other [a]	27(1.9)	3.37	27(1.9)	3.27	21(1.5)	2.54	48(1.7)	2.90
No. of urinalysis performed								
N	1387		1405		1396		2801	
Mean (SD)	5.2 (2.50)		5.7 (2.34)		5.6 (2.41)		5.6 (2.38)	
Median	6.0		7.0		7.0		7.0	
Range	(1;11)		(1;11)		(1;11)		(1;11)	
	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs
No. of subjects with any urinalysis performed outside of protocol specification	121 (8.7)	15.48	138 (9.8)	17.00	140 (10.0)	17.33	278 (9.9)	17.16
No. of subjects with all urinalysis performed per protocol specification	1266 (91.3)		1267 (90.2)		1256 (90.0)		2523 (90.1)	
Urine Blood	n(%)		n(%)		n(%)		n(%)	
Any post-baseline value	1387 (96.3)		1405 (97.2)		1396 (96.9)		2801 (97.1)	
Trace/+1/+2/+3	227 (16.4)		248 (17.7)		259 (18.6)		507 (18.1)	
Trace	153 (11.0)		156 (11.1)		165 (11.8)		321 (11.5)	
+1	79 (5.7)		99 (7.0)		96 (6.9)		195 (7.0)	
+2	40 (2.9)		47 (3.3)		44 (3.2)		91 (3.2)	
+3	15 (1.1)		7 (0.5)		12 (0.9)		19 (0.7)	

Note: Overall percentages calculated with the number of subjects in each group as denominator.
Note: Percentages calculated with the number of subjects who had any post-baseline urine blood measures in each group as denominator.
Note: incidence rates are per 1000 person-years and calculated as 1000*(the number of incidence divided by the total person-year follow up for all treated subjects who have a post-baseline urinalysis performed in each group).
[a] The other category consisted of plain films and scintigraphy studies.

Source: NDA 204042, IR response received September 27, 2018; Table 2

Table 9: Summary of Urinalysis Collection and Abnormal Urine Occult Blood in DIA4003 (On-Study Analysis Set)

	------- Placebo ------- ------- (N=2903) ------		--------- Cana -------- ------- (N=2904) ------	
	n(%)	Rate/1000 pt-yrs	n(%)	Rate/1000 pt-yrs
No. of subjects with any post-baseline urinalysis performed	114 (3.9)	19.02	105 (3.6)	17.44
No. of subjects without post-baseline urinalysis performed	2789 (96.1)		2799 (96.4)	

	n (%)	n (%)
Urine Occult Blood		
Any post-baseline value	114 (3.9)	105 (3.6)
Trace/+1/+2/+3	12 (10.5)	12 (11.4)
Trace	7 (6.1)	9 (8.6)
+1	3 (2.6)	1 (1.0)
+2	2 (1.8)	0
+3	1 (0.9)	2 (1.9)

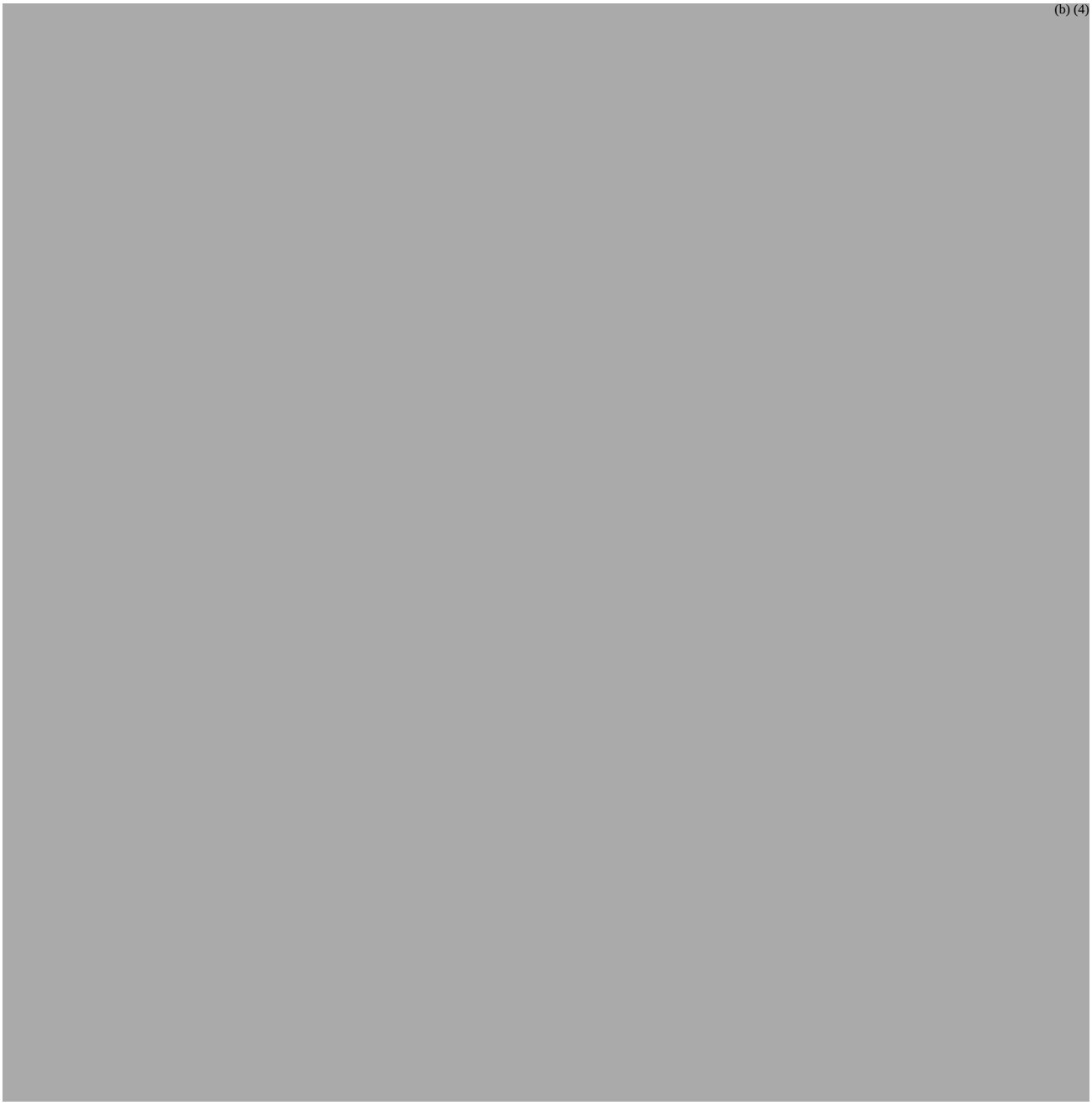
Note: incidence rates are per 1000 person-years and calculated as 1000*(the number of incidence divided by the total person-year follow up for all treated subjects in each group).
Note: Overall percentages calculated with the number of subjects in each group as denominator.
Note: Percentages calculated with the number of subjects who had any post-baseline urine occult blood measures in each group as denominator.
Note: CANVAS-R had 2 treatment groups: placebo and Cana (100 mg QD for the first 13 weeks, with up-titration to 300 mg QD thereafter at investigator discretion and based on tolerability and glycemic needs)

Source: NDA 204042, IR response received September 27, 2018; Table 3

Reviewer's comment: The Applicant's summary of imaging test and urinalysis done did not show an imbalance in the rate of imaging studies or urinalysis between treatment groups in DIA3008

(summarized above; see Table 8). Information on imaging studies were not available in DIA4003. The rate of urinalysis done was not observed to be different between treatment groups in DIA4003; in fact, urinalysis appeared to have been collected less in the canagliflozin group compared to placebo (see Table 9). These data do not support a concern for detection bias for RCC cases in the canagliflozin group.

8. Division of Pharmacovigilance (DPV)'s Enhanced Pharmacovigilance Interim Report Review:



(b) (4)

9. Consideration of Conducting an Observational Study and ARIA (Active Risk Identification and Analysis) Assessment:

Based on the available information discussed above, the Agency determined that an observational study should be conducted to further evaluate the RCC safety signal for canagliflozin.

While the re-reviewed and new nonclinical data suggested that the original conclusion at the time of initial approval of canagliflozin remains likely to be true, i.e. unlikely clinical relevance, it was also noted that the clinical imbalance in RCC cases, even when a very specific definition of 'case' was used, still showed a two-fold imbalance, and because the kidney is the target organ of the drug, the signal should not be dismissed.

Data from the CANVAS program, as noted above, did not raise concern for detection bias that would greatly impact interpretation of an observational study. Also, it was apparent from the clinical trial data that the rarity of the RCC event and the duration of follow up required to have enough data to conduct a meaningful analysis would introduce feasibility issues with regard to requiring another randomized controlled trial to assess the signal.

The Agency conducted virtual Signal Assessment Meeting (SAM), and it was determined that the ARIA System would be sufficient to evaluate the potential association between canagliflozin and RCC. See Dr. Christian Hampp's memo dated October 12, 2018 for detailed discussion of ARIA assessment.

Sentinel data (January 2008 through June 2018) currently includes 345,000 initiators of canagliflozin, with 46,000 patients >1 year duration; 95,000 initiators of dapagliflozin, with 9400 patients >1 year duration; and 127,000 initiators of empagliflozin, with 10,300 patients >1 year duration. In comparison, sitagliptin, a DPP-4 inhibitor, have 1,630,000 initiators with 266,000 patients >1 year duration. Regardless of exposure, the Sentinel currently includes the following duration of follow-up: average of 11.3 months for SGLT2 inhibitors; 13.8% have 24-36 months, 4.6% have 36-48 months, and 0.6% have >48 months of follow-up. This compares to average duration of follow-up of 29.6 months for all DPP-4 inhibitors. Based on this available exposure data, the total number of patients exposed to canagliflozin was considered to be substantial but exposure duration may be considered inadequate to evaluate RCC association with SGLT2 inhibitors. However, this was felt to be due to recent approval of canagliflozin (2013) compared to DPP-4 inhibitors which was first approved in 2005, and it is expected that the available follow-up time will be improved for SGLT2 inhibitors with additional years of data

accumulation. Therefore, once adequate follow-up time has accumulated, ARIA would be sufficient to investigate the potential association between canagliflozin and RCC.

Further, it was determined that absence of a validated endpoint algorithm to identify RCC would not render ARIA insufficient.

DEPI staff will outline a plan to monitor accumulation of canagliflozin exposure and follow-up time in Sentinel to determine when ARIA could be used to evaluate possible association between canagliflozin and RCC.

Reviewer's comment: As ARIA was determined to be sufficient to investigate the possible association between canagliflozin and RCC; therefore, a PMR for this safety signal will not be required.

10 Labeling:

Because the majority of RCC cases were seen in DIA3008, and RCC cases from DIA3008 remained after exclusion of cases that are unlikely to be related to the study drug based on temporal relationship and underlying disease, incidence rate of RCC in DIA3008 was calculated by our Statistical colleague Dr. Eugenio Andraca-Carrera (please note that there is small discrepancy between his analysis and Applicant's analysis due to the difference in the number calculating overall study population [i.e., N] in the dataset submitted; the overall imbalance does not change and we will use confirmed data by the Applicant during labeling discussions):

		events/N (%)	events/PY (IR per 10,000 PY)
CANVAS	Canagliflozin	8/2649 (0.30%)	8/11525 (6.9)
	Placebo	2/1296 (0.15%)	2/5225 (3.8)

In DIA3008, the incidence of RCC in the canagliflozin arm was 6.9/10,000 PY (0.30%) compared to 3.8/10,000 PY (0.15%) in the placebo arm. There is still almost 2-fold increased risk of RCC in the canagliflozin arm compared to placebo arm in DIA3008.

Table 10 describes characteristics of these 10 cases with RCC in DIA3008. Most of these subjects had underlying risk factors for developing RCC such as hypertension (9/10), obesity (8/10), and smoking (5/10). All except for one case occurred in males and the average age at the time of diagnosis was 64 years. The time to onset of RCC was ~5 years in half of cases associated with canagliflozin (4/8 cases).

Based on the residual uncertainty about the imbalance in RCC not favoring canagliflozin in the CANVAS Program due to small number of reported cases, I recommend labeling the imbalance in renal cancer seen in the CANVAS study in Section 6.1, Adverse Reactions. A Warning and Precaution is not warranted. The *FDA Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed*

Warning Sections of Labeling for Human Prescription Drug and Biological Products states that "the Warnings and Precautions section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or *otherwise clinically significant* because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitely established." Although RCC is "serious and otherwise clinically significant", the observed cases that led to imbalance was small and the causal association between canagliflozin and RCC remains uncertain. Further, at this time there is no recommended mitigating action for prescribers that would warrant a Warning and Precaution. As additional data regarding RCC are generated in the planned observational study, a change to the labeling of canagliflozin-containing products may be considered.

11 Planned Regulatory Action:

1. The imbalance in renal cancer seen in the CANVAS study will be labeled in Section 6.1, Adverse Reactions with the following language:

(b) (4)

2. An observational study to provide additional data on this safety issue is warranted. Based on the ARIA sufficiency, FDA will conduct such an observational study at which time sufficient follow up time has been accrued as is generally needed for a malignancy signal. A Postmarketing Requirement based on the RCC signal will not be issued.

Table 10: Characteristics of Ten Subjects with Renal Cell Carcinoma (RCC) in the CANVAS Study – Excluded Subjects with Exposure <90 Days, Onset <180 Days after Exposure, and History of Renal Cancer or Renal Cyst

Subject	Tx	Age at dx	Sex	Race	Country	BMI	HTN	Smoking	Day Onset (years)	Tumor size	Histology	How was tumor detected
(b) (6)	Cana 100	75	Male	White	Netherlands	29.6	Yes	No	705 (1.9)	10 x 12 cm	No, but renal mass was large with metastasis	S/sx (high ESR and CRP, decreased appetite, and pain in the lower abdomen)
	Cana 300	65	Male	White	Netherlands	31.3	Yes	No	1356 (3.7)	25 cm	Yes	Enlarged kidney found during evaluation of unexplained tachycardia
	Cana 300	50	Male	White	Australia	36	Yes	No	1806 (4.9)	3 cm	Yes	CT angiogram (indication not reported, but reported to be routine screening)
	Cana 100	62	Male	White	Australia	33.1	No	No	849 (2.3)	8.5 x 7 x 10.5 cm	Yes	S/sx (severe back pain [initial back pain occurred about 18 months]) leading to CT scan of abdomen and pelvis
	Cana 100	69	Male	White	Russia	30.3	Yes	Yes	450 (1.2); recurrence on Day 1257 (3.4)	2 cm; 2.5 cm	Yes	Planned annual examination
	Cana 300	66	Female	White	Estonia	37.5	Yes	No	1767 (4.8)	7 cm	Yes	S/sx (abdominal pain) leading to ultrasound of abdomen
	Cana 300	54	Male	African-American/ American Indian	US	40	Yes	Yes	1777 (4.9)	4.9 cm	Yes	S/sx (hematuria) leading to CT scan of kidney
	Cana 100	78	Male	White	Israel	35.2	Yes	Yes	1767 (4.8)	Not reported	Yes	CT abdomen (indication not reported, but reported to be routine screening)
	Placebo	60	Male	White	Russia	29.1	Yes	Yes	710 (1.9)	8.2 x 7.4 x 7.3 cm	No, but large renal mass	S/sx (pain in left lumbar area, dizziness, headache) leading to chest radiograph and CT scan of abdominal cavity
	Placebo	63	Male	White	Russia	30.1	Yes	Yes	1343 (3.7)	3.1 x 3 cm	Yes	Ultrasound scan of abdomen (indication not reported)

*Died due to RCC

#had recurrence of renal cancer

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYON J KWON
10/29/2018

LISA B YANOFF
10/29/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy supplement
Application Number(s)	NDA 204042, S-27/ NDA 204353, S-25/ NDA 205879, S-07
Priority or Standard	Standard
Submit Date(s)	September 29, 2017
Received Date(s)	September 29, 2017
PDUFA Goal Date	October 29, 2018 (3-month clock extension)
Division / Office	DMEP/ODE 2
Reviewer Name(s)	Hyon Kwon
Review Completion Date	October 25, 2018
Established Name	Canagliflozin, canagliflozin and metformin hydrochloride, canagliflozin and metformin hydrochloride extended release
Trade Name	Invokana, Invokamet, Invokamet XR
Therapeutic Class	SGLT2 inhibitor
Applicant	Janssen Pharmaceuticals, Inc
Formulation(s)	Tablets
Dosing Regimen	Invokana: 100 mg and 300 mg once daily; Invokamet and Invokamet XR (canagliflozin/metformin): 50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg twice daily
Indication(s)	To improve glycemic control in adults with diabetes mellitus
Intended Population(s)	Adults with diabetes mellitus

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend **approval** of this efficacy supplement for patients with established cardiovascular disease (CVD). (b) (4) See section 1.2 for my rationale.

In addition to supporting a new indication of reduction of the risk of MACE in adults with type 2 diabetes mellitus, the Applicant submitted the meta-analysis results combining DIA3008 and DIA4003 data to fulfill the post-marketing requirement for PMR#2027-5:

> **2027-5:** A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

The primary analysis of hazard ratio for MACE with canagliflozin compared to placebo was 0.86, with the upper bound of 95% CI less than 1.3. (95% CI: 0.75, 0.97). Therefore, this supplement application contained the final report for postmarketing requirement PMR 2027-5 and fulfills this requirement.

1.2 Risk Benefit Assessment

In order to meet the post-marketing regulatory requirement for cardiovascular (CV) risk assessment where the upper bound of the 2-sided 95% confidence interval (CI) of the risk ratio of test drug to comparator is less than 1.3, the Applicant conducted two CV outcome studies with pre-specified plan to conduct a meta-analysis of these two studies on the primary composite endpoint of major adverse cardiovascular events (MACE; CV death, nonfatal myocardial infarction [MI], or nonfatal stroke). The meta-analysis of DIA3008 (CANVAS) and DIA4003 (CANVAS-R) (also called 'The CANVAS Program') was agreed upon with FDA (prior to submission) to assess canagliflozin's cardiovascular risk.

The Applicant submitted the results of this meta-analysis to both fulfill the post-marketing requirement (PMR #2027-5) and to support a new indication of reduction of the risk of MACE in adults with type 2 diabetes mellitus (T2DM) who have established cardiovascular disease (CVD) (b) (4)

The primary endpoint was time to the first positively adjudicated occurrence of any component of the MACE composite endpoint (i.e., time from randomization to the first occurrence of CV death, non-fatal MI or non-fatal stroke). In the CANVAS Program, a total of 585 subjects (10%; 26.93/1000 PY) randomized to canagliflozin and 426 subjects (9.8%; 31.48/1000 PY) randomized to placebo had MACE event. Based on the stratified Cox proportional hazard model analysis, canagliflozin ruled out a 30% relative increase in MACE. Statistical superiority, although not pre-specified in the hierarchical hypothesis testing, was also shown with a 14% reduction in the risk of MACE for canagliflozin compared to placebo (HR 0.86; 95% CI: 0.75, 0.97; p=0.0158); see Table 16.

Notably, all components of MACE showed a similar point estimate of the hazard ratio of <1 as the overall MACE, although none of the individual components were statistically significant. Canagliflozin failed to show benefit in all-cause mortality or cardiovascular death. This result is somewhat different from CV benefit seen with another SGLT2 inhibitor, empagliflozin, which is labeled for cardiovascular benefit based on its dedicated CV outcomes study (EMPA-REG OUTCOME). Empagliflozin is not indicated for MACE reduction and is only indicated for reduction in the risk of cardiovascular death because the result of EMPA-REG showed that the differences in MACE were largely driven by a large difference in the number of CV deaths between treatment groups, and the other components of MACE outcome were not internally consistent; there was an imbalance in stroke not favoring empagliflozin (although not statistically significant). We did not see a similar imbalance in strokes with canagliflozin as the hazard ratio for stroke was less than 1 (HR for all strokes was 0.87 [95% CI; 0.69, 1.09]).

The robustness of the primary endpoint findings was supported by the overall low extent of missing data in the ascertainment of MACE. In total, ~4% of patients (408 patients) did not complete the trial, and of these patients, vital status was unavailable for 22 and 20 patients for canagliflozin and placebo, respectively.

However, because the superiority of canagliflozin compared to placebo in MACE was not pre-specified, and because the superiority met statistical significance based on meta-analysis of two studies and was not confirmed in each individual study, there were some concerns whether the results of this meta-analysis was statistically robust and considered to be sufficient evidence of CV benefit, as this meta-analysis would be considered to be ‘one study’. The evidentiary standards to support an efficacy claim has typically relied on two or more clinical trials[1], but the FDA has previously relied on a single, well conducted and controlled study in circumstances where a single trial has provided “highly reliable and statistically strong evidence of an important clinical benefit,

[1] Section 505 (d) of the Federal Food, Drug, and Cosmetic Act

such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds."[2]

Our Statistical colleague concluded that the results of meta-analysis as 'one study' were sufficiently robust to support the CV benefit for canagliflozin; please refer to Dr. Roberto Crackel's Statistical Review for further details. Also, there has been a regulatory precedence for accepting the results of a meta-analysis for a new indication. Herceptin was approved for adjuvant breast cancer based on a pre-specified meta-analysis that combined the results from 2 studies (BLA 103792/5050, Approved November 16, 2006). In addition, liraglutide was approved for MACE reduction in adults with T2DM who have established cardiovascular disease (CVD) based on one CV study (LEADER), because LEADER was concluded to be adequate substantial evidence.

The mechanism by which canagliflozin compared to placebo may lead to lower cardiovascular events is unknown, but potential mediators that may explain the result include the larger reduction in HbA1c, weight loss, and decrease in systolic and diastolic blood pressure with canagliflozin compared to placebo. However, canagliflozin does increase the total cholesterol, HDL-C, and LDL-C levels compared to placebo, but the clinical significance of a small increase in these lipid parameters in the overall MACE results is unknown. It is also notable that a numerically larger proportion of subjects in the canagliflozin group initiated statins compared to placebo.

The patient population in both studies were enriched for CV events by enrolling patients with a prior history of CV disease or without history of CV disease but at high CV risk. Both DIA3008 and DIA4003 were targeted to enroll 70% of total subjects with CV disease and 30% of total subjects without CV disease but at high risk for CVD. Approximately 65% of pooled DIA3008 and DIA4003 study population had established CV disease (Table 9). (b) (4)

(b) (4)

[2] Guidance for Industry. Providing clinical evidence of effectiveness for human drug and biological products. Silver Spring, MD: Food and Drug Administration, May 1998.

During my safety review of pooled DIA3008 and DIA4003 data, an imbalance in the incidence of renal cell carcinoma not favoring canagliflozin compared to placebo was noted (14 subjects versus 3 subjects with a 2:1 randomization ratio). Renal cell carcinoma has been an adverse event of interest because carcinogenicity studies with canagliflozin in rats have shown an increased risk for renal tubular adenoma and carcinoma in male and female rats at doses 12x exposure of 300 mg clinical dose. The Applicant had previously provided *in vitro* data to support the hypothesis that carbohydrate malabsorption related to the high dose of canagliflozin caused the renal tumors in rats, and clinical studies have not shown that carbohydrate malabsorption occurs in humans at doses up to 2x the clinical dose of 300 mg. We have been monitoring renal cancers closely during the clinical development program for canagliflozin as well as after approval by requiring post-marketing enhanced pharmacovigilance for renal cancers.

The imbalance in renal cell carcinoma was mostly due to reported cases from study DIA3008. This was not surprising given the latency associated with malignancies in general and DIA3008 had much longer duration of follow-up. The mean duration of exposure was 223 weeks (almost 4.3 years) in DIA3008 compared to 94 weeks (~1.8 years) in DIA4003; the mean duration of overall follow-up was 296 weeks (~5.7 years) in DIA3008 and 108 weeks (~2 years) in DIA4003. Thirteen subjects in the canagliflozin group compared to 3 subjects in the placebo group reported renal cell cancers in DIA3008, and one additional subject receiving canagliflozin from study DIA4003 reported renal cell cancer. Of these, one canagliflozin subject from DIA3008 and the only subject from DIA4003 reported renal cancer <180 days after study drug initiation, and these two renal cancers are very unlikely to be related to the study drug due to long latency for malignancies. Most of the subjects had underlying risk factors for developing renal cell carcinoma such as hypertension, obesity, and smoking, and two subjects had pre-existing conditions related to renal cancer (one renal cyst and another had history of renal cancer; both received canagliflozin 100 mg). Because of small numbers of reported cases and confounding factors found in most of these renal cancer cases, it is difficult to determine whether these reported renal cancers are causality related to the canagliflozin treatment or whether this is a spurious finding.

Another notable finding during this safety review was that the increased risk for fractures noted in DIA3008 was not observed in DIA4003. The reason for this discrepancy is unclear at this time, since both studies had same inclusion and exclusion criteria and as a result the patient population of these two studies were very similar in baseline characteristics. The difference in duration of follow-up between DIA3008 and DIA4003 would not explain the observed differences in fracture risk between these two studies, as the increase in the risk of fractures with canagliflozin was observed at around 26 weeks in DIA3008. Bone fracture is currently labeled as Warnings and Precautions, and we will update the labeling to reflect that the increased risk of fracture was observed with canagliflozin in DIA3008 only.

In conclusion, the overall MACE finding suggests that the use of canagliflozin may result in a substantial cardiovascular benefit in patients with established cardiovascular disease. Although an imbalance in the incidence of renal cell cancer not favoring canagliflozin was observed in the CANVAS program, the causal relationship remains unclear and therefore the overall benefit risk remains favorable for canagliflozin.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

This application triggers the Pediatric Research Equity Act (PREA) because of a new indication. We agree with the Applicant's request for full waiver for this indication because pediatric studies are impossible or highly impractical as cardiovascular disease in type 2 diabetic patients primarily occurs in the adult population and is rare in pediatric patients. At the PeRC meeting on Mary 30, 2018, PeRC members agreed with our recommendation for full waiver.

2 Introduction and Regulatory Background

2.1 Product Information

Canagliflozin an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and increases urinary glucose excretion, thereby lowering plasma glucose levels in patients with T2DM. The direct glucose lowering effect of canagliflozin does not depend on augmenting endogenous insulin secretion or improving insulin sensitivity. Its effect is dependent on the ability to excrete glucose in the urine, which is correlated to both plasma glucose levels and glomerular filtration rate (GFR), and thus the glucose lowering effect of canagliflozin is expected to decline with decreasing renal function. Canagliflozin was approved for the treatment of T2DM in the US on March 29, 2013 at daily doses of 100 mg and 300 mg.

Invokamet, the fixed dose combination of canagliflozin/metformin immediate release (IR), was approved on August 8, 2014, and is currently indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate. Invokamet XR, the fixed dose combination of canagliflozin/metformin extended release (XR) was approved for the same indication on September 20, 2016.

2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved treatment of T1DM and T2DM (glycemic control), used either alone or in combination include:

- Insulin and insulin analogs
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Alpha-glucosidase inhibitors
- Glucagon-like peptide 1 (GLP-1) agonists
- Synthetic analogues of human amylin
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Bile acid sequestrant
- Dopamine agonists
- SGLT-2 inhibitors

Recently, several products completed large CV outcome studies. The CV studies in DPP-4 inhibitors such as saxagliptin did not show macrovascular risk reduction but was not inferior to comparator, i.e. did not demonstrate excess CV risk.

The large CV outcome study for liraglutide, the LEADER trial, showed CV benefit, and liraglutide is indicated “to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes and established cardiovascular disease”.

The large CV outcome study for another SGLT2-inhibitor empagliflozin, EMPA-REG, also showed CV benefit, and empagliflozin is indicated “to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease”.

2.3 Availability of Proposed Active Ingredient in the United States

Canagliflozin was first approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus on March 29, 2013.

2.4 Important Safety Issues With Consideration to Related Drugs

Currently there are four SGLT2 inhibitors approved by the FDA: canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin.

Safety concerns related to SGLT inhibitors include hypotension, diabetic ketoacidosis, urosepsis and urinary tract infection, genital mycotic infections including phimosis, acute

kidney injury, increases in hematocrit and increases in LDL-C. Pancreatitis, hypersensitivity reactions, photosensitivity reactions, hepatic abnormalities are other safety issues for consideration with SGLT2 inhibitors.

Increased risk for fractures and amputations have only been seen in the canagliflozin studies so far.

Possible concerns exist for certain malignancies based on animal findings and include pheochromocytoma, Leydig cell tumors, and renal cell carcinoma. Imbalances in breast and bladder cancer were also observed in the premarketing dapagliflozin program and are malignancies of interest.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

To support the initial marketing application for canagliflozin, the Applicant conducted a pre-specified meta-analysis of CV events from all randomized subjects in 9 controlled Phase 2 and Phase 3 studies, which included interim data from DIA3008. The primary endpoint was MACE-plus, which was a composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization due to unstable angina. There were 130 MACE-plus events among 6396 subjects in the canagliflozin group and 71 MACE-plus events among 3327 subjects in the comparator group. Interim data from Study DIA3008 represented the majority of the events, contributing 108 MACE-plus events among 2886 subjects in the canagliflozin group and 53 MACE-plus events among 1441 subjects in the placebo group. The estimated hazard ratio of canagliflozin versus all comparators was 0.91 with 95% CI (0.68, 1.21). The upper bound of 95% confidence interval was below 1.8 required to show adequate cardiovascular safety of new antidiabetic products according to the FDA Diabetes Guidance for assessing cardiovascular safety (2008).

The following table summarizes important pre-submission regulatory activity related to this efficacy supplement:

Date	Meeting
July 13, 2009	End-of-Phase 2 (EOP2) Meeting occurred on April 28, 2009, and this was a revised meeting minutes to correct an error. At the EOP2 meeting, DMEP encouraged using MACE composite of CV death, nonfatal MI, and nonfatal stroke.
Nov 12, 2009	Advice letter related to evaluation of safety for DIA3008; however, at this time, DIA3008 was to continue as a dedicated CV study after interim analysis for pre-marketing assessment.
Feb 25, 2011	Advice letter for Statistical Analysis Plan
June 13, 2012	Pre-NDA meeting for the initial application submission for canagliflozin about the content and format of the NDA.

March 15, 2013	Feedback on PMRs, including CV PMR 2027-5. Final report submission date is September 30, 2017.
March 29, 2013	Approval of Invokana
September 16, 2013	FDA feedback on DIA4003 protocol and Statistical Analysis Plan (SAP) for meta-analysis of DIA3008 and DIA4003 for assessment of CV safety
September 24, 2013	Applicant response to Agency Feedback on DIA4003 from September 16, 2013 about the visit schedule in DIA4003.
September 26, 2013	Email acceptance by FDA of Applicant's September 24, 2013 response regarding the revised visit schedule.
June 14, 2016	Written Response to Type C meeting on CV Pooling Strategy for DIA3008 and DIA4003
October 21, 2016	Written Response to Type C meeting with feedback on SAP
March 6, 2017	Written Response to Type C meeting about operational questions to support efficacy supplement submission of CV outcomes data
July 25, 2017	Amended pre-NDA (Type B) meeting minutes that occurred on June 6, 2017, where the Applicant provided topline results of the CANVAS Program. We provided some suggestions on analyses for fractures, and amputation was further discussed

In addition, based on the Division of Pharmacovigilance's review of post-marketing cases of diabetic ketoacidosis with SGLT inhibitors including canagliflozin, a Drug Safety Communication (DSC) regarding SGLT inhibitors and the risk of diabetic ketoacidosis was issued on May 15, 2015. The Applicant was also notified to designate ketoacidosis as an adverse event of special interest and collect as much information as possible to characterize this risk in their ongoing trials, including DIA3008 and DIA4003. On December 4, 2015, the labeling for SGLT2 inhibitors including canagliflozin was updated to add a Warnings and Precautions section about the risk of ketoacidosis.

On March 17, 2016, the Applicant submitted a 15-day safety report entitled, "Invokana (canagliflozin) update to health authorities on aggregate analysis of safety data from CANVAS (DIA3008)". This report informed us about 2-fold increase in the rate of lower-limb amputations in patients treated with canagliflozin in DIA3008 based on the review of interim safety data by the Independent Data Monitoring Committee (IDMC). The IDMC recommended that DIA3008 continue, and the Applicant updated the Informed Consent Form and Investigator Brochure and issued a Letter to Investigator and a Dear Healthcare Provider letter on this topic. FDA issued a DSC related about this on May 18, 2016. Subsequent updates submitted by the Applicant (March 17, 2017 and April 10, 2017) continued to show a 2-fold increase in the risk of lower limb amputations in DIA3008, and also showed similar increased risk in DIA4003. On July 25, 2017, the labeling for canagliflozin was updated to add a Boxed Warning to warn the healthcare professionals about the risk of lower limb amputation.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well-organized and information was not difficult to find. The overall quality of the submission was acceptable.

3.2 Compliance with Good Clinical Practices

All trials were conducted according to Good Clinical Practice.

3.3 Financial Disclosures

The following investigators had financial disclosure Form 3455 from DIA3008:

- (b) (6) reported significant equity interest in Johnson & Johnson in excess of $50,000 owned by spouse. This investigator enrolled (b) (6);
- (b) (6) reported significant payment of other sorts, the total of which exceeds $25,000. This investigator enrolled (b) (6);
- (b) (6) reported significant payment of other sorts, the total of which exceeds $25,000. This investigator enrolled (b) (6);
- (b) (6) did not disclose financial interest but the Applicant's financial systems check found payments tagged as honoraria in total exceeding $25,000. This investigator enrolled (b) (6);
- (b) (6) did not disclose financial interest but the Applicant's financial systems check found payments tagged as honoraria in total exceeding $25,000. This investigator enrolled (b) (6);
- (b) (6) reported a significant equity interest in Johnson & Johnson of $50,000. This investigator enrolled (b) (6);
- (b) (6) reported significant payment of other sorts, the total of which exceeds $25,000. This investigator enrolled (b) (6).

The following investigator had financial disclosure Form 3455 from DIA4003:

- (b) (6) reported significant payment of other sorts, the total of which exceeds $25,000. This investigator enrolled (b) (6).

DIA3008 enrolled 4330 subjects in the study, and DIA4003 enrolled 5812 subjects in the study. It is unlikely that the above investigators' financial interest had an impact on the findings from the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new CMC, clinical microbiology, preclinical pharmacology/toxicology, or clinical pharmacology information was submitted in this efficacy supplement. Therefore, subsections are deleted from this section.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In support of this efficacy supplement, the Applicant submitted complete study reports (CSRs) for studies DIA3008 and DIA4003, as well as results of meta-analysis of these two studies.

DIA3008 (**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy, or CANVAS) and DIA4003 (**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy**-R**enal, or CANVAS-R) are two CV outcome studies in subjects who had or who were at high risk for CV disease. Since only these two studies are submitted to support this efficacy supplement, the studies will not be presented as a table.

The integrated data from DIA3008 and DIA4003 is sometimes referred to as “the CANVAS Program” in this document. DIA3008 was initiated in November 2009 and DIA4003 was initiated in January 2014.

DIA3008 enrolled 4330 subjects in the study, and DIA4003 enrolled 5812 subjects.

5.2 Review Strategy

The review of efficacy (CV benefit) is based on the results of a meta-analysis of the two CV studies DIA3008 and DIA4003.

Review of CV safety was based on the meta-analysis to rule out a 1.3 risk margin. A separate efficacy statistical analysis was conducted by Roberto Crackel, Ph.D.

Non-CV safety was mainly focused on reviewing updated data of adverse events of interest since the initial NDA approval for canagliflozin as well as other safety issue that arose since approval (discussed in sections 7.3.5), as well as screening for imbalances between treatment groups for serious adverse events or adverse events leading to study drug discontinuation. This was mainly done based on pooled data for both DIA3008 and DIA4003.

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant submitted integrated analyses of two CV outcome studies, DIA3008 (CANVAS) and DIA4003 (CANVAS-R), which is also called 'The CANVAS Program', to assess canagliflozin's cardiovascular risk.

Initially, CV-meta analysis results (and results from DIA3008) were only to be unblinded to the canagliflozin program Independent Data Monitoring Committee (IDMC) and were not to be unblinded to the sponsor at the time of application submission. DIA3008 was to continue on to become their dedicated CV outcome study to meet the CV risk assessment post-marketing. However, due to an increase in low-density lipoprotein-cholesterol (LDL-C) seen with canagliflozin during the clinical development program, the Applicant decided to review unblinded results of CV meta-analysis to understand the impact of LDL-C changes on CV risk, and therefore became unblinded to the MACE events in DIA3008. Additional unblinding of DIA3008 data occurred to respond to safety updates and requests by regulatory agency as shown in Table 1**Error! Reference source not found.**. The last unblinding of MACE data from DIA3008 occurred in November 2012.

DIA4003 remained unblinded until the study completion.

Table 1: Unblinding of DIA3008

Data Cutoff Date	Type of Unblinded DIA3008 Data	Primary Reason
15 Sept 2011	Safety[a]	Required for evaluation of general safety (not MACE-plus) for the initial marketing applications and preparation of the DIA3008 Interim Safety Report, 18-week substudy reports, and Integrated Summary of Safety
31 Jan 2012	MACE-Plus	Data were used for the CV meta-analysis including DIA3008 and all other Phase 3 studies
01 July 2012	Safety[a]	Required for a Day 120 Safety Update (not MACE-plus) for NDA204042
19 Nov 2012	MACE-plus	MACE-plus data required for the second integrated CV analysis in response to a request arising during review of the canagliflozin Marketing Authorization Application by the Committee for Medicinal Products for Human Use (CHMP)
31 Dec 2012	Safety[a]	Required for a 120-day safety update for the canagliflozin immediate release fixed dose combination with metformin
15 May 2013	Safety[a]	Required for a Health Authority safety update on bone fracture. The same dataset was also used for DKA analyses.
07 Oct 2015	Safety[a]	Required to prepare a 15-day safety notification on amputation, following IDMC notification in February 2016.
27 Mar 2017	Final database lock	

[a] This unblinding of the DIA3008 data did not include any unblinding for any CV endpoint (MACE).
Key: CV=cardiovascular, DKA=diabetic ketoacidosis, MACE=major adverse cardiovascular events.
Source: ISE, Table 2

The Applicant stated that steps were taken to ensure the integrity of the ongoing DIA3008 study by not unblinding subject-level treatment assignments to the investigators, study subjects, Endpoint Adjudication Committee (EAC), sponsor staff

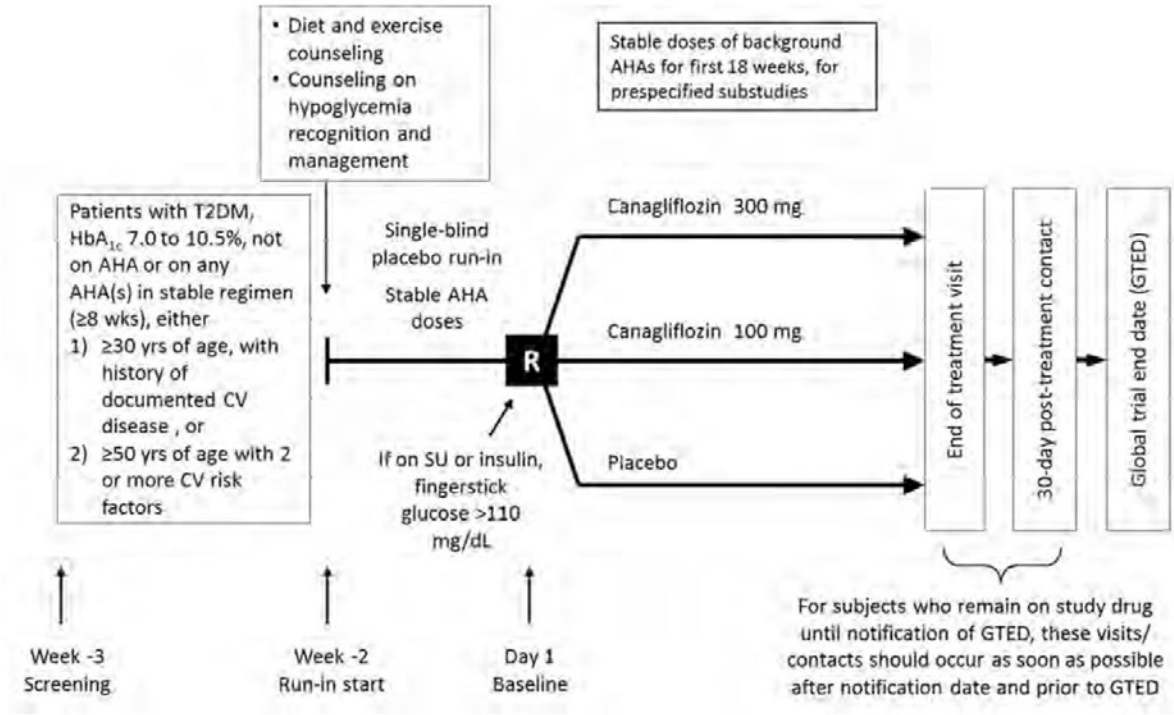
responsible for day-to-day interactions with the sites, and sponsor staff responsible for requesting and reviewing endpoint adjudication packages from sites. The Applicant also stated that a limited number of sponsor staff had access to unblinded subject-level data from DIA3008 to prepare documents for Health Authority submissions and were not provided to the sponsor's medical staff interacting with the investigative sites or handling endpoint adjudication-related activities. In addition, an external, independent Statistics Reporting Group which support the IDMC had access to unblinded data and did not share unblinded data or analyses with the sponsor unless a potential safety signal was identified from DIA3008 (e.g., amputation).

In order to meet the post-marketing CV risk assessment requirement, we recommended that the Applicant initiate a new dedicated study or expansion of DIA3008 enrollment to randomize 10,000 subjects. However, the Applicant proposed to conduct a second DIA3008-like study and to pool the results of these 2 studies (i.e., meta-analysis) to demonstrate that the upper bound of the 2-sided 95% CI of the CV risk ratio of canagliflozin compared to placebo for MACE is less than 1.3.

To pool the results of these two studies, the Applicant designed the new study, DIA4003, identical to DIA3008 such as inclusion/exclusion criteria, event definitions, etc. We agreed to the Applicant's plan for meta-analysis of 2 CV studies, DIA3008 and DIA4003, to evaluate the CV safety of canagliflozin.

CANVAS (DIA3008) was a randomized, double-blind, placebo-controlled, 3 parallel-group, multi-center study to evaluate the safety, tolerability, and CV risk with canagliflozin compared to placebo in subjects with T2DM, both in addition to standard of care for management of CV risk factors and glycemic control. The study was originally designed to include 2 sequential cohorts with up to 18,500 subjects, with recruitment of 4500 subjects in the initial cohort (Cohort A) and 14,000 subjects into the second cohort (Cohort B). See Figure 1 for an overview of study design for DIA3008.

Figure 1: Overview of Study Design for DIA3008 (CANVAS)

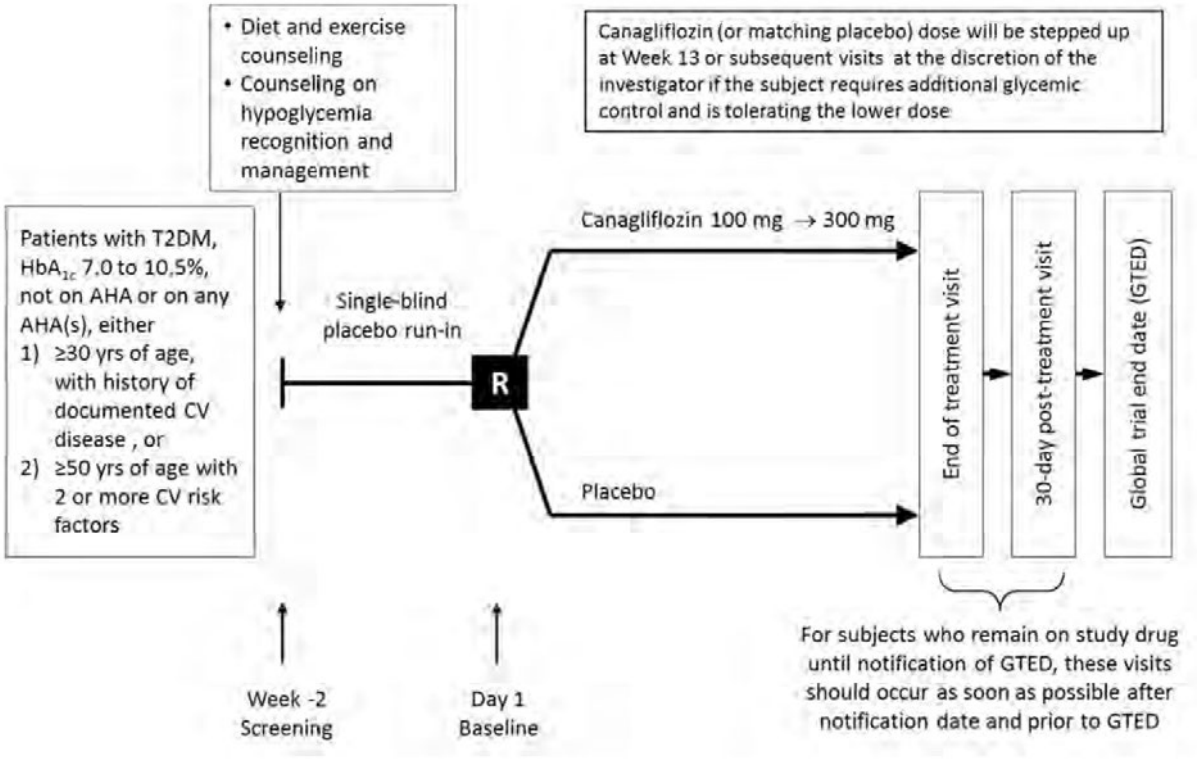


Key: AHA=antihyperglycemic agents, CV=cardiovascular, GTED=global trial end date, R=randomization, SU=sulfonylurea, T2DM=type 2 diabetes mellitus.

Source: ISE, Figure 1

CANVAS-R (DIA4003) was a randomized, double-blind, placebo-controlled, 2 parallel-group, multi-center study to evaluate the effects of canagliflozin compared to placebo in subjects with T2DM, both in addition to standard of care for management of CV risk factors and glycemic control. The planned total sample size was about 5700 subjects. See Figure 2 for an overview of study design for DIA4003.

Figure 2: Overview of Study Design for DIA4003 (CANVAS-R)



Key: AHA=antihyperglycemic agents, CV=cardiovascular, GTED=global trial end date, R=randomization, T2DM=type 2 diabetes mellitus.

ISE, Figure 2

As discussed above, DIA4003 was designed to be similar to DIA3008 in population, study procedures, and study assessments, so that the data from these two studies could be combined for evaluation of CV outcomes, i.e. pre-planned meta-analysis. In both studies, investigators were to manage the CV risk factors (e.g., blood pressure, lipids) and hyperglycemia according to national guidelines, except for the use of SGLT2 inhibitors which were not allowed. Background therapies were to be adjusted per investigator's discretion per standard of care, except for the first 18 weeks for antihyperglycemic agents (AHAs) in DIA3008 because of substudies.

See Table 2 below showing the main characteristics of the study designs. Major difference between 2 studies were:

- Randomization to 3 treatment arms in DIA3008 in a 1:1:1 ratio (Cana 100, Cana 300, or placebo) versus 2 treatment arms in DIA4003 in a 1: 1 ratio (Cana or placebo, where Cana 100 can be up-titrated Week 13 or after);
- Study drug treatment, where study drug dose can be titrated to 300 mg 13 weeks or thereafter based on glycemic response and tolerability in DIA4003, whereas in DIA3008 subjects stayed on the same dose throughout the study;

- Stable doses of background AHA for the first 18 weeks due to substudies in DIA3008 (and adjustable thereafter at the investigator's discretion), whereas in DIA4003 background AHA could be adjusted at the investigator's discretion at any time.

Table 2: Summary of Study Design Elements for DIA3008 and DIA4003

	DIA3008	DIA4003
Subjects Randomized	4330	5812
Study population	Men or women with T2DM with inadequate glycemic control (HbA1c 7-10.5%, inclusive) with either known CV disease or 2 or more CV risk factors	
AHA background therapy	AHA monotherapy or combination therapy	
AHA Background Therapies	Could not be adjusted during the first 18 weeks (due to sub-studies); can be adjusted after 18 weeks per standard of care	Could be adjusted per standard of care at any time
Renal function at entry	eGFR ≥30 mL/min/1.73m^2	
Renal function for study drug discontinuation	eGFR <15 mL/min/1.73m^2	
Randomization	1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo	1:1 to canagliflozin 100 mg or matching placebo
Study Drug Treatment	Treatment remained the same	After Week 13, titration to 300 mg was permitted based on tolerability and glycemic needs
Committee	Single Academic Steering Committee, Independent Data Monitoring Committee, and CV and Renal Endpoint Adjudication Committees	
First subject randomized	December 2009	January 2014
Last subject randomized	March 2011	May 2015

Both studies were event- and time-driven. Both studies were scheduled to end when 688 subjects experienced an adjudicated MACE and the last subject randomized had about 78 weeks of follow-up. The global trial end date (GTED) was the completion date of the study (i.e., when the last subject completed the last study visit), and all visits including 30-day off-drug follow-up visit were to be completed before GTED.

The patient population for both studies included both patients with history of CV disease and at high risk for CV disease. For both studies, an overall 70%:30% ratio for subjects with history of CV disease:at high risk for CV disease was targeted.

Subject criteria for inclusion in study were virtually the same in both DIA3008 and DIA4003 and are summarized in Table 3.

Table 3: Key Inclusion and Exclusion Criteria for DIA3008 and DIA4003

	DIA3008	DIA4003
Key Inclusion Criteria	Diagnosis of T2DM with HbA1C of 7-10.5% at screening, inclusive	
	Not currently on AHA therapy (i.e. drug naïve) or on AHA monotherapy or combination therapy with any approved agent (except SGLT2 inhibitor)	
	History or high risk of CV events based on either: • Age ≥30 years with documented symptomatic atherosclerotic CV disease; including stroke, MI, hospitalized admission for unstable angina, coronary artery bypass graft, percutaneous coronary intervention (with or without stenting), peripheral revascularization (angioplasty or surgery), symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease, or amputation secondary to vascular disease; • Age ≥50 years with 2 more of the following risk factors at screening: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg at screening (average of 3 readings) while on at least one blood-pressure lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria within 1 year of screening, or documented HDL-C of <39 mg/dL within 1 year of screening.	
Key Exclusion Criteria	History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy	
	At Baseline/Day 1, fasting fingerstick glucose >270 mg/dL; and <110 mg/dL if on a sulfonylurea or on insulin	
	History of one or more severe hypoglycemic episodes within 6 months of screening	
	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months of screening, or a planned revascularization procedure, or history of NYHA Class 4 cardiac disease	
	History of hepatitis B surface antigen or hepatitis C antibody positive, or other clinically active liver disease	
	ALT >2x ULN or total bilirubin >1.5x ULN at screening	
	Any history or planned bariatric surgery	
	eGFR <30 mL/min/1.73m^2 at screening; renal disease that required treatment with immunosuppressive therapy or history of chronic dialysis or renal transplant	

Source: Adapted from Table 3, ISS

In addition, the following were required only for study DIA3008:

- Stable AHA regimen ≥8 before randomization was required to evaluate glycemic efficacy in 18-week sub-studies;
- Findings on ECG were obtained at screening (instead of simply “known” findings within 3 months before screening;
- Additional eGFR criterion for subjects taking metformin, where subjects taking metformin were excluded if serum creatinine ≥1.4 mg/dL for men or ≥1.3 mg/dL for women at screening; as well as if there was a contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site;
- Exclusion of patients taking rosiglitazone within 8 weeks of screening (implemented on March 2011 during amendment INT-3)

Both DIA3008 and DIA4003 were multinational, multicenter studies and had the same external committees that were involved with study design, endpoint collection and adjudication, as follows:

- An Academic Research Organization (ARO), which provided scientific and academic oversight of the study, and site monitoring for some sites;
- A Steering Committee (SC) consisting of external scientific experts, providing scientific advice about the study design, conduct, and data collection; both DIA3008 and DIA4003 were overseen by a single SC;
- An Independent Data Monitoring Committee (IDMC) which reviewed unblinded serious adverse events and CV events at regular intervals with the authority to recommend specific decisions to the sponsor; an external, independent Statistical Reporting Group which support the IDMC had access to the unblinded data, and did not share unblinded data or analyses with the sponsor unless a potential safety issue was identified from DIA3008 (e.g., amputation);
- An independent Event Adjudication Committee (EAC), reviewing blinded data for specific adverse events, including MACE, hospitalized heart failure, venous thromboembolism/pulmonary embolism, and all deaths; events from both DIA3008 and DIA4003 were reviewed by the same EAC and used same set of standard definitions for both studies;
- Separate adjudication committees for selected adverse events of interest such as fracture, pancreatitis, renal events, and diabetic ketoacidosis;
- A Renal Endpoint Adjudication Committee (R-EAC), which adjudicated cases of doubling of serum creatinine (SCr), end-stage kidney disease, and 40% decreases in eGFR for both studies.

Each study had a 30-day follow-up period to assess safety events after study drug discontinuation.

Statistical Methods:

Refer to Dr. Roberto Crackel's Statistical Review for a detailed discussion of statistical methods.

The key primary and secondary objectives for the meta-analysis of DIA3008 and DIA4003 were:

- *Primary:* To demonstrate that canagliflozin is not associated with an unacceptable increase in CV risk (i.e., MACE) by demonstrating that the upper bound of the 2-sided 95% CI for the risk ratio of canagliflozin to placebo is <1.3; risk ratio is measured by hazard ratio;

- *Secondary:* To demonstrate the superiority of canagliflozin in the reduction of the following mortality endpoints compared to the placebo:
  - All-cause mortality (i.e., death from any cause)
  - CV death (i.e., death from CV cause)

Testing for superiority of canagliflozin for MACE was not pre-specified in the testing hierarchy (Figure 3).

The primary CV endpoint is MACE, which is a composite of CV outcomes that includes CV death, nonfatal MI (excluding silent MIs), or nonfatal stroke. Adjudication of these outcomes was done blinded by the EAC.

The secondary endpoints were all-cause mortality and CV death, and adjudications were done blinded by the EAC.

Additional CV endpoints included: all-cause hospitalization, adjudicated hospitalization for heart failure, fatal and nonfatal MI and stroke, and the composite of adjudicated hospitalization for heart failure or CV death.

The Applicant also conducted pooled analyses of renal endpoints, which were also considered exploratory: progression of albuminuria, regression of albuminuria, urinary albumin/creatinine ratio (ACR), eGFR, renal composite.

Other exploratory endpoints include change in HbA1c, body weight, blood pressure, and fasting plasma lipids over time.

Reviewer's comment: Since renal endpoints were considered exploratory, I will not discuss these endpoints further in this review, except for changes in eGFR which are discussed in Section 7.3.5.2 as part of renal safety assessment. Other biomarker changes such as change in HbA1c, body weight, blood pressure, and fasting plasma lipids over time are discussed since these are relevant biomarkers for CV risk assessment.

Datasets used for the analysis of efficacy endpoints are described in 4 below. All canagliflozin treatment arms regardless of dose were pooled and compared to the placebo.

Table 4: Summary of Analysis Sets for Pooled Analysis of DIA3008 and DIA4003

Analysis Set	Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date up to GTED
On-Study	Treated subjects	Day 1 to the last trial contact date up to GTED
On-Treatment	Treated subjects	Day 1 to the last dose date plus 2 days for laboratory (except ACR) and vital signs, and 30 days for CV, mortality, renal endpoints, and adverse events, or the last trial contact date, whichever is earlier
Truncated ITT (only applicable for all-cause mortality and CV mortality)	For DIA3008, subjects who were at risk for death after Nov 19, 2012; for DIA4003, all randomized subjects	For DIA3008, November 20, 2012 to the last trial contact date up to GTED. For DIA4002, Day 1 to the last trial contact date up to GTED.

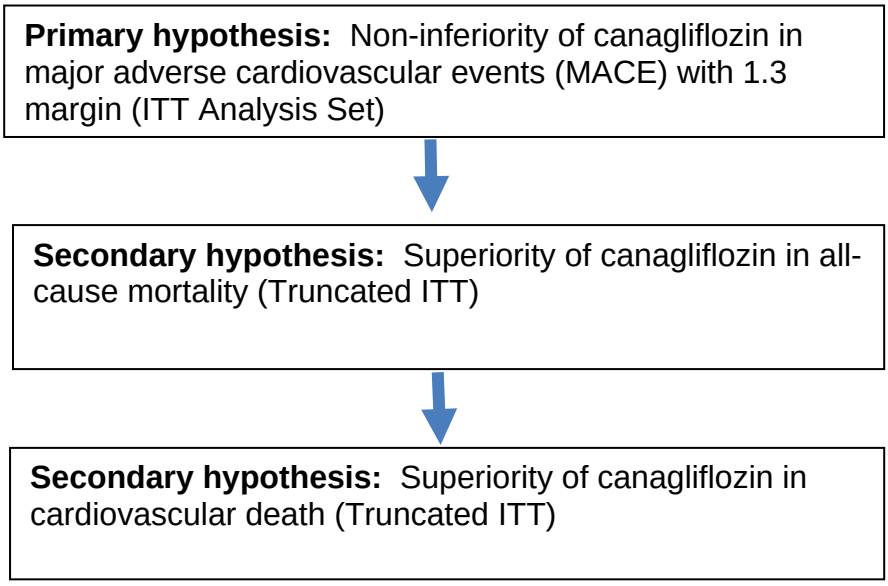
Source: ISE, Table 5

The primary analysis was based on the time to occurrence of MACE using the ITT Analysis Set, and supportive analysis was done in the On-Treatment Analysis Set. A separate supportive analysis was done for each individual MACE component in both the ITT Analysis Set and On-Treatment Analysis Set. Analyses of fatal/nonfatal MI and fatal/nonfatal stroke were also done.

Because there was an unblinded interim analysis of DIA3008 in 2012, the secondary analyses of all-cause mortality and CV death was done using the Truncated ITT Analysis Set as described in Table 44, where data for DIA3008 was left-truncated in 2012 (meaning that only deaths that occurred after unblinded interim analysis on November 19, 2012 were included and deaths up to the date of interim analyses were excluded). Supportive analysis of the 2 secondary mortality endpoints was also done using the ITT Analysis Set (without data truncation).

Reviewer's comment: The statistical testing and datasets were agreed on prior to sNDA submission with involvement of our Statistical colleagues.

Figure 3: Hypothesis Testing Sequence and Dataset in Pooled Analysis



Source: Adapted from ISE, Figure 3

Type 1 error was controlled at 5% by testing the primary and secondary hypotheses sequentially, where subsequent hypothesis testing was conditional on the statistical significance of the previous test at the 5% significance level, as shown in Figure 3.

The HR of all canagliflozin compared to placebo and 95% CI was estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable, and study (DIA3008 and DIA4003) and prior CV disease subgroup (either history of prior CV disease or at high risk for CV disease) as the stratification factors.

Changes from baseline in HbA1c, percent change in body weight, and blood pressure were analyzed using mixed model for repeated measures (MMRM) in the On-Treatment Analysis Set. The MMRM analysis included the fixed categorical effects of treatment, visit, study, and treatment-by-visit interaction, and the continuous, fixed covariates of baseline and baseline-by-visit interaction.

For subjects who were lost to follow-up or withdrew consent before MACE in the ITT analysis set, data between the last trial contact date and the GTED were considered missing. The proportion of data missing is defined as the ratio of the duration of missing follow-up (days between last contact date + 1 day and GTED) and the duration of intended follow-up (days between randomization date and GTED).

Because the meta-analysis of the CANVAS Program combined data from 2 studies with different randomization ratio and different duration of follow-up, counts or proportions of subjects would not be a reliable estimate for the effects of the study drug. Efficacy as well as safety data are mainly provided as annualized event rates to compare effects of canagliflozin against placebo.

Protocol Amendments:

The initial DIA3008 protocol was issued in August 2009, the first subject was screened on November 17, 2009, and first subject was randomized on December 9, 2009. The amendments in DIA3008 protocol and CV EAC Charter are summarized in Table 5 below.

Table 5: DIA3008 Study Milestones and Amendments to the DIA3008 Protocol and Cardiovascular Endpoint Adjudication Committee Charter

Date	Event	Reason
9/16/2009	Amendment INT-1	Further clarified interim analysis and adaptation plan for the study; described the initial cohort and subsequent cohort
9/16/2009	Cardiovascular EAC Charter 1.0 issued	
4/27/2010	Amendment INT-2	Added data from Phase 1 studies which showed that clinical doses of canagliflozin did not have photosensitizing effect and photoprotective measures (such as topical sunscreen or clothing as appropriate) were removed; photoprotective measures were placed in clinical studies because in vitro and animal tests showed that canagliflozin may be photosensitizing. Digoxin removed as disallowed therapy based on Phase 1 drug-drug interaction study.
2/22/2011	Cardiovascular EAC Charter 2.0 issued	Incorporated endpoint definition wording consistent with FDA Standardized Definition for Endpoint Events in Cardiovascular Trials: Draft Recommendations (Oct 20, 2010), Appendix 1; added endpoint definitions for venous thromboembolic (VTE) events in Appendix 1; events adjudicated before this version were re-reviewed by the EAC
3/11/2011	Amendment INT-3	Addressed regulatory action taken with rosiglitazone and to add new follow-up procedures for subjects who prematurely discontinued the study drug; subjects who was

		taking rosiglitazone within 8 weeks of screening were not allowed to participate and rosiglitazone was added to exclusionary drugs because rosiglitazone was withdrawn or restrictions were in place on its use in several markets worldwide due to concerning cardiovascular risk
9/8/2011	Amendment INT-4	Removed the preplanned re-estimation of the sample size for Cohort B since a fixed sample size approach was chosen, and to specify that an interim analysis of DIA3008 was required for reporting safety data in support of filing the marketing applications
9/29/2011	Cardiovascular EAC Charter 3.0 issued	Clarification of wording for various procedures. In definitions for MI, stroke, and hospitalized unstable angina, EAC to consider information based on its source and likely reliability in some instances where a specific source document may not be available.
4/25/2012	Cardiovascular EAC Charter 4.0 issued	Added a statement about adjudication of VTE events, including providing for assessment of provoking risk factors.
12/13/2012	Amendment INT-5	Applicant had been unblinded to the CV endpoint results from DIA3008, and the Steering Committee determined that the second cohort (Cohort B) originally planned for future enrollment in CANVAS would not be conducted; the original cohort (Cohort A, which completed enrollment in March 2011) was to continue.
11/8/2013	Amendment INT-6	Changes were implemented for compliance with the FDA postmarketing requirement for canagliflozin; CV safety was to be assessed on a composite of 3-point MACE, and hospitalized unstable angina events no longer required adjudication and were to be reported as AEs. CV meta-analysis was to occur when at least 688 events are accumulated from CANVAS plus another planned study CANVAS-R. AE collection on eCRF was being limited to SAEs, AEs leading to study drug discontinuation, and AEs of interest specified by US FDA in the post-marketing requirement.
4/30/2014	Cardiovascular EAC Charter 5.0 issued	Enhanced the provision for EAC reporting on death adjudication from “potential or proximate cause of death is cardiovascular” to “cause of

		death – death will be classified as deaths due to CV causes, non-CV causes, and undetermined. If possible, the cause of death should be stated according to the categories described in Appendix 1.1 distinguishing proximate and underlying causes.
10/16/2014	Cardiovascular EAC Charter 6.0 issued	Revised instructions for handling of findings of the QC reviews
9/23/2015	Amendment INT-7	Incorporate request by Health Authority to include DKA safety information and handling of subjects for this event based on post-marketing cases of serious DKA; subjects with SAE of biochemically-confirmed DKA were to be withdrawn from study drug, DKA was added as an AE of special interest, and DKA was to be reported to the sponsor within 24 hours
5/5/2016	Amendment INT-8	Include new safety information and guidance about managing subjects surrounding the event of lower-extremity amputations (e.g., foot examination was added to be consistent with standard diabetes management, and added guidance regarding foot care and reducing the risk of amputation) based on IDMC's review of interim safety data from CANVAS where it showed that there was an increase in lower limb amputations in those treated with canagliflozin; amputation was added as AE of special interest
2/22/2017	Global Trial End Date upon completion of the last subject's last visit	

Source: Modified from ISE, Table 3

The initial DIA4003 protocol was issued in September 2013, and there were 5 global amendments to the protocol. The first (INT-1 on October 16, 2013; to modify protocol language for consistency) and second (INT-2 on December 20, 2013; to add a baseline urinary measurement) amendment to the protocol were considered to be non-substantial and were implemented before any study-related procedures began. The primary reason for Amendment INT-3 (September 17, 2015) was to incorporate a request by Health Authorities to include DKA safety information and the disposition of subjects with DKA. The Amendment INT-4 (May 5, 2016) was to include new safety information and guidance regarding subject management with the event of lower extremity amputations. The Amendment INT-5 (September 1, 2016) was to add the composite endpoint of CV death or hospitalization for heart failure, and CV death as a secondary CV objective, as well as to add exploratory renal composite endpoint objectives; some of these changes were based on the results from the EMPA-REG OUTCOME study with empagliflozin.

6 Review of Efficacy

Efficacy Summary

The glycemic lowering efficacy of canagliflozin was established during the initial NDA submission. The CANVAS Program, which was a meta-analysis of CANVAS (DIA3008) and CANVAS-R (DIA4003) studies, was a post-marketing program to assess the cardiovascular safety (and efficacy) of canagliflozin in patients with type 2 diabetes mellitus. This section mainly discusses the pre-specified primary and multiplicity-adjusted secondary endpoints in the CANVAS Program.

Subjects and Disposition:

As shown in Table 9, about 65% of the overall population in pooled DIA3008 and DIA4003 had established CV disease per inclusion criteria. Canagliflozin and placebo had similar medical histories and baseline anti-diabetic and cardiovascular drug therapies. Despite having similar baseline use of anti-diabetic and antihypertensive medications, post-baseline initiation of these medications was higher in subjects randomized to placebo than canagliflozin. However, numerically higher proportion of subjects randomized to canagliflozin initiated anti-thrombotics and statins compared to placebo (Table 17**Error! Reference source not found.**).

About 4.2% and 3.9% of subjects randomized to placebo and canagliflozin respectively did not complete the trial, and the vital status was unavailable in 0.5% (20/4348) and 0.4% (22/5795) of subjects, respectively.

Primary efficacy results:

The primary endpoint was time to the first positively adjudicated occurrence of any component of the MACE composite endpoint (i.e., time from randomization to the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). In the CANVAS Program, a total of 585 subjects (10%; 26.93/1000 PY) randomized to canagliflozin and 426 subjects (9.8%; 31.48/1000 PY) randomized to placebo had a MACE event. Based on the stratified Cox proportional hazard model analysis, canagliflozin ruled out a 30% relative increase in MACE. Statistical superiority, although not pre-specified in hierarchical testing, was also shown with a 14% relative decrease for canagliflozin compared to placebo (p=0.0158); see Table 16. Notably, all components of MACE showed hazard ratio of <1 consistent with the overall MACE.

The Applicant is currently proposing indication to reduce the risk of MACE in adults with T2DM with CV disease [redacted] (b) (4) The hazard ratio

for MACE in patient population with CV disease was 0.82 (95% CI: 0.72, 0.95), which was consistent with the primary analysis.

Secondary efficacy results:

The key secondary endpoints were all-cause mortality and cardiovascular death; hypothesis testing for cardiovascular death was to be done after statistical significance was seen in all-cause mortality to control for type 1 error. However, canagliflozin was not found to be statistically superior compared to placebo in all-cause mortality; the hazard ratio for all cause-morality was 0.90 (95% CI: 0.76, 1.07; p=0.25). Although further hypothesis testing was stopped, canagliflozin did not reduce the risk of cardiovascular death compared to placebo; the hazard ratio was 0.96 (95% CI: 0.77, 1.18).

Changes in traditional CV risk factors (body weight, blood pressure, lipids, and HbA1c):

There was a larger reduction in body weight with canagliflozin versus placebo after 2 years of study (treatment difference of -2.8%). A larger mean decrease in systolic and diastolic blood pressure were also seen with canagliflozin compared to placebo (treatment difference of -4.17 in systolic and -1.23 mmHg in diastolic) after 2 years of treatment. There was a mean increase in total cholesterol (treatment difference of 7.9 mg/dL), HDL-C (treatment difference of 2.3 mg/dL), and LDL-C (treatment difference of 5.1 mg/dL) with canagliflozin compared to placebo after 2 years of study. In addition, a larger reduction in HbA1c was seen after 2 years with canagliflozin compared to placebo (treatment difference of -0.47%), despite more subjects in placebo initiating new anti-diabetic therapy during their participation in the trial (**Error! Reference source not found.**).

6.1 Indication

Canagliflozin is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

The Applicant aims to expand the indication for canagliflozin: to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease (CVD) (b) (4)

It is important to note that the proposed indication encompasses (b) (4) prevention (i.e., those with established CVD) for cardiovascular events. This is further discussed during the subgroup analysis in section 6.1.7.

6.1.1 Methods

As discussed in Section 5.1, two CV outcome studies, DIA3008 and DIA4003, were conducted and data from these two studies were combined to conduct a CV assessment for canagliflozin. Therefore, the integrated data from DIA3008 and DIA4003 (the CANVAS Program) will be presented here, and any notable differences from individual study results compared to the overall integrated data will be described in each relevant section.

The primary composite endpoint of MACE includes CV death, nonfatal MI, or nonfatal stroke, which will be mainly discussed in the efficacy section. Silent MIs were not systemically collected and were excluded from MACE. All the events in the primary endpoint were adjudicated by the CEC.

Secondary confirmatory endpoints include: all-cause mortality and CV death. All mortality events were blindly adjudicated by the EAC.

Additional CV-related endpoints included the first occurrence of: adjudicated hospitalization for heart failure, fatal and nonfatal MI and stroke, and the composite of adjudicated hospitalization for heart failure or CV death. All-cause hospitalization was also additional exploratory endpoint.

Renal endpoints were exploratory in nature, as well as changes in HbA1c, body weight, blood pressure, and fasting plasma lipids over time.

The pooled dataset of DIA3008 and DIA4003 combine data from 2 studies with different duration of follow-up and different randomization ratios between active and placebo groups. Therefore, comparative efficacy data are presented as annualized event rate to adjust for different duration of follow-up, rather than counts or proportions of subjects, to compare the effect of canagliflozin versus placebo.

6.1.2 Demographics

The baseline demographic characteristics in the pooled data are summarized in Table 6. Overall, there were no notable differences in the baseline demographic characteristics between treatment groups in the ITT Analysis Set. The median age of subjects was 63 years, and 64% of subjects were men. The majority of subjects were White (78%), followed by Asians (~13%), and a small proportion of subjects (3.3%) were African-American.

Compared to DIA4003, there was a higher percentage of Asian subjects in DIA3008 (18.4% vs 8.4%). No other notable differences in the baseline demographic characteristics was seen between DIA3008 and DIA4003.

Table 6: Baseline Demographic Characteristics (Pooled Data, ITT Analysis Set)

	----- Placebo ---- (N=4347)	------ Cana ------ (N=5795)	------ Total ----- (N=10142)
Sex, n (%)			
N	4347	5795	10142
Male	2750 (63.3)	3759 (64.9)	6509 (64.2)
Female	1597 (36.7)	2036 (35.1)	3633 (35.8)
Age (Years)			
N	4347	5795	10142
Category, n (%)			
< 65	2369 (54.5)	3209 (55.4)	5578 (55.0)
≥ 65	1978 (45.5)	2586 (44.6)	4564 (45.0)
Mean (SD)	63.4 (8.21)	63.2 (8.27)	63.3 (8.25)
Median	64.0	63.0	63.0
Range	(30;89)	(30;90)	(30;90)
Race, n (%)			
N	4347	5795	10142
White	3436 (79.0)	4508 (77.8)	7944 (78.3)
Black or African-American	160 (3.7)	176 (3.0)	336 (3.3)
Asian	507 (11.7)	777 (13.4)	1284 (12.7)
American Indian or Alaska Native	22 (0.5)	16 (0.3)	38 (0.4)
Native Hawaiian or Other Pacific Islander	10 (0.2)	13 (0.2)	23 (0.2)
Multiple	20 (0.5)	30 (0.5)	50 (0.5)
Other	191 (4.4)	272 (4.7)	463 (4.6)
Unknown	1 (<0.1)	3 (0.1)	4 (<0.1)
Ethnicity, n (%)			
N	4347	5795	10142
Hispanic or Latino	735 (16.9)	871 (15.0)	1606 (15.8)
Not Hispanic or Latino	3591 (82.6)	4907 (84.7)	8498 (83.8)
Not Reported	12 (0.3)	10 (0.2)	22 (0.2)
Unknown	9 (0.2)	7 (0.1)	16 (0.2)
Region, n (%)			
N	4347	5795	10142
North America	1005 (23.1)	1425 (24.6)	2430 (24.0)
Central/South America	484 (11.1)	537 (9.3)	1021 (10.1)
Europe	1566 (36.0)	2043 (35.3)	3609 (35.6)
Rest of the World	1292 (29.7)	1790 (30.9)	3082 (30.4)

Note: Percentage calculated with the number of subjects with non-missing values in each group as denominator.
Source: ISE, Table 9

As shown in Table 7, at baseline the median body weight was 88 kg and the median BMI was 31.3 kg/m^2 in the overall study population, and this was similar between treatment groups. About 59% subjects had baseline BMI of ≥30 kg/m^2, (obese). There was no notable difference in the baseline anthropometric characteristics between DIA3008 and DIA4003.

Table 7: Baseline Anthropometric Characteristics (Pooled Data, ITT Analysis Set)

	----- Placebo ---- (N=4347)	------ Cana ------ (N=5795)	------ Total ----- (N=10142)
Baseline Weight (kg)			
N	4347	5795	10142
Mean (SD)	90.0 (20.37)	90.3 (20.17)	90.2 (20.26)
Median	88.0	88.5	88.2
Range	(40;208)	(38;205)	(38;208)
Baseline BMI (kg/m²)			
N	4341	5787	10128
Category, n (%)			
< 30	1768 (40.7)	2351 (40.6)	4119 (40.7)
≥ 30	2573 (59.3)	3436 (59.4)	6009 (59.3)
Mean (SD)	32.0 (5.95)	31.9 (5.91)	32.0 (5.93)
Median	31.3	31.3	31.3
Range	(17;60)	(18;71)	(17;71)

Note: Percentages calculated with the number of subjects with non-missing values in each group as denominator.
Source: ISE, Table 10

There were no notable difference between treatment groups in baseline diabetic characteristics in the overall study population. The mean baseline HbA1c was 8.2% and were similar between treatment groups. Subjects had diabetes for about 14 years on average. About 46% of overall subjects had a history of one or more microvascular complications (e.g. retinopathy, neuropath, nephropathy) of diabetes at baseline, and 'other diabetic neuropathy' (diabetic neuropathy other than automatic neuropathy) was most frequent. These data are summarized in Table 8.

The baseline eGFR was 76.5 mL/min/1.73m^2, and about 20% of subjects had baseline eGFR <60 mL/min/1.73m^2. The majority of subjects had normal albuminuria (~79%).

About 2.3% of overall study population had history of amputation, and was same between treatment groups (Table 8). There was a slight difference in this baseline characteristic between two studies. In DIA3008, about 1.1% and 2.1% subjects had a history of amputation in the placebo and pooled canagliflozin groups, respectively. In DIA4003, about 3% and 2.5% of subjects had a history of amputation in the placebo and canaglifozin groups, respectively. No other notable difference in baseline diabetic characteristics was seen between DIA3008 and DIA4003.

Table 8: Baseline Diabetic Characteristics (Pooled Data, ITT Analysis Set)

	--- Placebo --- (N=4347)	----- Cana ---- (N=5795)	---- Total ---- (N=10142)
Baseline Hemoglobin A1c (%)			
N	4347	5795	10142
Category, n (%)			
< 7	204 (4.7)	289 (5.0)	493 (4.9)
7 - < 8	1676 (38.6)	2242 (38.7)	3918 (38.6)
8 - < 9	1469 (33.8)	1928 (33.3)	3397 (33.5)
9 - ≤ 10	819 (18.8)	1081 (18.7)	1900 (18.7)
> 10	179 (4.1)	255 (4.4)	434 (4.3)
Mean (SD)	8.2 (0.93)	8.2 (0.94)	8.2 (0.94)
Median	8.1	8.1	8.1
Range	(5.9;11.8)	(5.4;13.1)	(5.4;13.1)
Duration of Diabetes (Years)			
N	4341	5790	10131
Category, n (%)			
<10	1303 (30.0)	1783 (30.8)	3086 (30.5)
≥ 10	3038 (70.0)	4007 (69.2)	7045 (69.5)
Mean (SD)	13.7 (7.82)	13.5 (7.71)	13.5 (7.76)
Median	12.7	12.6	12.6
Range	(0.0;54.0)	(0.0;65.0)	(0.0;65.0)
Subjects with microvascular complications of diabetes, n (%)			
N	1989	2678	4667
Any	1989 (100)	2678 (100)	4667 (100)
Autonomic Neuropathy	218 (11.0)	281 (10.5)	499 (10.7)
Other Diabetic Neuropathy	1166 (58.6)	1582 (59.1)	2748 (58.9)
Diabetic Retinopathy	926 (46.6)	1203 (44.9)	2129 (45.6)
Diabetic Nephropathy	780 (39.2)	994 (37.1)	1774 (38.0)
Subjects with number of microvascular complications of diabetes, n (%)			
N	4347	5795	10142
0	2358 (54.2)	3117 (53.8)	5475 (54.0)
1	1149 (26.4)	1630 (28.1)	2779 (27.4)
2	640 (14.7)	790 (13.6)	1430 (14.1)
3	200 (4.6)	258 (4.5)	458 (4.5)
≥ 1	1989 (45.8)	2678 (46.2)	4667 (46.0)
Baseline eGFR (mL/min/1.73m2)			
N	4346	5794	10140
Category, n (%)			
< 15	0	2 (<0.1)	2 (<0.1)
15 - < 30	17 (0.4)	9 (0.2)	26 (0.3)
30 - < 45	239 (5.5)	287 (5.0)	526 (5.2)
45 - < 60	673 (15.5)	812 (14.0)	1485 (14.6)
60 - < 90	2360 (54.3)	3265 (56.4)	5625 (55.5)
≥ 90	1057 (24.3)	1419 (24.5)	2476 (24.4)
Mean (SD)	76.2 (20.84)	76.7 (20.28)	76.5 (20.52)
Median	75.0	76.0	76.0
Range	(17.0;196.0)	(10.0;284.0)	(10.0;284.0)
Baseline ACR (mg/mmol)			
N	4293	5740	10033
Mean (SD)	14.0 (51.04)	12.3 (49.03)	13.0 (49.90)
Median	1.4	1.4	1.4
Range	(0.3;868.7)	(0.2;1366)	(0.2;1366)
Baseline Albumin/Creatinine (mg/g)			
N	4293	5740	10033
Mean (SD)	123.6 (451.27)	108.7 (433.51)	115.0 (441.24)
Median	12.1	12.4	12.3
Range	(2.3;7681)	(1.8;12075)	(1.8;12075)
Baseline Albuminuria, n (%)			
N	4293	5740	10033
Normo-albuminuria	2995 (69.8)	4012 (69.9)	7007 (69.8)
Micro-albuminuria	944 (22.0)	1322 (23.0)	2266 (22.6)
Non-nephrotic range macro-albuminuria	326 (7.6)	377 (6.6)	703 (7.0)
Nephrotic range macro-albuminuria	28 (0.7)	29 (0.5)	57 (0.6)

	--- Placebo --- (N=4347)	----- Cana ---- (N=5795)	---- Total ---- (N=10142)
Baseline Systolic Blood Pressure (mmHg)			
N	4347	5795	10142
Category, n (%)			
≤ 140	2595 (59.7)	3525 (60.8)	6120 (60.3)
>140	1752 (40.3)	2270 (39.2)	4022 (39.7)
Mean (SD)	136.9 (15.75)	136.4 (15.77)	136.6 (15.76)
Median	137.0	136.3	137.0
Range	(80.0;209.0)	(73.0;215.0)	(73.0;215.0)
Baseline Diastolic Blood Pressure (mmHg)			
N	4347	5795	10142
Mean (SD)	77.8 (9.71)	77.6 (9.63)	77.7 (9.66)
Median	78.3	78.0	78.0
Range	(44.0;116.0)	(43.0;116.0)	(43.0;116.0)
Baseline Serum HDL Cholesterol (mmol/L) - Fasting			
N	4288	5734	10022
Category, n (%)			
< 1.01	1329 (31.0)	1777 (31.0)	3106 (31.0)
≥ 1.01	2959 (69.0)	3957 (69.0)	6916 (69.0)
Mean (SD)	1.18 (0.305)	1.18 (0.322)	1.18 (0.315)
Median	1.14	1.13	1.14
Range	(0.32;2.89)	(0.26;3.57)	(0.26;3.57)
Baseline Serum HDL Cholesterol (mg/dL) - Fasting			
N	4288	5734	10022
Mean (SD)	45.49 (11.818)	45.56 (12.451)	45.53 (12.184)
Median	44.00	44.00	44.00
Range	(12.00;112.0)	(10.00;138.0)	(10.00;138.0)
Baseline Serum LDL Cholesterol (mmol/L) - Fasting			
N	4287	5731	10018
Category, n (%)			
≤ 1.81	1499 (35.0)	1990 (34.7)	3489 (34.8)
>1.81	2788 (65.0)	3741 (65.3)	6529 (65.2)
Mean (SD)	2.30 (0.937)	2.29 (0.933)	2.29 (0.935)
Median	2.12	2.12	2.12
Range	(0.12;6.60)	(0.03;8.61)	(0.03;8.61)
Baseline Serum LDL Cholesterol (mg/dL) - Fasting			
N	4287	5731	10018
Mean (SD)	88.97 (36.249)	88.41 (36.074)	88.65 (36.148)
Median	82.00	82.00	82.00
Range	(5.00;255.0)	(1.00;333.0)	(1.00;333.0)
Baseline Triglycerides (mmol/L)			
N	4288	5733	10021
Mean (SD)	2.03 (1.520)	2.02 (1.330)	2.02 (1.414)
Median	1.69	1.68	1.68
Range	(0.36;30.70)	(0.37;20.68)	(0.36;30.70)
History of Amputation, n (%)			
N	4347	5795	10142
Yes	102 (2.3)	136 (2.3)	238 (2.3)
No	4245 (97.7)	5659 (97.7)	9904 (97.7)

Note: Percentage calculated with the number of subjects with non-missing values in each group as denominator.
Source: ISE, Table 11

About 66% of overall population in pooled data had history of prior CV disease, and about 72% of study population had history of atherosclerotic vascular disease. The proportion of subjects with baseline history of cardiovascular disease appear to be balanced between treatment groups (Table 9).

Subjects with 'prior CV disease' do not exactly correspond to subjects with any history of 'atherosclerotic vascular disease' which include subjects with any history of coronary, cerebrovascular, or peripheral vascular disease (PVD) because of different way these

were captured per Applicant. 'Prior CV disease' was planned grouping based on the investigator's designation on the eCRFs at baseline in order to determine whether the subject was in the primary or secondary prevention category. In order to be in the secondary prevention category, protocol-specified disease criteria had to be documented (e.g., documented history of stroke, MI, or CABG). The 'atherosclerotic vascular disease' was compiled during the study from reported medical history in order to better understand the amputation adverse reaction, with no effect on the 'prior CV disease' designation. Therefore, a subject could have had coronary, cerebrovascular, or PVD that did not meet the specific criteria for the secondary prevention group because it was less severe or not documented (e.g., carotid or PVD that was not symptomatic or not documented as hemodynamically significant), in which case the subject would have been captures under 'atherosclerotic vascular disease history' but not under 'prior CV disease'.

Between studies, subjects in DIA3008 had lower proportion of subjects with prior CV disease compared to subjects in DIA4003, 59% versus 71% respectively.

Table 9: Baseline History of Cardiovascular Disease (Pooled Data, ITT Analysis Set)

	Placebo (N=4347) n (%)	Cana (N=5795) n (%)	Total (N=10,142) n (%)
Prior CV Disease	2900 (66.7)	3756 (64.8)	6656 (65.6)
Atherosclerotic vascular disease history*			
History of coronary	2487 (57.2)	3234 (55.8)	5721 (56.4)
History of cerebrovascular	845 (19.4)	1113 (20.3)	1958 (19.3)
History of peripheral vascular disease	937 (21.6)	1176 (20.3)	2113 (20.8)
Any	3197 (73.5)	4127 (71.2)	7324 (72.2)
History of hypertension	3937 (90.6)	5188 (89.5)	9125 (90.0)
History of heart failure	658 (15.1)	803 (13.9)	1461 (14.4)

*Some subjects had ≥1 type of atherosclerotic disease
Source: ISE, Table 12

At baseline, about 44% of study population were taking 2 antihyperglycemic agents (AHAs), ~36% of total subjects were taking 3 or more AHAs, and ~19% of subjects were taking only 1 AHA (not shown here; see TSICM12, ISE). The antihyperglycemic agents (AHA) that subjects were taking were similar between treatment groups (Table 10). Metformin was the most common AHA drug used (~77%), followed by insulin (~50%) and sulfonylurea (43%) with smaller percentages of other drugs.

Table 10: Antihyperglycemic Agents at Baseline (Pooled Data, On-Treatment Analysis Set)

Concomitant Medication	Placebo (N=4344) n (%)	Cana (N=5790) n (%)	Total (N=10134) n (%)
Total no. subjects with therapy	4287 (98.7)	5710 (98.6)	9997 (98.6)
Alpha glucosidase inhibitors	126 (2.9)	126 (2.2)	252 (2.5)
Biguanides	3377 (77.7)	4443 (76.7)	7820 (77.2)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	564 (13.0)	697 (12.0)	1261 (12.4)
GLP 1	185 (4.3)	222 (3.8)	407 (4.0)
Insulin	2204 (50.7)	2889 (49.9)	5093 (50.3)
SGLT2	1 (<0.1)	0	1 (<0.1)
Sulfonylurea	1833 (42.2)	2526 (43.6)	4359 (43.0)
Thiazolidinediones (PPARy)	185 (4.3)	307 (5.3)	492 (4.9)
Other AHA agents	98 (2.3)	134 (2.3)	232 (2.3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 13

Overall, 98% of overall study population were taking cardiovascular therapies at baseline, with 80% of subjects taking a renin-angiotensin-aldosterone system (RAAS) inhibitor, 75% of subjects taking statins, ~74% of subjects taking anti-thrombotics, and ~54% of total subjects taking a beta-blocker (Table 11). These appear to be balanced between treatment groups.

Table 11: Cardiovascular Therapies at Baseline (Pooled Data; On-Treatment Analysis Set)

Concomitant Medication	Placebo (N=4344) n (%)	Cana (N=5790) n (%)	Total (N=10134) n (%)
Total no. subjects with therapy	4254 (97.9)	5675 (98.0)	9929 (98.0)
Anti-thrombotics (including aspirin)	3235 (74.5)	4232 (73.1)	7467 (73.7)
Beta-blocker	2382 (54.8)	3038 (52.5)	5420 (53.5)
Calcium channel blocker	1513 (34.8)	1930 (33.3)	3443 (34.0)
Diuretic Loop	592 (13.6)	716 (12.4)	1308 (12.9)
Diuretic Non-Loop	1563 (36.0)	2083 (36.0)	3646 (36.0)
RAAS Inhibitor	3471 (79.9)	4642 (80.2)	8113 (80.1)
Statins	3270 (75.3)	4326 (74.7)	7596 (75.0)

Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 16

Reviewer's comments: The baseline characteristics appear to be balanced between treatment groups in the overall pooled patient population.

6.1.3 Subject Disposition

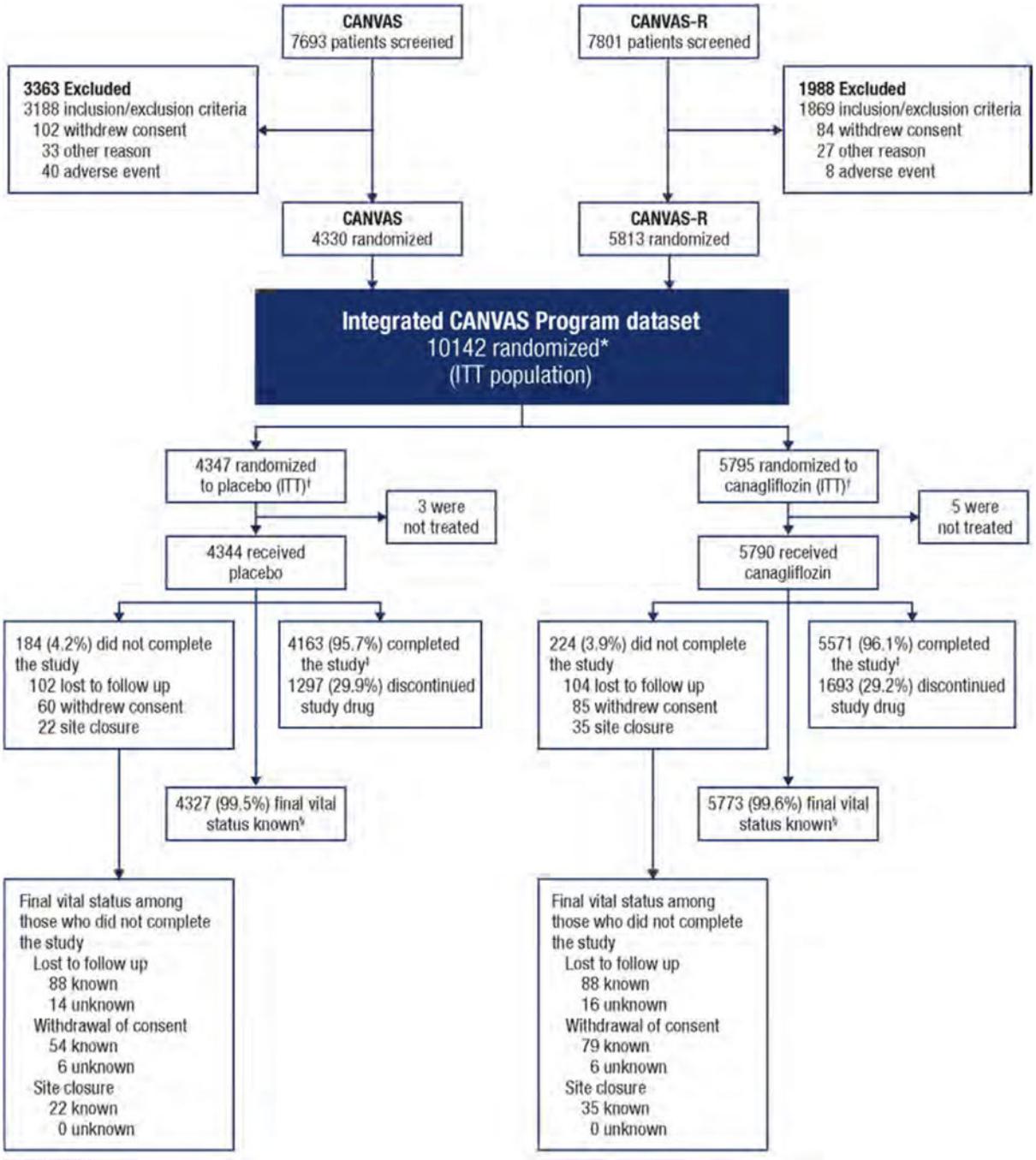
A total of 15,494 subjects were screened, and 10,143 subjects were randomized with 4347 and 5795 subjects to placebo and canagliflozin respectively. The overall subject disposition by each study is shown in Figure 4.

One subject was randomly assigned twice (assigned 2 different subject IDs at 2 different sites). This subject was originally randomized at one site to placebo and was discontinued from study drug due to an adverse event, and then went to another site and was randomized a second time without informing the second site of the previous randomization. This subject was discontinued from the second site and was followed by the first site until the end of study. This subject is included in the analysis only once in the ITT, On-Study, and On-Treatment Analysis Sets, and therefore the ITT Analysis Set includes 10,142 unique subjects.

A total of 8 subjects (5 subjects in the canagliflozin group and 3 subjects in the placebo group) were randomly assigned to treatment but did not take the study drug, so the On-Treatment and On-Study Analysis Sets include 10,134 subjects.

Subjects were enrolled at 359 centers in 24 countries in DIA3008 and at 419 centers in 24 countries in DIA4003.

Figure 4: Subject Disposition in CANVAS (DIA3008) and CANVAS-R (DIA4003)



Key: ITT=intent-to-treat.
*One patient was randomized at 2 different sites and therefore the second randomized ID was excluded from the ITT analysis set.
† Percentages calculated based on the ITT analysis set.
‡ A patient is considered as having completed the study, regardless of whether the patient is on or off study drug, if the patient is followed until a time point between the notification of the trial end date (1 November 2016) and the trial end date (February 23, 2017), or until the time of death for those who died prior to the trial end date.
§ Including results from the search of public records.
Source: ISE, Figure 4

Study completion and vital status of subjects from the pooled data are shown in Table 12 and by each study in Table 13. Overall, ~96% of subjects randomized to canagliflozin or placebo completed the study, and this means that for about 4% of randomized subjects, follow-up information for MACE was not available for the entire period. However, the vital status was obtained for 99.6% of subjects randomized in the trial, and thus vital status information at the end of the study was known for all but 42 subjects.

Table 12: Study Completion and Vital Status (Pooled Data: All Randomized Subjects)

	Placebo (N=4348) n (%)	Cana (N=5795) n (%)	Total (N=10,143) n (%)
Subjects in ITT Analysis Set	4347	5795	10,142
Completed Study*	**4163 (95.7%)**	**5571 (96.1%)**	**9734 (96%)**
Discontinued from Study	184 (4.2%)	224 (3.9%)	408 (4%)
Experienced MACE before discontinuation	36 (0.8%)	39 (0.7%)	75 (0.7%)
Did not experience MACE before discontinuation	148 (3.4%)	185 (3.2%)	333 (3.3%)
Final vital status known**	**4327 (99.5%)**	**5773 (99.6%)**	**10,100 (99.6%)**
Alive	4046 (93.1%)	5371 (92.7%)	9417 (92.8%)
Died	281 (6.5%)	402 (6.9%)	683 (6.7%)
Final Vital Status Unknown	20 (0.5%)	22 (0.4%)	42 (0.4%)

*A subject is considered having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until a time point between the notification of GTED and GTED, or until the time of death for subjects who died before GTED (GTED=the stopping date of the study and end of all visits, including the 30-day off-drug follow-up visit)
**Includes results from the search of public records.
Source: Modified from ISE, Table 7, TSIDS01A

Table 13: Study Completion and Vital Status by Study (ITT Analysis Set)

	DIA3008			DIA4003	
	Placebo n (%)	Cana 100 n (%)	Cana 300 n (%)	Placebo n (%)	Cana n (%)
ITT Analysis Set	**1442**	**1445**	**1443**	**2905**	**2907**
Completed study*	1297 (89.9%)	1344 (93%)	1355 (93.9%)	2866 (98.6%)	2872 (98.8%)
Did not complete study	145 (10.1%)	101 (7%)	88 (6.1%)	39 (1.3%)	35 (1.2%)
Lost to follow-up	74	47	37	28	20
Withdrew consent	50	36	35	10	14
Site closure	21	18	16	1	1
Final vital status known**	1429 (99.1%)	1437 (99.4%)	1435 (99.4%)	2898 (99.7%)	2901 (99.8%)
Alive	1254 (87%)	1280 (88.6%)	1289 (89.3%)	2792 (96.1%)	2802 (96.4%)
Died	175 (12.1%)	157 (10.9%)	146 (10.1%)	106 (3.6%)	99 (3.4%)
Final vital status unknown	13 (0.9%)	8 (0.6%)	8 (0.6%)	7 (0.2%)	6 (0.2%)

*A subject is considered having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until a time point between the notification of GTED and GTED, or until the time of death for subjects who died before GTED (GTED=the stopping date of the study and end of all visits, including the 30-day off-drug follow-up visit)
**Includes results from the search of public records.
Source: CSR DIA3008, Table 6; CSR DIA4003, Table 6

Premature discontinuation of study drug for pooled data is summarized in Table 14 and by study in Table 15. The discontinuation rate per 100 person-years (PY) was slightly higher in the placebo group compared to the canagliflozin group, 11.8 versus 9.4 per 100 PY respectively.

The most frequent reasons for premature discontinuation of study drug were subjects deciding to discontinue the study drug treatment for “personal reasons”, and this occurred in about 14% of subjects in the placebo group and ~11% of subjects in the canagliflozin group. Personal reasons were not specified since it was subject decision to discontinue, but these subjects agreed to be contacted and followed after study drug discontinuation. Subjects who “decided to discontinue the study treatment for personal reasons” were different from subjects who “withdrew consent” in that subjects withdrawing consent refused any further follow-up, as well as subjects who were “noncompliance with study drug” who were persistently in poor compliance with study treatment or procedures.

The second most common reason for discontinuation of study drug was adverse events, which was slightly higher in the canagliflozin group (9.7%) compared to placebo (6%). Adverse events leading to study drug are discussed further in Section 7.3.3.

Table 14: Reasons for Premature Discontinuation from Study Drug (Pooled Data; On-Treatment Analysis Set)

	Placebo n (%)	Cana n (%)	Total n (%)
On-treatment analysis set	**4344**	**5790**	**10,134**
Primary reason for Discontinuation	1297 (29.9)	1693 (29.2)	2990 (29.5)
Discontinuation rate per 100 person-years	11.80	9.41	10.32
Adverse event	301 (6.0)	559 (9.7)	860 (8.5)
Lost to follow-up	8 (0.2)	19 (0.3)	27 (0.3)
Noncompliance with study drug	45 (1.0)	60 (1.0)	105 (1.0)
Physician decision	75 (1.7)	100 (1.7)	175 (1.7)
Product quality complaint	1 (<0.1)	1 (<0.1)	2 (<0.1)
Protocol violation	14 (0.3)	20 (0.3)	34 (0.3)
Study terminated by the sponsor	3 (0.1)	5 (0.1)	8 (0.1)
Decided to discontinue study treatment for personal reasons	606 (14.0)	630 (10.9)	1236 (12.2)
Withdrew consent	61 (1.4)	79 (1.4)	140 (1.4)
eGFR withdrawal criteria	4 (0.1)	6 (0.1)	10 (0.1)
Other	179 (4.1)	214 (3.7)	393 (3.9)

Source: ISE, Table 8

There were no meaningful differences between treatment groups for study drug discontinuation reasons within each study. A higher proportion of subjects discontinued the study drug in DIA3008 compared to DIA4003 (Table 15). This is likely due to the longer duration of DIA3008 study compared to DIA4003, as longer study in general has higher attrition of enrolled subjects. The annualized rate of study drug discontinuation was same in canagliflozin group in both studies (9.4/100 PY) and similar in placebo group in DIA3008 and DIA4003 (12.2 and 11.4/100 PY, respectively). The Kaplan-Meier-plot of time to discontinuation from study confirmed a larger dropout after 104 weeks as the study continued in DIA3008 (see Figure 3 in DIA3008 CSR, not shown here).

Table 15: Reasons for Premature Discontinuation from Study Drug by Study (On-Treatment Analysis Set)

	DIA3008			DIA4003	
	Placebo n (%)	Cana 100 n (%)	Cana 300 n (%)	Placebo n (%)	Cana n (%)
On-treatment analysis set	**1441**	**1445**	**1441**	**2903**	**2904**
Premature discontinuation of study drug	706 (49%)	605 (41.9%)	582 (40.4%)	591 (20.4%)	506 (17.4%)
Adverse event	136 (9.4%)	163 (11.3%)	208 (14.4%)	165 (5.7%)	188 (6.5%)
Lost to follow-up	8 (0.6%)	11 (0.8%)	8 (0.6%)		
Noncompliance with study drug	32 (2.2%)	30 (2.1%)	21 (1.5%)	13 (0.4%)	9 (0.3%)
Physician decision	46 (3.2%)	39 (2.7%)	32 (2.2%)	29 (1.0%)	29 (1.0%)
Product quality complaint	0	1 (0.1%)	0	1 (<0.1%)	0
Protocol violation	9 (0.6%)	7 (0.5%)	11 (0.8%)	5 (0.2%)	2 (0.1%)
Study terminated by the sponsor	3 (0.2%)	2 (0.1%)	3 (0.2%)		
Decided to discontinue study treatment for personal reasons	342 (23.7%)	263 (18.2%)	204 (14.2%)	264 (9.1%)	163 (5.6%)
Withdrew consent	55 (3.8%)	38 (2.6%)	33 (2.3%)	6 (0.2%)	8 (0.3%)
eGFR withdrawal criteria	3 (0.2%)	1 (0.1%)	4 (0.3%)	1 (<0.1%)	1 (<0.1%)
Other	72 (5%)	50 (3.5%)	58 (4%)	107 (3.7%)	106 (3.7%)

Source: CSR DIA3008, Table 7; CSR DIA4003, Table 7

6.1.4 Analysis of Primary Endpoint

The analyses discussed below are the Applicant's results. Please refer to the Statistical Review by Dr. Roberto Crackel for the FDA analyses of the primary endpoint.

The primary efficacy endpoint was time to first occurrence of adjudicated 3-point MACE composite endpoint which was defined as CV death, non-fatal myocardial infarction, or non-fatal stroke. The primary analysis of time to first occurrence of MACE was in the ITT Analysis Set, and data in DIA3008 and DIA4003 were pooled to conduct a meta-analysis. A stratified proportional hazard model which included treatment was used to conduct the analysis and was stratified by study and prior CV disease subgroup.

Table 16 summarizes the first adjudicated MACE events by treatment arm. About 10.1% of subjects (26.93/1000 PY) randomized to canagliflozin compared to 9.8% of subjects (31.48/1000 PY) randomized to placebo experienced first MACE event. It should be noted that when looking at percentage of patients who experienced MACE, the percentage is higher in the canagliflozin arm compared to placebo; this is due to the fact that we are pooling two studies with unequal randomization (DIA3008 had 2:1 ratio and DIA4003 had 1:1 ratio of canagliflozin to placebo), and a larger number of subjects in DIA3008 had MACE due to longer follow-up than DIA4003. This was accounted by including study as a stratification factor in the MACE analysis (Table 16). Event rate takes difference in exposure into account and are less affected by unequal randomization across pooled studies. Slight numerical differences in the event rate were seen for each component of MACE, which tended to be slightly higher for placebo than canagliflozin.

Table 16: Time to First MACE – Pooled DIA3008 and DIA4003 (Intent-to-Treat Analysis Set)

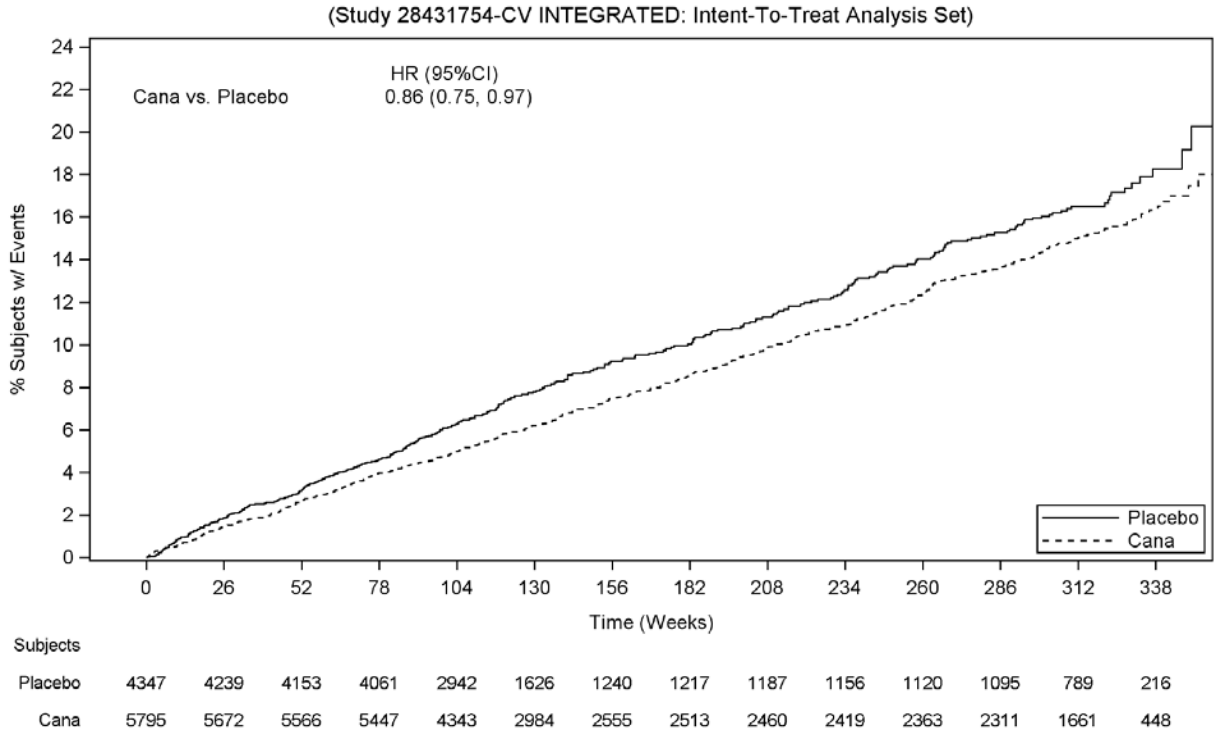
	Placebo (N=4347)		Canagliflozin (N=5795)			
	N (%)	Event rate*		Event rate*	HR (95% CI)	p-value**
3-point MACE	426 (9.8%)	31.48	585 (10.1%)	26.93	0.86 (0.75, 0.97)	0.0158
CV death	185 (4.3%)	12.84	268 (4.6%)	11.60	0.87 (0.72, 1.06)	0.1658
Nonfatal MI	159 (3.7%)	11.61	215 (3.7%)	9.74	0.85 (0.69, 1.05)	0.1257
Nonfatal stroke	116 (2.7%)	8.39	158 (2.7%)	7.12	0.90 (0.71, 1.15)	0.3967

*Event rate per 1000 patient-years;
**p-value corresponds to a test of superiority at two-sided significance level at 0.05; p-value for a test of non-inferiority for an HR margin of 1.3 at a one-sided significance level of 0.025 was <0.0001.
Source: ISE, Tables 18, 19

The hazard ratio (HR) for time to first adjudicated MACE of canagliflozin vs. placebo was 0.86 with a 95% CI of (0.75, 0.97). This result excludes a 30% excess increased CV risk since the upper 95% CI is below 1.3 and confirmed the pre-specified hypothesis of noninferiority of canagliflozin compared to placebo (p<0.0001). The exposure-adjusted incidence rate of each component of MACE was numerically less in the canagliflozin compared to placebo, although none of the individual component demonstrated statistical significance (Table 16).

The Kaplan-Meier estimation of time to first 3-point MACE for all canagliflozin compared to placebo is shown in Figure 5. The curve for canagliflozin and placebo appear to separate relatively early in the study, around as early as Week 26, and continue to remain separated throughout the study.

Figure 5: Kaplan-Meier Estimates of First Occurrence of Adjudicated 3-Point MACE in Pooled DIA3008 and DIA4003 (ITT Analysis Set)



Source: ISE, Figure 6

Reviewer's comment: This finding of non-inferiority for the primary MACE endpoint in the CANVAS Program is consistent with the findings of another SLGT2-inhibitor, empagliflozin, where reduction in MACE endpoint was observed in similar patient population.

The Applicant also tested for superiority of canagliflozin compared to placebo in reducing the risk of MACE, and the p-value was 0.0158 for the test of superiority at two-sided significance level at 0.05.

Although not pre-specified in the Statistical Analysis Plan, because the upper bound of 95% CI for the first adjudicated 3-point MACE was less than 1, this evidence was considered to support the claim that canagliflozin is superior to placebo in reducing the overall risk for MACE. However, none of the individual components showed statistical significance.

Reviewer's comment: Because the superiority of canagliflozin compared to placebo in MACE was not pre-specified in the meta-analysis, and because the superiority met statistical significance based on meta-analysis of two CV studies and not seen in each individual study, I had some concerns whether the results of this meta-analysis were statistically robust and considered to be sufficient

evidence of CV benefit, as this meta-analysis would be considered to be 'one study' and we typically require more than one adequate and well-controlled study to support a claim for a new benefit/indication.

However, the FDA Statistical Reviewer concluded that the meta-analysis of the CANVAS Program is statistically rigorous and sufficiently robust to support the CV benefit claim for canagliflozin in patients with T2DM who are at risk for CVD and can be considered 'one study'. Please refer to Dr. Roberto Crackel's Statistical Review for his analysis and conclusion.

Based on the combined analysis of CANVAS and CANVAS-R, the Applicant aims to add an indication of: to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease (CVD) (b) (6).

The relative risk reduction of canagliflozin is about 14% reduction in the risk of MACE in the integrated analysis of DIA3008 and DIA4003.

This decrease is similar to the relative risk reduction of empagliflozin, the first anti-diabetic drug product labeled for a cardiovascular benefit: the three-point MACE in the EMPA-REG OUTCOME study was 0.85 (95% CI: 0.74, 0.99; p=0.0382). Of note, the current indication of empagliflozin is "to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease". Empagliflozin does not have an indication for MACE in part because the Applicant for empagliflozin did not request this indication. FDA analysis showed that the "this result is almost exclusively due to the benefit observed with empagliflozin on the CV death component of the primary outcome"; the components of the MACE outcome of EMPA-REG were not internally consistent (although the hazard ratios for CV death and non-fatal MI were less than 1, the hazard ratio for non-fatal stroke was >1).[3]

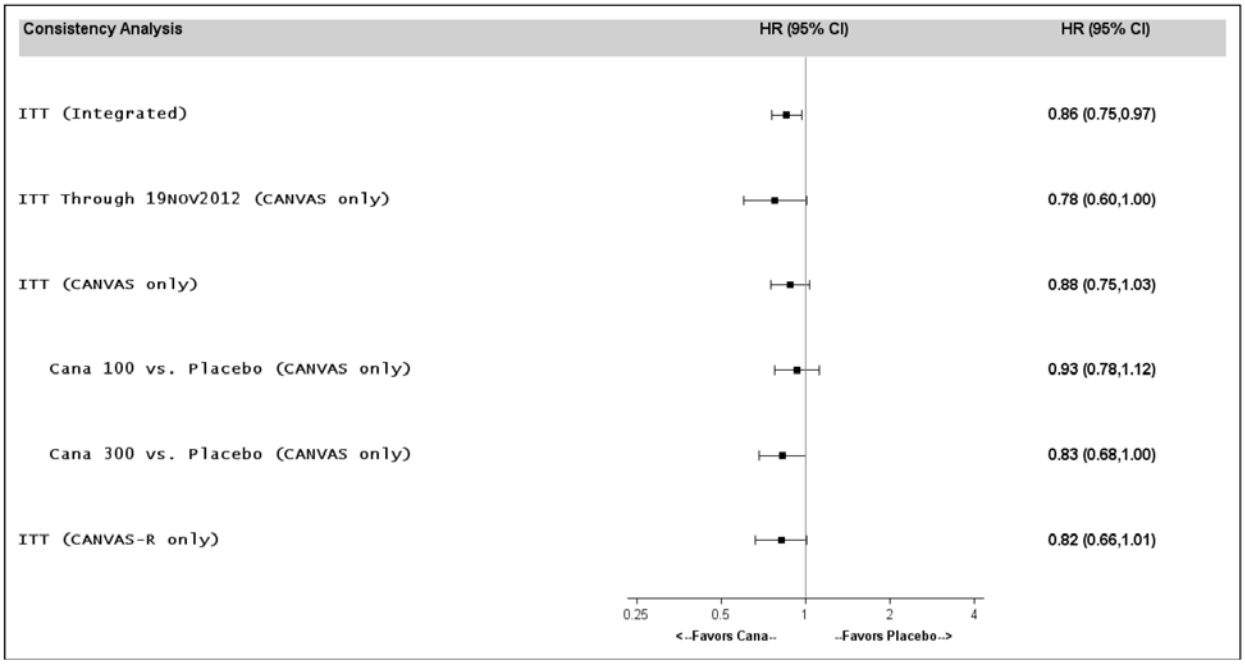
This decrease is also similar to the relative risk reduction of liraglutide, the second anti-diabetic drug product labeled for cardiovascular benefit: the three-point MACE in the LEADER was 0.87 (95% CI: 0.78, 0.97; p=0.005). The current indication of liraglutide is "to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease". Liraglutide only has indication for MACE in patients with established cardiovascular disease because LEADER was a study in patients with type 2 diabetes mellitus and largely enrolled patients with established cardiovascular disease (~80%).

[3] Dr. Andreea O. Lungu's Clinical Review, NDA 204629, November 3, 2016

MACE in CANVAS and CANVAS-R:

As shown in Figure 6, the HR for time to first adjudicated 3-point MACE in DIA3008 and DIA4003 showed similar trend with the hazard ratio in positive direction, although the 95% CI cross 1 for each study by itself, most likely due to insufficient statistical power to show the CV benefit.

Figure 6: Forest Plot of Hazard Ratios and 95% CI of Time to First MACE in the CANVAS Program, CANVAS, CANVAS-R (ITT Analysis Set)



Source: ISE, Figure 15

Within DIA3008, the HR for 3-point MACE with 300 mg dose of canagliflozin reached statistical significance (0.83 [95% CI: 0.68, 1.00]) whereas 100 mg dose of canagliflozin did not reach statistical significance (0.93 [95% CI: 0.78, 1.12]). When both canagliflozin groups are pooled, the hazard ratio for 3-point MACE is 0.88 with 95% CI of (0.75, 1.03).

As previously discussed in study design section, within DIA4003 canagliflozin treatment was initiated at 100 mg dose and up-titrated to 300 mg at Week 13 or thereafter if additional glycemic control was needed and lower dose was tolerated.

In order to assess whether there is a difference in CV outcomes by dosage levels, we sent an Information Request (IR) to the Applicant on February 16, 2018 as following:

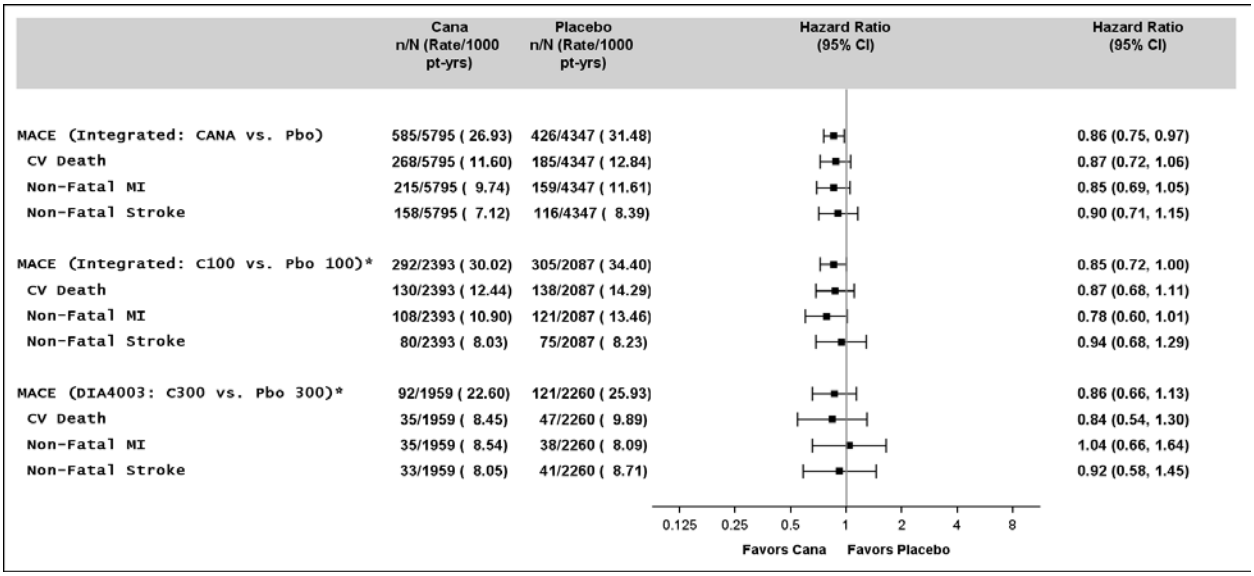
We are interested in evaluating CV outcomes by dosage levels. Please perform the following 2 analyses:

1. Please integrate studies 3008 and 4003 and perform a time to first occurrence of MACE analysis (including individual components) that compares Cana 100 vs placebo. The Cana 100 group should consist of: 1445 patients in the Cana 100 mg arm from study 3008, 929 patients who only took Cana 100 mg in study 4003, and 3 patients who had missing dose information in study 4003. The placebo group should consist of: 1442 patients in the Placebo arm from study 3008, 623 patients who only took Placebo 100 mg in study 4003, 1 patient who had missing dose information in study 4003, and any patient who experienced a non-fatal event while on Placebo 100 mg and was later up-titrated to Placebo 300 mg in study 4003.

2. For study 4003, please perform a time to first occurrence of MACE analysis (including individual components) that compares patients who up-titrated to Cana 300 mg vs Placebo. The Cana group should consist of patients who up-titrated to Cana 300 mg (but exclude patients who experienced a non-fatal event while on Cana 100 mg). The placebo group should consist of patients who up-titrated to Placebo 300 mg (but exclude patients who experienced a non-fatal event while on Placebo 100 mg).

On March 12, 2008, the Applicant responded to the IR and the results are shown in Figure 7. In both the integrated and DIA4003 analyses, the HR point estimates for MACE by dose was very similar to the MACE in pooled canagliflozin dose.

Figure 7: Forest Plot of Hazard Ratios and 95% CI of First Occurrence of MACE and Components in Pooled DIA3008 and DIA4003 (ITT Analysis Set)



*Denotes analysis based on the treatment groups from the FDA's pooling strategy received in their RFI dated Feb 16, 2018
Source: Response to IR on March 12, 2018, Figure 1

Reviewer's comment: There do not appear to be dose differences in the CV reduction for canagliflozin.

<u>MACE within the first 30 Days Post-randomization:</u>

During the review of the CV meta-analysis supporting the original approval of canagliflozin (i.e. submitted to support the 1.8 goalpost), the FDA statistician Dr. Andraca-Carrera noted an imbalance in the early CV events in DIA3008. Thirteen CV events occurred on canagliflozin and 1 CV event occurred on placebo during the first 30 days after randomization (0.45% vs 0.07%) with an estimated HR of 6.5, although 95% CI was not significant due to small number of events (95% CI: 0.85,49.66). Due to this observation, we requested that the Applicant conduct an analysis of MACE during the first 30 days after randomization in the new CV study, DIA4003.

During 30 days post-randomization in DIA4003, 3-point MACE occurred in 8/2907 subjects in the canagliflozin group compared to 9/2905 subjects in the placebo group, with an estimated HR of 0.89 (95% CI: 0.34, 2.31). The HR of 3-point MACE comparing canagliflozin versus placebo during 30 days post-randomization for the pooled DIA3008 and DIA4003 was 1.51 (95% CI: 0.70, 3.26), and this appears to be driven by the imbalance observed in DIA3008.

Reviewer's comments: Numerically higher number of CV events during the first 30 days of treatment with canagliflozin compared to placebo seen in DIA3008 but

was not seen in DIA4003. We have no scientific reason to believe that canagliflozin treatment may lead to a higher CV risk during first 30 days of treatment, and thus the imbalance seen in DIA3008 is likely a chance finding.

Sensitivity Analyses (On-Study and On-Treatment Analysis Sets):

The Applicant performed 3-point MACE analyses using the On-Study Analyses Set (data used from the same data period as ITT Analysis Set but restricted to dosed subjects) and the On-Treatment Analysis Set (only data from first dose of study drug to 30 days after the last dose of study drug was used).

The HR of 3-point MACE for canagliflozin compared to placebo was 0.86 (95% CI: 0.75, 0.97) using the On-Study Analysis Set and was 0.88 (95% CI: 0.76, 1.02) using the On-Treatment Analysis Set.

Reviewer's comment: The On-Study Analysis Set includes treated subjects but was restricted to dosed subjects, and the result of this sensitivity analysis supports the primary analysis. The On-Treatment Analysis Set included data from the first dose of study drug to 30 days after the last dose of the study drug, and as a result lowers the statistical power because MACE events that occur during follow-up while not on study drug are excluded from the analysis. Although the 95% CI did cross 1 for the On-Treatment Analysis Set, the point estimate remains similar to the primary analysis which is reassuring.

Assessment of Missing Data for MACE:

The proportion of missing subject-years in the canagliflozin group was 2.0% (454 PY missing follow-up in 153 subjects) and 2.4% (335 PY missing follow-up in 127 subjects) in the placebo group. A multiple imputation analysis was done by the Applicant to assess the impact of missing data from subjects who were either lost to follow-up or withdrew their consent before MACE event. Event imputation was done from a model using the observed data, adjusted for treatment and baseline characteristics, and the imputed events and follow-up times were merged with the observed data. The primary efficacy model was re-analyzed with the imputed dataset, and this process was repeated 1000 times. The HR of 3-point MACE for canagliflozin compared to placebo for the multiple imputation analysis was 0.85 (95% CI: 0.75, 0.97).

Reviewer's comment: Please refer to Dr. Roberto Crackel's review for the FDA's sensitivity analyses and missing data analysis. Dr. Crackel concluded that the missing data had very little impact on the results of the primary analysis based on his multiple imputation analysis.

Concomitant Cardiovascular Therapy:

The proportion of total subjects initiating new cardiovascular therapies was ~25-26% (Table 17**Error! Reference source not found.**). More subjects in the placebo group appear to have initiated calcium channel blockers (7.8% vs 5.5%) and non-loop diuretics (6.4% vs 4.7%) compared to placebo during their participation in the study. This is likely due to the fact that canagliflozin reduce blood pressure, and therefore subjects in the placebo initiated more anti-hypertensives such as calcium channel blockers and diuretics.

In comparison, more subjects in the canagliflozin group initiated anti-thrombotics (5.2% vs 4.2%) and statins (5.8% vs 4.8%) compared to placebo. This is likely due to increase in lipid levels seen with canagliflozin therapy (see Section 6.1.6 for discussion of Changes in Fasting Plasma Lipids).

It is not clear whether these differences between treatment groups in newly initiated concomitant CV therapies impacted the MACE outcome of the study.

Between studies, a larger proportion of subjects initiated new CV drug in DIA3008 (~36% in placebo and ~33% in the combined canagliflozin group) compared to DIA4003 (~22% in placebo and ~17% in the canagliflozin group). This may be related to the fact that DIA3008 compared to DIA4003 enrolled fewer subjects with prior CV history (59% vs 71%) and more subjects at high CV risk (41% vs 29%), and therefore subjects at high CV risk ended up requiring additional CV drugs during study as part of natural disease progression. DIA3008 also had much longer duration of study compared to DIA4003 (mean total follow-up of 296 weeks versus 108 weeks).

Table 17: Newly Initiated Cardiovascular Therapies (Pooled Data; On-Treatment Analysis Set)

Concomitant Medication	Placebo (N=4344) n (%)	Cana (N=5790) n (%)	Total (N=10134) n (%)
Total no. subjects with concomitant therapy	1153 (26.5)	1428 (24.7)	2581 (25.5)
Anti-thrombotics (including aspirin)	181 (4.2)	300 (5.2)	481 (4.7)
Beta-blocker	242 (5.6)	305 (5.3)	547 (5.4)
Calcium channel blocker	339 (7.8)	317 (5.5)	656 (6.5)
Diuretic Loop	250 (5.8)	307 (5.3)	557 (5.5)
Diuretic Non-Loop	277 (6.4)	274 (4.7)	551 (5.4)
RAAS Inhibitor	171 (3.9)	232 (4.0)	403 (4.0)
Statins	207 (4.8)	338 (5.8)	545 (5.4)

Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 17

6.1.5 Analysis of Secondary Endpoints

In this section I will discuss the results for 'confirmatory' CV secondary endpoints, all-cause mortality and CV death, as well as relevant CV endpoints such as all MIs (fatal or non-fatal),all strokes (fatal or non-fatal), and hospitalization for heart failure.

All-cause Mortality:

The key confirmatory secondary endpoint after confirmation of non-inferiority in 3-point MACE was all-cause mortality. The analysis was to test for superiority of canagliflozin compared to placebo, using the Truncated ITT Analysis Set (where all study time and mortality events before November 20, 2012 are removed from DIA3008, as previously discussed).

A total of 553 deaths were reported during the trial, which occurred in 19.05/1000 PY of subjects randomized to canagliflozin and 20.12/1000 PY of subjects randomized to placebo. The HR for canagliflozin versus placebo for all-cause mortality was 0.90 (95% CI: 0.78, 1.01). Thus, although the point estimate of HR for all-cause death was <1, canagliflozin was not found to be statistically superior compared to placebo in reducing the risk for all-cause mortality. As hypothesis testing in this second step of hierarchical testing (Figure 3) did not reach statistical significance, formal statistical testing did not proceed further.

Table 18: Time to All-Cause Mortality – Pooled DIA3008 and DIA4003 (Truncated ITT Analysis Set)

	Placebo (N=4288)		Canagliflozin (N=5711)			
	N (%)	Event rate*		Event rate*	HR (95% CI)	p-value**
All-cause mortality	229 (5.3%)	20.12	324 (5.7%)	19.05	0.90 (0.76, 1.07)	0.2452

HR (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
*Event rate per 1000 patient-years;
**p-value for all-cause mortality corresponds to a test of superiority at a two-sided significance level at 0.05.
Source: ISE, Table 25

The sensitivity analyses based on the ITT Analysis Set (without truncation) also showed similar result with HR of 0.87 (95% CI: 0.74, 1.01) for all-cause mortality with canagliflozin compared to placebo group.

All-cause mortality by study showed that most deaths occurred in DIA3008, and as a result the 95% CI was much narrower compared to all-cause death in DIA4003 (Table 19).

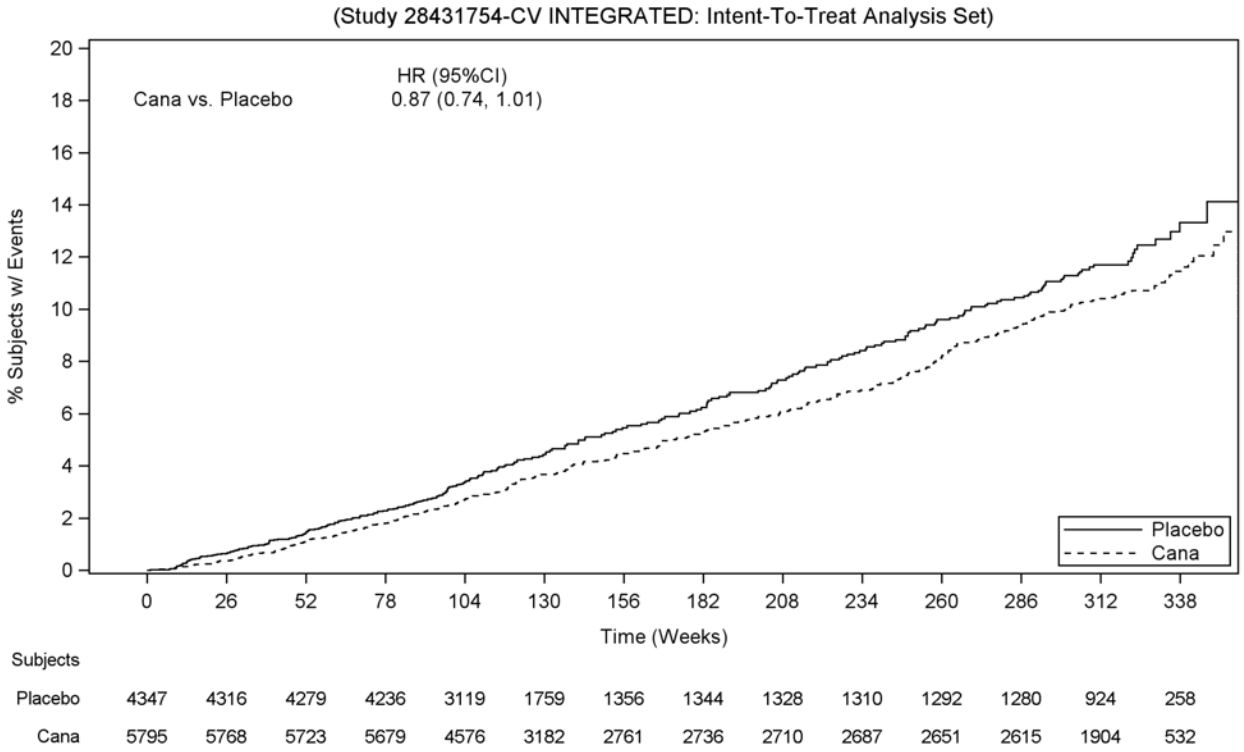
Table 19: All-Cause Mortality By Study (ITT Analysis Set)

	Placebo	All Canagliflozin	
	n/N (%)	n/N (%)	HR (95% CI)
DIA3008	175/1442 (12.1%)	301/2888 (10.4%)	0.84 (0.70, 1.01)
DIA4003	106/2905 (3.6%)	99/2907 (3.4%)	0.92 (0.70, 1.21)

HR (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 prior CV disease subgroup.
Source: ISE, Table 28

The Kaplan-Meier plot of time to all-cause mortality for the pooled DIA3008 and DIA4003 ITT Analysis Set is shown in Figure 8, where you can see an early separation of curves between treatment groups that remained separated for the duration of follow-up, albeit not statistically significant.

Figure 8: Kaplan-Meier Estimates of Time to All-Cause Mortality in Pooled DIA3008 and DIA4003 (ITT Analysis Set)



Source: ISE, GEFCV01_ACM

In order to assess the impact of missing follow-up data on all-cause mortality, a worst-case scenario analysis was done by the Applicant where among subjects with unknown vital status at study completion, subject on canagliflozin were assumed to have died on the date of censoring while the placebo subjects remained censored. In this single imputation analysis, the HR of all-cause mortality in the truncated ITT analysis set was

0.94 (95% CI: 0.80, 1.12) for the imputed. This missing data analysis continue to show HR <1 of all-cause mortality for canagliflozin compared to placebo, supporting the primary analysis.

The EAC was asked to assign subjects who died 1 proximate and 1 or more underlying causes of death, and as a result a subject may have more than one category for causes of death. The adjudicated causes of death, both proximate and underlying causes, are summarized in Table 20. Review of causes of death by proximate cause had similar trends (not shown here; see TEFDEATH01A_ADJ in ISE). Deaths where the cause could not be determined by EAC were pre-specified to be treated as CV death in analyses.

Most causes of death for both the proximate and underlying causes were determined to be cardiovascular deaths, which accounted for about ~64% (146/226) and ~68.5% (222/324) of deaths in the placebo and canagliflozin groups. The causes of deaths were undetermined in about 17% (39/229) of deaths with placebo and 14% (46/324) of deaths with canagliflozin. Review of sample of deaths classified as having an "undetermined" death showed that either there were multiple possible contributing factors or very few details surrounding death to obtain the cause of death.

Among CV deaths, the exposure-adjusted incidence rate of death due to acute myocardial infarction as proximate and underlying cause appear to be almost twice higher with canagliflozin compared to placebo (2.34 vs 1.25/1000 PY; see Table 20). The incidence of adjudicated death by proximate cause due to acute MI was 40/5795 (0.7%) in the canagliflozin group and 17/4347 (0.4%) in the placebo group; I estimated the event rate to be about 2.23/1000 PY in the placebo group compared to 1.54/1000 PY in the canagliflozin group.

Deaths in DIA4003 appear to have largely contributed to this imbalance in acute MI not favoring canagliflozin, as 15 subjects (0.5%; 2.5/1000 PY) in the canagliflozin group compared to 4 subjects (0.1%; 0.7/1000 PY) in the placebo group died due to acute MI based on proximate and underlying cause; of these, 10 subjects (0.3%) in the canagliflozin group and 3 subjects (0.1%) in the placebo group died due to acute MI as proximate cause. In comparison, in DIA3008, 20 subjects (1.4%) in canagliflozin 100 mg and 19 subjects (1.3%) in canagliflozin 300 mg compared to 14 subjects (1.0%) in the placebo group died due to acute MI as both proximate and underlying causes.

Review of narratives[4] of subjects who died due to acute MI as either proximate or underlying cause did not identify possible reason or specific concern related to this imbalance, since all of these cases had prior CV history, had multiple underlying

[4] Four cases with acute MI either as proximate or underlying cause with placebo were (b) (6) ; fifteen cases with canagliflozin were (b) (6)

diseases that placed them at high risk for MI, and was consistent with cause of death classification. The reason for this is unclear, and it is reassuring that the analysis for all MIs including both fatal and non-fatal events did not show an increased risk for MI with canagliflozin (

Table 24).

Table 20: Adjudicated Death By Both Proximate and Underlying Causes in Pooled DIA3008 and DIA4003 (ITT Analysis Set)

Type of Death	Placebo (N=4347)		Cana (N=5795)	
Cause of Death	N (%)	Rate*	N (%)	Rate*
All Deaths	**229 (5.3)**	**20.12**	**324 (5.7)**	**19.05**
CV Death	**146 (3.4)**	**10.13**	**222 (3.8)**	**9.61**
Acute myocardial infarction	18 (0.4)	1.25	54 (0.9)	2.34
Heart failure or cardiogenic shock	35 (0.8)	2.43	68 (1.2)	2.94
Other CV causes	39 (0.9)	2.71	61 (1.1)	2.64
Stroke	23 (0.5)	1.60	28 (0.5)	1.21
Sudden cardiac death	85 (2.0)	5.90	111 (1.9)	4.80
Non-CV Death	**96 (2.2)**	**6.66**	**132 (2.3)**	**5.71**
Accidental/trauma	5 (0.1)	0.35	10 (0.2)	0.43
Drug overdose	2 (<0.1)	0.14	1 (<0.1)	0.04
Gastrointestinal causes	17 (0.4)	1.18	14 (0.2)	0.61
Hemorrhage, not intracranial	1 (<0.1)	0.07	5 (0.1)	0.22
Hepatobiliary causes	11 (0.3)	0.76	17 (0.3)	0.74
Infection (includes sepsis)	31 (0.7)	2.15	40 (0.7)	1.73
Malignant causes	56 (1.3)	3.89	77 (1.3)	3.33
Non-cardiovascular surgery	2 (<0.1)	0.14	1 (<0.1)	0.04
Non-cardiovascular system organ failure	8 (0.2)	0.56	12 (0.2)	0.52
Non-infectious	1 (<0.1)	0.07	1 (<0.1)	0.04
Other non-CV	2 (<0.1)	0.14	7 (0.1)	0.30
Pancreatic causes	13 (0.3)	0.90	8 (0.1)	0.35
Pulmonary causes	39 (0.9)	2.71	56 (1.0)	2.42
Renal causes	17 (0.4)	1.18	20 (0.3)	0.87
Suicide	0	0	3 (0.1)	0.13
Undetermined	**39 (0.9)**	**2.71**	**46 (0.8)**	**1.99**

*Rate=/1000 patient-years
NOTE: A subject may have one proximate cause and multiple underlying causes.
Source: ISE, TEFDEATH01_ADJ_IR

Cardiovascular Death:

Since all-cause mortality did not reach statistical significance, statistical testing for superiority of canagliflozin compared to placebo in CV death was not done. The p-value in Table 32 is considered nominal.

Canagliflozin did not significantly reduce the risk of CV death when compared to placebo in the Truncated ITT Analysis Set (Table 32), and the HR for CV death was 0.96 with wide 95% CI (0.77, 1.18). Of note, the event rate of CV death was numerically higher in the canagliflozin group compared to placebo, 12.82 versus 12.74 per 1000 PY in the Truncated ITT Analysis Set, despite the HR being <1. This may be due to truncation of data since data for DIA3008 were left-truncated in 2012 when MACE events were unblinded for interim analysis. In supportive analysis of CV death using ITT Analysis Set (which was not left-truncated and included all DIA3008 data), the overall event rate of CV death was lower with canagliflozin (11.60/1000 PY in the canagliflozin group and 12.84/1000 PY in the placebo group), and the HR for CV death was 0.87 for canagliflozin vs. placebo with narrower 95% CI (0.74, 1.01) (Table 22).

Table 21: CV Death – Pooled DIA3008 and DIA4003 (Truncated ITT Analysis Set)

	Placebo (N=4288)		Canagliflozin (N=5711)			
	N (%)	Event rate*		Event rate*	HR (95% CI)	p-value**
CV Death	145 (3.4)	12.74	218 (3.8)	12.82	0.96 (0.77, 1.18)	0.6739

HR (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
*Event rate per 1000 patient-years;
**p-value for all-cause mortality corresponds to a test of superiority at a two-sided significance level at 0.05.
Source: ISE, Table 30

Table 22: Supportive Analysis of CV Death – Pooled DIA3008 and DIA4003 (ITT Analysis Set)

	Placebo (N=4347)		Canagliflozin (N=5795)		
	N (%)	Event rate*		Event rate*	HR (95% CI)
CV Death	185 (4.3)	12.84	268 (4.6)	11.60	0.87 (0.72, 1.06)

HR (canagliflozin compared to placebo), 95% CI and p-value are estimated using a Cox proportional hazard model stratified by study and prior CV disease subgroup
*Event rate per 1000 patient-years;
Source: ISE, Table 32

The effect of left-truncation of DIA3008 data on CV death can be fully seen by looking at the study-level data (Table 23). In DIA3008, HR of CV death until November 19, 2012 was 0.62 for canagliflozin compared to placebo with 95% CI nominally significant (0.41, 0.94), and the event rate for CV death in the canagliflozin group was significantly lower (8.20/1000 PY) compared to placebo (13.21/1000 PY). Excluding this data through November 19, 2012 in DIA3008, the event rate for canagliflozin was numerically higher (14.35/1000 PY) compared to placebo (14.02/1000 PY), and the HR of CV death was 1.02 for canagliflozin compared to placebo (95% CI: 0.77, 1.34). Therefore, in DIA3008, it appears that CV death occurred less in the canagliflozin group compared to placebo until November 19, 2012 and then subsequently occurred slightly more in the

canagliflozin group compared to placebo. The reason for this trend over time course is unclear.

Table 23: CV Death By Study (ITT Analysis Set)

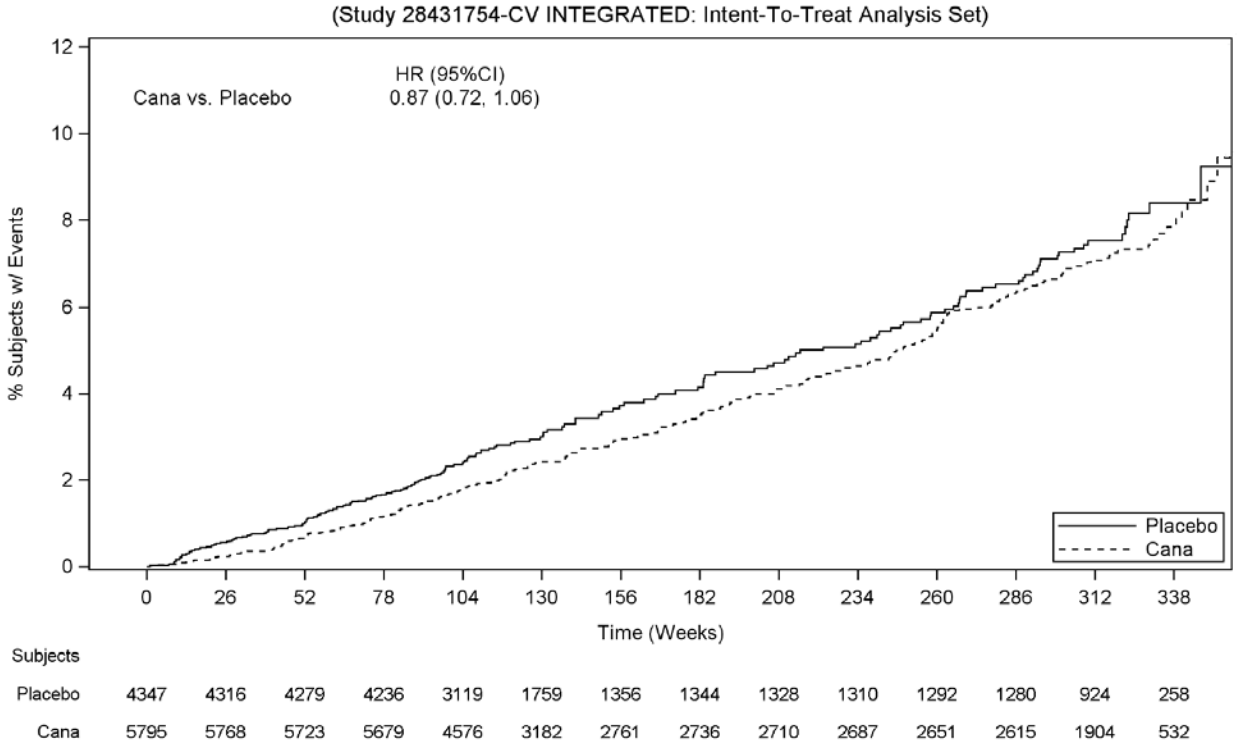
	Placebo		All Canagliflozin		
	n/N (%)	Event Rate*	n/N (%)	Event Rate*	HR (95% CI)
DIA3008	115/1442 (8%)	13.73	207/2888 (7.2%)	12.15	0.88 (0.70, 1.10)
DIA 3008 Through Nov 19, 2012	40/1442 (2.8%)	13.21	50/2888 (1.7%)	8.20	0.62 (0.41, 0.94)
DIA 3008 Truncated ITT (excludes subjects through Nov 19, 2012)	75/1383 (5.4%)	14.02	157/2804 (5.6%)	14.35	1.02 (0.77, 1.34)
DIA4003	70/2905 (2.4%)	11.60	61/2907 (2.1%)	10.06	0.86 (0.61, 1.22)

HR (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 prior CV disease subgroup
*Event rate per 1000 patient-years;
Source: ISE, Table 34

In the sensitivity analysis, the proportional hazard assumption was not satisfied in the ITT Analysis Set of pooled DIA3008 and DIA4003 data (without truncation), but the results are similar based on the analysis using the log-rank test which does not require the assumption of proportional hazards (0.87 [95% CI: 0.72, 1.06]).

See Figure 9 for the Kaplan-Meier curve for time to CV death for the ITT Analysis Sets. Similar to all-cause mortality, there is an early separation of curves between treatment groups, but the curves seem to merge by ~5 years (~260 weeks), although the number of subjects drop off significantly by then.

Figure 9: Kaplan-Meier Estimates of Time to CV Death in Pooled DIA3008 and DIA4003 (ITT Analysis Set)



Source: ISE, GEFCV01_CVD

To assess the impact of missing data on CV death, a worst-case scenario analysis was done where in subjects with unknown vital status at study completion, subject on canagliflozin were assumed to have died on the date of censoring while the placebo subjects remained censored. In this single imputation analysis, the HR of all-cause mortality in the truncated ITT analysis set was 1.02 (95% CI: 0.83, 1.26) for the imputed.

For causes of deaths, including CV deaths, see Table 20 and discussions in section 'All-cause Mortality' above.

All Myocardial Infarctions (Fatal or Nonfatal):

The HR for all MIs, whether fatal or nonfatal, for canagliflozin compared to placebo in the ITT Analysis Set was 0.89 (95% CI: 0.73, 1.09) (

Table 24). Only events adjudicated as CV deaths where proximate cause was MI was used to define fatal MI. The majority of MIs were nonfatal, as 92% (159/173) of MIs in the placebo and 87% (215/248) of MIs in the canagliflozin group were nonfatal MIs. Fatal MIs were discussed in 'All-cause Mortality' section above.

Table 24: Myocardial Infarction (Fatal/Nonfatal) – Pooled DIA3008 and DIA4003 (ITT Analysis Set)

	Placebo (N=4347)		Canagliflozin (N=5795)			
	N (%)	Rate*	N (%)	Rate*	HR (95% CI)	p-value**
MI (Fatal/Nonfatal)	173 (4.0)	12.64	248 (4.3)	11.24	0.89 (0.73, 1.09)	0.2588
Nonfatal MI	159 (3.7)	11.61	215 (3.7)	9.74	0.85 (0.69, 1.05)	0.1257

HR (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
*Event rate per 1000 patient-years;
**p-value for corresponds to a test of superiority at a two-sided significance level at 0.05.
Source: ISE, Table 37, Table 19

Fatal or non-fatal MIs by study show that there was a higher incidence of MI in DIA3008 compared to DIA4003, but the point estimate for HR for all MIs was consistent with the overall results combining both studies (Table 19).

Table 25: Fatal or Non-Fatal Myocardial Infarction By Study (ITT Analysis Set)

	Placebo n/N (%)	All Canagliflozin n/N (%)	HR (95% CI)
DIA3008	97/1442 (6.7%)	177/2888 (6.1%)	0.88 (0.68, 1.12)
DIA4003	76/2905 (2.6%)	71/2907 (2.4%)	0.92 (0.67, 1.27)

HR (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 prior CV disease subgroup.
Source: ISE, Table TEFCV04_MI

Subgroup analysis for all MIs, without adjustment for multiplicity, showed 5 subgroups where the interaction p-value was <0.05 (Table 26). Of note, subjects with prior history of CV disease appear to have less relative risk for MI with canagliflozin treatment compared to subjects without prior history of CV disease. Similarly, less relative risk of MI was seen with canagliflozin treatment in subjects with baseline use of diuretics, subjects with diabetes ≥10 years, and eGFR 30 to <60 mL/min/1.73 m^2. Except for baseline use of diuretics, the other subgroups had a marginal p-value for interaction. Applicant further computed Gail-Simon p-value for the interaction of treatment group and baseline subgroup when interaction p-value was significant at 0.05, and baseline use of diuretics (yes or no) was the only subgroup with marginally significant Gail-Simon p-value of 0.0490. Although the baseline use of loop diuretics was slightly higher in subjects receiving placebo compared to canagliflozin (13.6% versus 12.4% respectively; Table 11), this is unlikely to have had significant effect in the overall estimate of risk for MI.

Table 26: Subgroup Analysis of Fatal or Nonfatal Myocardial Infarction With Significant Interaction Value – Pooled DIA3008 and DIA4003 (ITT Analysis Set)

	Placebo n/N (%)	Canagliflozin n/N (%)	HR (95% CI)	Interaction value
Baseline eGFR (mL/min/1.73 m²)				
30-<60	52/912 (5.7)	49/1099 (4.5)	0.63 (0.42, 0.93)	0.0431
60-<90	85/2360 (3.6)	156/3265 (4.8)	1.14 (0.87, 1.49)	
≥90	35/1057 (3.3)	43/1419 (3.0)	0.72 (0.46, 1.13)	
History of CV disease				
Yes	150/2900 (5.2)	194/3756 (5.2)	0.82 (0.66, 1.01)	0.0431
No	23/1447 (1.6)	54/2039 (2.6)	1.38 (0.84, 2.26)	
Baseline use of diuretics				
Yes	103/1954 (5.3)	108/2536 (4.3)	0.64 (0.48, 0.84)	0.0015
No	70/2393 (2.9)	140/3259 (4.3)	1.28 (0.96, 1.71)	
Baseline use of diuretics				
Loop	43/592 (7.3)	32/716 (4.5)	0.47 (0.30, 0.76)	0.0023
Non-Loop	60/1362 (4.4)	76/1820 (4.2)	0.75 (0.53, 1.06)	
None	70/2393 (2.9)	140/3259 (4.3)	1.28 (0.96, 1.71)	
Duration of diabetes ≥10 years				
Yes	134/3038 (4.4)	168/4007 (4.2)	0.77 (0.61, 0.98)	0.0362
No	39/1303 (3.0)	80/1783 (4.5)	1.30 (0.88, 1.91)	

HR (canagliflozin compared to placebo) and 95% CI are estimated using a stratified Cox proportional hazard model including treatment as the explanatory variable and stratified by study and prior CV disease subgroup. Subgroup of history of CV disease is not stratified by prior CV disease subgroup.*Event rate per 1000 patient-years;
*p-value for interaction of treatment by subgroup is based on the Cox proportional hazards model including treatment, baseline subgroup and their interaction.
Source: ISE, TEFCV04_MI

All Strokes (Fatal or Nonfatal):

The HR for all strokes, whether fatal or nonfatal, for canagliflozin compared to placebo in the ITT Analysis Set was 0.87 (95% CI: 0.67, 1.09) (Table 27). Only events adjudicated as CV deaths where proximate cause was stroke was used to define fatal stroke. The majority of strokes were non-fatal, as 87.2% (116/133) and 89.7% (158/176) strokes in placebo and canagliflozin groups respectively were non-fatal strokes, and the HR for non-fatal stroke was also <1.

Table 27: Stroke (Fatal/Nonfatal) – Pooled DIA3008 and DIA4003 (ITT Analysis Set)

	Placebo (N=4347)		Canagliflozin (N=5795)		HR (95% CI)	p-value**
	N (%)	Rate*	N (%)	Rate*		
Stroke (Fatal/Nonfatal)	133 (3.1)	9.62	176 (3.0)	7.93	0.87 (0.69, 1.09)	0.2342
Nonfatal stroke	116 (2.7)	8.39	158 (2.7)	7.12	0.90 (0.71, 1.15)	0.3967

HR (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
*Event rate per 1000 patient-years;
**p-value for corresponds to a test of superiority at a two-sided significance level at 0.05.
Source: ISE, Table 38, Table 19

Fatal or non-fatal stroke by study show that there was a higher incidence of stroke in DIA3008 compared to DIA4003, and the point estimate for HR for sroke was slightly higher in DIA3008 (Table 19).

Table 28: Fatal or Non-Fatal Stroke By Study (ITT Analysis Set)

	Placebo n/N (%)	All Canagliflozin n/N (%)	HR (95% CI)
DIA3008	62/1442 (4.3%)	119/2888 (4.1%)	0.93 (0.69, 1.27)
DIA4003	71/2905 (2.4%)	57/2907 (2.0%)	0.80 (0.56, 1.13)

HR (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 prior CV disease subgroup.
Source: ISE, Table TEFCV04_STROK

Subgroup analysis for all strokes, without adjustment for multiplicity, showed 5 subgroups where the interaction p-value was <0.05 (Table 29). Less relative risk for stroke was seen with canagliflozin in subjects with baseline use of antithrombotics, elderly subjects who were ≥65 years of age, and eGFR 30 to <60 mL/min/1.73 m^2. Computation of Gail-Simon p-value for interaction of treatment group and baseline subgroup was all not significant and was >0.05.

Table 29: Subgroup Analysis of Fatal or Nonfatal Stroke With Significant Interaction Value – Pooled DIA3008 and DIA4003 (ITT Analysis Set)

	Placebo n/N (%)	Canagliflozin n/N (%)	HR (95% CI)	Interaction value
Baseline eGFR (mL/min/1.73 m^2)				
30-<60	38/912 (4.2)	25/1099 (2.3)	0.50 (0.30, 0.83)	0.0058
60-<90	73/2360 (3.1)	100/3265 (3.1)	0.89 (0.65, 1.21)	
≥90	22/1057 (2.1)	51/1419 (3.6)	1.42 (0.86, 2.36)	
Baseline use of antithrombotics				
Yes	113/3235 (3.5)	131/4236 (3.1)	0.79 (0.61, 1.02)	0.0352
No	20/1112 (1.8)	45/1559 (2.9)	1.32 (0.78, 2.26)	
Age				
<65	50/2369 (2.1)	95/3209 (3.0)	1.17 (0.83, 1.65)	0.0064
≥65	83/1978 (4.2)	81/2586 (3.1)	0.68 (0.50, 0.93)	

HR (canagliflozin compared to placebo) and 95% CI are estimated using a stratified Cox proportional hazard model including treatment as the explanatory variable and stratified by study and prior CV disease subgroup. Subgroup of history of CV disease is not stratified by prior CV disease subgroup.*Event rate per 1000 patient-years;
*p-value for interaction of treatment by subgroup is based on the Cox proportional hazards model including treatment, baseline subgroup and their interaction.
Source: ISE, TEFCV04_STROK

Reviewer's comment: Each component of MACE, which included CV death, myocardial infarction and stroke, were consistent with the overall MACE analysis with the hazard ratio <1, although the 95% CIs all crossed 1 most likely due to insufficient power.

Hospitalization for Heart Failure:

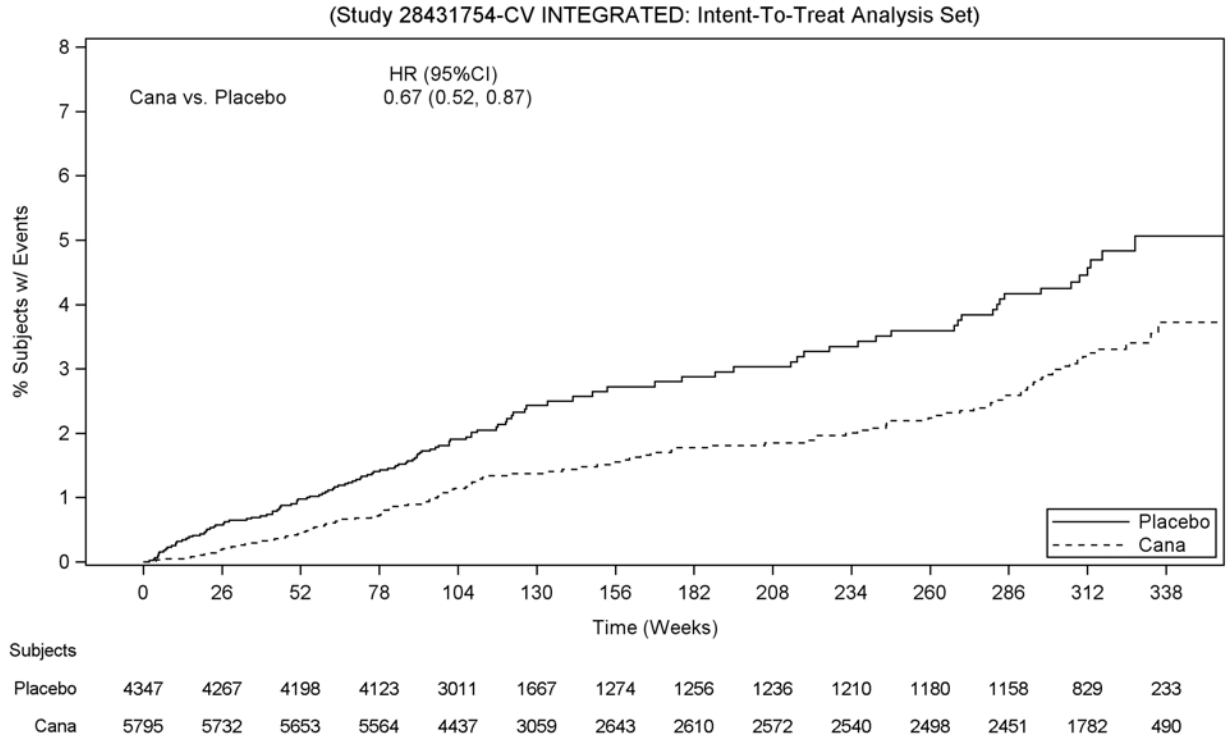
Hospitalization for heart failure was an adjudicated event. As shown in Table 30, the HR for time to the first occurrence of hospitalization for heart failure for canagliflozin compared placebo in the ITT Analysis Set was 0.67 and was nominally significant (95% CI: 0.52, 0.87). The time to the first occurrence of hospitalization for heart failure can be seen in Figure 10, showing early separation of curves between treatment groups shortly after randomization which was maintained throughout the study.

Table 30: Time to First Hospitalization for Heart Failure in The CANVAS Program (ITT Analysis Set)

	Placebo		Canagliflozin			
	n/N (%)	Rate*	n/N (%)	Rate*	HR (95% CI)	p-value**
Pooled DIA3008 & DIA4003	120/4347 (2.8)	8.68	123/5795 (2.1)	5.50	0.67 (0.52, 0.87)	0.0021
DIA3008	53/1442 (3.7)	6.71	85/2888 (2.9)	5.19	0.77 (0.55, 1.08)	
DIA4003	67/2905 (2.3)	11.29	38/2907 (1.3)	6.34	0.56 (0.38, 0.83)	

HR (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
*Event rate per 1000 patient-years;
**p-value for corresponds to a test of superiority at a two-sided significance level at 0.05.
Source: ISE, Table 35; CSR DIA3008, Table 22; CSR DIA4003, Table 21

Figure 10: Kaplan-Meier Estimates of First Occurrence of Hospitalization of Heart Failure

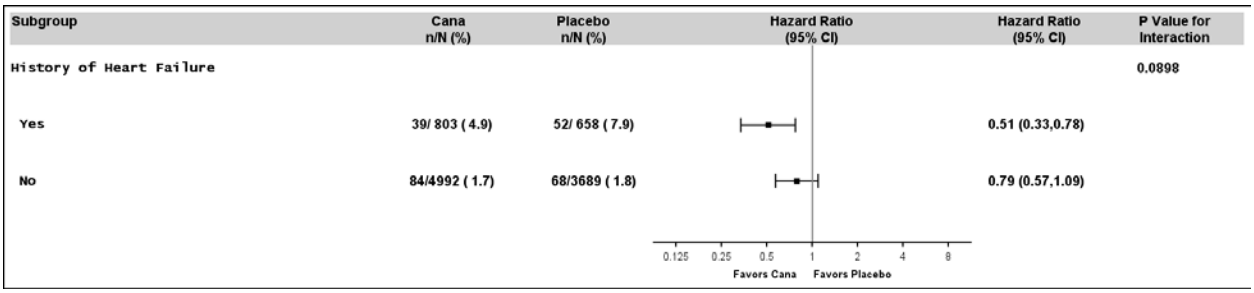


Source: ISE, Figure 19

At baseline, past history of heart failure was balanced between treatment groups; 15% (658/4347) of subjects in the placebo group and 14% (803/5795) of subjects in the combined canagliflozin group reported history of heart failure. However, details regarding ejection fraction or New York Heart Association Classification were not collected. In addition, it appears that more subjects receiving placebo compared to subjects receiving canagliflozin initiated diuretics therapy during their participation in study (Table 17).

Subgroup analysis showed that the reduced risk of HR for time to the first occurrence of hospitalization for heart failure for canagliflozin was mainly seen in those with history of heart failure at baseline. As discussed in Table 3, heart failure patients with history of NYHA Class 4 cardiac disease were excluded from DIA3008 and DIA4003.

Figure 11: Forest Plot of Hazard Ratios and 95% CI of First Occurrence of Hospitalization for Heart Failure by History of Heart Failure – Pooled DIA3008 and DIA4003 (ITT Analysis Set)



Source: ISE, GEFCV04A_HHF

Reviewer's comment: A decrease in heart failure events is plausible given the mechanism of action for canagliflozin, which has a diuretic effect. However, it should be noted that DIA3008 and DIA4003 enrolled a broad population of heart failure patients, and patients with heart failure were not directed to optimize their medical therapy for heart failure before enrollment and during the study. As discussed before, heart failure was an exploratory endpoint in these studies, and the Applicant is currently investigating the effect of canagliflozin in heart failure patients under IND with an oversight by the Division of Cardiovascular and Renal Products to conduct appropriate well-designed studies in patients with heart failure.

6.1.6 Other Endpoints/Exploratory Endpoints

In this section, relevant biomarker changes for CV risk is described, such as changes in HbA1c, body weight, blood pressure, and fasting plasma lipids. Renal efficacy endpoints were considered exploratory and will not be further discussed, and it should be noted that the Applicant is conducting further studies to evaluate the renal benefit for canagliflozin in discussion with Division of Cardiology and Renal Products.

Changes in HbA1c:

The change from baseline in HbA1c was measured at Weeks 12/13, 26, and every 26 weeks thereafter. Measurements beyond Week 104 were mainly from subjects in DIA3008. In order to summarize data from both studies, change from baseline to Week 104 is presented here. In DIA3008, background AHAs were not to be adjusted up to Week 12 if possible due to sub-studies, whereas in DIA4003 adjustment of background AHAs were allowed at the investigator's discretion at any time.

At baseline, the mean HbA1c was similar between treatment groups (8.24% in the placebo and 8.25% in the canagliflozin group). At Week 104, the mean HbA1c was 8.1% in the placebo group compared to 7.6% in the canagliflozin group, with the

placebo-subtracted LS mean change from baseline of -0.47% (95 CI: -0.518, -0.420) per On-Treatment Analysis Set. The placebo arm HbA1c at Week 104 did not show any significant changes in HbA1c compared to baseline (LS mean change from baseline was -0.10), while canagliflozin arm showed significant reduction as early as 12 weeks of study (Figure 12). It is unclear what may have led to the differences in HbA1c between treatment groups over time during their participation in the study, as subjects were supposed to be treated per standard of care.

As can be seen in Table 31**Error! Reference source not found.**, more subjects in the placebo arm initiated additional AHAs during the study compared to canagliflozin arm per standard of care About 22% of overall subjects initiated a new AHA, most commonly a DPP-4 inhibitor (~7%) or insulin (~6%). Despite this, subjects randomized to placebo did not see much improvement in their glycemic control in comparison to those randomized to canagliflozin. Since dosage for concomitant medications were not obtained, we cannot assess whether these treatments were optimized.

A larger proportion of subjects initiated a new AHA in DIA3008 (37% in placebo and 25% in canagliflozin group) compared to DIA4003 (22% in placebo and 11% in canagliflozin group), most likely due to longer duration of study as the mean follow-up was 296 weeks for DIA3008 compared to 108 weeks for DIA4003. Baseline HbA1c was similar for both studies.

Table 31: Newly Initiated Concomitant AHA Medication (Pooled Data, On-Treatment Analysis Set)

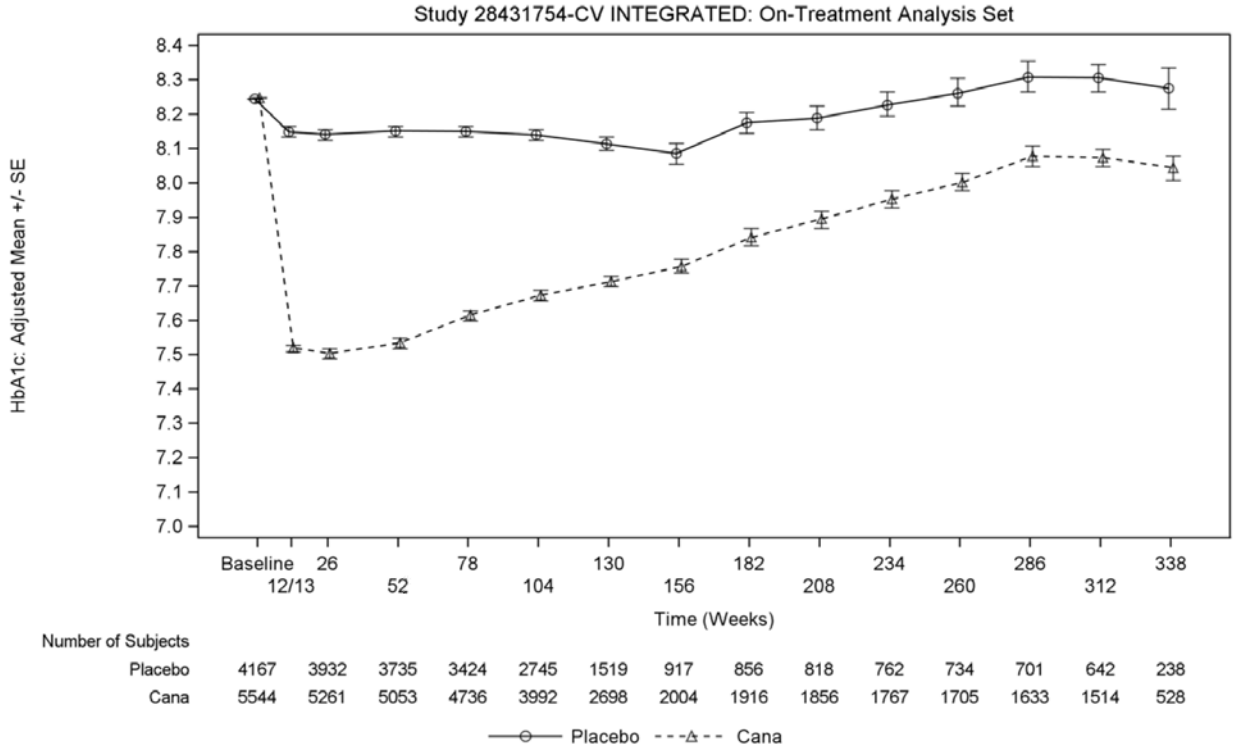
Concomitant Medication	Placebo (N=4344) n (%)	Cana (N=5790) n (%)	Total (N=10134) n (%)
Total no. subjects with concomitant therapy	1173 (27.0)	1029 (17.8)	2202 (21.7)
Alpha glucosidase inhibitors	59 (1.4)	59 (1.0)	118 (1.2)
Biguanides	209 (4.8)	188 (3.2)	397 (3.9)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	385 (8.9)	340 (5.9)	725 (7.2)
GLP 1	148 (3.4)	138 (2.4)	286 (2.8)
Insulin	380 (8.7)	271 (4.7)	651 (6.4)
SGLT2	21 (0.5)	29 (0.5)	50 (0.5)
Sulfonylurea	251 (5.8)	218 (3.8)	469 (4.6)
Thiazolidinediones (PPARy)	81 (1.9)	53 (0.9)	134 (1.3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Source: ISE, Table 14

The adjusted mean HbA1c over time in pooled DIA3008 and DIA4003 is shown in Figure 12, where the reduction of HbA1c in the canagliflozin group can be seen at around Week 12. The HbA1c levels in the canagliflozin group appear to rise slowly after Week 52, but the reduction in HbA1c with canagliflozin compared to placebo remained statistically significant through Week 338. The placebo-subtracted LS mean

change from baseline to Week 338 was 0.24% (95% CI: -0.37, -0.10), however only 6% (238/4167) subjects and 9.5% (528/5544) subjects in canagliflozin had Week 338 value.

Figure 12: Adjusted* Mean HbA1c Over Time in the Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)



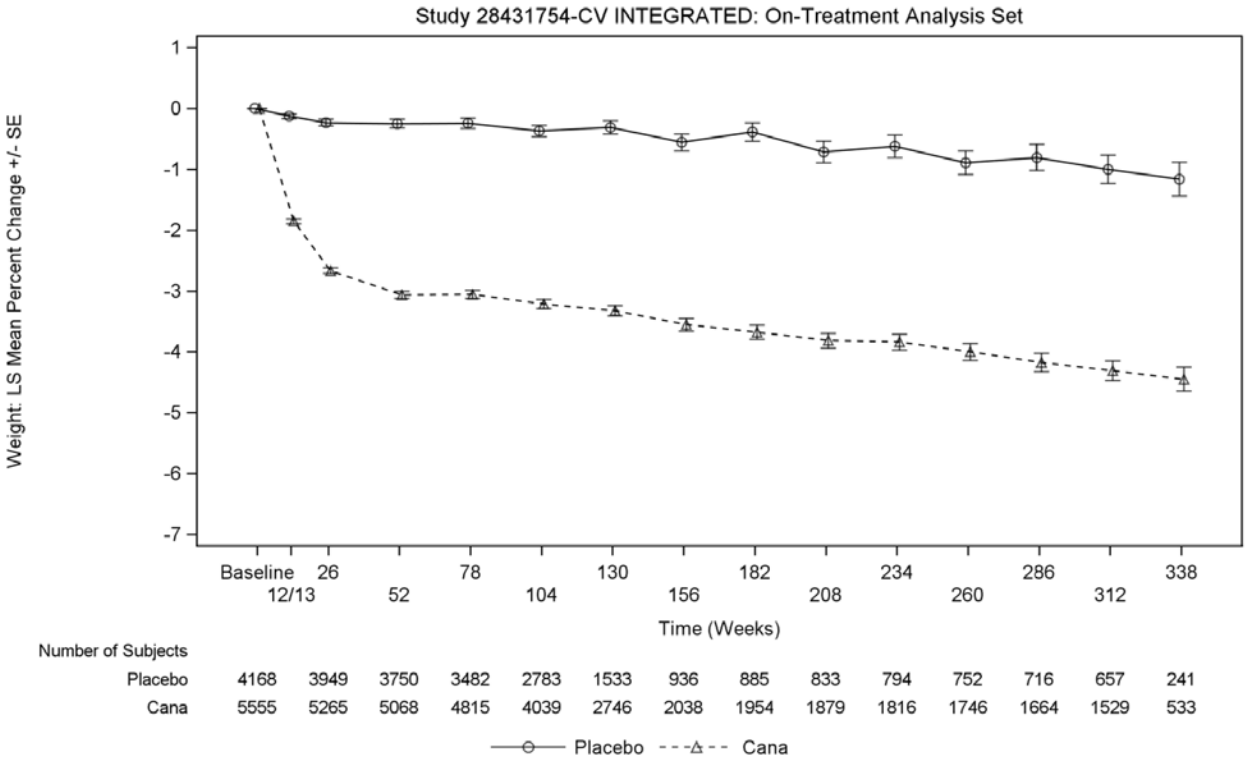
*ANCOVA model with treatment as a fixed effect and the corresponding baseline value as covariate
Source: ISE, Figure 32

Changes in Body Weight:

Similar to HbA1c, the change from baseline in body weight was measured at Weeks 12/13, 26, and every 26 weeks thereafter, and measurements beyond Week 104 were mainly from subjects in DIA3008. In order to summarize data from both studies, change from baseline to Week 104 is presented here.

In the On-Treatment Analysis Set, a reduction in body weight at Week 104 was seen with canagliflozin compared to placebo, with the placebo-subtracted LS mean change from baseline of -2.8% (95 CI: -3.1, -2.6). The decline in body weight was most noticeable up to Week 26, after which there was a progressive smaller decline up to Week 338 in the canagliflozin treatment group (Figure 13). The decline in the placebo group was minimal.

Figure 13: LS Mean Percent Change from Baseline in Body Weight Over Time in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)



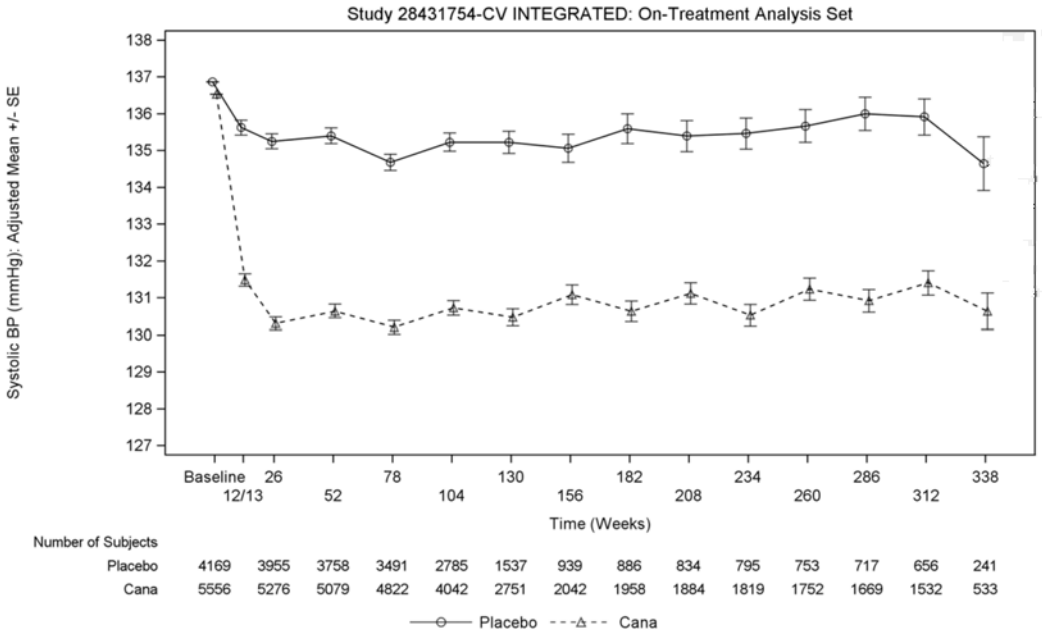
Based on a mixed model for repeated measures including the fixed effects of treatment, visit, treatment-by-visit interaction, baseline value, baseline-by-visit interaction.
Source: ISE, Figure 33

Changes in Blood Pressure:

The change from baseline in blood pressure was measured at Weeks 12/13, Week 26, and every 26 weeks thereafter. Measurements after Week 104 was mainly from subjects in DIA3008.

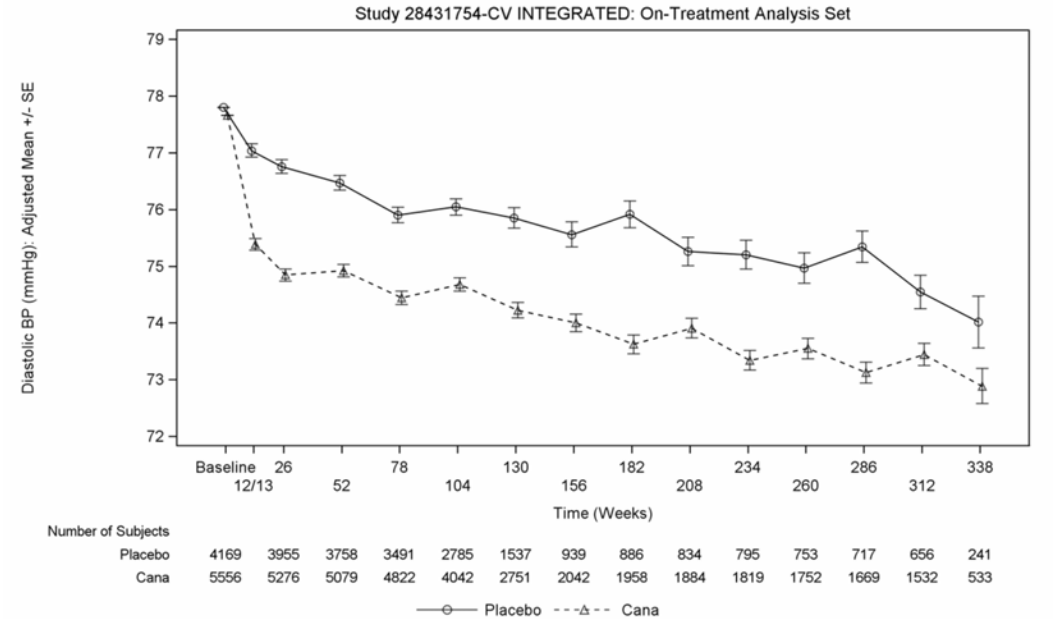
In the On-Treatment Analysis Set, the LS mean reductions in systolic blood pressure and diastolic blood pressure at Week 104 was seen with canagliflozin compared to placebo, with the placebo-subtracted LS mean change from baseline of -4.17 mmHg (95% CI: -4.79,-3.55) and -1.23 mmHg (95% CI: -1.59,-0.86). See Figure 14 for the mean changes in systolic blood pressure over time, and Figure 15 for the mean changes in diastolic blood pressure over time.

Figure 14: Adjusted Mean Systolic Blood Pressure Over Time in the Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)



Source: ISE, Figure 34

Figure 15: Adjusted Mean Diastolic Blood Pressure Over Time in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)



Source: ISE, Figure 35

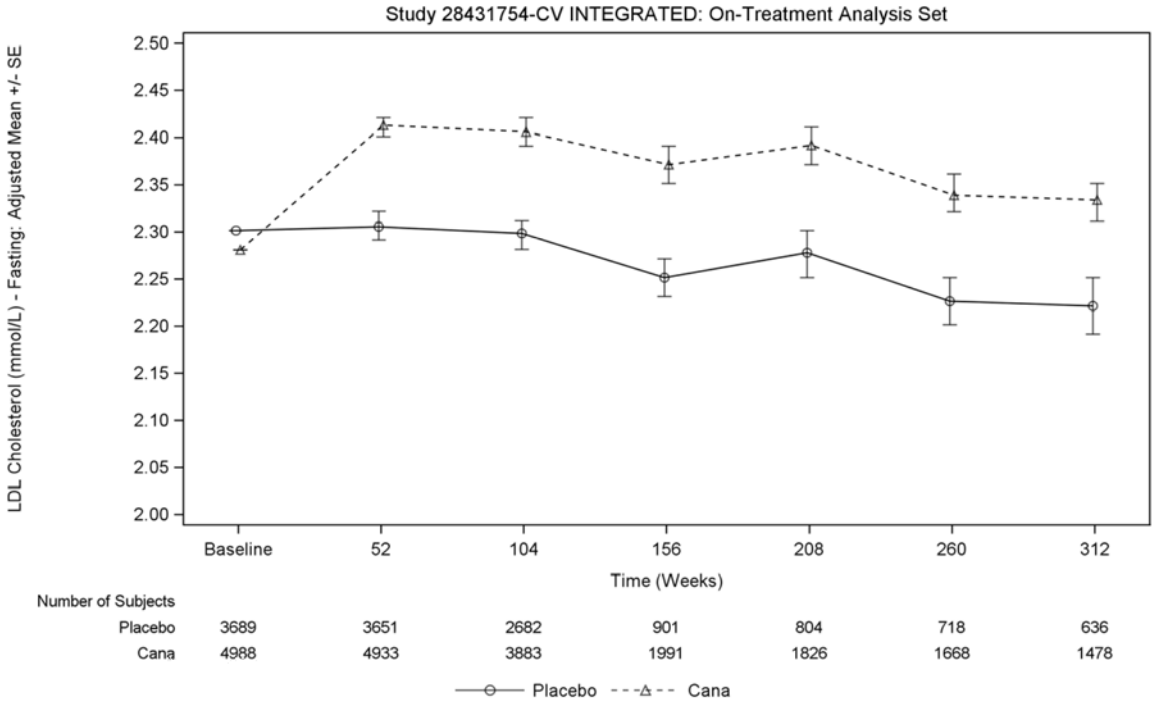
Changes in Fasting Plasma Lipids:

The changes from baseline in lipid parameters was measured at Weeks 18 in DIA3008 and at Week 26 in DIA4003, and every 26 weeks thereafter. Measurements after Week 104 was mainly from subjects in DIA3008.

In the On-Treatment Analysis Set, increased in lipid parameters at Week 104 was seen with canagliflozin compared to placebo. The placebo-subtracted LS mean changes from baseline in total cholesterol was 7.9 mg/dL (95% CI: 6.1, 9.6), HDL-C was 2.3 mg/dL (95% CI: 1.9, 2.6), and LDL-C was 5.1 mg/dL (95% CI: 3.7, 6.5). There were no differences between canagliflozin and placebo for the ratio of LDL-C to HDL-C, total cholesterol to HDL-C, and triglycerides from baseline to Week 104.

The LS mean increase of LDL-C with canagliflozin reached peak at around Week 52 and did not increase further (Figure 15).

Figure 16: Adjusted* Mean LDL Cholesterol Over Time in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)



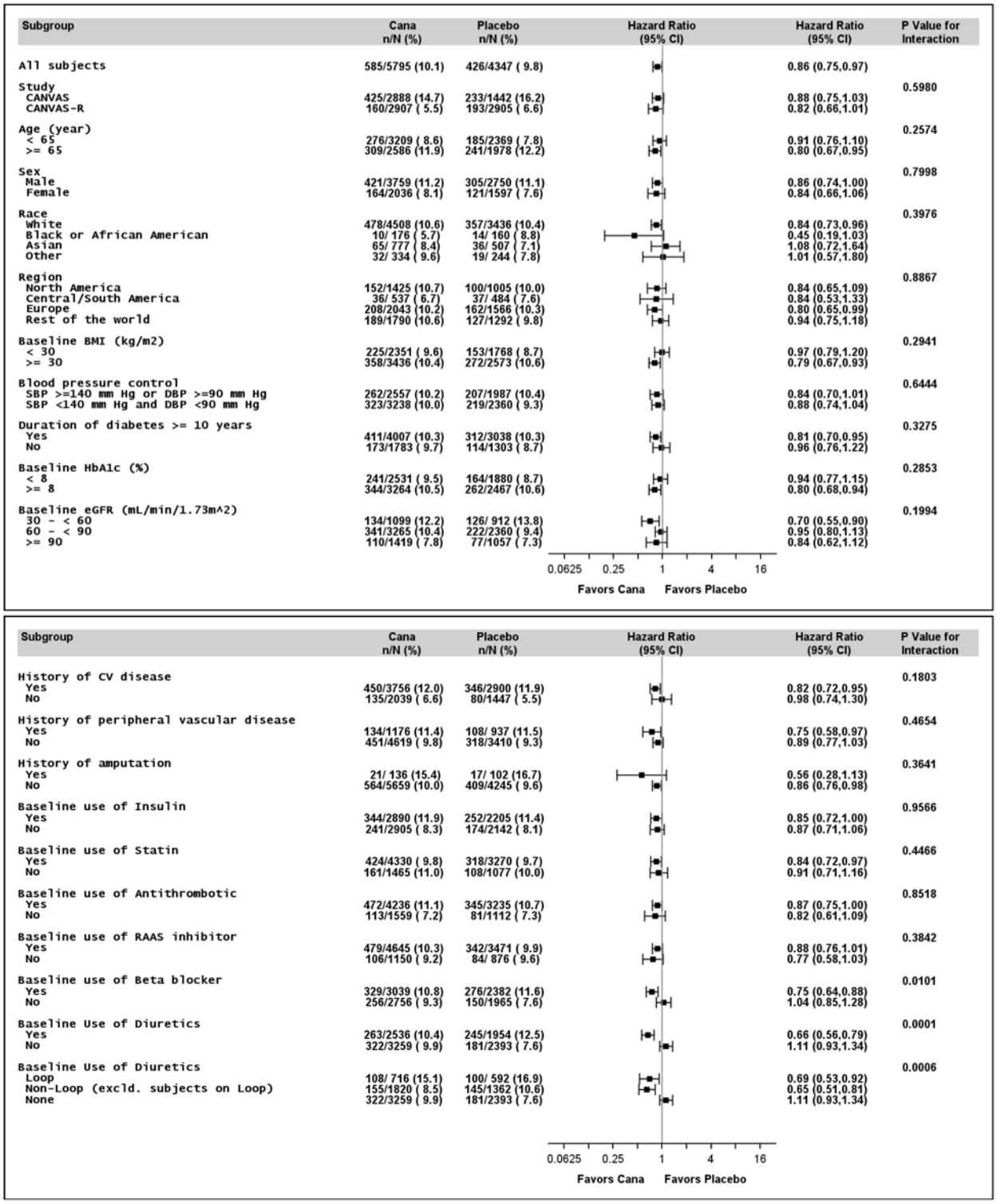
*Mixed model for repeated measures including the fixed effect of study, treatment, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction.
Source: ISE, GEFOLDL02_AM

6.1.7 Subpopulations

As pre-specified, the Applicant performed subgroup analyses for MACE. These analyses were done without adjustment for multiplicity. Across subgroups, the HR for MACE showed similar trend as the overall population with HR for MACE <1 with canagliflozin compared to placebo except for the following subgroups: Asians, 'other' race, subjects not using beta-blocker at baseline, and subjects not using diuretics at baseline (Figure 17).

The interaction p-value showed significance in the subgroups defined by baseline use of beta-blocker and diuretics.

Figure 17: Forest Plot of Hazard Ratios and 95% CI of First Occurrence of 3-point MACE by Subgroup in Pooled DIA3008 and DIA4003 (ITT Analysis Set)



Source: ISE, Figure 14

Beta-Blocker Use at Baseline:

As shown in Figure 17, the HR for 3-point MACE for subjects using beta-blocker at baseline was 0.75 (95% CI: 0.64, 0.88) compared to 1.04 (95% CI: 0.85, 1.28) for subjects not using a beta-blocker at baseline. However, qualitative interaction using Gail-Simon test was not significant (p=0.3365).

Compared to subjects not on beta-blockers at baseline, subjects on beta-blockers at baseline had slightly higher proportion of subjects with age ≥65 years (47.3% versus 42.4%), more Whites (81.8% versus 74.3%), had prior CV disease (78.8% vs 50.5%) or atherosclerotic vascular disease history (84.7% vs 57.8%), had baseline eGFR <60 mL/min/1.72m^2 (23.5% vs 16.1%) and were more likely to be on a diuretic (50.6% vs 37%). Since subjects with age ≥65 years, Whites, prior CV disease, eGFR <60 mL/min/1.72m^2, and on diuretic at baseline were at a numerically lower risk for 3-point MACE with canagliflozin, lower proportion of subjects with these baseline characteristics among subjects not using beta-blocker may have contributed to the slightly elevated risk for MACE seen in this subgroup .

To assess whether there was a difference in relevant biomarkers for CV risk during study between those who were on and not on beta-blockers at baseline, changes in HbA1c, body weight, and blood pressure were compared between these groups. The LS mean changes in HbA1c from baseline to Week 52 in subjects using a beta-blocker at baseline was -0.6% compared to -0.65% in subjects not on beta-blockers at baseline. The LS mean changes in body weight from baseline to Week 52 in subjects using a beta-blocker and not using a beta-blocker at baseline was -2.51 kg in both groups. The placebo-subtracted LS mean changes in SBP/DBP from baseline to Week 52 were -5.02/-1.48 mmHg in subjects using a beta blocker and -3.76/-1.33 mmHg in subjects not using a beta-blocker at baseline. Although there was a numerically larger reduction in blood pressure from baseline in subjects using a beta-blocker compared to those who were not using a beta-blocker at baseline, this would be anticipated from the pharmacological effect of beta-blocker on blood pressure. There appear to be no difference in changes in HbA1c or body weight between these two groups.

Reviewer's comments: Overall, the changes from baseline to Week 52 in HbA1c and body weight were not meaningfully different between subjects who were on beta blocker and not on beta blocker. The statistical heterogeneity seen in this subgroup appear to be related to the imbalance in the distribution of baseline subject characteristics that may affect the CV risk.

Diuretic Use at Baseline:

As shown in Figure 17, the HR for 3-point MACE for subjects using diuretic at baseline was 0.66 (95% CI: 0.56, 0.79) compared to 1.11 (95% CI: 0.93, 1.34) for subjects not

using a diuretic at baseline, with interaction p-value of 0.0001. However, qualitative interaction using Gail-Simon test was not significant (p=0.1254).

Compared to subjects not on diuretics at baseline, subjects on diuretics at baseline had slightly higher proportion of subjects with age ≥65 years (49.3% versus 41.6%), more Whites (83.4% versus 74.3%), have baseline BMI ≥30 kg/m^2 (69% vs 51%), eGFR <60 mL/min/1.72m^2 (27.2% vs 14.4%) and were more likely to be using beta-blockers at baseline (61% vs 47%). Since subjects with age ≥65 years, Whites, baseline BMI ≥30 kg/m^2, eGFR <60 mL/min/1.72m^2, and on beta-blockers at baseline were at a numerically lower risk for 3-point MACE with canagliflozin, lower proportion of subjects with these baseline characteristics among subjects not using diuretics at baseline may have contributed to the higher risk for MACE seen in this subgroup.

To assess whether there was a difference in relevant biomarkers for CV risk during study between those who were on and not on diuretics at baseline, changes in HbA1c, body weight, and blood pressure were compared between these groups. The LS mean changes in HbA1c from baseline to Week 52 in subjects using a diuretic at baseline was -0.58% compared to -0.65% in subjects not on diuretics at baseline. The LS mean changes in body weight from baseline to Week 52 in subjects using a diuretic and not using a diuretic at baseline was -2.48 kg and -2.55 kg respectively. The placebo-subtracted LS mean changes in SBP/DBP from baseline to Week 52 were -4.33/-1.54 mmHg in subjects using a diuretic and -4.52/-1.31 mmHg in subjects not using a diuretic at baseline. There appear to be no difference in changes in HbA1c, body weight, or blood pressure between these two groups.

Reviewer's comments: Overall, the changes from baseline to Week 52 in HbA1c, body weight, and blood pressure were not meaningfully different between subjects who were on diuretic and not on diuretic at baseline. The statistical heterogeneity seen in these subgroups appear to be related to the imbalance in the distribution of baseline subject characteristics that may affect the CV risk. It is theoretically possible that concomitant use of canagliflozin with diuretics may have synergistic effect on cardiovascular outcomes, particularly in patients with heart failure, but it is difficult to assess whether this may have contributed to the lower CV risk in patients on diuretics.

Cardiovascular History:

As shown in Figure 17, in the pooled DIA3008 and DIA4003 dataset, the HR for 3-point MACE for subjects with history of CV disease was 0.82 (95% CI: 0.72, 0.95) compared to 0.98 (95% CI: 0.74, 1.30) for subjects without prior CV disease. Although the p-value for interaction was not statistically significant at 0.1803, this merits further discussion.

As discussed in section 5.3, both DIA3008 and DIA4003 enrolled adults with T2DM who either 1) have history of CV disease, or 2) without history of CV disease but at high risk

of CV disease. As discussed in section 6.1.2, about 65% of overall population in pooled DIA3008 and DIA4003 data had history of prior disease (Table 9). Based on the results of this meta-analysis of DIA3008 and DIA4003, the Applicant is currently proposing indication to reduce the risk of MACE in adults with T2DM with history of CV disease (b) (4)

About 59% of total subject in DIA3008 had prior CV disease and 71% of total subjects in DIA4003 had prior CV disease.

In DIA3008, the HR for 3-point MACE in subjects with history of CV disease was 0.83 (95% CI: 0.69, 0.99) compared to 1.06 (95% CI: 0.77, 1.47) in subjects without prior CV disease. Therefore, the subgroup analysis for MACE in DIA3008 showed similar finding as the subgroup analysis of pooled MACE data, as the point estimate for MACE was around 1 and the 95% CI for HR crossed 1 with the upper bound of 1.47 in subjects without prior CV disease.

In DIA4003, the HR for 3-point MACE for subjects with history of CV disease was 0.82 (95% CI: 0.66, 1.03) compared to 0.78 (95% CI: 0.44, 1.38) for subjects without prior CV disease. Although the HR for MACE in subjects without prior CV disease in DIA4003 was not similar to the pooled data or DIA3008 with HR of 0.78, the 95% CI was very wide (0.44, 1.38) and the upper bound of 95% CI was 1.38. The subgroup analysis for DIA4003 may not have sufficient power and not as reliable as only about 35% of overall MACE events occurred in DIA4003.

Reviewer's comment: The subgroup analysis in two different patient population enrolled in DIA3008 and DIA4003 (i.e., subjects with history of CV disease or without history of CV disease but at high risk) suggest that the CV benefit shown in meta-analysis may only be relevant for patients with prior history of CV disease.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There are no changes to the currently approved dosing recommendation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable to this efficacy supplement.

6.1.10 Additional Efficacy Issues/Analyses

Additional efficacy analyses were discussed at relevant sections above.

7 Review of Safety

Safety Summary

Since the overall safety of canagliflozin was established at the time of initial approval, safety review for this supplement mainly focused on re-evaluating some of the well-known adverse events that were of interest with canagliflozin as well as to determine new safety issues with longer duration of follow-up available from two large CV outcome studies, DIA3008 and DIA4003. It should be noted that the adverse events were streamlined after Amendment INT-6 (up to January 7, 2014) for DIA3008 and during the whole study for DIA4003, where except for certain adverse events of interest (see Section 7.3.5.1) only serious adverse events (SAE) and adverse events (AEs) leading to study drug discontinuation were collected.

The exposure-adjusted incidence rate of serious adverse events (SAE) and adverse events (AEs) leading to study drug discontinuation were similar between canagliflozin and treatment groups, and there did not appear to be clear preferred terms driving numerical differences in specific SAEs or AEs leading to study drug discontinuation in DIA3008, DIA4003, or in pooled dataset of these two studies.

An imbalance in the incidence of renal cell carcinoma not favoring canagliflozin compared to placebo was noted, and this imbalance was mostly due to cases from study DIA3008. This was not surprising given the latency associated with malignancies in general and DIA3008 had much longer duration of follow-up. The mean duration of exposure was 223 weeks in DIA3008 compared to 94 weeks in DIA4003. Thirteen subjects in the canagliflozin group compared to 2 subjects in the placebo group reported renal cell cancers in DIA3008, and one additional subject from canagliflozin group reported renal cell cancer from study DIA4003. Of these, one canagliflozin subject from DIA3008 and the only subject from DIA4003 reported renal cancer <180 days after study drug initiation, which is very unlikely to be due to study drug exposure. Most of the subjects had underlying risk factors for developing renal cell carcinoma such as hypertension, obesity, and smoking, and two subjects had pre-existing conditions related to renal cancer (one renal cyst and another had history of renal cancer; both received canagliflozin 100 mg). Because of small numbers of reported cases and confounding factors found in most of these renal cancer cases, it is difficult to determine whether these reported renal cancers are causality related to the canagliflozin treatment or whether this is a spurious finding.

Another notable finding during this safety review was that the increased risk for fractures noted in DIA3008 was not observed in DIA4003. The reason for this

discrepancy is unclear at this time, since both studies had same inclusion and exclusion criteria and as a result the patient population of these two studies was very similar in baseline characteristics. The different duration of follow-up between DIA3008 and DIA4003 would not explain the observed differences in fracture risk between these two studies as the increase in the risk of fractures with canagliflozin was observed at around 26 weeks in DIA3008.

7.1 Methods

The safety and tolerability of canagliflozin was evaluated by combining the safety data from two large CV studies, DIA3008 and DIA4003, through GTED.

In DIA3008, all adverse events (AEs) (serious and non-serious) were collected from the beginning of the study until Amendment INT-6 (up to January 7, 2014), after which the collection of certain AEs were streamlined. In DIA4003, certain AE collection was streamlined from the beginning of the study, since the study began after approval of canagliflozin, where the safety profile of canagliflozin was believed to have been well-established during the Phase 3 program. Streamlined collection meant only serious AEs or AEs that led to study drug discontinuation and/or affected the following AEs of interest: osmotic diuresis, volume depletion, hypoglycemia, urinary tract infection, female mycotic genital infection, severe hypersensitivity/cutaneous reactions, pancreatitis, hepatic injury, and renal-related adverse events (including nephrotoxicity/acute kidney injury).

The collection of following AEs of interest were not streamlined in either DIA3008 or DIA4003 throughout the study (i.e., all serious and non-serious events were collected): male mycotic genital infection (balanitis, phimosis, events leading to circumcision), malignancy (renal cell cancer, bladder cancer, pheochromocytoma, Leydig cell tumors, and breast cancer), photosensitivity, venous thromboembolic events, amputation, fracture, and diabetic ketoacidosis (DKA).

Unless otherwise specified, the majority of adverse events will be summarized using the On-Treatment Analysis Set (i.e., treatment-emergent). Treatment-emergent adverse events (TEAEs) are those that occur after initiation of double-blind study drug and before the last dose of study drug plus 30 days. Adverse events that began before starting the study drug and increased in intensity, or adverse events that are attributed to have a relationship with the study drug by the investigator (possible, probably, or very likely related) after initiation of study drug were also considered as TEAEs.

Since DIA3008 and DIA4003 have different duration of follow-up and different randomization ratios between active and placebo groups, safety data are summarized as annualized event rates for comparison rather than proportions of subjects. Therefore, incidence rates adjusted for exposure (i.e., adjusted-incidence rate) rather than incidence, are used for evaluation of AEs. The adjusted-incidence rate was

calculated as the total number of subjects with the AE divided by the follow-up time in subject-years.

The Applicant screened for potential imbalances in AEs, using a 95% CI for the adjusted-incidence rate difference (IRD) of canagliflozin minus placebo. Events were considered imbalanced if this 95% CI excluded 0, or if there were at least 4 reported events in a treatment group and the adjusted incidence rate was greater in the canagliflozin group. If there were 0 placebo events, AEs were further assessed when there were 4 or more events in at least one of the canagliflozin dose groups or the combined canagliflozin group.

Reviewer's comments: Given the thorough safety evaluation of canagliflozin during the original submission, the Applicant's method for identifying potential AEs for further evaluation was reasonable.

In both studies, safety events were monitored and adjudicated by the same adjudication committees, including:

- An independent Endpoint Adjudication Committee (EAC) reviewed blinded data for MACE, hospitalized congestive heart failure, venous thromboembolism/pulmonary embolism, and all deaths;
- And Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events and CV events at regular intervals;
- Separate adjudication committees reviewed cases of venous thromboembolic events (VTEs; only in DIA3008), diabetic ketoacidosis (DKA), fractures, and pancreatitis.

Cardiovascular safety was discussed in the efficacy section 6, as the main objective of these CV studies were to show that canagliflozin is not associated with an unacceptable increase in CV risk based on evaluation of MACE. Section 7 will discuss other adverse events, along with clinical laboratory test and vital sign findings from these CV studies.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of safety was mainly based on safety data from two CV studies, DIA3008 and DIA4003.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the time of database lock.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from DIA3008 and DIA4003 (i.e., CANVAS Program) were pooled for evaluation. Subjects treated with canagliflozin, regardless of dose, were pooled as the 'combined canagliflozin' group.

Adverse events of non-CANVAS studies were pooled similarly to the CANVAS Program to allow for an assessment of whether there is a meaningful difference in the safety profile seen in the CANVAS Program where patients with established CV disease and high risk CV patient population is enrolled compared to the safety profile seen in general diabetes population at lower CV risk (i.e., non-CANVAS). In addition, the duration of exposure to study drug is longer in the CANVAS Program (median of about 109 weeks; range 0.1 to 365 weeks) compared to non-CANVAS studies (median of about 51 weeks; range 0.1 to 109 weeks). Pooled data from non-CANVAS studies will be described when applicable during discussion of safety.

For certain less common AEs (diabetic ketoacidosis, pancreatitis, photosensitivity, bladder cancer, renal cancer), CANVAS and non-CANVAS studies will all be pooled and referred to as the pooled Phase 3/4 dataset.

See Table 32 for definitions of safety dataset including pooled datasets

Table 32: Safety Dataset Definitions including Pooled Datasets

Datasets	Definition
CANVAS Program	Pooled data from 2 studies, DIA3008 (CANVAS) and DIA4003 (CANVAS-R)
CANVAS INT-6	DIA3008 up to Amendment INT-6 (January 7, 2014)
Non-CANVAS studies	Pooled data from 12 non-CANVAS Phase 3 and Phase 4 studies: DIA3002, DIA3004, DIA3005, DIA3006, DIA3009, DIA3010, DIA3011, DIA3012, DIA3014, DIA3015, DIA4002, and DIA4004
All Cana Phase 3 and Phase 4 studies	Pooled data from all 14 Phase 3 and Phase 4 canagliflozin studies (i.e., CANVAS Program and 12 non-CANVAS studies)

Source: Clinical Overview, Table 3

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 10,142 subjects were randomized across two studies, DIA3008 and DIA4003, and 10,134 subjects comprise the On-Treatment and On-Study analysis sets for evaluation of safety.

In DIA3008, the overall mean duration of exposure to study drug was ~223 weeks, and was ~229 weeks for the combined canagliflozin group versus ~210 weeks for the placebo group. About 35% of subjects had ≥312 weeks (6 years) of exposure and the upper range of exposure was 365 weeks (~7 years). The total exposure to study drug was 12,678.8 subject years in the combined canagliflozin group and 5795.3 subject-years in the placebo group.

In DIA4003, the overall mean duration of exposure to study drug was ~94 weeks, and was ~95 weeks for the canagliflozin group versus ~93 weeks for the placebo group. About 6.7% of subjects had ≥130 weeks (2.5 years) and the upper range of exposure was 149 weeks. The total exposure to study drug was 5310.7 subject years in the canagliflozin group and 5199.9 subject years in the placebo group.

In the pooled dataset of DIA3008 and DIA4003 (CANVAS Program), the overall mean exposure to study drug was higher in the canagliflozin group (about 162 weeks) compared to placebo group (about 132 weeks). The total exposure to study drug was 17,989.5 subject-years in the combined canagliflozin group and 10,995.2 subject-years in the placebo group.

See Table 33 for summary of exposure for different safety datasets.

Table 33: Duration of Exposure to Study Drug in DIA3008, DIA4003 and Pooled Dataset

DIA3008	**Placebo**	**Cana 100**	**Cana 300**	**Cana Total**
N	1441	1445	1441	2886
Mean (SD)	209.9 (123.9)	229.8 (117.5)	228.7 (121.4)	229.2 (119.4)
Median	277.9	300.4	301.0	300.9
Range	0.1; 365	0.1; 365	0.1; 364	0.1; 365
Total exposure (patient years)	5795.3	6363.7	6315.1	12678.8
DIA4003	**Placebo**			**Cana**
N	2903			2904
Mean (SD)	93.5 (30.1)			95.4 (29.4)
Median	99.0			100.9
Range	0.1; 145			0.1; 149
Total exposure (patient years)	5199.9			5310.7
CANVAS Program	**Placebo**			**All Cana**
N	4344			5790
Mean (SD)	132.1 (93.3)			162.1
Median	104.1			115.6
Range	0.1; 365			0.1; 365
Total exposure (patient years)	10995.2			17898.5
Non-CANVAS Pooled	**Placebo**	**Cana 100**	**Cana 300**	**All Cana**
N	2826	2401	2887	5288
Mean (SD)	93.5 (30.1)	50.6 (32.9)	47.7 (30.7)	49.0 (31.7)
Median	51.4	51.9	51.1	51.4
Range	0.1; 107	0.1; 109	0.1; 108	0.1; 109
Total exposure (patient years)	2594.7	2328.2	2640.7	4968.8

Source: Clinical Overview, Tables 4, 5, 6, and 7

Reviewer's comment: Overall, the mean duration of exposure to study drug was much longer in DIA3008 compared to DIA4003. The longer mean duration of exposure in the canagliflozin group compared to the placebo in the pooled dataset is likely due to contribution from subjects in DIA3008 as there were two canagliflozin treatment arms in that study.

For the proportion of time on treatment compared to the extent of follow-up (total follow-up time includes both on-drug and off-drug), 79% of total patient-years of follow-up was on study drug, with 80% in the canagliflozin group and 78% in the placebo group. In DIA3008, subjects were on study drug about 72 to 77% of time, compared to about 87 to 88% of time that subjects were on study drug in DIA4003.

As discussed in Section 6.1.2, the baseline demographic characteristics were similar between treatment groups in the pooled dataset.

7.2.2 Explorations for Dose Response

Discussion of dose-response for MACE based on the results of DIA3008 are discussed in section 6.1.4. All doses of canagliflozin were pooled for the primary analysis of

safety, as DIA4003 had one treatment group for canagliflozin with dose titration based on glycemic response.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Both studies had routine testing at specified intervals to measure vital signs and laboratory tests and was appropriate for safety evaluation of canagliflozin.

7.2.5 Metabolic, Clearance, and Interaction Workup

None.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Safety of canagliflozin has already been thoroughly evaluated in the original submission and adverse reactions were also identified from the post-marketing experience. Adverse events of interest for SGLT2 inhibitors including canagliflozin were analyzed and described in Section 7.3.5.

7.3 Major Safety Results

7.3.1 Deaths

Deaths are discussed in Section 6. Causes of deaths were adjudicated in both studies, and CV deaths and all-cause mortality were part of efficacy endpoints.

7.3.2 Serious Adverse Events

In the pooled DIA3008 and DIA4003 dataset, the serious adverse events (SAEs) with incidence of ≥0.5% of subjects in any treatment group are listed in Table 34.

Table 34: Serious Adverse Events (N [%]) in At Least 0.5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)

System Organ Class or Preferred Term	Placebo (N=4344)	Cana (N=5790)
Subjects with SAEs	**1359 (31.3)**	**1921 (33.2)**
Cardiac disorders	**448 (10.3)**	**584 (10.1)**
Acute myocardial infarction	36 (0.8)	50 (0.9)
Angina pectoris	57 (1.3)	67 (1.2)
Angina unstable	62 (1.4)	94 (1.6)
Atrial fibrillation	44 (1.0)	53 (0.9)
Cardiac failure	60 (1.4)	61 (1.1)
Cardiac failure congestive	38 (0.9)	40 (0.7)
Coronary artery disease	53 (1.2)	81 (1.4)
Myocardial infarction	40 (0.9)	60 (1.0)
Eye disorders	**26 (0.6)**	**55 (0.9)**
Cataract	11 (0.3)	28 (0.5)
General disorders and administration site conditions	**111 (2.6)**	**165 (2.8)**
Chest pain	40 (0.9)	61 (1.1)
Infections and infestations	**291 (6.7)**	**445 (7.7)**
Cellulitis	30 (0.7)	39 (0.7)
Osteomyelitis	12 (0.3)	29 (0.5)
Pneumonia	67 (1.5)	83 (1.4)
Urinary tract infection	29 (0.7)	32 (0.6)
Metabolism and nutrition disorders	**124 (2.9)**	**124 (2.1)**
Diabetes mellitus	28 (0.6)	17 (0.3)
Hypoglycemia	17 (0.4)	30 (0.5)
Musculoskeletal and connective tissue disorder	**128 (2.9)**	**192 (3.3)**
Osteoarthritis	43 (1.0)	66 (1.1)
Nervous system disorders	**173 (4.0)**	**265 (4.6)**
Cerebrovascular accident	47 (1.1)	41 (0.7)
Transient ischemic attack	25 (0.6)	31 (0.5)
Renal and urinary disorders	**68 (1.6)**	**104 (1.8)**
Acute kidney injury	28 (0.6)	30 (0.5)
Reproductive system and breast disorders	**16 (0.4)**	**59 (1.0)**
Benign prostatic hyperplasia	6 (0.1)	27 (0.5)
Skin and subcutaneous tissue disorders	**28 (0.6)**	**77 (1.3)**
Diabetic foot	13 (0.3)	29 (0.5)
Skin ulcer	7 (0.2)	31 (0.5)
Vascular disorders	**121 (2.8)**	**187 (3.2)**
Peripheral arterial occlusive disease	13 (0.3)	32 (0.6)
Peripheral vascular disorder	11 (0.3)	27 (0.5)

Source: ISS, TSFSAE01C

The following are SAEs that were not part of adverse events of interest (AEs of interest are described in section 7.3.5) and were identified by screening as described in Section 7.1 Methods (i.e., if the 95% CI of the incidence rate difference between placebo and canagliflozin group exclude 0, or if there were no subjects with events in the placebo group and 4 or more subjects with events in the canagliflozin group):

- SAE meeting criteria where 0 placebo events and ≥4 canagliflozin events:
  - Adenocarcinoma gastric
  - Craniocerebral injury
  - Neuralgia
  - Prostatomegaly
  - Small intestinal obstruction
  - Soft tissue infection
  - Staphylococcal sepsis
  - Urethral stenosis
- SAE meeting criteria where 95 % CI excluded 0 and ≥4 canagliflozin events:
  - Benign prostatic hyperplasia
  - Gangrene
  - Influenza
  - Skin ulcer

These events are briefly summarized here:

Adenocarcinoma gastric (5 canagliflozin vs 0 placebo): Four subjects were from DIA3008 and 1 from DIA4003. One was fatal event. None led to study discontinuation and none were considered related to the study drug. In the CANVAS Program, there were no imbalances in other events of gastric malignancies such as gastric cancer (5 canagliflozin vs 3 placebo) or gastric adenoma (0 canagliflozin vs 1 placebo). No other cases reported in the non-CANVAS pooled studies.

Craniocerebral injury (6 canagliflozin vs 0 placebo): Three were fatal, and all three fatal cases were associated with motor vehicle accidents. The other 3 involved falls, 2 of which were on stairs (in one case there was no precipitating event before the fall, in the other the subject tripped) and the final case felt dizziness and weakness and fell and hit her head, and this final case was adjudicated as an ischemic stroke.

Neuralgia (5 canagliflozin vs 0 placebo): In the AEs in DIA3008 through INT-6, events of neuralgia was balanced between treatment groups (2.49 vs 2.22/1000 PY in canagliflozin vs placebo groups). No SAEs of neuralgia was reported in non-CANVAS pooled dataset.

Small intestinal obstruction (7 canagliflozin vs 0 placebo): Five were reported from DIA3008 and 2 from DIA4003. Three SAEs were considered to be associated with sequelae from prior surgeries, another was considered to be possibly related to food, and another had a prior history of small intestinal obstruction. None appeared to be related to constipation. In the AEs in DIA3008 through INT-6, the overall number of reported events for small intestinal obstruction were infrequent (1 subject each in canagliflozin 100 mg and 300 mg versus none in placebo). In the non-CANVAS pooled

dataset, there were no imbalances between canagliflozin and non-canagliflozin groups for small intestinal obstruction.

Soft tissue infection (3 canagliflozin vs 0 placebo): In the pooled non-CANVAS studies, soft tissue infection occurred at similar rates between placebo (0.36/1000 PY) and combined canagliflozin (0.19/1000 PY) group.

Staphylococcal sepsis (5 canagliflozin vs 0 placebo): In the AEs in DIA3008 through INT-6, 4 subjects in the canagliflozin versus none in placebo reported staphylococcal sepsis. Concurrent illnesses included preceding or concurrent infection (osteomyelitis of right great toe, pneumonia, erysipelas) in 3 cases, and in 2 cases subjects were hospitalized for other conditions (hepatic cirrhosis, renal failure and cardiac decompensation). In one fatal case, no concurrent AE was reported and the source of infection was never identified. In the pooled non-CANVAS studies, there were no events of staphylococcal sepsis.

Urethral stenosis (6 canagliflozin vs 0 placebo): Five subjects were from DIA3008 and 1 from DIA4003. One female subject had a history of UTI. Of 4 male subjects, one has a history of BPH and balanoposthitis, one had a history of UTI and balanoposthitits, another had a history of BPH, and another had a history of prostate adenoma. In DIA3008 through INT-6, urethral stenosis was infrequent with 1 subject on canagliflozin 100 mg and 2 subjects on canagliflozin 300 mg versus none with placebo.

Influenza (10 canagliflozin vs 1 placebo): In DIA3008 through INT-6, influenza occurred at similar rates between treatment groups (21.84/1000 PY in placebo, 23.09/1000 PY in canagliflozin 100 mg, and 19.22/1000 PY in canagliflozin 300 mg). In the pooled non-CANVAS studies, no SAE of influenza was reported and the incidence of influenza was similar between treatment groups (34.89/1000 PY in placebo, 38.98/1000 PY in canagliflozin 100 mg, and 37.76/1000 PY in canagliflozin 300 mg).

Reviewer's comments: These events that showed an imbalance in SAEs because of ≥4 events with canagliflozin compared to none with placebo do not appear to be a new safety concern with canagliflozin treatment.

Gangrene and skin ulcer are discussed further in section 7.3.4, Significant Adverse Events.

7.3.3 Dropouts and/or Discontinuations

The common AEs (occurring in at least 0.2% subjects in any treatment group) that led to study drug discontinuations are summarized by Preferred Terms in Table 35.

Table 35: Adverse Events Leading to Study Drug Discontinuations in At Least 0.2% of Subjects in Any Treatment Group in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)

System Organ Class or Preferred Term	Placebo (N=4344)	Cana (N=5790)
Subjects with AEs	**371 (8.5)**	**654 (11.3)**
Cardiac disorders	**40 (0.9)**	**61 (1.1)**
Cardiac failure	10 (0.2)	11 (0.2)
Myocardial infarction	2 (<0.1)	15 (0.3)
Gastrointestinal disorders	**44 (1.0)**	**51 (0.9)**
Diarrhea	9 (0.2)	9 (0.2)
General disorders and administration site conditions	**27 (0.6)**	**44 (0.8)**
Death	3 (0.1)	11 (0.2)
Sudden death	8 (0.2)	7 (0.1)
Infections and infestations	**47 (1.1)**	**135 (2.3)**
General infection fungal	3 (0.1)	14 (0.2)
Pneumonia	6 (0.1)	12 (0.2)
Urinary tract infection	5 (0.1)	26 (0.4)
Vulvovaginal candidiasis	3 (0.1)	10 (0.2)
Vulvovaginal mycotic infection	2 (<0.1)	13 (0.2)
Investigations	**18 (0.4)**	**41 (0.7)**
Blood creatinine increased	5 (0.1)	9 (0.2)
Neoplasms benign, malignant and unspecified	**67 (1.5)**	**77 (1.3)**
Lung neoplasm malignant	8 (0.2)	4 (0.1)
Pancreatic carcinoma	7 (0.2)	1 (<0.1)
Nervous system disorders	**36 (0.8)**	**46 (0.8)**
Cerebrovascular accident	10 (0.2)	9 (0.2)
Renal and urinary disorders	**32 (0.7)**	**52 (0.9)**
Renal impairment	7 (0.2)	14 (0.2)
Reproductive system and breast disorders	**10 (0.2)**	**50 (0.9)**
Balanoposthitis	5 (0.1)	41 (0.7)

Source: ISS, TSFSAE06C

The following are AEs that led to study drug discontinuation that were not part of adverse events of interest (AEs of interest are described in section 7.3.5) and were identified by screening (as described in Section 7.1, Methods):

- Meeting criteria where 0 placebo events and ≥4 canagliflozin events:
  - Alanine aminotransferase increased
  - Cardiac arrest
  - Dyspnea
- SAE meeting criteria where 95 % CI excluded 0 and ≥4 canagliflozin events:
  - Myocardial infarction

AEs with Preferred Terms ‘cardiac arrest’ and ‘myocardial infarction’ are adjudicated for MACE endpoints and will not be discussed further. The other events are briefly summarized here:

Alanine aminotransferase increased (5 canagliflozin vs 0 placebo): No imbalance in the incidence rate for any AEs of increased alanine aminotransferase was seen between treatment groups in DIA3008 INT-6 dataset (5.81 and 2.87/1000 PY in placebo and combined canagliflozin) or in the pooled non-CANVAS studies (6.41 and 5.39/1000 PY in all non-cana vs all cana).

Dyspnea (4 canagliflozin vs 0 placebo): One subjects was from DIA3008 and 3 subjects were from DIA4003. Two events were also SAEs. In the CANVAS Program, the incidence of SAEs of dyspnea was same between treatment groups (1.41/1000 PY in both placebo and canagliflozin groups). In non-CANVAS studies, there were no events of dyspnea leading to study drug discontinuation, and the overall incidence of all dyspnea was similar between treatment groups (5.70 and 4.46/1000 PY in all non-cana and all cana).

Reviewer's comments: These events that showed an imbalance in study drug discontinuation because of ≥4 events with canagliflozin compared to none with placebo do not appear to be a new safety concern with canagliflozin.

7.3.4 Significant Adverse Events

Table 36 lists AEs by Preferred Terms (for DIA3008 INT-6 for events that were streamlined or in the pooled DIA3008 and DIA4003 dataset for events that were not streamlined) that were identified by comparing the incidence between treatment groups, using the screening method described in Section 7.1 Methods (i.e., if the 95% CI of the incidence rate difference between placebo and canagliflozin group exclude 0, or if there were no subjects with events in the placebo group and 4 or more subjects with events in the canagliflozin group).

Table 36: Adverse Events Meeting Screening Criteria in Pooled DIA3008 and DIA4003

Preferred Term	Preferred Term	Preferred Term
Criteria Met: 0 placebo; ≥4 canagliflozin		
Abscess	Nail disorder	Staphylococcal sepsis
Acarodermatitis	Oesophageal candidiasis	Throat irritation
Appendicitis	Pertussis	Thyroid adenoma
Ataxia	Post procedural complication	Tracheobronchitis
Biliary dyskinesia	Postoperative wound complication	Ulcerative keratitis
Burns second degree	Renal function test abnormal	Upper-airway cough syndrome
Cataract nuclear	Rosacea	Urge incontinence
Chills	Skin cancer	Vitreous haemorrhage
Colon cancer metastatic	Skin candida	Vulvovaginal pruritus
Decubitus ulcer	Soft tissue infection	Wheezing
Delirium	Hepatic cancer	
Dental discomfort	Hunger	
Diabetic foot infection	Hydronephrosis	
Diastolic dysfunction	Incontinence	
Ear discomfort	Lacunar infarction	
Electrocardiogram T wave inversion	Limb discomfort	
Eyelid Ptosis	Limb traumatic amputation	
Fluid retention	Malignant melanoma in situ	
Gastrointestinal disorder	Metrorrhagia	
Haemorrhagic anaemia	Musculoskeletal discomfort	
Criteria Met: 95% CI excluded 0 and ≥4 canagliflozin		
Dizziness	Hyperlipidaemia	Rectal haemorrhage
Dysuria	Non-cardiac chest pain	Skin lesion
Gangrene	Peripheral artery occlusion	Skin ulcer
		Urinary incontinence

Source: ISS, Table 18

Based on review of the number of events and characteristics of AEs in Table 36 as presented by the Applicant in Attachment SCREEN_AES of ISS, most appeared to be not causality associated with canagliflozin treatment. I will briefly describe gangrene, peripheral artery occlusion and skin ulcer, as these could be related to amputation. I will also discuss data about Fournier's gangrene, which is a safety issue that Division of Pharmacovigilance recently identified with canagliflozin during their surveillance of post-marketing reports.

Gangrene:

In the DIA3008 INT-6 dataset, gangrene occurred at higher incidence in the canagliflozin 100 mg (14/1445 subjects, 1.0%; 3.63/1000 PY) compared to placebo (3/1441 subjects, 0.2%; 0.83/1000 PY) or canagliflozin 300 mg (3/1441 subjects, 0.2%; 0.79/1000 PY) group, with the 95% CI for the IRD excluding 0 (Table 37).

In the pooled DIA3008 and DIA4003 dataset, the incidence of SAE of gangrene was higher in the combined canagliflozin compared to placebo, 1.41 versus 0.53/1000 PY (26 vs 6 subjects) respectively. This is mostly due to DIA3008 data.

As discussed in section 7.3.5.1, gangrene is one of the most common events that led to amputation with canagliflozin.

Table 37: Summary of Gangrene AEs with Canagliflozin

	Gangrene			
Any Adverse Event through INT-6	Placebo (N=1441)	Cana 100 mg (N=1445)	Cana 300 mg (N=1441)	All Cana (N=2886)
n(%)	3(0.2)	14(1.0)	3(0.2)	17(0.6)
IR (/1000 subject-years)	0.83	3.63	0.79	2.22
IRD (/1000 subject-years) (95% CI) (minus placebo)		2.80 (0.52, 5.08)	-0.04 (-1.63, 1.55)	1.39 (-0.19, 2.97)
Serious adverse events – Integrated	Placebo (N=4344)			All Cana (N=5790)
n(%)	6(0.1)			26(0.4)
IR (/1000 subject-years)	0.53			1.41
IRD (/1000 subject-years) (95% CI) (minus placebo)				0.88 (0.16, 1.60)
Adverse events leading study drug discontinuation – Integrated	Placebo (N=4344)			All Cana (N=5790)
IR (/1000 subject-years)	0			0.16
IRD (/1000 subject-years) (95% CI) (minus placebo)				0.16
Non-CANVAS Any Adverse Event	All Non-Cana (N=2826)	Cana 100 mg (N=2401)	Cana 300 mg (N=2887)	All Cana (N=5288)
IR (/1000 subject-years)	0.36	0.00	0.00	0.00
IRD (95% CI) (minus all non-cana)		-0.36	-0.36	-0.36
Non-CANVAS serious adverse event	All Non-Cana (N=2826)	Cana 100 mg (N=2401)	Cana 300 mg (N=2887)	All Cana (N=5288)
IR (/1000 subject-years)	0.36	0	0	0
IRD (95% CI) (minus all non-cana)		-0.36	-0.36	-0.36
Non-CANVAS adverse events leading study drug discontinuation	All Non-Cana (N=2826)	Cana 100 mg (N=2401)	Cana 300 mg (N=2887)	All Cana (N=5288)
IR (/1000 subject-years)	0	0	0	0
IRD (95% CI) (minus all non-cana)		0	0	0

Key: cana=canagliflozin, CI=confidence interval, IR=incidence rate, IRD=incidence rate difference
Note: Percentages calculated with the number of subjects in each group as the denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Source: ISS, Table 68

Reviewer's comments: Gangrene is listed in the labeling as one of the common precipitating medical events leading to the need for an amputation.

Fournier's Gangrene:

The Division of Pharmacovigilance identified Fournier's gangrene as a potential safety issue during their review of postmarketing cases, and on October 10, 2017, FDA issued a Tracked Safety Issue for all the SGLT2 inhibitors including products containing canagliflozin regarding Fournier's gangrene. The safety data in this submission was reviewed for potential imbalance in Fournier's gangrene with canagliflozin therapy.

I used the ADAE dataset to identify cases that reported the 'Fournier's gangrene' at Lower Level Term, or the following Preferred Terms: Necrotising fasciitis, Necrotising fasciitis fungal, Necrotising fasciitis staphylococcal, Necrotising fasciitis streptococcal, Necrotising soft tissue infection, Fasciitis, Fascial infection, Perineal abscess, Perineal cellulitis, Perineal necrosis, Perineal infection, Perineal operation, Scrotal abscess, Scrotal gangrene, Vulval abscess, Vulval cellulitis. I also text searched for "Fournier" to identify further cases that may have been miscoded (none were identified).

In DIA3008, a total of 14 subjects were identified by above search criteria, 7 subjects (0.6%) with placebo, 3 subjects (0.2%) with canagliflozin 100 mg, and 4 subjects (0.3%) with canagliflozin 300 mg. See

Table 38.

Seven of 14 AEs had serious outcome. All necrotizing fasciitis and perineal abscess events, and one vulval abscess were SAEs. The majority of necrotizing fasciitis occurred in the placebo group.

Table 38: DIA3008 – Fournier's Gangrene (On-Treatment Analysis Set)

Preferred Term	Placebo (N=1441)	Cana 100 (N=1445)	Cana 300 (N=1441)	Total
Subjects with AE, N (%)	7 (0.5%)	3 (0.2%)	4 (0.3%)	14
Necrotizing fasciitis	3*	1	1	5
Scrotal abscess	2	2	1	5
Vulval abscess	1	0	1	2
Perineal abscess	1*	0	1	2
Scrotal infection	1	0	0	1

Note: One subject in the placebo group had both necrotizing fasciitis and perineal abscess.
Source: Reviewer generated from ADAE

In DIA4003, 1 subject in the canagliflozin group reported 'scrotal abscess' (subject 300926) and 1 subject in the placebo group reported 'left perineal abscess' (subject 300546). Both were SAEs.

Reviewer's comment: There was no imbalance between treatment groups in the incidence of Fournier's gangrene in DIA3008 and DIA4003 studies.

Peripheral Artery Occlusion:

In the DIA3008 INT-6 dataset, peripheral artery occlusion occurred at higher incidence in the canagliflozin 100 mg (10/1445 subjects, 0.7%; 2.59/1000 PY) compared to placebo (1/1441 subjects, 0.1%; 0.28/1000 PY) or canagliflozin 300 mg (1/1441

subjects, 0.1%; 0.26/1000 PY) group, with the 95% CI for the IRD excluding 0 (Table 39).

In DIA3008, the incidence of SAE for peripheral artery occlusion was higher with canagliflozin 100 mg (7/1445; 1.08/1000 PY) compared to where only 1 subjects in both placebo and canagliflozin 300 mg group having an SAE of peripheral artery occlusion.

In DIA4003, 3 subjects in the canagliflozin group compared to one subject in the placebo group experienced peripheral artery occlusion.

Table 39: Summary of Peripheral Artery Occlusion AEs with Canagliflozin

	Peripheral Artery Occlusion			
Any Adverse Event through INT-6	**Placebo (N=1441)**	**Cana 100mg (N=1445)**	**Cana 300mg (N=1441)**	**All Cana (N=2886)**
n(%)	1(0.1)	10(0.7)	1(0.1)	11(0.4)
IR (/1,000 subject-years)	0.28	2.59	0.26	1.44
IRD (/1,000 subject-years) (95% CI) (minus placebo)		2.31 (0.45, 4.17)	-0.02 (-1.08, 1.04)	1.16 (-0.02, 2.34)
Serious adverse events – Integrated	**Placebo (N=4344)**			**All Cana (N=5790)**
IR (/1,000 subject-years)	0.18			0.65
IRD (95% CI) (minus placebo)				0.47 (-0.05, 0.99)
Adverse events leading study drug discontinuation – Integrated	**Placebo (N=4344)**			**All Cana (N=5790)**
IR (/1000 subject-years)	0			0
IRD (95% CI) (minus placebo)				0
Non-CANVAS Any Adverse Event	**All Non-Cana (N=2826)**	**Cana 100mg (N=2401)**	**Cana 300mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0.36	0.00	0.00	0.00
IRD (95% CI) (minus all non-cana)		-0.36	-0.36	-0.36
Non-CANVAS serious adverse events	**All Non-Cana (N=2826)**	**Cana 100mg (N=2401)**	**Cana 300mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0	0	0	0
IRD (95% CI) (minus all non-cana)		0	0	0
Non-CANVAS adverse events leading study drug discontinuation	**All Non-Cana (N=2826)**	**Cana 100mg (N=2401)**	**Cana 300mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0	0	0	0
IRD (95% CI) (minus all non-cana)		0	0	0

Key: cana=canagliflozin, CI=confidence interval, IR=incidence rate, IRD=incidence rate difference
Note: Percentages calculated with the number of subjects in each group as the denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Source: ISS, Table 69

Reviewer's comment: The imbalance in the incidence of 'peripheral artery occlusion' was only seen in the canagliflozin 100 mg dose group in DIA3008, and the overall number of SAEs was small in both DIA3008 and DIA4003 where patients with peripheral vascular disease were enrolled. There were no cases with canagliflozin in non-CANVAS studies.

Skin Ulcer:

In the DIA3008 INT-6 dataset, there was a slightly higher incidence of skin ulcer in both canagliflozin treatment compared to the placebo, as shown in Table 40. About 90% of these skin ulcers occurred in the lower extremity.

In DIA3008, more SAEs of skin ulcer occurred with canagliflozin 100 mg (10/1445 [1%)]) and canagliflozin 300 mg (14/1441 [1%]) compared to placebo (2/1441 [0.1%]). In DIA4003, the incidence of SAEs were balanced between treatment groups (7/2904 [0.2%] with canagliflozin and 5/2903 [0.2%] with placebo).

Table 40: Summary of Skin Ulcer with Canagliflozin

	Skin Ulcer			
Any Adverse Event through INT-6	**Placebo (N=1441)**	**Cana 100 mg (N=1445)**	**Cana 300 mg (N=1441)**	**All Cana (N=2886)**
n(%)	24(1.7)	38(2.6)	48(3.3)	86(3.0)
IR (/1,000 subject-years)	6.64	9.86	12.64	11.24
IRD (/1,000 subject-years) (95% CI) (minus placebo)		3.22 (-0.96, 7.40)	6.00 (1.48, 10.52)	4.60 (0.98, 8.22)
Serious adverse events – Integrated	**Placebo (N=4344)**			**All Cana (N=5790)**
IR (/1,000 subject-years)	0.62			1.68
IRD (/1,000 subject-years) (95% CI) (minus placebo)				1.06 (0.28, 1.84)
Adverse events leading study drug discontinuation – Integrated	**Placebo (N=4344)**			**All Cana (N=5790)**
IR (/1,000 subject-years)	0.35			0.22
IRD (/1,000 subject-years) (95% CI) (minus placebo)				-0.13 (-0.60, 0.34)
Non-CANVAS Any Adverse Event	**All Non-Cana (N=2826)**	**Cana 100 mg (N=2401)**	**Cana 300 mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	4.63	3.58	3.49	3.53
IRD (95% CI) (minus all non-cana)		-1.05 (-4.66, 2.56)	-1.14 (-4.61, 2.33)	-1.10 (-4.19, 1.99)
Non-CANVAS serious adverse events	**All Non-Cana (N=2826)**	**Cana 100 mg (N=2401)**	**Cana 300 mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0.36	0	0.35	0.19
IRD (95% CI) (minus all non-cana)		-0.36	-0.01 (-1.76, 1.74)	-0.17 (-1.43, 1.09)
Non-CANVAS adverse events leading study drug discontinuation	**All Non-Cana (N=2826)**	**Cana 100 mg (N=2401)**	**Cana 300 mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0.36	0	0	0
IRD (95% CI) (minus all non-cana)		-0.36	-0.36	-0.36

Source: ISS, Table 70

As discussed in section 7.3.5.1, skin ulcer was part of broader groupings of skin and subcutaneous tissue ulcerations as a possible etiology for amputation in 'ulcer groupings' (Table 52) and there did not seem to be an imbalance between treatment groups as one of the possible preceding events for amputation.

Vitreous Hemorrhage:

In DIA3008 through IND-6, vitreous hemorrhage was reported in 4 subjects (0.3%; 1.04/1000 PY) in canagliflozin 100 mg, 7 subjects (0.5%; 1.84/1000 PY) in canagliflozin 300 mg group versus none in placebo (Table 41). In DIA3008, two subjects in canagliflozin 100 mg and 1 subject in canagliflozin 300 mg reported SAEs of vitreous hemorrhage, and none led to study discontinuation. No cases of vitreous hemorrhage were reported in DIA4003.

In the non-CANVAS pooled dataset, the incidence of vitreous hemorrhage was low and similar between non-canagliflozin and canagliflozin groups, and the overall incidence was much lower in comparison to DIA3008. See Table 41 for a summary of vitreous hemorrhage in different pool of studies.

Table 41: Summary of Vitreous Hemorrhage Adverse Events

	Vitreous Haemorrhage			
Any Adverse Events through INT-6	**Placebo (N=1441)**	**Cana 100 mg (N=1445)**	**Cana 300 mg (N=1441)**	**All Cana (N=2886)**
n(%)	0	4(0.3)	7(0.5)	11(0.4)
IR (/1,000 subject-years)	0	1.04	1.84	1.44
IRD (/1,000 subject-years) (95% CI) (minus placebo)		1.04	1.84	1.44
Serious adverse events – Integrated	**Placebo (N=4344)**			**All Cana (N=5790)**
IR (/1,000 subject-years)	0			0.16
IRD (/1,000 subject-years) (95% CI) (minus placebo)				0.16
Adverse events leading study drug discontinuation - Integrated	**Placebo (N=4344)**			**All Cana (N=5790)**
IR (/1,000 subject-years)	0	0	0	0
IRD (/1,000 subject-years) (95% CI) (minus placebo)		0	0	0
Non-CANVAS Any Adverse Event	**All Non-Cana (N=2826)**	**Cana 100 mg (N=2401)**	**Cana 300 mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0.36	0.00	0.35	0.19
IRD (95% CI) (minus all non-cana)		-0.36	-0.01 (-1.76, 1.74)	-0.17 (-1.43, 1.09)
Non-CANVAS serious adverse events	**All Non-Cana (N=2826)**	**Cana 100 mg (N=2401)**	**Cana 300 mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0.36	0	0	0
IRD (95% CI) (minus all non-cana)		-0.36	-0.36	-0.36
Non-CANVAS adverse events leading study drug discontinuation	**All Non-Cana (N=2826)**	**Cana 100 mg (N=2401)**	**Cana 300 mg (N=2887)**	**All Cana (N=5288)**
IR (/1,000 subject-years)	0	0	0	0
IRD (95% CI) (minus all non-cana)		0	0	0

Integrated=pool of DIA3008 and DIA4003 studies.
Source: ISS, Table 72

The Applicant summarized the change in HbA1c from baseline to Week 18 as well as to the HbA1c nearest to the event onset, which are listed in Table 42. The median day of onset was 392 days (range 86 to 1104 days). There was no particular pattern in the change in HbA1c from baseline to nearest the event onset; HbA1c reduction ranged from 0.2 to 1.6%.

Table 42: Change in HbA1c from Baseline to Week 18 and Closest Visit to Onset of Vitreous Hemorrhage Onset in DIA3008 INT-6

		Week 18		Closest HbA_{1c}		Vitreous Hemorrhage Adverse Event	
Subject	Baseline HbA_{1c} (%)	Study Day of Week 18 Visit	HbA_{1c} (%)	Study Day of Visit Closest to Adverse Event Onset	HbA_{1c} (%)	Adverse Event Onset Day	Change from Baseline to Closest HbA_{1c}
802009	9.3	129	8.9	351	8.5	319	-0.8
802340	8	126	6.8	1092	7.6	1025	-0.4
802921	8.7	127	8.4	85	7.9	86	-0.8
803264	8.5	131	8.1	909	7.4	892	-1.1
803458	10.8	127	8.6	911	6.8	853	-4
803886	8.6	108	8.2	366	7	356	-1.6
804982	8.5	135	7.6	275	7.5	268	-1
805144	8.9	125	8.1	1079	8.3	1104	-0.6
805169	8	127	6.3	377	7	392	-1
805238	8.5	127	7.2	372	8.3	461	-0.2
805817	7.2	127	7	85	6.8	92	-0.4

Source: ISS, Table 73

In order to further assess vitreous hemorrhage, DIA3008 through INT-6 were evaluated by group of related PTs such as eye hemorrhage, retinal hemorrhage, and hemorrhagic retinopathy. In this PT grouping, the adjusted-incidence rate was similar between treatment groups. The adjusted-incidence rate for this grouping of terms were also similar in the non-CANVAS studies. See Table 43.

Table 43: Grouping of Vitreous Hemorrhage Adverse Events for DIA3008 INT-6 Through January 7, 2014

Eye Hemorrhage Grouping			
DIA3008 INT-6	**Placebo (N=1441)**	**Cana 100 (N=1445)**	**Cana 300 (N=1441)**
Subjects with AEs	12 (0.8)	11 (0.8)	13 (0.9)
Incidence rate per 1000 person-years	3.32	2.85	3.42
Eye hemorrhage	7 (0.5)	5 (0.3)	2 (0.1)
Retinal hemorrhage	5 (0.3)	2 (0.1)	4 (0.3)
Retinopathy hemorrhage	2 (0.1)	0	0
Vitreous hemorrhage	0	4 (0.3)	7 (0.5)
Non-CANVAS	**All non-Cana (N=2826)**	**Cana Total (N=5288)**	
Incidence rate per 1000 person-years	0.36	0.37	

Source: ISS, Table 74, Table 75

Since vitreous hemorrhage can be manifestation of diabetic retinopathy and as the imbalance in vitreous hemorrhage was only observed in DIA3008, I looked at all the reported AEs in Eye Disorders System Organ Class that may be indicative of worsening in diabetic retinopathy, see the selected listing in Table 44.

Although the number of reported events for certain AE terms indicative of proliferative retinopathy was sometimes higher in the canagliflozin group, it does not appear to consistently show the imbalance not favoring canagliflozin. For example, whereas 3 subjects with canagliflozin 300 mg versus none in the other treatment groups reported ‘retinopathy proliferative’, other AE terms such as ‘retinal detachment’ occurred more often in the placebo group (6 events [0.4%]) compared to the canagliflozin groups (2 events [0.1%] each in canagliflozin 100 mg and 300 mg groups). The highest reported PTs were ‘cataract’ and ‘diabetic retinopathy’, and there was no notable difference in the incidence for these events between treatment groups.

Table 44: Selected Eye Events in DIA3008 through January 7, 2014 (DIA3008 INT-6)

Preferred Terms	Placebo (N=1441)	Cana 100 (N=1445)	Cana 300 (N=1441)
Eye Disorders System Organ Class	**177 (12.3)**	**194 (13.4)**	**219 (15.2)**
Arteriosclerotic retinopathy	2 (0.1)	0	1 (0.1)
Blindness unilateral	0	2 (0.1)	0
Cataract	65 (4.5)	77 (5.3)	80 (5.6)
Cataract nuclear	0	2 (0.1)	2 (0.1)
Cataract subcapsular	3 (0.2)	0	1 (0.1)
Chorioretinopathy	1 (0.1)	0	0
Conjunctival hemorrhage	3 (0.2)	2 (0.1)	2 (0.1)
Conjunctival edema	0	1 (0.1)	0
Cystoid macular edema	0	0	2 (0.1)
Diabetic eye disease	1 (0.1)	0	2 (0.1)
Diabetic retinal edema	1 (0.1)	4 (0.3)	2 (0.1)
Diabetic retinopathy	36 (2.5)	40 (2.8)	39 (2.7)
Eye hemorrhage	7 (0.5)	5 (0.3)	2 (0.1)
Eye inflammation	2 (0.1)	1 (0.1)	0
Eye edema	0	1 (0.1)	0
Macular degeneration	4 (0.3)	3 (0.2)	1 (0.1)
Macular fibrosis	2 (0.1)	1 (0.1)	3 (0.2)
Macular hole	0	1 (<0.1)	1 (0.1)
Maculopathy	1 (0.1)	4 (0.3)	3 (0.2)
Optic ischemic neuropathy	2 (0.1)	0	0
Retinal artery occlusion	1 (0.1)	0	0
Retinal detachment	6 (0.4)	2 (0.1)	2 (0.1)
Retinal disorder	2 (0.1)	1 (0.1)	1 (0.1)
Retinal hemorrhage	5 (0.3)	2 (0.1)	4 (0.3)
Retinal tear	1 (0.1)	1 (0.1)	0
Retinal vascular disorder	0	0	2 (0.1)
Retinal vascular thrombosis	0	0	1 (0.1)
Retinopathy	2 (0.1)	7 (0.5)	7 (0.5)
Retinopathy hemorrhage	2 (0.1)	0	0
Retinopathy hypertensive	3 (0.2)	0	3 (0.2)
Retinopathy proliferative	0	0	3 (0.2)
Ulcerative keratitis	0	0	4 (0.3)
Visual impairment	7 (0.5)	5 (0.3)	6 (0.4)
Vitreous degeneration	0	1 (0.1)	0
Vitreous detachment	1 (0.1)	2 (0.1)	2 (0.1)
Vitreous floaters	4 (0.3)	1 (0.1)	4 (0.3)
Vitreous hemorrhage	0	4 (0.3)	7 (0.5)
Vitreous loss	0	0	1 (0.1)

Source: DIA3008 CSR, abstracted from TSFAE01_S1

Reviewer's comments: Vitreous hemorrhage was only reported with canagliflozin compared to none with placebo, which is a concern given that this may suggest events related to diabetic retinopathy. However, the overall number of events was small and grouping with other related events did not appear to suggest a

concern for canagliflozin. The overall review of reported events related to eye disease do not appear to suggest a concern for possible worsening of diabetic retinopathy with canagliflozin at this time.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Adverse Events of Interest Collected Regardless of Seriousness or Study Drug Discontinuation

This section will discuss the following adverse events of interest that were collected throughout both DIA3008 and DIA4003 regardless of seriousness or study drug discontinuation and where a predefined MedDRA terms were used to identify these AEs: male genital infections, selected malignancies (i.e., breast cancer, bladder cancer, renal cell carcinoma, Leydig cell tumor, and pheochromocytoma), photosensitivity, venous thromboembolic events, amputation, fracture, and DKA.

Unless described in specific section as otherwise, these AEs were collected using grouping of pre-specified list of MedDRA preferred terms and are described in Appendix 1 of the Integrated Statistical Analysis Plan.

Reviewer's comments: The groupings of pre-specified list of terms were acceptable.

Male Genital Infections:

The following MedDRA terms were used to identify male genital mycotic infection and phimosis: balanitis, balanitis candida, balanoposthitis, balanoposthitis infective, erosive balanitis, gangrenous balanitis, genital candidiasis, genital infection, genital infection fungal, genital infection male, penile infection, and posthitis.

Events of circumcision were identified by searching the Diagnostic or Therapeutic Procedures (DTPs) in DIA3008, but DIA4003 did not have DTP. The Applicant searched both studies for specific terms on the AE page, and stated that they systemically queried phimosis to determine if they led to circumcision.

In the CANVAS and CANVAS-R pooled dataset, the adjusted-incidence rates of any male mycotic genital infections were 31.74 versus 9.62 per 1000 PY in the combined canagliflozin and placebo groups respectively, with the IRD of 22.12 (95% CI: 18.22, 26.02). This compares to the adjusted incidence rate of 51.98 and 9.09 per 1000 PY in the combined canagliflozin and non-canagliflozin groups respective in the non-CANVAS pooled dataset, with IRD of 42.89 (95% CI: 33.04, 52.74).

The most commonly reported terms were balanoposthitis and fungal genital infection. See Table 45 for summary of reported AEs for male mycotic genital infections in the pooled dataset.

Table 45: Male Mycotic Genital Infection and Phimosis - Pooled Dataset (On-treatment Analysis Set)

	Placebo (N=2747) N (%)	Cana (N=3756) N (%)
Subjects with male mycotic genital infections	70 (2.5)	386 (10.3)
Incidence rate per 1000 PY*	9.62	31.74
Balanitis candida	6 (0.2)	39 (1.0)
Balanoposthitis	50 (1.8)	282 (7.5)
Balanoposthitis infective	0	1 (<0.1)
Genital candidiasis	1 (0.1)	11 (0.3)
Genital infection	0	2 (0.1)
Genital infection fungal	10 (0.4)	67 (1.8)
Penile infection	3 (0.1)	6 (0.2)
Subjects with phimosis	7 (0.3)	61 (1.6)
Incidence rate per 1000 PY*	0.96	5.02

*Incidence is calculated on the number of subjects having at least one AE, not the number of events; the denominator is the total of each subject's exposure of the study drug plus 30 days; PY=person-years.
Source: ISS, Table 23

Of male mycotic genital infections, 2 were serious AEs and both were from canagliflozin group; one subject was hospitalized in DIA3008 and one subject had 'other medically important condition' in DIA4003, and both events resolved. Fifty-four events (1.4%; 4.44/1000 PY) in the canagliflozin group and 7 events (0.3%; 0.96/1000 PY) led to discontinuation.

In the combined canagliflozin versus placebo groups, ~18% (70/386) and ~9% (6/70) had 2 events, and ~13% (49/386) and ~1.4% (1/70) had 3 or more events, respectively. The median duration of male genital mycotic infections was 31 days and 15.5 days in the combined canagliflozin and placebo groups respectively.

In DIA3008, baseline medical history collected the circumcision status in men, whereas in DIA4003 this was not collected. The majority of males in DIA3008 were not circumcised, as 2072 men were not circumcised and 788 men were circumcised. The adjusted-incidence rates of male mycotic genital infections in uncircumcised males were 34.61 and 10.86 per 1000 PY (15.4% [208/1354] and 4.5% [32/718]) in the combined canagliflozin and placebo groups, respectively. The adjusted-incidence rates of male mycotic genital infections in circumcised males were 13.41 and 3.06 per 1000 PY (6.4% [35/551] and 1.3% [3/237]) in the combined canagliflozin and placebo groups, respectively.

In addition, a prior history of balanitits/balanoposthitis was reported in ~21% (59/278) subjects who experienced male genital mycotic infection compared to ~3% (79/2582) of subjects who did not experience male genital mycotic infection in DIA3008.

In the pooled dataset, the adjusted-incidence rate of phimosis was 5.02 and 0.96 per 1000 subject-years in combined canagliflozin and placebo groups, respectively (Table 45). Of these, 7 subjects on canagliflozin reported serious phimosis due to hospitalization and 2 subjects reported leading to discontinuation, compared to none in the placebo group. Six of 7 SAEs had a circumcision completed and 7th had a "phimosis surgery", and all were recovered/resolved.

In the pooled dataset, the adjusted-incidence rate of circumcision in the overall male population was 3.25 (1.3% [48/3756]) and 1.00 (0.3% [9/2747]) per 1000 PY in the combined canagliflozin and placebo groups respectively.

Reviewer's comment: Current labeling warns about the increased risk of genital mycotic infections with canagliflozin in the Warnings and Precautions in Section 5.8 as well as in Adverse Reactions Section 6.1 along with phimosis. Based on evaluation of current data, no further labeling changes are indicated for male genital mycotic infections.

Selected Malignancies:

Canagliflozin was not found to be genotoxic. However, nonclinical findings during clinical development of canagliflozin showed possible increase in Leydig cell tumors, renal tubular tumors, and pheochromocytomas. Mechanistically, this finding was thought to be related to rat-specific mechanisms that may not be relevant for humans. Please see the PharmTox review by Dr. Fred Alavi during the original NDA review for further details of nonclinical carcinogenicity studies.

In the clinical program for another SLGT2 inhibitor (dapaglifozin), an imbalance in breast cancer and bladder cancer not favoring those receiving the active drug treatment was noted.

Thus, breast cancer, bladder cancer, renal tubular tumors, Leydig cell tumors, renal tubular tumors, and pheochromocytomas were malignancies of interest.

There were no Leydig cell tumors or pheochromocytomas reported with canagliflozin so far, and the rest of malignancies of interest are discussed here.

Breast cancer:

The adjusted-incidence rates for breast cancer in the combined canagliflozin and placebo groups were 3.09 and 2.62 per 1000 PY, respectively, in the pooled dataset.

Eight of these occurred during the first 180 days after study drug initiation, 4 in each treatment group; excluding these events, the adjusted-incidence rate was 2.96 and 2.15 per 1000 PY in the combined canagliflozin and placebo groups, respectively. Except for one in each treatment group, the remaining breast cancer events were SAEs; there were 4 fatal breast cancer AEs in the canagliflozin group and 3 fatal AEs in the placebo group. Breast cancer AEs led to discontinuation in 7 subjects and 4 subjects in the combined canagliflozin group and placebo group, respectively.

Table 46: Breast Cancer (Females Only) – Pooled Dataset (On-Study Analysis Set)

	Placebo (N=1597) N (%)	Cana (N=2034) N (%)
Subjects with breast cancer	13 (0.8%)	24 (1.2%)
Incidence rate per 1000 PY*	2.62	3.09
Breast cancer	8 (0.5)	17 (0.8)
Breast cancer metastatic	0	2 (0.1)
Breast cancer recurrent	0	1 (<0.1)
Breast cancer stage 1	0	1 (<0.1)
Breast cancer stage 2	0	1 (<0.1)
Breast cancer stage 3	0	1 (<0.1)
Invasive ductal breast carcinoma	4 (0.3)	2 (0.1)
Invasive lobular breast carcinoma	0	1 (<0.1)
Lobular breast carcinoma in situ	1 (0.1)	0

*Incidence is calculated on the number of subjects having at least one AE; PY=person-years.
Source: ISS, Table 26

In DIA3008, a single case of breast cancer (Subject (b) (6) [reported term: right breast carcinoma]) occurred in a male subject after taking canagliflozin 300 mg on Day 1564. Study drug continued and he underwent modified radical mastectomy. He subsequently developed metastases (reported term: worsening right breast carcinoma) on Day 1746. He was withdrawn from the study and was still alive at the end of study.

Reviewer's comment: Numerically the incidence of breast cancer is slightly larger in the canagliflozin arm compared to placebo but the difference is very small and is not concerning. One case of breast cancer in male is likely due to chance.

Bladder cancer:

In the pooled dataset, the adjusted-incidence rate of bladder cancer was 0.98 per 1000 PY (0.4% [16/4344]) in the combined canagliflozin and 1.14 per 1000 PY (0.4% [22/5790]) in the placebo group. One and two events in the canagliflozin and placebo group, respectively, occurred during the first 180 days after study drug initiation;

excluding these events, the adjusted-incidence rate was 1.12 and 1.26 per 1000 PY in the combined canagliflozin and placebo groups, respectively. Except for one in each group, all bladder cancer AEs were SAEs, and 5 were fatal bladder cancer AEs with canagliflozin and one was fatal with placebo.

Renal cancer:

In the pooled dataset of DIA3008 and DIA4003, there were 14 subjects (0.2%) in the canagliflozin group and 3 subjects (0.1%) in the placebo group that reported renal cell carcinoma, and the adjusted-incidence rates were 0.62 and 0.21 per 1000 PY in the combined canagliflozin group and the placebo groups, respectively (IRD 0.41; 0.95% CI: -0.04, 0.86); see Table 47. The median onset for first event was ~1177 days in the canagliflozin and 710 days in the placebo group.

Table 47: Renal Cancer in Pooled DIA3008 and DIA4003

	Placebo (N=4344) N (%)	Cana (N=5790) N (%)
All renal cancer	**3 (0.1%)**	**14 (0.2%)**
Incidence rate per 1000 PY	0.21	0.62
Incidence rate difference vs placebo (95% CI)		0.41 (-0.04, 0.86)
Renal cancer >180 days after study drug initiation	**3 (0.1%)**	**12 (0.2%)**
Incidence rate per 1000 PY	0.25	0.61
Incidence rate difference vs placebo (95% CI)		0.36 (95% CI: -0.14, 0.86)

Table 48: Renal Cancer in DIA3008

	Placebo (N=1414)	Cana 100 (N=1433)	Cana 300 (N=1425)	All Cana (N=2858)
All renal cancer	**3 (0.2%)**	**7 (0.5%)**	**6 (0.4%)**	**13 (0.5%)**
Incidence rate per 1000 PY	0.37	0.85	0.73	0.79
Renal cancer >180 days after study drug initiation	**3 (0.2%)**	**7 (0.5%)**	**5 (0.4%)**	**12 (0.4%)**
Incidence rate per 1000 PY	0.41	0.93	0.66	0.79
Incidence rate difference vs placebo (95% CI)		0.52 (-0.42, 1.46)	0.25 (-0.61, 1.11)	0.38 (-0.36, 1.12)

One renal cancer was reported from DIA4003 in a subject receiving canagliflozin, and the remaining 16 renal cancer cases were reported from DIA3008. The one subject from DIA4003 was a 59-year old Caucasian female from Germany with history of hypertension, obesity (BMI 38.2 kg/m^2), and a smoker who was diagnosed with renal tumor incidentally during CT scan for evaluation of microalbuminuria on Day 40 (Subject

(b) (6)). A subject from DIA3008 (Subject (b) (6) a 60-year old Caucasian man from Ukraine with history of hypertension and obesity (BMI 41.5 kg/m^2) experienced pain in the lumbar area with low grade fever and weakness on Day 30, and an abdominal ultrasound scan and CT scan showed mass in the lower area of the left kidney and was diagnosed with renal cancer on Day 32 after study drug initiation. He underwent left nephrectomy with adrenalectomy, and the histology showed a highly differentiated clear cell renal carcinoma of left kidney.

Reviewer's comment: The renal cell carcinoma occurring in these 2 subjects occurring 30 and 40 days after starting canagliflozin are unlikely to be related to the study drug given the long latency associated with malignancy.

The adjusted-incidence rates excluding these two subjects were 0.61 and 0.25 per 1000 PY in the combined canagliflozin group and the placebo groups (12 versus 3 subjects), respectively (IRD 0.36; 0.95% CI: -0.14, 0.86).

In addition, two other subjects in DIA3008 (one from the canagliflozin 100 mg [subject (b) (6)] and one from the placebo group [subject (b) (6)]) were exposed to study drug <90 days but were diagnosed with renal malignancy later in the study:

- Subject (b) (6) (canagliflozin 100 mg; Netherlands): A 69-year old Caucasian man with hypertension, obesity (BMI 31.1 kg/m^2), history of smoking and resection of benign brain tumor enrolled into the study. He had a non-serious event of allergic skin reaction to study drug on Day 7, study drug was discontinued on Day 77, and he was withdrawn from the study on Day 85. On Day 1099, a tumor of right kidney was reported based on routine screening (unspecified what this routine screening was), and he underwent resection of right kidney tumor on Day 1140. Pathology report of the resected tumor showed a **clear cell renal cell carcinoma** with a diameter of 6 cm. He underwent resection of right kidney tumor. ***Reviewer's comment: He received canagliflozin for only about 2 months, and the renal cell carcinoma was reported about 3 years after initiation of study drug. It appears unlikely that his renal cell carcinoma may be related to the study drug given the limited exposure.***

- Subject (b) (6) (placebo; Argentina): A 71-year old Caucasian woman with a history of hypertension with BMI of 28.9 kg/m^2 decided to withdraw from the study on Day 51 for personal reasons and received the last dose of study drug on Day 42. On Day 227, a routine ultrasound scan of the abdomen showed a possible right renal mass, a CT scan of the abdomen without contrast showed a round image in the anterior right kidney. A CT scan of the abdomen with contrast on Day 235 showed a solid tumor in the right kidney, and she underwent a total right nephrectomy. Histology showed renal cell carcinoma of 6cm diameter.

Reviewer's comments: Given the long latency associated with drug-related malignancies, it is unlikely that the reported renal cancer in 4 subjects discussed above (3 in the canagliflozin group [Subjects (b) (6)] and 1 in the placebo group [Subject (b) (6)]) was related to the study drug where renal cancer occurred within <180 days after study drug initiation or after receiving the study drug for <90 days.

In the canagliflozin groups, two subjects had pre-existing conditions related to renal cancer: one subject had a history of renal cancer (Subject (b) (6)) and another had a history of renal cyst (Subject (b) (6)):

- Subject (b) (6) (canagliflozin 100 mg; US): A 59-year old Caucasian obese(BMI 36 kg/m^2) man with history of smoking, renal cell carcinoma and two cryogenic surgeries (about 6 years before study entry), hypertension, hyperlipidemia, CAD, MI, and GERD discontinued the study drug on Day 664 due to non-serious event of increased blood creatinine and BUN levels, and was withdrawn from the study on Day 680 due to these events. On Day 1254, AE of ***renal cancer*** (reported term: malignant neoplasm of right kidney) was reported, and on Day 1380, a non-serious AE of renal cancer (reported term: malignant neoplasm of left kidney) was reported, both during routine screening. He underwent a CT-directed cryoablation of the right kidney malignant neoplasm for the small enhanced mass of the right kidney, and renal cancer was reported as resolved. On Day 1492, a non-serious AE of renal cancer (reported term: neoplasm of right kidney) was reported again, and was reported as resolved on Day 1688. Histology was not provided. ***Reviewer's comment: This patient had history of smoking and renal cell carcinoma, received canagliflozin for almost 2 years before discontinuing the study drug, and was subsequently diagnosed with renal cancer almost 2 years after discontinuation of study drug (4 years after starting the study drug). Thus, the renal cancer is likely to be recurrence of renal cancer and appears unlikely to be related to the study drug.***

- Subject (b) (6) (canagliflozin 100 mg; Germany): A 66-year old Caucasian woman with multiple medical history significant for hyperlipidemia, hypertension, obesity (BMI of 43.9 kg/m^2), pyoderma gangrenosum, pain in the lumbar region for many years, and left renal cyst (3 years before study entry) experienced multiple AEs which included SAE of coronary artery stenosis (Day 270), rib fracture and sternal fracture after a car accident (Day 276), non-serious AE of skin ulcer, SAE of lumbar spinal stenosis (Day 357), non-serious AE of micturition urgency (Day 636), non-serious AE of UTI (Day 662), SAE of atrial fibrillation and coronary artery disease (Day 743 and Day 751), SAE of staphylococcal sepsis, cardiac failure, and renal failure on Day 753 along with *E coli* UTI that resolved on Day 781. On Day 911, cystoscopy showed plantar redness in bladder roof and lateral wall, and she underwent a transurethral resection of the suspected areas in the region of the bladder roof. Histology

showed focal urothelial carcinoma in situ and SAE of ***bladder cancer*** stage 0. She underwent transurethral resection and received intravesicular treatments with BCG for 6 weeks. On Day 916 bladder cancer was reported as resolved. On Day 1185, she was hospitalized for pyrexia of an unknown origin, which resolved on Day 1189. On Day 1596 she had lumbar deterioration and CT scan showed suspected area of left kidney carcinoma along with lumbar region issues. ***Renal cancer carcinoma*** was reported (onset Day 1614) along with SAE of intervertebral discitis. She was hospitalized and underwent left nephrectomy on Day 1738; renal cancer carcinoma was reported to have been resolved on Day 1750. Histology confirmed diagnosis of partial necrotic moderate differentiated clear cell renal cell carcinoma, which was partly cystic, restricted to renal parenchyma. She was withdrawn on Day 2206 due to physician's decision (subject was unable to come to study center due to wounds on lower leg and bad medical control at home). ***Reviewer's comment: This subject had past history of renal cyst, developed bladder cancer about 2.5 years after study drug initiation. This patient also had lumbar pain issues and was found to have renal cancer about 4.5 years after study drug initiation during evaluation of exacerbated back pain. She had pre-existing left renal cyst 3 years before study entry. The investigator considered these events as doubtfully related to the study drug.***

Reviewer's comment: It is likely that the renal cancer in Subject (b) (6) was a recurrence of pre-existing renal cancer. In Subject (b) (6) it is also highly plausible that pre-existing left renal cyst before study entry became cancerous. Therefore, these two cases had underlying pre-existing conditions related to renal cancer, making the reported renal cancer during their participation in the study less likely to be causally related to the study drug.

One subject had concurrent bladder cancer and renal cancer, both considered to be primary site per report:

- Subject (b) (6) (canagliflozin 300 mg; Australia): A 85-year old Caucasian man with BMI of 26.1 kg/m^2 had past history of hypertension, angina, conduction disorder, and myocardial ischemia. He had no known exposure to chemicals. He had multiple AEs during the study including unstable angina on Day 162 and Day 590. On an unspecified date, he had frank hematuria, and a renal tract ultrasound scan on Day 721 showed suspicious areas of malignancy, which included a 2.7 cm right renal mass superiorly, and a 3.6 cm bladder mass posteroinferiorly, a 1.8 cm right renal parapelvic cyst. On Day 722, a CT scan of abdomen and pelvis showed lobulated enhancing mass within the left posterolateral aspect of urinary bladder closely adjacent to vesicoureteric junction, suggestive of transitional cell carcinoma, and a 3.2 cm enhancing mass at the peripheral lateral aspect of midsection of the right kidney suggestive of a renal cell carcinoma. He was hospitalized on Day 734 and underwent

cystoscopic transurethral resection of the bladder tumor. Histopathology report on Day 735 showed Grade 3 papillary urothelial carcinoma with lamina propria invasion; stage pT1. SAE of ***bladder transitional cell carcinoma*** and ***renal cell carcinoma*** were reported. He was withdrawn from the study on Day 788. He did not receive any additional treatment and died on Day 1113 due to metastases to liver with possible primary site being the bladder and bladder transitional cell carcinoma. Autopsy was not done. The investigator considered these to be doubtfully related to the study drug. ***Reviewer's comment: Histology only confirmed urothelial cancer and not renal cell carcinoma.***

Two subjects who received canagliflozin and died due to metastatic renal carcinoma are summarized:

- Subject (b) (6) (canagliflozin 100 mg; Netherlands): A 73-year old Caucasian man with BMI of 29.6 kg/m^2 with history of hypertension had a SAE of presyncope on Day 544. On Day 690 he had high erythrocyte sedimentation rate and C-reactive protein (unspecified values), decreased appetite, and pain in the left lower abdomen. A CT scan on Day 705 showed an image (10x12 cm) suspected of a primary ***renal cell carcinoma*** and extension of tumor through renal vein into the inferior vena cava just below the right atrium; the right lower lobe of the lungs showed three nodular abnormalities and a small solitary hypodense abnormality in the liver (6 mm) suggesting metastasis. It also showed slight nodular enlargement of the left adrenal gland. The chest radiograph on the same day showed lung metastasis. He did not receive any treatment for these events, study drug was discontinued on Day 742, and he was withdrawn from the study. On Day 856, he died due to renal cell carcinoma. No autopsy was done. ***Reviewer's comment: This subject had signs and symptoms that led to diagnostic evaluations leading to detection of renal cell carcinoma after about 2 years of study drug initiation.***

- Subject (b) (6) (canagliflozin 100 mg; Australia): A 60-year old Caucasian man with obesity (BMI of 33.1 kg/m^2) with no smoking history experienced multiple AEs including right eyelid papilloma around Day 370, lower back pain on Day 485, benign monoclonal hypergammaglobulinemia on Day 735, and thyroid mass on Day 743. On Day 792, back pain worsened, and on Day 849 he was hospitalized due to severe low back pain. A CT scan of abdomen and pelvis showed a complex left renal mass (8.5 x7x10.5 cm) with extension to perinephric compartment and involvement of the Gerota's fascia, enlarged lymph node in the left para-aortic region below the left renal vein, and lytic lesion in the L3 consistent with a solitary metastatic deposit. A SAE of ***metastatic renal cell carcinoma*** was reported. A whole body bone scan with single proton emission CT scan on Day 852 showed solitary bony metastasis in L3 secondary to left renal tumor. On Day 853, CT scan of brain and chest showed multiple small pulmonary nodules with 3 nodules measuring 4 to 6 mm in dize, suspicious for

lung metastasis, but no cerebral metastasis, and MRI of spine showed possible metastasis in T4 left pedicle and in L3. Study drug was discontinued and he was withdrawn from the study on Day 854. He underwent a left radical nephrectomy on Day 856 and left laparoscopic nephrectomy on Day 859. Histopathology confirmed renal cell carcinoma of clear cell type with sarcomatoid and rhabdoid differentiation (stage pT3a; nucleolar grade 4). He was subsequently hospitalized due to metastatic renal cell carcinoma on Day 1279 and died on Day 1315. ***Reviewer's comment: He began having initial back pain about 18 months which worsened ~2.2 years after study drug initiation, leading to diagnosis of RCC.***

Remaining six renal cancer events in the canagliflozin group are summarized:

- Subject (b) (6) (canagliflozin 100 mg; Russia): A 68-year old Caucasian man with BMI 30.3 kg/m^2 had history of hypertension, smoking, urinary calculus, an ectopic kidney (lumbar of left kidney). On Day 450, an ultrasonography of abdomen and retroperitoneal space (reported to have been done for planned annual examination for general assessment of abdominal organs) showed suspected tumor of the right kidney; lower and middle segment of the right kidney was visualized on the back of the dense tumor to 2 cm in diameter extra-renal type of growth. He was hospitalized on Day 664 and underwent lumbotomy radiofrequency resection of right kidney on Day 666. Histology showed moderately differentiated ***renal cell cancer clear cell variant***, Stage 1. Subsequently, on Day 1257, an ultrasound of kidneys and adrenal glands showed volume of formation of right kidney. On Day 1263, a MRI of abdomen and retroperitoneum showed volume of formation in the middle third of the right kidney with clear contours 2.5 x 2.4 x 2.4 cm. On Day 1281, he underwent lumbotomy resection of right kidney; macroscopy of suspected tumor showed node of 2.5 cm in diameter. Histology showed ***renal cell carcinoma of the right kidney, clear cell variant***, second degree of cellular anaplasia, and 2 point Fuhrman. Study drug was interrupted due to this event, renal cancer resolved on Day 1291, and study drug was restarted on an unspecified day. He decided to discontinue study drug early for personal reasons and was withdrawn on Day 1456. ***Reviewer's comment: This subject had renal cancer about 22 months after starting canagliflozin and had another incidence of renal cell carcinoma at about 42 months after starting canagliflozin.***

- Subject (b) (6) (canagliflozin 300 mg; Estonia): A 61-year old Caucasian woman with BMI 37.5 kg/m^2 had history of hypertension but no smoking history. During the study, she had multiple AEs including macular degeneration on Day 192, SAE of AV block on Day 988, and syncope on Day 1034. On Day 1731, a non-serious AE of abdominal pain was reported, and on Day 1767 she underwent an ultrasound of abdomen which diagnosed a **renal cancer** (reported term: malignant tumor of left kidney). A CT scan confirmed tumor of left kidney

on Day 1808, and ultrasound scan of abdominal and pelvic region on Day 1897 showed tumor mass of 7 cm diameter in the upper pole of left kidney. She underwent resection of left kidney on Day 1899 and also underwent plastic surgery of renal ureter. Histology showed renal cell carcinoma, chronic inflammation in surrounding tissue and glomerular sclerosis. Renal cancer was resolved on Day 1913 and abdominal pain was resolved on Day 1919. She subsequently developed perinephric abscess after the kidney surgery, which was not resolved at the time of report (up to Day 2026). She was withdrawn from the study on Day 1998. ***Reviewer's comment: This subject had abdominal pain which led to renal cancer diagnosis.***

- Subject (b) (6) (canagliflozin 300 mg; US): A 50-year old African-American/American Indian man with BMI 40.0 kg/m^2 and history of smoking, hypertension, myocardial infarction, hypercholesterolemia, obesity, prostate enlargement, and arthritis experienced bladder outlet obstruction on Day 718, and was hospitalized due to worsening of benign prostatic hyperplasia (BPH) on Day 779. He also had concurrent non-serious UTI that resolved on Day 789. He underwent bipolar transurethral prostate resection on Day 790, and his BPH resolved on Day 792. On Day 1527, he developed signs and symptoms of hematuria and a CT scan of right kidney on Day 1569 showed an intermediate right renal lesion. On Day 1777, repeat CT scan showed heterogenous renal mass involving the lower pole of the right kidney measuring 4.9 cm mass for renal cell carcinoma, and an additional smaller exophytic mass of 1.2 cm was noted just above the larger mass. On Day 1808, histology showed renal cell carcinoma stage 2, clear cell type. He underwent right renal cryoablation to remove carcinoma as well as 1.2 cm renal mass on Day 1909. He completed the study on Day 2101. Event of renal cell carcinoma stage 2 was not resolved at the time of this report.

- Subject (b) (6) (canagliflozin 100 mg; Israel): A 73-year old Caucasian man with history of hypertension, smoking, and obesity (BMI 35.2 kg/m^2) had multiple AEs during study participation including SAE of exertional dyspnea on Day 330, SAE of unstable angina on Day 883, and SAE of squamous cell carcinoma of skin (left ear) on Day 1215. On Day 1767, renal cancer was reported after a CT of abdomen (indication not reported) earlier that month showed a space occupying lesion in the right kidney. Biopsy indicated renal cancer, but further description of histology was not available. He underwent radiofrequency ablation of right kidney mass on Day and cancer resolved on Day 1801.

- Subject (b) (6) (canagliflozin 300 mg; Australia), renal cell carcinoma: A 45-year Caucasian man with BMI 36 kg/m^2 and history of hypertension underwent aorto-bifemoral CT angiogram for an unspecified reason, which showed chronic, heavily calcified extensive atherosclerotic disease bilaterally from the mid superficial femoral artery level extending distally, and showed renal cell

carcinoma (reported term: right multifocal renal cell carcinoma) on Day 1806. On Day 1814, a CT scan of chest and abdomen showed three discrete, solid lesions in the right kidney, the largest measuring 3.3 cm in diameter, consistent with multifocal renal cell carcinoma. On Day 1837, the subject was hospitalized and underwent CT-guided core biopsy of the right renal lesions. Histology confirmed three separate conventional ***clear cell renal cell carcinoma***, largest 3 cm, Fuhrman Grade 3, confined to kidney with surgical margins clear. On Day 1871, he underwent laparoscopic right nephrectomy without complications, and event was reported as resolved on Day 1875. He completed the study on Day 2290 without interrupting the study drug.

- Subject (b) (6) (canagliflozin 300 mg; Netherlands): A 61-year old Caucasian man with BMI 31.3 kg/m^2 and history of hypertension had a CT scan of thorax and abdomen on Day 1356 which showed right kidney tumor (about 25 cm). An enlarged right kidney was noted on Day 1360 during consultation for unexplained tachycardia. On Day 1377, a needle biopsy examination of the renal tumor showed Fuhrmann Grade 3 clear cell kidney tumor. A CT scan on unspecified day showed intrathoracic lymph node metastasis, three pulmonary lesions suspicious for metastasis and possible rib lesions possible for metastasis; the cancer staging was reported as pT2bN2M1. The Investigator considered the event possibly related to the study drug and study drug was discontinued on Day 1365. He was withdrawn from the study on Day 1398. He was hospitalized and underwent a total right nephrectomy on Day 1407. A repeat CT scan on Day 1434 showed a slight growth (<10%) of metastatic lesions and he received medical therapy. The event of ***clear cell renal cell carcinoma*** was not resolved at the time of report.

Two cases of renal cancer reported with placebo are summarized, and in one case the subject died (b) (6):

- Subject (b) (6) (placebo, Russia): A 58-year old Caucasian man, baseline BMI of 29.1 kg/m^2 had history of hypertension and smoking. On an unspecified day, he complained of pain in the left lumbar area, dizziness, and headache. On Day 703, chest radiograph showed suggestion of metastatic changes in lungs. A CT scan of the abdominal cavity on Day 710 showed cancer of the left kidney with metastases to the lungs and adrenal glands. The upper and middle thirds of the left kidney mass size was 7.4x8.2x7.3 cm, adrenal gland mass size was 6.2x8x8.2 cm on right and 4.4x6.6x5cm on the left, and basal segments of the lungs with masses up to 1 cm. The cancer was not operated on because of late stage of cancer and concurrent conditions of CAD and T2DM. He received the last dose of study drug on Day 723 and died on Day 898 due to metastatic renal cancer. ***Reviewer's comment: No histology was reported for RCC, but the renal mass was large with metastatic lesions***.

- Subject (b) (6) (placebo, Russia): A 59-year old Caucasian man, with baseline BMI 30.1 kg/m^2, history of hypertension and smoking experienced diabetic hyperosmolar coma due to alcohol poisoning on Day 399, and on Day 401 an abdominal ultrasound scan showed left kidney cysts. He had other gastrointestinal and medical complications related to alcohol poisoning. He was hospitalized and an ultrasound scan of the abdomen on Day 1343 (indication not specified) showed a formation in the left kidney (3.7x3.6 cm), and a CT scan of the abdomen and retroperitoneum showed a mass lesion of the left kidney on Day 1345. Doppler ultrasound scan of renal vessels on Day 1346 showed hypervascularization with formation in the left kidney with mixed blood flow. He was hospitalized on Day 1363 for removal of left kidney lesion on Day 1365. Histopathology showed clear cell renal cell carcinoma (RCC), Grade 2 (3.1x3.0 cm). The RCC resolved on Day 1374.

Table 49: Renal Cancer Cases in DIA3008 and DIA4003

	Placebo (N=3)	Cana (N=14)
Onset Day <180 after study drug initiation	0	2
Days of study drug exposure <90 but diagnosis >180 days after study drug initiation	1	1
Prior renal abnormality	0	2
BMI >30 kg/m^2	1	12
Smoking history	2	6
History of hypertension	3	12

Source: Reviewer generated from narratives

In the non-CANVAS studies with canagliflozin, one subject (Subject ID (b) (6) who received canagliflozin 300 mg had an adverse event of renal cell cancer. This non-smoking 62-year old subject had a history of hypertension, obesity (BMI 35 kg/m^2), and cyst on left kidney, and on Day 174 discovered a 45x47 tumor of the left kidney on a routine follow-up exam of the left renal cyst. Histology after nephrectomy on Day 289 showed a Grade 2 renal cell cancer of cellular anaplasia (by Kurman nuclear grade). ***Reviewer's comment: This patient had history of renal cyst on left kidney and renal cell cancer was discovered on a routine follow-up exam of left renal cyst on Day 174. The renal cancer appears to be unlikely to be related to canagliflozin treatment.***

When all Phase 3 and 4 canagliflozin studies were pooled, the adjusted-incidence rates of renal cell carcinoma were 0.53 per 1000 PY (15/11,078 [0.1%]) in the total canagliflozin and 0.17 per 1000 PY (3/7170 [<0.1%]) in the non-canagliflozin groups (IRD: 0.36; 95% CI: -0.0, 0.72). Excluding 3 events occurring <180 days after study drug initiation (all in the canagliflozin group), the adjusted-incidence rates was 0.52 and 0.22 per 1000 PY in the total canagliflozin and non-canagliflozin groups respectively (IRD: 0.30; 95% CI: -0.13, 0.73).

Reviewer's comments: Carcinogenicity studies with canagliflozin in rats have shown an increased risk for renal tubular adenoma and carcinoma in male and female rats at doses 12x exposure from 300 mg clinical dose. The Applicant provided in vitro data to support the hypothesis that carbohydrate malabsorption related to the high dose of canagliflozin caused the renal tumors in rats, and clinical studies have not shown that carbohydrate malabsorption occurs in humans at doses up to 2x the clinical dose of 300 mg. We have been monitoring renal cancers closely during the clinical development program for canagliflozin as well as after approval by requiring post-marketing enhanced pharmacovigilance for renal cancers.

It is not surprising that most reported renal cancers occurred in DIA3008, given that cancers have long latency and this study had much longer duration compared to DIA4003 and other clinical studies. Numerically there is a small imbalance not favoring canagliflozin in DIA3008 alone, when combined with DIA4003, and when combined with all the Phase 3 and 4 clinical studies. However, the number of overall events was small, and the events were confounded by either baseline risk factors for increase in renal cancers such as hypertension, obesity, smoking history, or renal abnormalities (i.e., previous history of renal cancer, renal cyst), and it is difficult to conclude that this imbalance in renal cancer can be causality related to canagliflozin at this time.

Photosensitivity:

Because preclinical testing suggested that canagliflozin may potentially be photosensitizing, photosensitivity was considered to be an adverse event of interest.

In the pooled dataset of DIA3008 and DIA4003, the adjusted incidence rate of photosensitivity events was 1.03 per 1000 PY (0.3% [19/5790]) in the combined canagliflozin group and 0.26 per 1000 PY (0.1% [3/4344]) in the placebo group. Of these, sunburn was reported in 8 subjects (0.1%) and 2 subjects (<0.1%) in the canagliflozin and placebo group, respectively. None were SAEs and one subject from DIA3008 discontinued the study drug.

Reviewer's comment: Photosensitivity reactions are currently labeled in Adverse Reactions Section 6.1.

Venous Thromboembolic Events (VTEs):

Venous embolic and thrombotic events were AE of interest because of increase in hemoglobin/hematocrit as well as volume depletion related to canagliflozin treatment. Venous thromboembolic events were adjudicated in DIA3008 but not in DIA4003 where events were captured using a predefined MedDRA PTs. As the overall concordance

between adjudicated results and investigator reported cases were observed to be almost 94% in DIA3008, this was acceptable.

In the pooled dataset, the overall incidence of VTE was 1.85 per 1000 PY (0.5% [21/4344]) in the placebo group and 1.68 per 1000 PY (0.5% [31/5790]) in the combined canagliflozin group. The majority of VTEs were pulmonary embolism (21 subjects [0.4%] in the combined canagliflozin group versus 12 subjects [0.3%] in the placebo group) and deep vein thrombosis (19 subjects [0.3%] in the combined canagliflozin group versus 7 subjects [0.2%] in the placebo group).

Reviewer's comment: There was no imbalance in the incidence of VTEs.

Amputation:

Amputation is a newly identified safety issue of canagliflozin in DIA3008 that was initially brought to us by the Applicant in March 2016 based on a review by the Independent Data Monitoring Committee. On May 18, 2016, we issued a Drug Safety Communication regarding canagliflozin and increased risk of leg and foot amputations based on interim analysis of data from DIA3008. Subsequently, the labeling was updated on July 25, 2017 to include information about the increased risk of amputation in the Warnings and Precautions section and Adverse Reactions section along with a boxed warning.

In DIA3008, events of amputations were being recorded by the investigators within the Adverse Events and the Diagnostic Therapeutic Procedures (DTPs) eCRFs. In DIA4003, DTPs page was not being used due to streamlining of data collection, and the investigators were to record procedures in the verbatim description of the AE term. After amputation was identified as a safety issue, the Adverse Events and the DTPs eCRFs continued to be used but the Applicant also created a specific eCRF to systemically collect data. Investigators were asked to complete amputation eCRFs for every new event of amputation as well as for every amputation event that occurred before the introduction of amputation eCRFs. In addition, the Applicant conducted a search of their clinical database (eCRFs for Adverse Events in DIA3008 and DIA4003, and DTPs in DIA3008) and their pharmacovigilance dataset using the search terms 'ampu', 'remov', 'resection', 'necrosectomy', 'disarticulation', 'exarticulation', 'BKA', and 'AKA' to identify any additional event of amputations.

Reviewer's comment: Their method of capturing potential cases of amputation is reasonable.

Investigators completed a separate eCRF for every date of amputation event, and each date/eCRF counted as an event. If more than one amputation on same anatomical location occurred on the same day, the amputation was counted as one event and one location and not counted as multiple amputations. If a subject had amputations in more

than one anatomical location, s/he was counted in each day of different locations regardless of whether it occurred on the same day or on separate days, and s/he was included in the count of subjects with multiple amputations.

Upper extremity amputations

Nine subjects (10 amputation events) reported an upper extremity (finger) amputations, 6 from DIA3008 and 3 from DIA4003.

The upper extremity amputations in 6 subjects (5 with canagliflozin and 1 with placebo) were traumatic and were related with different type of accidents (e.g., wood splitter, table saw, conveyer belt, etc).

The upper extremity amputations in 3 subjects (1 with canagliflozin and 2 with placebo) were non-traumatic. The one subject who had atraumatic finger amputation was due to osteomyelitis, and the patient also had experienced an episode of 'finger cellulitis' 2 years before the amputation event.

Lower extremity amputations

In the overall pooled dataset, 188 subjects reported a lower limb amputation during their participation in the study. One case was traumatic amputation with canagliflozin and excluded in the summary; remaining 187 atraumatic lower limb amputations will be discussed further in this section.

As shown in Table 50, the exposure-adjusted incidence rate shows about 3 more amputations per 1000 PY of atraumatic lower extremity amputation with canagliflozin compared to placebo group, with almost 2-fold increase in the risk of amputation with canagliflozin compared to placebo. About 35-36% of subjects had 2 or more amputation events and this was similar between treatment groups.

Table 50: Atraumatic Lower Limb Amputations - DIA3008 and DIA4003 Pooled (On-Study Analysis Set)

	Placebo (N=4344)	Cana (N=5790)
Subjects with event, N (%)	47 (1.1)	140 (2.4)
Subjects with one amputation	30 (64%)	91 (65%)
Subjects with > one amputation	17 (36%)	49 (35%)
Number of events	69	221
Exposure to first event, PY	13935	22207
Incidence rate* (/1000 PY)	3.37	6.30
IRD (95% CI)		2.93 (1.50, 4.36)
HR** (95% CI)		1.97 (1.41, 2.75)

*Incidence is calculated with number of subjects with at least one amputation and not number of events; incidence rate where a subject's follow-up is calculated from Day 1 to the first amputation event rate.
**HR calculated from a stratified Cox proportional hazard model including treatment as explanatory variable, and stratified by study.
PY=patient-years; IRD=incidence rate difference; HR=hazard ratio; CI=confidence interval
Source: ISS, Table 32, Attachment "AMP"

The locations of atraumatic lower limb amputation are summarized in Table 51, and separated as major (ankle, below-knee, above-knee) and minor (toes and trans-metatarsal). The 2-fold increased risk of overall lower limb amputation with canagliflozin was also seen in both major and minor amputations. The difference in the incidence of amputations between combined canagliflozin group and placebo was seen as early as 26 weeks (not shown here; see Figure 2 of ISS). The majority of lower limb amputations were minor and most of the amputations involved toe.

Table 51: Lower Limb Amputation by Location – DIA3008 and DIA4003 Pooled (On-Study Analysis Set)

	Placebo (N=4344)		Cana (N=5790)		Cana vs Placebo	
	n (%)	Incidence rate (/1,000 subject-years)	n (%)	Incidence rate(/1,000 subject-years)	IRD (95%CI) (/1,000 subject-years)	HR (95%CI)
Total no. subjects with events	47 (1.1)	3.37	140 (2.4)	6.30	2.93 (1.50, 4.36)	1.97 (1.41, 2.75)
Minor	40 (85.1)	2.87	113 (80.7)	5.08	2.21 (0.91, 3.51)	1.85 (1.28, 2.66)
Toe	37 (78.7)	2.64	96 (68.6)	4.26	1.62 (0.40, 2.84)	
Trans-metatarsal	7 (14.9)	0.50	29 (20.7)	1.29	0.79 (0.17, 1.41)	
Major	13 (27.7)	0.93	41 (29.3)	1.82	0.90 (0.12, 1.67)	2.03 (1.08, 3.82)
Ankle	1 (2.1)	0.07	1 (0.7)	0.04	-0.03 (-0.25, 0.19)	
Below-knee	10 (21.3)	0.71	26 (18.6)	1.15	0.44 (-0.21, 1.09)	
Above-knee	3 (6.4)	0.21	14 (10.0)	0.62	0.41 (-0.04, 0.86)	

Note: Overall percentages calculated with the number of subjects in each group as denominator.
Note: Location percentages calculated with the number of subjects with amputation events in each group as denominator.
Note: Subject can be counted in more than one location.
Note: One of the amputations included in the count of trans-metatarsal was a Chopart's amputation.
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 adjusted incidence rate difference (IRD).
Note: Hazard ratio (HR) is from a stratified Cox proportional hazard model including treatment as the explanatory variable, and stratified by study
Note: Hazard ratio for minor amputation is based on an analysis which includes all subjects (ie, including those with major amputation).
Note: For "Total", "Minor" and "Major": Incidence rates are per 1000 subject-years, where a subject's follow-up is calculated from Day 1 to the first amputation event date. For the other rows: Incidence rates are per 1000 subject-years, where a subject's follow-up is the total follow-up time (study duration).Cross reference: TSFAE32BB_AMP_OS_SC, TSFAE32BB_AMP_OS_SC_MINOR_EXP2, TSFAE32BB_AMP_OS_SC_EXP TSFAE32B_AMP_OS_IRD2

Source: ISS, Table 33

In the amputation eCRF, investigator selected one of the following pre-specified options (more than one could be selected) as the proximate etiology leading to amputations: infection, gangrene, ulcer, peripheral arterial disease, acute limb ischemia, neuropathy, and/or other. As summarized in Table 52, the most common etiology for lower limb amputation appeared to be due to infection, ~57% in the placebo group and ~48% in the canagliflozin group. In comparison to placebo, more proportion of lower limb amputation in the canagliflozin group were due to gangrene (~38% vs ~28%) and acute limb ischemia (~13% vs ~6%). More proportion of lower limb amputation in the placebo group were due to neuropathy compared to canagliflozin group (~21% vs ~13%).

Table 52: Atraumatic Lower Limb Amputation by Etiology – Pooled DIA3008 and DIA4003 (On-Study Analysis Set)

	Placebo (N=4344) n (%)	Cana (N=5790) n (%)
Total no. subjects with events	47 (1.1)	140 (2.4)
Infection	27 (57.4)	67 (47.9)
Gangrene	13 (27.7)	53 (37.9)
Peripheral Arterial Disease	13 (27.7)	46 (32.9)
Ulcer	17 (36.2)	43 (30.7)
Acute Limb Ischemia	3 (6.4)	18 (12.9)
Neuropathy	10 (21.3)	18 (12.9)
Other	0	2 (1.4)

Note: Overall percentages calculated with the number of subjects in each group as denominator.
Note: Percentages calculated with the number of subjects with amputation events in each group as denominator.
Note: Subjects can be counted in more than one etiology.
Source: ISS, Table 35

In order to evaluate conditions leading to lower extremity amputations, the Applicant created 4 groupings of AEs that could potentially lead to amputations with MedDRA Preferred Terms as following, in addition to High Level Term (HLT) of "Skin and subcutaneous tissue ulcerations", before unblinded analyses:

- Infections and infestations – infected skin ulcer, skin infection, staphylococcal skin infection, gangrene, osteomyelitis, diabetic gangrene, localized infection, wound abscess, wound infection, subcutaneous abscess, abscess limb, staphylococcal osteomyelitis, diabetic foot infection, staphylococcal skin infection, soft issue infection, bone abscess, osteitis, cellulitis, wound, dry gangrene, postoperative wound infection, postoperative wound complication, wound dehiscence, burn infection, extremity necrosis ; and further analyzed in the following 3 groups:
  - Reversible infections – abscess limb, burn infection, cellulitis, diabetic food infection, infected skin ulcer, localized infection, skin infection, soft tissue infection, staphylococcal skin infection, subcutaneous abscess, wound, wound dehiscence, wound infection;
  - Irreversible infections – diabetic gangrene, dry gangrene, extremity necrosis, gangrene;
  - Osteomyelitis – bone abscess, osteitis, osteomyelitis, staphylococcal osteomyelitis, osteomyelitis chronic;
- Skin and subcutaneous disorders – diabetic ulcer, neuropathic ulcer, fungating wound, diabetic foot, diabetic neuropathic ulcer, skin erosion;
- Vascular disorders – arteriosclerosis, peripheral arterial occlusive disease, peripheral vascular disorder, peripheral artery stenosis, peripheral ischemia, arterial stenosis, diabetic microangiopathy, arterial occlusive disease, angiopathy, intermittent claudication, arterial disorder, impaired healing, peripheral arterial occlusion;

- Nervous system disorders – paresthesia, hypoesthesia, diabetic neuropathy, peripheral neuropathy, areflexia, hyporeflexia, polyneuropathy, automatic neuropathy, burning sensation, diabetic automatic neuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, sensory disturbance, diabetic neuropathic ulcer.

The incidence rates and HRs for combined canagliflozin compared to placebo for above AE groupings are summarized in Table 53. Because only SAEs and AEs leading to study drug discontinuations were collected in DIA3008 after amendment IND-6 and in DIA4003 throughout its study, the data presented only represents SAEs.

Except for 'reversible infections' and 'nervous system disorders', the other groupings of SAEs was higher in the canagliflozin groups compared to placebo, and the HR was 1 or greater in 'irreversible infections' and Skin and subcutaneous tissue ulcerations HLT. Within the groupings, the following terms had IRD with the lower limit of 95% CI >0 in canagliflozin versus placebo: skin ulcer (1.6 vs 0.64/1000 PY; IRD 0.96/1000 PY), gangrene (1.4 vs 0.5/1000 PY; IRD 0.9/1000 PY), peripheral artery occlusion (0.62 vs 0.14/1000 PY; IRD 0.48/1000 PY), peripheral artery stenosis (1.1 vs 0.5/1000 PY; IRD 0.6/1000 PY).

Table 53: Incidence and Hazard Ratio for Serious Adverse Events of Interest – Pooled DIA3008 and DIA4003 (On-study Analysis Set)

	------ Placebo (N=4344) -----		----- Cana (N=5790) -----		- Cana Total vs. Placebo -
Adverse Events Grouping	n (%)	Event Rate (/1,000 subject-years)	n (%)	Event Rate (/1,000 subject-years)	Hazard Ratio (95%CI)
HLT Skin and subcutaneous tissue ulcerations	31 (0.7)	2.21	80 (1.4)	3.55	1.73 (1.14, 2.63)
Infections and infestations	92 (2.1)	6.57	170 (2.9)	7.54	1.14 (0.89, 1.48)
Reversible infections	67 (1.5)	4.78	103 (1.8)	4.57	0.95 (0.70, 1.30)
Irreversible infections	15 (0.3)	1.07	44 (0.8)	1.95	1.80 (1.00, 3.26)
Osteomyelitis	14 (0.3)	1.00	40 (0.7)	1.77	1.76 (0.95, 3.26)
Skin and subcutaneous tissue disorders	15 (0.3)	1.07	33 (0.6)	1.46	1.50 (0.81, 2.79)
Vascular disorders	63 (1.5)	4.50	129 (2.2)	5.72	1.34 (0.98, 1.81)
Nervous system disorders	5 (0.1)	0.36	6 (0.1)	0.27	0.81 (0.24, 2.70)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Event rate per 1,000 subject-years is based on the number of subjects experiencing at least one adverse event, not the number of events. The denominator is the total follow-up time (study duration).
Note: Hazard ratio (canagliflozin compared to placebo) and its 95% CI are estimated using a stratified Cox proportional hazard model including treatment as the explanatory variable, and stratified by study
Note: 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: ISS, Table 36

Baseline characteristics of subjects who had amputation versus those without amputation were more likely to be men (83% vs 64%), had diabetes for longer duration (mean 16.3 years vs 13.5 years), had baseline history of amputation (27% vs 2%), CV disease (82% vs 65%), and microvascular diabetic complications (75% vs 45%). Subjects with amputations were also more likely to be on insulin (70% vs 50%) and on loop diuretic (22% vs 13%) at baseline compared to those without amputations.

A logistic regression modeling to assess whether certain baseline risk factors were associated with an increased risk for amputation using a proportional hazard model with

only the factor included as a term in the model (i.e, univariate analysis) showed that the following baseline factors were found to be significant with HR of ~2: amputation history, peripheral vascular disease, neuropathy, HbA1c >8%, gender (being male), CV disease, insulin use, loop diuretic use, nephropathy, retinopathy, diabetes ≥10 years, and eGFR <60 mL/min/1.73m^2. It is notable that past history of amputation had a hazard ratio of 21.4 (95% CI: 15.5, 29.6).

A pooled analysis of all non-CANVAS Phase 3 and 4 studies did not show an increased incidence rates of lower limb amputation with canagliflozin (2.2 in all non-cana vs 0.5/1000 PY in all cana; see Table 43 in ISS). These studies enrolled subjects at who were not at high risk for CV disease, as only about 6% of subjects had prior CV disease.

Reviewer's comments: Lower limb amputation information is currently described in a Boxed Warning, Warnings and Precautions Section 5.1, Adverse Reactions Section 6.1, and Patient Counseling Information Section 17 of labeling. No changes are warranted at this time.

Revascularization Analysis:

This was not an adverse event of interest but will be discussed here due to its possible relatedness to amputations.

In the 4-Month Safety Update submitted on January 24, 2018, the Applicant conducted a summary of revascularization analysis. The Applicant stated that analyses to assess the risk of peripheral lower extremity revascularization with canagliflozin in DIA3008 and DIA4003 were done while exploring the etiology for the amputation risk with canagliflozin.

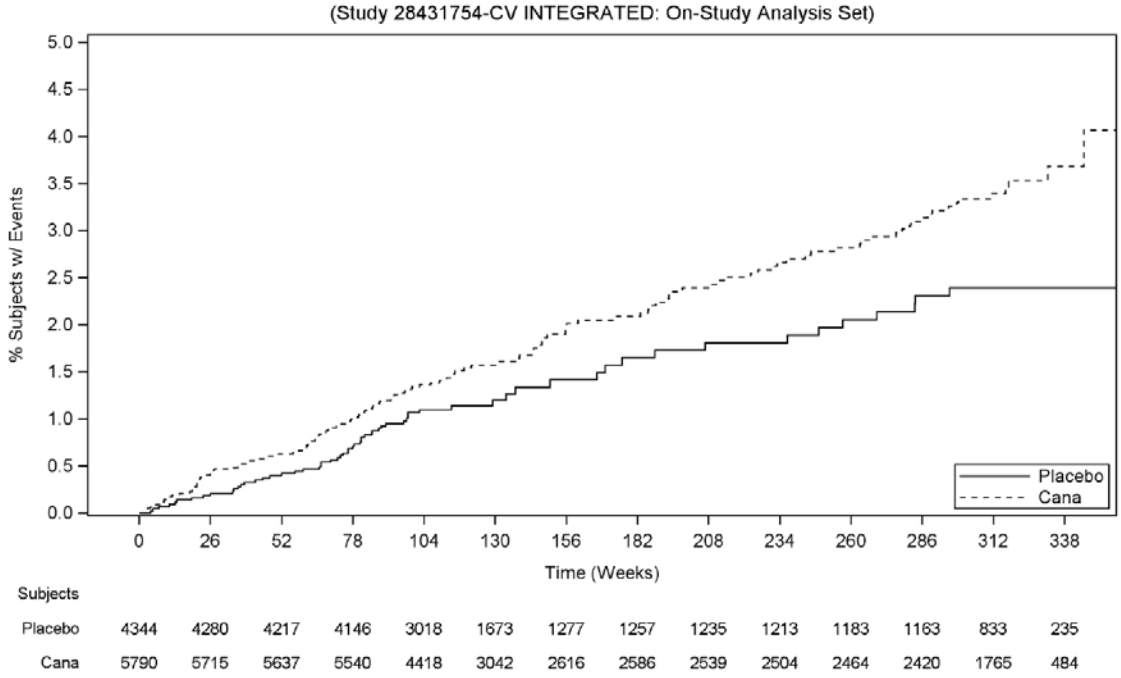
Since peripheral revascularization procedures were not systemically collected during the CANVAS Program, the Applicant searched the clinical trial databases (electronic case report forms for Adverse Events and for Diagnostic/Therapeutic Procedure pages (DTPs) in DIA3008, and for Adverse Events in DIA4003), and pharmacovigilance database (CIOMS reports) using the terms 'Fem', 'Popl', 'Iliac', 'Tib', 'Leg', 'Endart', 'By pass', 'Bypass', 'By-pass', 'Stent', 'Angio', 'Revasc', 'PTA', 'PCI', 'Ather', 'Ater', 'Percut', 'Periph'. DTP was not used in DIA4003 study. A sponsor physician reviewed these cases and identified subjects who had undergone lower extremity peripheral revascularization procedures.

This identified 197 unique subjects who underwent a lower extremity peripheral revascularization procedure, 135 subjects on canagliflozin and 62 subjects on placebo. Of 197 subjects identified, 114 were reported in the clinical database (96 found in the DTP page, 13 in the Adverse Event forms, and 5 found in both DTP and Adverse Event pages) and additional 83 subjects were found by searching the pharmacovigilance database.

In the pooled DIA3008 and DIA4003 data, the incidence rate of peripheral revascularization procedures was 4.5 in placebo and 6.1 per 1000 PY in the pooled canagliflozin group, with a HR for pooled canagliflozin group versus placebo of 1.37 (95% CI: 1.01, 1.85). As shown in Figure 18, an increase in peripheral revascularization procedures with canagliflozin compared to placebo was apparent within 26 weeks of treatment initiation.

In DIA3008, the incidence rate in the placebo, canagliflozin 100 mg, and canagliflozin 300 mg groups were 4.3, 6.7, and 5.5 per 1000 PYs, respectively. The HRs for 100 mg and 300 mg canagliflozin compared to placebo were 1.55 (95% CI: 1.01, 2.39) and 1.29 (95% CI: 0.83, 2.02), respectively.

Figure 18: Kaplan-Meier Plot of Revascularization in Pooled DIA3008 and DIA4003 (On-Study Analysis Set)



Source: 4MSU, Figure 1

Of 135 subjects in the canagliflozin group and 62 subjects in the placebo group who had peripheral revascularization procedure, 92 subjects (68%) and 47 subjects (76%) in the canagliflozin and placebo group respectively did not have amputations. Of 43 subjects and 15 subjects in the canagliflozin and placebo group who underwent an amputation, 14 (8.5%) subjects in canagliflozin and 6 (9.7%) subjects in placebo also underwent a major lower extremity amputation (e.g., ankle, below knee or above knee). In 11 cases with canagliflozin and 4 cases with placebo, the revascularization was antecedent to and occurred on the same side as the major amputation, and in 8 cases with

canagliflozin and 3 cases with placebo the revascularization procedure was considered to have failed and major amputation occurred within 3 months from revascularization.

In DIA3008 up to Amendment INT-6, a MedDRA grouping of 'vascular disorders' AEs (as discussed above in amputation) was used to identify events related to peripheral vascular disease (PVD) to assess a possible relationship between PVD-related AEs and peripheral revascularization procedure. The incidence rate of vascular disorders was numerically higher and was 15.77/1000 PY in the combined canagliflozin group compared to 13.47/1000 PY in the placebo group with HR of 1.18 (95% CI: 0.87,1.59).

In the pooled DIA3008 and DIA4003, SAEs of 'vascular disorder' grouping showed an imbalance not favoring canagliflozin, where the incidence rate was 5.72/1000 PY in the combined canagliflozin group and 4.50/1000 PY in the placebo group, with HR 1.34 although the 95% CI crossed 1 (HR 1.34 [95% CI: 0.98, 1.81]) (Table 53).

The Applicant discussed that the early increased risk for peripheral revascularization procedure and lower extremity amputations, both seen as early as within 26 weeks of randomization, is likely due to an acute hemodynamic mechanism and not related to increased progression of macrovascular disease.

Reviewer's comment: A modest increase in the risk for a peripheral revascularization procedure with canagliflozin was found in the pooled DIA3008 and DIA4003 (HR of 1.37 [95% CI: 1.01, 1.85]). There was an imbalance in SAEs of 'vascular disorder' groupings not favoring canagliflozin. The peripheral revascularization procedure was not always associated with amputations, since 68% of canagliflozin and 76% of placebo subjects who had peripheral revascularization procedure did not have amputations. Therefore, I recommend that increased incidence of peripheral revascularization procedure with canagliflozin be added to the labeling.

Fracture:

Potential fracture events were reported on the AE eCRF and on the supplemental fracture eCRF. The Applicant also stated that they reviewed AEs in the clinical database and alerted the investigator if a fracture suggestive of an AE was not identified on the supplemental fracture eCRF.

All fracture AEs were adjudicated by the independent Fracture Adjudication Committee (FAC), and defined as to whether it's high trauma, low trauma, pathological, stress, or other. The analysis is based on all adjudicated fractures in the On-Study Analysis Set.

In the pooled dataset of DIA3008 and DIA4003, the adjudicated-incidence rate for all fractures was 15.40 and 11.93/1000 PY in the combined canagliflozin and placebo groups, respectively (Table 54), with an IRD of 3.47 (95% CI: 1.00, 5.94) and HR of

1.26 (95% CI: 1.04, 1.52). Most of fractures were due to low trauma, and the adjudicated-incidence rate for low-trauma fractures was 11.58 and 9.17 in the combined canagliflozin and placebo groups, respectively, with an IRD of 2.41 (95% CI: 0.26, 4.56) and HR of 1.23 (95% CI: 0.99, 1.52) (data not shown; ISS, Table TSFAE20BB_FR_OS).

The remainder of following discussions will involve all adjudicated fractures in the On-Study Analysis Set. Data that the Applicant presented on low trauma fractures was similar with all fracture data.

Table 54: Adjudicated Fractures - Pooled DIA3008 and DIA4003 (On-Study Analysis Set)

	------ Placebo (N=4344) -----		------- Cana (N=5790) -------		------- Cana vs. Placebo -------	
Fracture Type (a)	n(%)	Rate(/1000 subject-years)	n(%)	Rate(/1000 subject-years)	IRD(/1000 subject-years)	95% CI
Total no. subjects with adverse events	163 (3.8)	11.93	333 (5.8)	15.40	3.47	(1.00, 5.94)
Total no. subjects with adjudicated fracture type (a)	163 (100)	11.93	333 (100)	15.40	3.47	(1.00, 5.94)
High trauma	28 (17.2)	2.05	61 (18.3)	2.82	0.77	(-0.28, 1.82)
Low trauma	126 (77.3)	9.22	253 (76.0)	11.70	2.48	(0.31, 4.65)
Pathological	2 (1.2)	0.15	6 (1.8)	0.28	0.13	(-0.25, 0.51)
Stress	2 (1.2)	0.15	2 (0.6)	0.09	-0.06	(-0.40, 0.28)
Other	14 (8.6)	1.02	18 (5.4)	0.83	-0.19	(-0.87, 0.49)

Note: Overall percentages calculated with the number of subjects in each group as denominator.
Note: Percentages calculated with the number of subjects with fracture events 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: (a) Adjudicated fracture type for confirmed fractures by the FAC.
Note: Events not confirmed as a fracture or without information available to the FAC are excluded.
Note: The same subject may be counted under different fracture type categories.
Note: 95% CI is based on the Normal approximation for the incidence rate difference (IRD).
Source: ISS, TSFAE00_FR_OS

As summarized in Table 55, the IRD for adjudicated fractures in the combined canagliflozin group compared to placebo was 5.98/1000 PY (95% CI: 2.88, 9.08/1000 PY) with a HR of 1.55 (95% CI: 1.21, 1.97) in DIA3008. However, in DIA4003, the IRD for adjudicated fractures in the canagliflozin group compared to placebo and was -1.80/1000 PY (95% CI: -5.83, 2.22/1000 PY) with a HR of 0.86 (95% CI: 0.62, 1.19). For pooled canagliflozin Phase 3 and 4 studies excluding DIA3008 and DIA4003 (i.e., non-CANVAS studies), the IRD for adjudicated fractures in the combined canagliflozin group compared to non-canagliflozin group was -0.31 (95% CI: -5.39, 4.77) with a HR was 1.13 (95% CI: 0.74, 1.72).

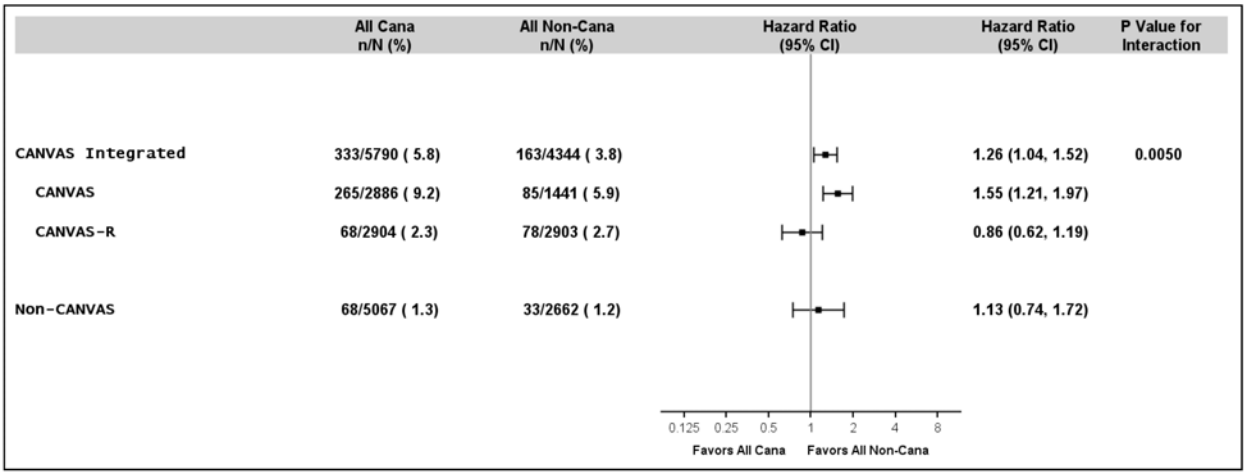
Table 55: Summary of Adjudicated Fractures in DIA3008, DIA4003, and non-CANVAS Studies

	DIA3008		DIA4003		Non-CANVAS studies	
	Placebo (N=1441)	All Cana (N=2886)	Placebo (N=2903)	All Cana (N=2904)	Non-Cana (N=2662)	All Cana (N=5067)
Subjects with fractures	**85 (5.9%)**	**265 (9.2%)**	**78 (2.7%)**	**68 (2.3%)**	**33 (1.2%)**	**62 (1.2%)**
Number of events	116	321	85	84		
Incidence Rate*	10.94	16.92	13.23	11.42	11.99	11.68
IRD (95% CI)		5.98 (2.88, 9.08)		-1.80 (-5.83, 2.22)		-0.31 (-5.39, 4.77)
HR (95% CI)		1.55 (1.21, 1.97)		0.86 (0.62, 1.19)		1.13 (0.74, 1.72)
By Fracture Region						
Lower limb (LL)	**39 (45.9%)**	**117 (44.2%)**	**36 (46.2%)**	**29 (42.6%)**	**18 (54.5%)**	**26 (42.6%)**
LL incidence rate*	5.02	7.47	6.10	4.87		
LL IRD (95% CI)		2.45 (0.35, 4.55)		-1.23 (-3.94, 1.48)		
Foot	13 (15.3%)	34 (12.8%)	7 (9%)	9 (13.2%)	7 (21.2%)	13 (21.3%)
Hip	10 (11.8%)	34 (12.8%)	12 (15.4%)	9 (13.2%)	0	3 (4.9%)
Ankle	10 (11.8%)	28 (10.6%)	7 (9%)	3 (4.4%)	6 (18.2%)	6 (9.8%)
Tibia	3 (3.5%)	10 (3.8%)	1 (1.3%)	4 (5.9%)	4 (12.1%)	1 (1.6%)
Patella	3 (3.5%)	6 (2.3%)	6 (7.7%)	3 (4.4%)	1 (3%)	0
Calcaneus	2 (2.4%)	0	0	0	1 (3%)	1 (1.6%)
Fibula	1 (1.2%)	7 (2.6%)	1 (1.3%)	2 (2.9%)	2 (6.1%)	0
Femur	0	4 (1.5%)	2 (2.6%)	1 (1.5%)	0	2 (3.3%)
Upper limb (UL)	**36 (42.4%)**	**103 (38.9%)**	**23 (29.5%)**	**22 (32.4%)**	**9 (27.3%)**	**26 (42.6%)**
UL incidence rate*	4.63	6.58	3.90	3.70		
UL IRD (95% CI)		1.95 (-0.05, 3.95)		-0.20 (-2.47, 2.07)		
Humerus	12 (14.1%)	38 (14.5%)	11 (14.1%)	6 (8.8%)	0	4 (6.6%)
Hand	9 (10.6%)	27 (10.2%)	2 (2.6%)	3 (4.4%)	4 (12.1%)	8 (13.1%)
Wrist	11 (12.9%)	25 (9.4%)	4 (5.1%)	6 (8.8%)	3 (9.1%)	10 (16.4%)
Radius	1 (1.2%)	9 (3.4%)	4 (5.1%)	5 (7.4%)	0	1 (1.6%)
Clavicle	4 (4.7%)	5 (1.9%)	0	1 (1.5%)	1 (3%)	2 (3.3%)
Ulna	2 (2.4%)	4 (1.5%)	1 (1.3%)	2 (2.9%)	1 (3%)	1 (1.6%)
Scapula	1 (1.2%)	0	1 (1.3%)	0	0	1 (1.6%)
Other	**24 (28.2%)**	**75 (28.3%)**	**23 (29.5%)**	**24 (35.3%)**	**8 (24.2%)**	**13 (21.3%)**
Other incidence rate*	3.09	4.79	3.9	4.03		
Other IRD (95% CI)		1.70 (0.03, 3.37)		0.13 (-2.19, 2.45)		
Thoracic cage	10 (11.8%)	38 (14.3%)	13 (16.7%)	11 (16.2%)	5 (15.2%)	4 (6.6%)
Spine	8 (9.4%)	23 (8.7%)	5 (6.4%)	7 (10.3%)	0	0
Skull or facial bone	3 (3.5%)	12 (4.5%)	4 (5.1%)	4 (5.9%)	1 (3%)	2 (3.3%)
Pelvis	4 (4.7%)	7 (2.6%)	1 (1.3%)	4 (5.9%)	0	2 (3.3%)
Lumbar	-	-	-	-	0	2 (3.3%)
Thoracic	-	-	-	-	1 (3%)	1 (1.6%)
Vertebra-unknown anatomical region	-	-	-	-	0	1 (1.6%)

*Incidence is based on the number of subjects with at least one fracture and not number of events; per 1000 Person-years
**Same subject may be counted under different anatomical region categories
HR=hazard ratio; calculated from a Cox proportional hazard including treatment as explanatory variable.
IRD=incidence rate difference
Source: DIA3008 CSR, Tables 67, 68; DIA4003 CSR, Tables 48, 49, 50; ISS, Tables 44, 47, TSFAE20A_FR_NC

There were discordant results in the fracture data between DIA3008 and DIA4003, and the p-value for interaction between studies was significant at (p=0.0050; Figure 19).

Figure 19: Forest Plot of Hazard Ratios (95% CI) of First Occurrence of Adjudicated Fracture by Pooled Data and Study (Safety Analysis Set)



Source: ISS, Figure 4

Reviewer's comment: Lack of increased incidence of overall fractures in non-CANVAS studies was not surprising given that the patient population in these studies were overall at lower risk for fractures (i.e., younger, less comorbidities) and were of shorter duration in compared to CANVAS. The increased risk for fractures seen in DIA3008 was not seen in DIA4003 is surprising given that the overall study population was very similar in baseline characteristics.

As summarized in Table 55, the overall pattern of anatomical region of fractures was generally similar between DIA3008, DIA4003, and non-CANVAS studies, and unlike previous trend at interim data where there was a higher incidence of upper limb fractures, there was a higher incidence of lower limb fractures across the studies.

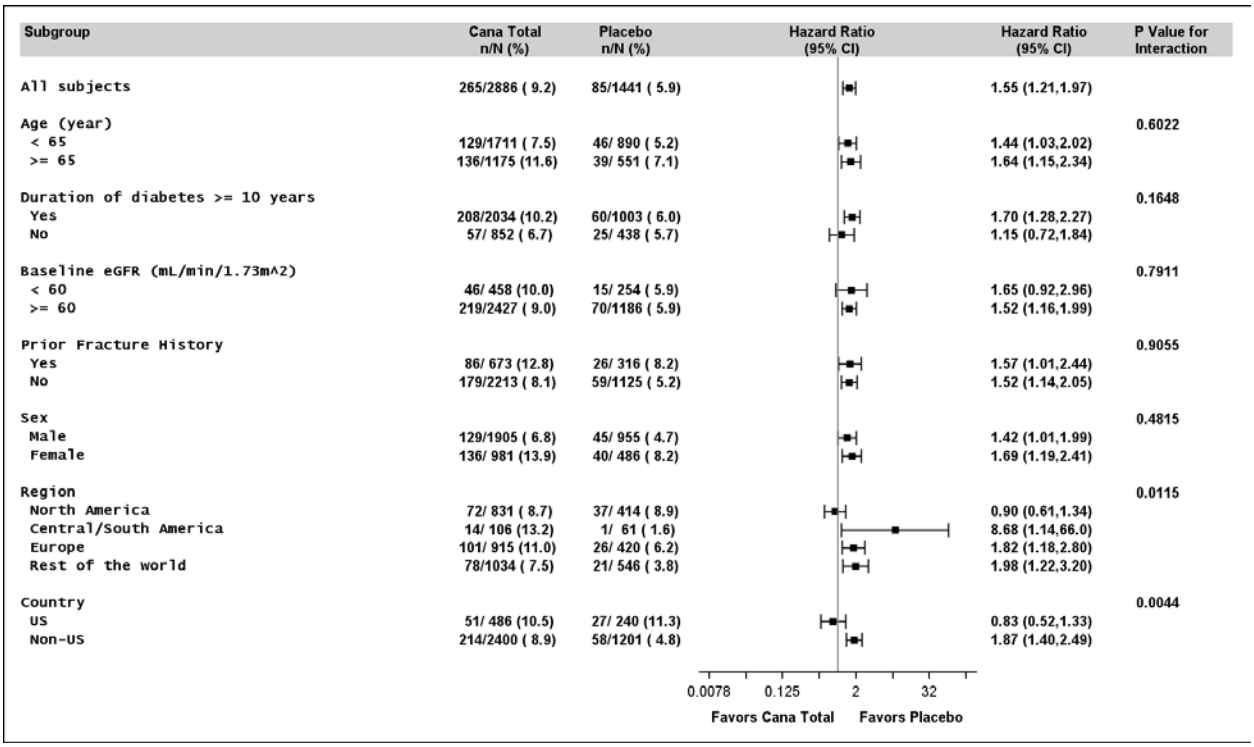
Because we wouldn't expect the risk of fractures to show in non-CANVAS studies where study population are generally younger and with less risk factors and co-morbidities for fractures, I will mainly focus on discussing the differences between DIA3008 and DIA4003.

There were canagliflozin treatment differences between DIA3008 and DIA4003, as discussed previously. In DIA3008, there were 2 canagliflozin treatment groups and subjects either received canagliflozin 100 mg or 300 mg during their participation in the study. In DIA4003, all subjects initially received canagliflozin 100 mg and were able to up-titrate to 300 mg if additional glycemic control was needed and they were tolerating 100 mg dose. But this treatment difference for canagliflozin between studies would not

explain the heterogeneity in the risk for fractures as the incidence of fractures was similar between 100 mg and 300 mg treatment groups in DIA3008.

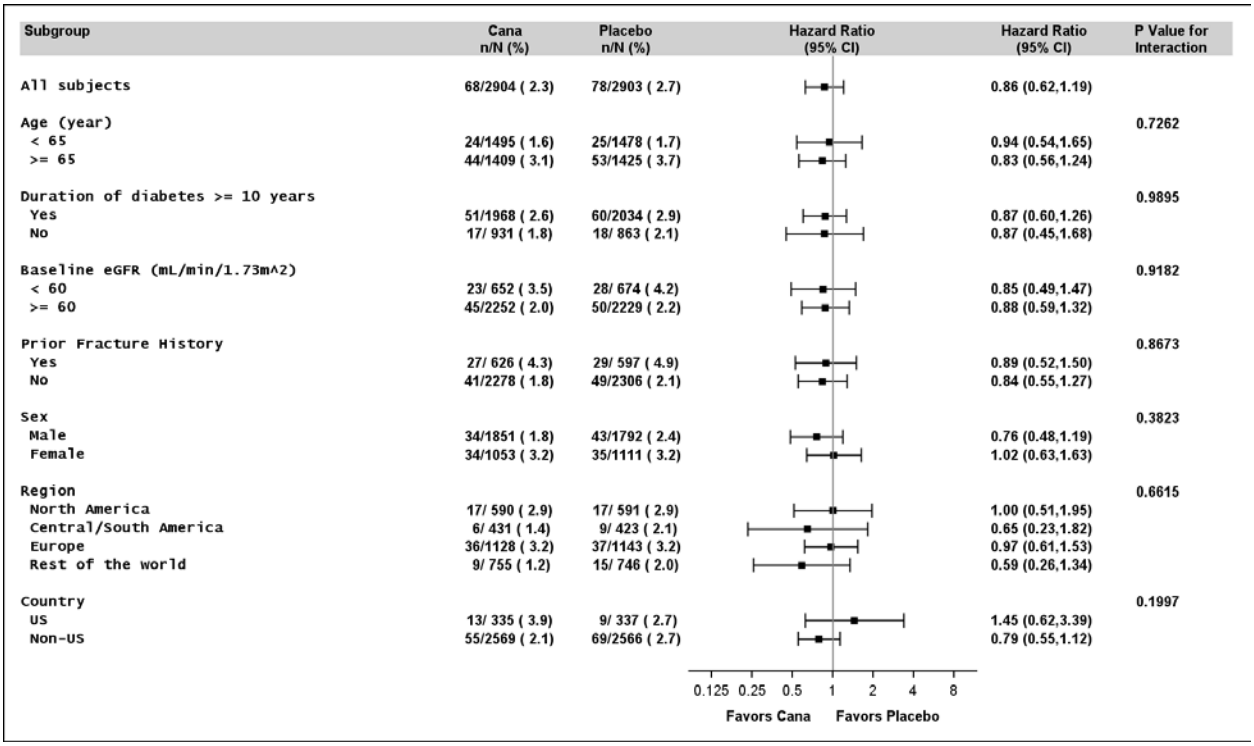
Subgroup analysis for risk of fractures showed that country (US vs non-US) was significant in DIA3008 with p-value for interaction of 0.0044. In non-US, the risk of fracture was higher with canagliflozin compared to US in DIA3008 (1.87 versus 0.83 respectively). However, in DIA4003, the risk of fracture was lower in non-US with canagliflozin compared to US (0.79 versus 1.45). Refer to Figure 20 and Figure 21 below. Subgroup analyses are considered exploratory, and it is unclear why the results are so dissimilar.

Figure 20: DIA3008 - Forest Plot of Hazard Ratios and 95% CI of Adjudicated Fracture by Subgroup (On-Study Analysis Set)



Source: DIA3008 CSR, Figure 27

Figure 21: DIA4003 - Forest Plot of Hazard Ratios and 95% CI of Adjudicated Fracture by Subgroup (On-Study Analysis Set)

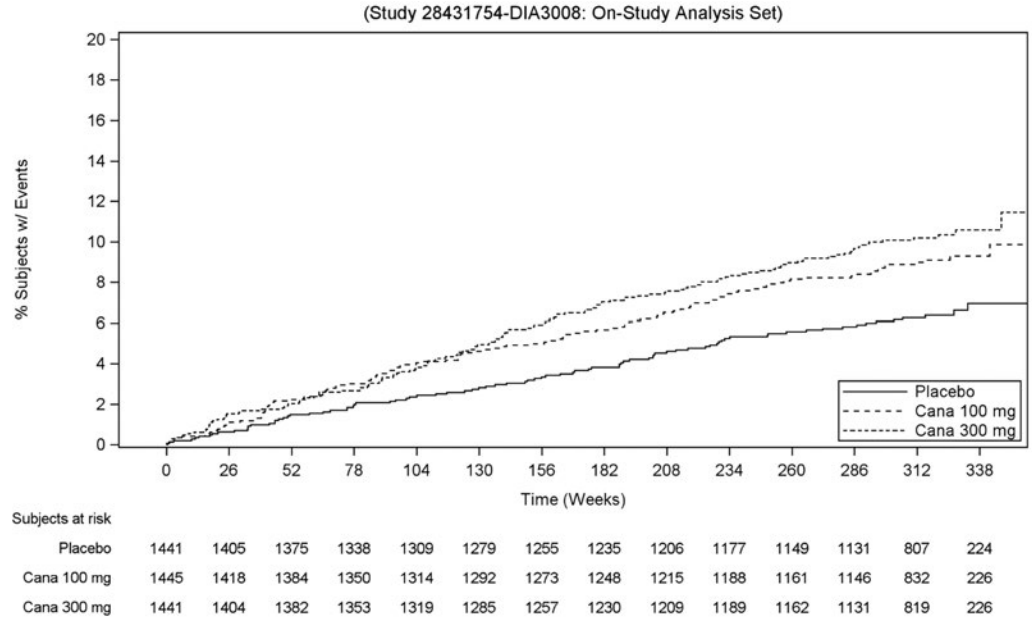


Source: DIA4003 CSR, Figure 33

The Kaplan-Meier plot of time to first adjudicated fractures for DIA3008 (Figure 22) shows that there is a separation of curves around Week 26 with a higher event rates in both doses of canagliflozin groups compared to placebo group, whereas there is a lower event rates with canagliflozin group compared to placebo in DIA4003 (Figure 23). The event rates for adjudicated fractures in non-CANVAS studies for all non-canagliflozin group appear to overlap with canagliflozin 100 mg up to around Week 52, and then seem to divulge after Week 52, with higher event rates in canagliflozin 100 mg and 300 mg groups are apparent by Week 78 (Figure 24); most of the non-CANVAS studies were 26-52 weeks in duration, and only 2 studies (DIA3009 and DIA3010) were 104 weeks in duration.

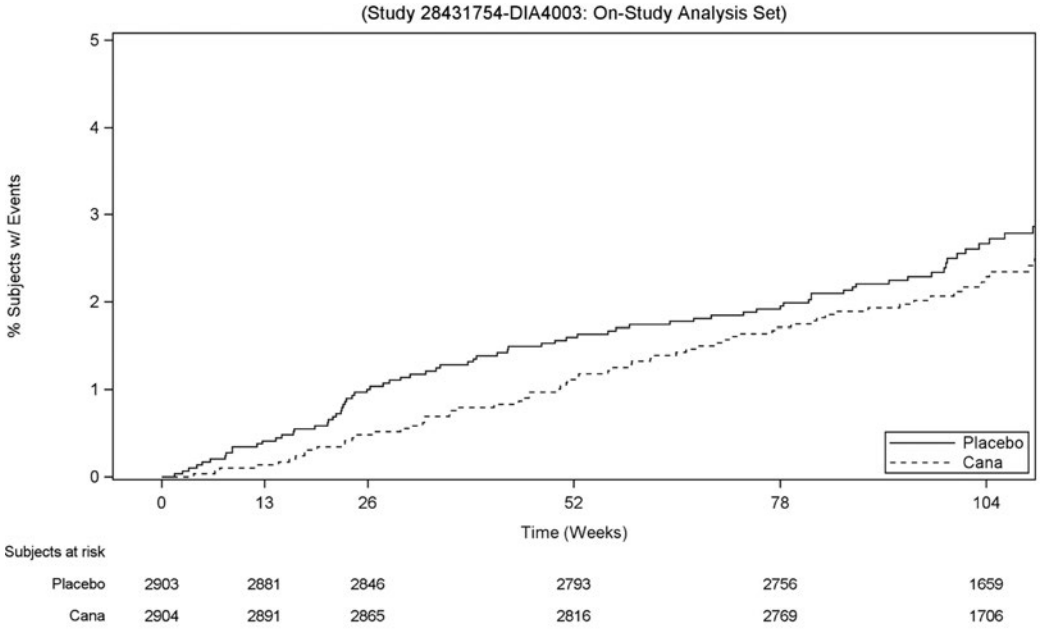
The median time to onset of adjudicated fracture was 898 days (range 782,1048 days) in DIA3008 and 348 days (range 270,413 days) in DIA4003.

Figure 22: DIA3008 - Kaplan-Meier Plot of Adjudicated Fractures



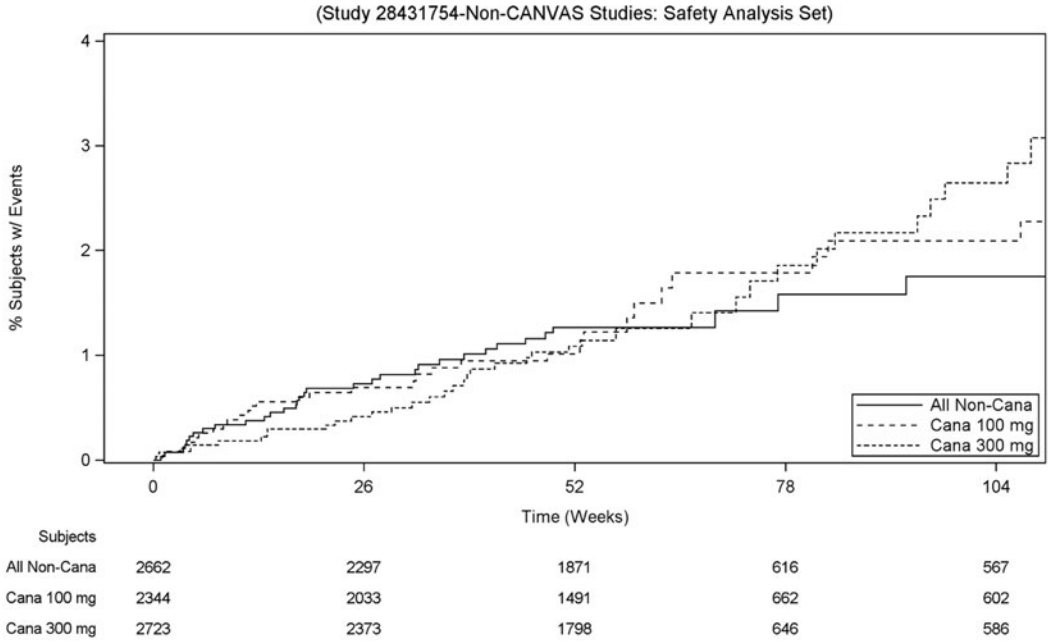
Source: ISS, Figure 5

Figure 23: DIA4003 - Kaplan-Meier Plot of Adjudicated Fractures



Source: ISS, Figure 6

Figure 24: Non-CANVAS Studies - Kaplan-Meier Plot of Adjudicated Fractures



Subjects					
All Non-Cana	2662	2297	1871	616	567
Cana 100 mg	2344	2033	1491	662	602
Cana 300 mg	2723	2373	1798	646	586

Source: ISS, Figure 7

There was some hypothesis that falls due to dizziness and loss of volume associated with canagliflozin may lead to fractures, as falls were increased with canagliflozin therapy; this is currently a labeled adverse reaction for canagliflozin. In DIA4003 only, CRF captured whether a fracture was associated with a fall. In the canagliflozin group, 72.1% of subjects with fracture reported a fall compared to 83.3% of subjects with fracture in the placebo group. Thus, this study did not show an imbalance in the falls in subjects who reported a fracture between canagliflozin and placebo.

Reviewer's comments: It is unclear why the increased risk of fractures that was observed with canagliflozin in DIA3008 was not observed in DIA4003. Risk of fracture is currently in the label as Warnings and Precautions; based on this final result, labeling changes in the language of fracture will be made to reflect that the increased risk of fracture was observed with canagliflozin only in DIA3008.

Diabetic Ketoacidosis (DKA):

Diabetic ketoacidosis was identified using a list of MedDRA terms prespecified and was adjudicated by an independent Clinical Event Committee (CEC). For AE that were not serious, only those presenting with signs and symptoms of DKA and/or those that required medical intervention were to be adjudicated, in order to eliminate those that had incidental findings of limited clinical relevance such as presence of urine ketones without symptoms or needing treatment. The main analysis of DKA was done in On-study analysis set, and a secondary analysis was done in On-treatment analysis set.

The adjudicated incidence rates of DKA were 0.62 and 0.29 per 1000 PY in the canagliflozin (14/5790 [0.2%]) and placebo (4/4344 [0.1%]) groups, respectively (IRD 0.33 [95% CI: -0.14, 0.80]), in the pooled data of DIA3008 and DIA4003.

Except for one subject in the placebo group, all other subjects did not report previous history of DKA. Five of 14 subjects in the canagliflozin group had autoimmune diabetes compared to none in the placebo group; one of these 5 subjects had reported history of type 1 diabetes mellitus (T1DM) and 4 subjects had evidence of latent autoimmune diabetes of adults (LADA) with positive GADA and insulin antibodies which was obtained after subjects had DKA. Precipitating factors (such as recent or concurrent illness or recent reduction in insulin dose) were identified in all placebo cases and in 75% (12/14) of canagliflozin cases. Except for one subject who was only on metformin before study entry in the canagliflozin group, all other subjects were on insulin treatment at the time of event, and concomitant blood glucose levels were >250 mg/dL in all cases. Aside from one subject in the canagliflozin group, all other cases were SAEs but none were fatal.

In the non-CANVAS pooled studies, the adjusted incidence rates of adjudicated DKA adverse events for canagliflozin was 0.56 per 1000 PY (3/5288 [0.1%]) compared to none in the non-canagliflozin groups. None of these 3 subjects had diagnosis of T1DM or LADA.

Changes in Bicarbonate:

The mean change in serum bicarbonate from baseline to Week 104 was slightly lower in the canagliflozin group (-0.6 mmol/L [SE 0.05]) compared to placebo (-0.3 mmol/L [SE 0.07]).

The pre-defined limit of change (PDLC) criterion for bicarbonate was <16 mEq/L. The incidence of *any* post-baseline value of bicarbonate <16 mEq/L was slightly higher in the combined canagliflozin group (4.6% [259/5616]) compared to placebo (3.6% [142/4208]), whereas the *last* post-baseline value of bicarbonate <16 mEq/L was similar between treatment groups (0.8% [46/5616] in the combined canagliflozin and 0.6% [25/4208] in the placebo group).

The significance of this finding in changes in bicarbonate is unclear.

Reviewer's comments: Numerically higher incidence of DKA was seen in the canagliflozin group compared to placebo, although the overall incidence is low. Ketoacidosis is a labeled adverse reaction for canagliflozin and for all SGLT2i drugs based on postmarketing reports.

7.3.5.2 Adverse Events of Interest Collected Only if They Were Serious or Led to Study Drug Discontinuation

As discussed previously, all AEs (serious and non-serious) were collected in DIA3008 through amendment INT-6 (date of January 7, 2014), after which only serious AEs or AEs that led to study drug discontinuation were collected except for those AEs in Section 7.3.5.1. In DIA4003, only serious AEs or AEs that led to study drug discontinuation were collected.

This section will discuss the following AEs of interest using a predefined MedDRA terms: female mycotic genital infection, urinary tract infection, osmotic diuresis, volume depletion, hypersensitivity/cutaneous reactions, hypoglycemia, pancreatitis, hepatic events, renal AEs.

All AEs (serious and non-serious) collected in DIA3008 through INT-6 will be summarized. Pooled AEs from DIA3008 and DIA4003 that were serious or led to study drug discontinuation will also be summarized. Pool of non-CANVAS studies will also be described.

Unless described in specific section as otherwise, most of these AEs were collected using a pre-specified list of MedDRA preferred terms and are described in Appendix 6 of the Integrated Statistical Analysis Plan.

Reviewer's comments: Grouping of terms were acceptable.

Female Mycotic Infection:

Table 56 summarizes the adjusted incidence rates of female mycotic genital infection adverse events in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison

Table 56: Female Mycotic Genital Infection Adverse Events (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=486)**	**All Cana (N=981)**
N (%)	21 (4.3%)	175 (17.8%)
Incidence rate (/1000 PY)	17.52	68.86
IRD vs placebo (95% CI)		51.33 (38.54, 64.12)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=1597)**	**Cana (N=2034)**
N (%)	0	1 (<0.1%)
Incidence rate (/1000 PY)		0.16
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=1597)**	**Cana (N=2034)**
N (%)	6 (0.4%)	44 (2.2%)
Incidence rate (/1000 PY)	1.48	7.03
Non-CANVAS All AEs	**All Non-Cana (N=1311)**	**All Cana (N=2595)**
N (%)	37 (2.8%)	279 (10.8%)
Incidence rate (/1000 PY)	29.17	107.06
IRD vs Non-Cana (95% CI)		77.89 (62.10, 93.68)
Serious AEs	0	0
AEs leading to discontinuation	0	14 subjects (0.5%); 5.37/1000 PY

Source: ISS Table TSFAE10_FGI_NC; CSR 3008, Table 72

Urinary Tract Infection (UTI):

Table 57 summarizes the adjusted incidence rates of UTIs in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison. The most frequently reported Preferred Terms were ‘urinary tract infection’ and ‘cystitis’.

The incidence rate of serious upper UTI was slightly higher in the combined canagliflozin group (1.30/1000 PY) compared to the placebo group (1.15/1000 PY).

Table 57: Urinary Tract Infection Adverse Events (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	134 (9.3%)	309 (10.7%)
Incidence rate (/1000 PY)	37.05	40.37
IRD vs placebo (95% CI)		3.32 (-4.42, 11.06)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	30 (0.7%)	37 (0.6%)
Incidence rate (/1000 PY)	2.65	2.01
IRD vs placebo (95% CI)		-0.64 (-1.81, 0.53)
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	5 (0.1%)	29 (0.5%)
Incidence rate (/1000 PY)	0.44	1.57
IRD vs placebo (95% CI)		1.13 (0.41, 1.85)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	169 (6%)	348 (6.6%)
Incidence rate (/1000 PY)	60.17	64.73
IRD vs Non-Cana (95% CI)		4.56 (-6.81, 15.93)
Serious AEs	2 (0.1%); 0.71/1000 PY	8 subjects (0.2%); 1.49/1000 PY
AEs leading to discontinuation	1 (0.1%); 0.36/1000 PY	9 subjects (0.2%); 1.67/1000 PY

Source: DIA3008 CSR, Table TSFAE00_S1_SC; ISS, Tables TSFAE00_SAE_B, TSFAE08_UTI_NC, TSFAE00D_SC

Osmotic Diuresis:

Table 58 summarizes the adjusted incidence rates of osmotic diuretic adverse events in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison. The most frequently reported Preferred Term was pollakiuria.

Table 58: Osmotic Diuretic Adverse Events (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	48 (3.3)	264 (9.1)
Incidence rate (/1000 PY)	13.27	34.49
IRD vs placebo (95% CI)		21.22 (15.58, 26.86)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	0	1 (<0.1)
Incidence rate (/1000 PY)	0	0.05
IRD vs placebo (95% CI)		0.05
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	4 (0.1)	14 (0.2)
Incidence rate (/1000 PY)	0.35	0.76
IRD vs placebo (95% CI)		0.41 (-0.16, 0.98)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	62 (2.2)	285 (5.4)
Incidence rate (/1000 PY)	22.08	53.01
IRD vs Non-Cana (95% CI)		30.93 (95% CI: 22.64, 39.22)
Serious AEs	0	0
AEs leading to discontinuation	1 subject (<0.1%)	3 subjects (0.1%)

Source: DIA3008 CSR, Table TSFAE00_S1_SC; ISS, Tables TSFAE00_SAE_B, TSFAE08_UTI_NC, TSFAE00D_SC, TSFAE24_OSMO_NC

Volume Depletion:

Table 59 summarizes the adjusted incidence rates of volume depletion adverse events in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison. Among serious volume depletion events in pooled DIA3008 and DIA4003, the most frequently reported Preferred Term was syncope (24 subjects [0.4%] in canagliflozin versus 15 subjects [0.3%] in placebo group).

Table 59: Volume Depletion Adverse Events (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	67 (4.6)	199 (6.9)
Incidence rate (/1000 PY)	18.52	26.00
IRD vs placebo (95% CI)		7.48 (1.73, 13.23)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	37 (0.9)	52 (0.9)
Incidence rate (/1000 PY)	3.27	2.82
IRD vs placebo (95% CI)		-0.45 (-1.77, 0.87)
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	7 (0.2)	7 (0.1)
Incidence rate (/1000 PY)	0.62	0.38
IRD vs placebo (95% CI)		-0.24 (-0.82, 0.34)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	47 (1.7)	119 (2.3)
Incidence rate (/1000 PY)	16.73	22.13
IRD vs Non-Cana (95% CI)		5.40 (-0.87, 11.67)
Serious AEs	3 subjects (0.1%)	8 subjects (0.2%)
AEs leading to discontinuation	2 subjects (0.1%)	3 subjects (0.1%)

Source: DIA3008 CSR, Table TSFAE00_S1_SC; ISS, Tables TSFAE00_SAE_B, TSFAE08_UTI_NC, TSFAE00D_SC, TSFAE30_VD_NC

Hypersensitivity/Cutaneous Reactions:

Table 60 summarizes the adjusted incidence rates of hypersensitivity/cutaneous reactions in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison.

Table 60: Hypersensitivity/Cutaneous Reactions (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	22 (1.5)	66 (2.3)
Incidence rate (/1000 PY)	6.08	8.62
IRD vs placebo (95% CI)		2.54 (-0.80, 5.88)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	8 (0.2)	13 (0.2)
Incidence rate (/1000 PY)	0.71	0.71
IRD vs placebo (95% CI)		0 (-0.66, 0.66)
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	2 (<0.1)	8 (0.1)
Incidence rate (/1000 PY)	0.18	0.43
IRD vs placebo (95% CI)		0.25 (-0.23, 0.73)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	23 (0.8)	44 (0.8)
Incidence rate (/1000 PY)	8.19	8.18
IRD vs Non-Cana (95% CI)		-0.01 (95% CI: -4.22, 4.20)
Serious AEs	1 subject (<0.1%)	5 subjects (0.1%)
AEs leading to discontinuation	2 subjects (0.1%)	5 subjects (0.1%)

Source: DIA3008 CSR, Table TSFAE00_S1_SC; ISS, Tables TSFAE00_SAE_B, TSFAE08_UTI_NC, TSFAE00D_SC, TSFAE19_HSEN_NC

Hypoglycemia:

In both DIA3008 and DIA4003, no discontinuation criteria for hypoglycemia were provided. In DIA3008, all hypoglycemic episodes were collected up to Amendment INT-6 and had a supplemental hypoglycemia eCRF. If the investigator thought the epiosode was considered to be an AE of hypoglycemia, then separate AE of hypoglycemia was reported on the AE eCRF, and this was used for the analysis of AE of hypoglycemia.

After INT-6, only SAEs of hypoglycemia or AEs leading to discontinuation were collected. In DIA4003, only SAEs of hypoglycemia or AEs leading to discontinuation were collected during the whole study. Investigators were to report hypoglycemia using standard definition of a SAE when reporting hypoglycemia.

In DIA3008 through INT-6, subjects were counted as having documented hypoglycemia episode when there was either a biochemically-confirmed hypoglycemic episode (concurrent fingerstick or plasma glucose ≤70 mg/dL) and/or severe hypoglycemia (requiring assistance or led to seizure or loss of consciousness). The overall incidence of documented hypoglycemia up to INT-6 in DIA3008 are summarized in Table 61. The overall incidence of subjects with any documented hypoglycemia was numerically higher in the canagliflozin groups (48.7% in 100 mg and 50.9% in 300 mg) compared to placebo (46.2%). The event rates of documented hypoglycemia episodes were similar across treatment groups (2.95 in placebo and 2.94 in the combined canagliflozin group).

Table 61: Documented Hypoglycemic Episodes through January 7, 2014 in DIA3008 INT-6 (On-Treatment Analysis Set)

	Placebo (N=1441) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1441) n (%)	Cana Total (N=2886) n (%)
Subjects with any documented hypoglycemia	666 (46.2)	704 (48.7)	734 (50.9)	1438 (49.8)
Biochemically documented hypoglycemia	665 (46.1)	701 (48.5)	731 (50.7)	1432 (49.6)
Severe hypoglycemia	69 (4.8)	74 (5.1)	88 (6.1)	162 (5.6)
Subjects with episodes of biochemically documented hypoglycemia*	665 (46.1)	701 (48.5)	731 (50.7)	1432 (49.6)
≤ 70 mg/dL (3.9 mmol/L)	665 (46.1)	701 (48.5)	731 (50.7)	1432 (49.6)
< 56 mg/dL (3.1 mmol/L)	369 (25.6)	370 (25.6)	366 (25.4)	736 (25.5)
< 36 mg/dL (2.0 mmol/L)	49 (3.4)	52 (3.6)	48 (3.3)	100 (3.5)
Total number of episodes of documented hypoglycemia	10685	11131	11348	22479
Subjects with numbers of documented hypoglycemia	666 (46.2)	704 (48.7)	734 (50.9)	1438 (49.8)
1 episode	134 (9.3)	134 (9.3)	141 (9.8)	275 (9.5)
2 episodes	69 (4.8)	81 (5.6)	75 (5.2)	156 (5.4)
≥ 3 episodes	463 (32.1)	489 (33.8)	518 (35.9)	1007 (34.9)
Event rate of documented hypoglycemia per subject-year exposure**	2.95	2.89	2.99	2.94

Note: Count and (%) are based on number of subjects, not number of episodes.
Note: *Subjects with any biochemically documented hypoglycemia episodes; Results of LOW are included in all the three glucose categories (i.e., = 70, <56, and/or <36 mg/dL).
Note: A subject may be counted in each of the three glucose categories.
Note: Glucose data could be reported in either mg/dL or mmol/L units. No conversion between the two units was made.
Note: The comparison between the reported glucose values and the cutoffs was based on the units in which the glucose values were reported.
Note: **The Denominator is the total of each subject's exposure of the study medication plus 30 days up to 07Jan2014.
Source: DIA3008 CSR, Table 87

Severe hypoglycemia episodes up to INT-6 in DIA3008 are summarized in Table 62. Numerically higher incidence of severe hypoglycemia occurred with canagliflozin (5.1% in 100 mg and 6.1% in 300 mg) compared to placebo group (4.8%). The event rate of severe hypoglycemia episodes per subject-year was same across treatment group (0.04).

Table 62: Severe Hypoglycemia Episodes through January 7, 2014 in DIA3008 INT-6 (On-Treatment Analysis Set)

	Placebo (N=1441) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1441) n (%)	Cana Total (N=2886) n (%)
Subjects with any severe hypoglycemia	69 (4.8)	74 (5.1)	88 (6.1)	162 (5.6)
Requiring the assistance of others to treat	68 (4.7)	67 (4.6)	82 (5.7)	149 (5.2)
With loss of consciousness	20 (1.4)	15 (1.0)	19 (1.3)	34 (1.2)
With a seizure	5 (0.3)	8 (0.6)	8 (0.6)	16 (0.6)
Total number of episodes	140	148	162	310
Subjects with numbers of severe hypoglycemia	69 (4.8)	74 (5.1)	88 (6.1)	162 (5.6)
1 episode	46 (3.2)	51 (3.5)	62 (4.3)	113 (3.9)
2 episodes	8 (0.6)	10 (0.7)	10 (0.7)	20 (0.7)
≥ 3 episodes	15 (1.0)	13 (0.9)	16 (1.1)	29 (1.0)
Event rate per subject-year exposure*	0.04	0.04	0.04	0.04

Note: Count (%) is based on number of subjects, not number of events.
Note: *The Denominator is the total of each subject's exposure of the study medication plus 30 days up to 07Jan2014.
Source: DIA3008 CSR, Table 88

Reviewer's comment: Looking at data collected through supplemental eCRF for hypoglycemia, there was no significant differences in the incidence of hypoglycemia between canagliflozin and placebo groups in documented hypoglycemia and severe hypoglycemic episodes.

Hypoglycemia reported as AE are summarized in Table 63 in DIA3008, both by itself through INT-6 and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison.

Table 63: Hypoglycemia Adverse Events (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	168 (11.7)	383 (13.3)
Incidence rate (/1000 PY)	46.45	50.04
Serious AEs	6 (0.4) 1.66/1000 PY	15 (0.5%) 1.96/1000 PY
AEs leading to discontinuation	1 (0.1) 0.28/1000 PY	4 (0.1) 0.52/1000 PY
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	18 (0.4)	30 (0.5)
Incidence rate (/1000 PY)	1.59	1.63
IRD vs placebo (95% CI)		0.04 (-0.92, 1.00)
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	3 (0.1)	6 (0.1)
Incidence rate (/1000 PY)	0.26	0.33
IRD vs placebo (95% CI)		0.07 (-0.39, 0.53)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	260 (9.2)	296 (5.6)
Incidence rate (/1000 PY)	92.57	55.06
IRD vs Non-Cana (95% CI)		-37.5 (-50.4, -24.6)
Serious AEs	2 (0.1%) 0.71/1000 PY	4 (0.1%) 0.74/1000 PY
AEs leading to discontinuation	5 (0.2%) 1.78/1000 PY	4 (0.1%) 0.74/1000 PY

Source: DIA3008 CSR Table 89; ISS TSFAE00_SAE_B_NC, TSFAE00D_SC, TSFAE00_SAE_B, TSFAE12_HYPO_NC

Pancreatitis:

Potential pancreatitis and related AEs identified through a pre-specified MedDRA terms were sent to an independent Pancreatitis Adjudication Committee (PAC) for adjudication. PAC were required to adjudicate the severity and identify any precipitating factors for cases adjudicated as acute pancreatic event.

The primary analysis of pancreatitis is based on adjudicated events in the On-treatment analysis set. Eighty-one events were submitted for adjudication, and of these, 16 were categorized as acute pancreatitis, 28 as not acute pancreatitis and 37 as undetermined. Because adjudication process was implemented close to the completion of the studies, measurements of amylase/lipase or imaging associated with these terms were not always available leading to a higher number of cases “unable to determine”.

In the pooled DIA3008 and DIA4003 data, the adjusted incidence rates of pancreatitis for canagliflozin was 0.49/1000 PY (9/5790 [0.2%]) and 0.35/1000 PY (4/4344 [0.1%]) for placebo.

An additional 3 cases of acute pancreatitis were identified in the canagliflozin group (and none in the non-canagliflozin group) through adjudication in the non-CANVAS pooled studies, and the incidence rate was 0.56/1000 PY in the combined canagliflozin group.

Reviewer's comment: Although there is a numerical imbalance not favoring canagliflozin for pancreatitis, the overall number of events is small. These data do not show an increased risk for pancreatitis with canagliflozin.

Hepatic Events:

Table 64 summarizes the adjusted incidence rates of hepatic adverse events in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison.

Table 64: Hepatic Adverse Events (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	33 (2.3)	57 (2.0)
Incidence rate (/1000 PY)	9.12	7.45
IRD vs placebo (95% CI)		-1.67 (-5.38, 2.04)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	9 (0.2)	15 (0.3)
Incidence rate (/1000 PY)	0.79	0.81
IRD vs placebo (95% CI)		0.02 (-0.67, 0.71)
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	3 (0.1)	7 (0.1)
Incidence rate (/1000 PY)	0.26	0.38
IRD vs placebo (95% CI)		0.12 (-0.35, 0.59)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	30 (1.1)	37 (0.1)
Incidence rate (/1000 PY)	10.68	6.88
IRD vs Non-Cana (95% CI)		-3.80 (-8.29, 0.69)
Serious AEs	2 (0.1%) 0.71/1000 PY	2 (<0.1%) 0.37/1000 PY
AEs leading to discontinuation	2 (0.1%) 0.71/1000 PY	1 (<0.1%) 0.19/1000 PY

Source: DIA3008 CSR, Table TSFAE00_S1_SC; ISS, Tables TSFAE00_SAE_B, TSFAE08_UTI_NC, TSFAE00D_SC, TSFAE26_HE_NC

Reviewer's comments: There does not appear to a concern for increased hepatic events with canagliflozin based on the incidence of hepatic AEs in DIA3008, pooled SAEs and AEs leading to discontinuation from DIA3008 and DIA4003 studies, and pooled non-CANVAS studies.

Four fatal cases, all from DIA3008, are summarized here (there were no serious hepatic AEs which were fatal in DIA4003):

- Subject (b) (6) **(canagliflozin 300 mg)** was a 66-year old man with a history of hypertension, hyperlipidemia, myocardial ischemia, and non-alcoholic steatohepatitis. At baseline, ALT was 44 U/L (nl 6-43 U/L), AST was 53 U/L (nl 11-36 U/L), GGT was 430 U/L (nl 10-50 U/L), and alkaline phosphatase (ALP) and bilirubin were normal. On Day 640, he became dizzy and fell at home due to ethanol consumption. He suffered a cranial contusion. On Day 661, his ALT was 194 IU (nl 0-41 IU), AST 161 U/L (nl 0-37 U/L), GGT 1109 IU (nl 5-45 IU) and bilirubin 51.7 µmol/L (nl 0-20.6 µmol/L). On Day 666, ultrasound showed hepatomegaly. An abdominal CT scan with contrast on Day 685 showed a slightly enlarged liver. He received spironolactone for abnormal liver function. Hepatomegaly and abnormal liver function was reported to have resolved on Day 695. On Day 728, AST was 37 U/L, GGT was 176 U/L and ALT, ALP and bilirubin were within normal. At Week 182 visit (Day 1274), AST was 111 U/L meeting the PDLC criteria of 3x ULN. ALT was 37 U/L, GGT was 721 U/L and ALP and bilirubin were normal. On Day 1820, AST was 71 U/L, GGT was 601 U/L, bilirubin was 32 µmol/L and ALT and ALP were normal. On Day 1851, ultrasound showed hepatic fibrosis, and he was hospitalized. On an unspecified day, nausea, decreased appetite, and recent consumption of more than the usual intake of alcohol were reported. Hepatic fibrosis was reported as resolved with sequelae on Day 1855 and he was discharged with lactulose and tiapride. On Day 1899 he was re-hospitalized for liver insufficiency, hepatic failure, and study drug was discontinued. On Day 1905, he was diagnosed with incarcerated umbilical hernia and underwent surgical repair. He died of hepatic failure the same day. ***Reviewer's comment: This patient had history of non-alcoholic steatohepatitis, and he also reported some degree of alcohol consumption around the time of hepatic event, confounding the assessment of causality related to the study drug.***

- Subject (b) (6) **(canagliflozin 100 mg)** was a 63-year old man with history of hyperlipidemia and cholelithiasis. At baseline, his AST was 22 U/L (nl 11-36 U/L), ALT was 18 U/L (nl 6-43 U/L), ALP was 80 U/L (nl 35-125 U/L) and bilirubin was 12 µmol/L (nl 3-21 µmol/L). On Day 1914, he was hospitalized with symptoms of jaundice and abdominal pain for 2 weeks, associated with tea colored urine. On an unspecified day, laboratory test showed AST of 82, ALT of 33, ALP of 486, total bilirubin of 147, direct bili of 109, and indirect bili of 38 (units not provided), and physical examination showed palpable liver and mild tenderness. On Day 1920, CT scan of abdomen were suggestive of liver infarction and showed bone and lung metastasis. He was diagnosed with SAE of gall bladder cancer and non-alcoholic steatohepatitis. On Day 1921 he was discharged, and he died at home on Day 1927. ***Reviewer's comment: This***

patient had history of cholelithiasis, and his liver impairment and death appear to be due to gall bladder cancer.

- Subject (b) (6) **(canagliflozin 300 mg)** was a 56-year old man with a history of heart failure, multiple coronary stents, dyslipidemia, abnormal liver function tests, elevated GGT, splenomegaly and fatty liver. No alcohol history was obtained. At baseline, ALT was 67 U/L (nl 6-43 U/L), AST was 76 U/L (nl 11-36), ALP was 75 U/L (nl 35-131), bilirubin was 15.39 µmol/L (nl 3.42-20.52), and GGT was 383 U/L (nl 10-61). He had no SAE during the study, and at the last visit on Day 1857 his liver function tests were within normal limits. On an unspecified day, the site discovered his name in obituaries, and the death certificate indicated that he died on Day 1891 of multiple organ dysfunction syndrome and decompensated cirrhosis, with onset 12 and 24 hours of death respectively. Autopsy was not done. His last dose of study drug was about Day 1890. ***Reviewer's comment: This subject had past medical history that included abnormal liver function tests, splenomegaly and fatty liver. His liver function tests were normal at the last visit, and it's unclear if his sudden onset of decompensated cirrhosis could be related to canagliflozin or due to his underlying comorbidities.***

- Subject (b) (6) **(canagliflozin 100 mg)** was a 69-year old man with history of hyperlipidemia, obesity, hypertension, left ventricular dysfunction and hypertrophy, and relevant concomitant drugs include atorvastatin and ezetimide. His hepatic tests were normal. On Day 754 he was hospitalized for SAE of right ventricular failure, myocardial ischemia, and non-serious AE of hepatic cirrhosis and splenomegaly. He had 8-day history of abdominal distension, exertional dyspnea, bilateral pedal edema, disturbed sleep and black colored stools. Abdominal ultrasound showed liver cirrhosis, portal hypertension, splenomegaly and moderate ascites. Laboratory tests showed total bilirubin of 1.34 mg/dL (nl 0.1-1.2 mg/dL), AST 48 U/L (nl <40 U/L), and AST 34 U/L (nl <42 U/L). Study drug was stopped, and treatment was given including spironolactone, but he developed hepatic encephalopathy. UTI was also reported on an unspecified day. On Day 757, CT scan and MRI of abdomen and pelvis showed cirrhosis of liver with portal hypertension and mild ascities. A focal lesion in the left lobe of liver was reported with malignant transformation, considered hepatocellular carcinoma. On Day 815, he was withdrawn from study, and on Day 826 he died due to hepatic cancer and hepatic encephalopathy. ***Reviewer's comments: This patient developed hepatic cirrhosis that eventually was determined to be hepatic cancer.***

There was one subject with a serious hepatic AE (hepatic cirrhosis) leading to discontinuation who had a PDLC elevation of ALT >3x ULN and AST >3x ULN in DIA3008:

- Subject (b) (6) **(canagliflozin 300 mg)**. A 62-year old man was on multiple therapy before study entry including sulfonylureas, metformin, sitagliptin, atorvastatin, telmisartan, and aspirin. At baseline ALT was 66 U/L (nl range 6-43), AST was 57 U/L (nl range 11-36), alkaline phosphatase (ALP) 144 U/L (nl range 35-125), GGT 390 U/L (nl range 10-50 U/L) and bilirubin was 18 µmol/L (nl range 3-21). On Day 911, the subject met the PDLC criteria for ALT >3x ULN (136 U/L), AST >3x ULN (124 U/L); alkaline phosphatase was 436 U/L, GGT was 1170 U/L and bilirubin was 35 µmol/L. An ultrasound was done, and it reported mild chronic liver disease On Day 1558, local lab showed ALT 71 U/L (nl 20-42), AST 92 U/L (nl 20-40, ALP 264 U/L (nl 58-128), and total bilirubin 2.57 mg/dL (nl 0.1-1.2), and a non-serious AE of worsening liver function was reported and he was treated with ursodeoxycholic acid. On Day 1559, subject was diagnosed with non-serious AE of hepatic cirrhosis and splenomegaly, and endoscopy showed Grade 1 esophageal varices. Treatment with the study drug was discontinued (last dose on Day 1571) and the subject was withdrawn from the study on Day 1612 due to hepatic cirrhosis, splenomegaly, erosive duodentitis, varices esophageal and hypochromic anemia. On Day 1612, ALT was 48 U/L, AST was 98 U/L, ALP was 292 U/L, and bilirubin was 41 µmol/L. ***Reviewer's comments: This subject entered the study with elevated liver function tests at baseline, and was on atorvastatin before study entry and during study participation which can cause liver impairment.***

Changes in Liver Enzymes:

The mean and median changes from baseline to Week 104 in ALT, AST, alkaline phosphatase, and bilirubin in DIA3008 were small and not clinically relevant (not shown here; see Table 103 in DIA3008 CSR).

The PDLC criteria for increase in ALT or AST were evaluated based on 'any' and 'last' (defined as up to a maximum of 2 days after the last dose of study drug) post-baseline value, and are summarized in Table 65 and Table 66 for the pooled DIA3008 and DIA4003 data.

The increased incidence of ALT elevations seen in the pooled data is mainly driven by the results from DIA3008 as shown in Table 67, as ALT elevations were balanced between treatment groups in DIA4003 (not shown here, see Table 73 of DIA4003 CSR).

Table 65: Subjects with Serum Alanine Aminotransferase (ALT) Elevations in the Pooled DIA3008 and DIA4003 Set (On-treatment Analysis Set)

	Placebo n (%)	Cana n (%)
Alanine Aminotransferase (U/L)		
Any post-baseline value	4208	5616
ALT > 3xULN	34 (0.8)	78 (1.4)
ALT > 5xULN	14 (0.3)	29 (0.5)
ALT > 8xULN	7 (0.2)	10 (0.2)
ALT > 10xULN	5 (0.1)	6 (0.1)
ALT > 20xULN	1 (<0.1)	2 (<0.1)
ALT > 3X ULN and Bilirubin > 2X ULN	0	3 (0.1)
Incidence rate per 1000 person-years exposure		
ALT > 3xULN	3.09	4.33
ALT > 5xULN	1.27	1.61
ALT > 8xULN	0.64	0.56
ALT > 10xULN	0.45	0.33
ALT > 20xULN	0.09	0.11
ALT > 3X ULN and Bilirubin > 2X ULN	0.00	0.17
Last post-baseline value	4208	5616
ALT > 3xULN	6 (0.1)	24 (0.4)
ALT > 5xULN	3 (0.1)	14 (0.2)
ALT > 8xULN	0	5 (0.1)
ALT > 10xULN	0	2 (<0.1)
ALT > 20xULN	0	1 (<0.1)
ALT > 3X ULN and Bilirubin > 2X ULN	0	3 (0.1)

Note: Percentages calculated with the number of subjects per time interval as denominator.
Note: ALT >3X ULN and Serum Bilirubin >2X ULN is composite criterion with the Serum Bilirubin elevation >2X ULN within 30 days following the ALT elevation >3X ULN.
Note: Exposure-adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with an elevation divided by the total person-year exposure for all treated subjects who have a post baseline lab value).
Source: ISS, Table 82

As seen in Table 66, similar pattern was seen with AST elevations, but the differences from placebo were less than the differences seen with ALT, and again this was mainly due to data from DIA3008.

Table 66: Subjects with Serum Aspartate Aminotransferase (AST) Elevations in the Pooled DIA3008 and DIA4003 Set (On-treatment Analysis Set)

	Placebo n (%)	Cana n (%)
Aspartate Aminotransferase (U/L)		
Any post-baseline value	4205	5613
AST > 3Xuln	26 (0.6)	51 (0.9)
AST > 5xULN	11 (0.3)	20 (0.4)
AST > 8xULN	3 (0.1)	7 (0.1)
AST > 10xULN	2 (<0.1)	5 (0.1)
AST > 20xULN	0	1 (<0.1)
AST > 3X ULN and Bilirubin > 2X ULN	0	4 (0.1)
Incidence rate per 1000 person-years exposure		
AST > 3xULN	2.36	2.83
AST > 5xULN	1.00	1.11
AST > 8xULN	0.27	0.39
AST > 10xULN	0.18	0.28
AST > 20xULN	0.00	0.06
AST > 3X ULN and Bilirubin > 2X ULN	0.00	0.22
Last post-baseline value	4205	5613
AST > 3xULN	6 (0.1)	16 (0.3)
AST > 5xULN	2 (<0.1)	9 (0.2)
AST > 8xULN	0	4 (0.1)
AST > 10xULN	0	3 (0.1)
AST > 3X ULN and Bilirubin > 2X ULN	0	3 (0.1)

Note: Percentages calculated with the number of subjects per time interval as denominator.
Note: AST >3X ULN and Serum Bilirubin >2X ULN is composite criterion with the Serum Bilirubin elevation >2 X ULN within 30 days following the AST elevation >3x ULN.
Note: Exposure adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with an elevation divided by the total person-year exposure for all treated subjects who have a post baseline lab value.)
Source: ISS, Table 83

As shown in Table 67, the incidence of 'any' post-baseline elevations in ALT was not consistently higher with canagliflozin or dose-dependent when exposure is considered. The number of events in the incidence of 'last' post-baseline elevations in ALT mostly occurred with canagliflozin but the number of events was small.

Table 67: Subjects with Serum Alanine Aminotransferase (ALT) Elevations in DIA3008 (On-Treatment Analysis Set)

	Placebo n (%)	Cana 100 mg n (%)	Cana 300 mg n (%)	Cana Total n (%)
Alanine Aminotransferase (U/L)				
Any post-baseline value	1395	1413	1382	2795
ALT > 3xULN	14 (1.0)	26 (1.8)	33 (2.4)	59 (2.1)
ALT > 5xULN	5 (0.4)	11 (0.8)	13 (0.9)	24 (0.9)
ALT > 8xULN	4 (0.3)	5 (0.4)	4 (0.3)	9 (0.3)
ALT > 10xULN	2 (0.1)	4 (0.3)	1 (0.1)	5 (0.2)
ALT > 20xULN	0	1 (0.1)	1 (0.1)	2 (0.1)
ALT > 3X ULN and Bilirubin > 2X ULN	0	0	3 (0.2)	3 (0.1)
Incidence rate per 1000 person-years exposure				
ALT > 3xULN	2.41	4.08	5.22	4.65
ALT > 5xULN	0.86	1.73	2.06	1.89
ALT > 8xULN	0.69	0.78	0.63	0.71
ALT > 10xULN	0.34	0.63	0.16	0.39
ALT > 20xULN	0.00	0.16	0.16	0.16
ALT > 3X ULN and Bilirubin > 2X ULN	0.00	0.00	0.47	0.24
Last post-baseline value	1395	1413	1382	2795
ALT > 3xULN	1 (0.1)	6 (0.4)	13 (0.9)	19 (0.7)
ALT > 5xULN	0	6 (0.4)	6 (0.4)	12 (0.4)
ALT > 8xULN	0	2 (0.1)	3 (0.2)	5 (0.2)
ALT > 10xULN	0	1 (0.1)	1 (0.1)	2 (0.1)
ALT > 20xULN	0	0	1 (0.1)	1 (<0.1)
ALT > 3X ULN and Bilirubin > 2X ULN	0	0	3 (0.2)	3 (0.1)

Note: Percentages calculated with the number of subjects per time interval as denominator.
Note: ALT >3X ULN and Serum Bilirubin >2X ULN is composite criterion with the Serum Bilirubin elevation >2X ULN within 30 days following the ALT elevation >3X ULN.
Note: Exposure adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with an elevation divided by the total person-year exposure for all treated subjects who have a post baseline lab value.)
Source: DIA3008 CSR, Table 104

Potential Hy's Law:

In the combined DIA3008 and DIA4003, there were 4 subjects in the canagliflozin group that met the biochemical definition of Hy's law with an ALT and/or AST >3x ULN and bilirubin >2x ULN.

Subject	Treatment Group	Possible alternative etiology
(b) (6)	Canagliflozin 300 mg	Cholangiocarcinoma
	Canagliflozin 300 mg	Gastric adenocarcinoma
	Canagliflozin 300 mg	Cardiac failure
	Canagliflozin 300 mg	Steatohepatitis

*Cases reviewed during the original NDA submission and agreed with the Applicant's assessment.

Two of these 4 cases were reviewed during the original NDA review when they submitted interim data for DIA3008, and we agreed with the Applicant's assessment for

the likely alternative etiology for the hepatic event. Two remaining cases are described here:

- Subject (b) (6) (canagliflozin 300 mg) was a 59 year-old man had medical history of hyperlipidemia, multiple myocardial infarctions, coronary artery bypass, and coronary angioplasty. At baseline, his liver function test was within normal limits. On Day 262, he was hospitalized with dizziness, dehydration, weakness, and blurred vision; his fasting glucose level was 27.9 mmol/L and systolic blood pressure was 77 mmHg. He had SAE of diabetes mellitus inadequate control and hypotension. He reported overeating and missing the morning dose of insulin, he received treatment and his study drug was interrupted, and these events were resolved on Day 263. During the study participation, his liver enzymes were within normal range. He completed the study on Day 2160, and he had gross swelling of thighs, elevated jugular venous pressure, crepitation on both lung bases, and was hospitalized; SAE of cardiac failure was reported. His ALA was 410 U/L (9.5x ULN; nl 6-43), AST was 413 U/L (11.5x ULN; 11-36 U/L), alkaline phosphatase was 236 U/L (1.9x ULN; nl 35-125 U/L), bilirubin was 49 µ/mol/L (2x ULN; nl 3-21), and GGT of 365 U/L (7x ULN; nl 10-50) on the same day. He received treatment with furosemide, fluid restriction, and lost weight. He was discharged and his cardiac failure resolved on Day 2196. ***Reviewer's comment: This patient's transient liver enzyme elevation is likely due to cardiac failure leading to liver congestion.***

- Subject (b) (6) (canagliflozin 300 mg) had a history of steatohepatitis and post-cholecystectomy syndrome. At baseline, ALT was 17 U/L (nl 6 to 34), AST was 15 U/L (nl 9 to 34), bilirubin was 14 µmol/L (nl 3 to 21), ALP was 105 U/L (nl 35 to 123 U/L), and GGT was elevated at 140 U/L (nl 4 to 49 U/L). On Day 368, the AST was elevated >3x ULN at 104 U/L and ALT was >2x ULN at 70 U/L and bilirubin was >2x ULN at 45 µmol/L. Subject was asymptomatic and remained on study drug, and lab values returned to normal range at the next study visit. ***Reviewer's comment: This transient increase in AST and bilirubin values may have been related to the patient's underlying liver disease conditions and it is unclear how much canagliflozin treatment may have caused it.***

Reviewer's comment: Overall, the evaluation of hepatic events and changes in liver enzymes do not suggest that canagliflozin causes liver impairment.

Renal Adverse Events (including Acute Kidney Injury):

Table 68 summarizes the adjusted incidence rates of renal adverse events, including AKI, in DIA3008, both by itself and pooled with DIA4003 for SAEs and AEs leading to discontinuation, and in the pool of non-CANVAS studies for comparison.

Table 68: Renal Adverse Events, Including AKI (On-Treatment Analysis Set)

DIA3008 through INT-6	**Placebo (N=1441)**	**All Cana (N=2886)**
N (%)	63 (4.4)	151 (5.2)
Incidence rate (/1000 PY)	17.42	19.73
IRD vs placebo (95% CI)		2.31 (-3.05, 7.67)
Serious AEs: DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	37 (0.9)	46 (0.8)
Incidence rate (/1000 PY)	3.27	2.50
IRD vs placebo (95% CI)		-0.77 (-2.06, 0.52)
AEs leading to discontinuation – DIA3008 and DIA4003 Pooled	**Placebo (N=4344)**	**Cana (N=5790)**
N (%)	25 (0.6)	41 (0.7)
Incidence rate (/1000 PY)	2.21	2.23
IRD vs placebo (95% CI)		0.02 (-1.10, 1.14)
Non-CANVAS All AEs	**All Non-Cana (N=2826)**	**All Cana (N=5288)**
N (%)	68 (2.4)	129 (2.4)
Incidence rate (/1000 PY)	24.21	23.99
IRD vs Non-Cana (95% CI)		-0.22 (-7.35, 6.91)
Serious AEs	6 (0.2%)	8 (0.2%)
AEs leading to discontinuation	16 (0.6%)	37 (0.7%)

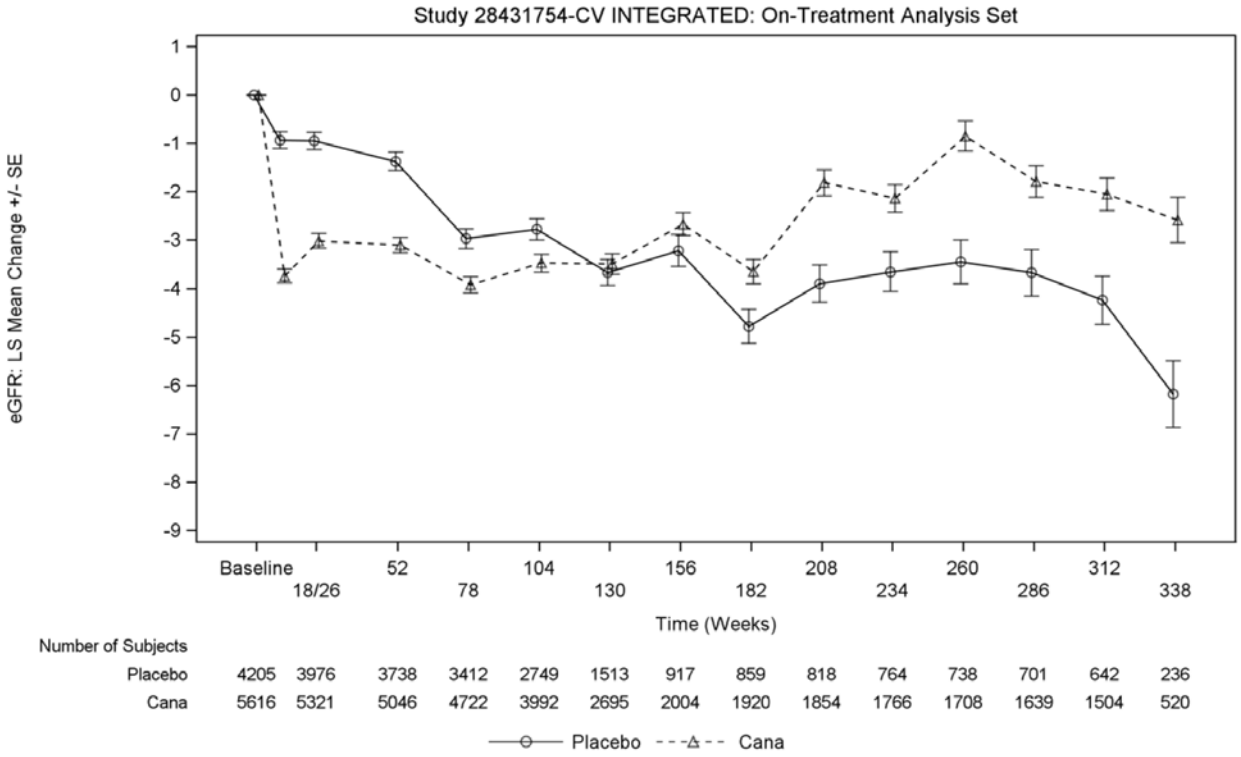
Source: DIA3008 CSR, Table TSFAE00_S1_SC; ISS, Tables TSFAE00_SAE_B, TSFAE08_UTI_NC, TSFAE00D_SC, TSFAE28_RN_NC

Changes in estimated glomerular filtration rate (eGFR):

Renal function was measured with eGFR at least every 26 weeks; in DIA4003, it was measured at Week 13, Week 26, and then every 26 weeks thereafter, and in DIA3008 it was measured at Week 6, Week 18, Week 39, Week 52, and then every 26 weeks thereafter. In DIA4003, off-treatment serum creatinine was measured 30 days after study drug discontinuation to evaluate eGFR changes off-drug.

In the pooled DIA3008 and DIA4003 dataset, the largest decline in mean eGFR in the canagliflozin group occurred at the earliest time point and did not decline further over the course of treatment, whereas the eGFR progressively declined in the placebo group (Figure 25). This steep decline was dose-dependent and more pronounced with 300 mg dose (Figure 27).

Figure 25: LS Mean Change From Baseline in eGFR Over Time in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)



Source: ISE, Table 30

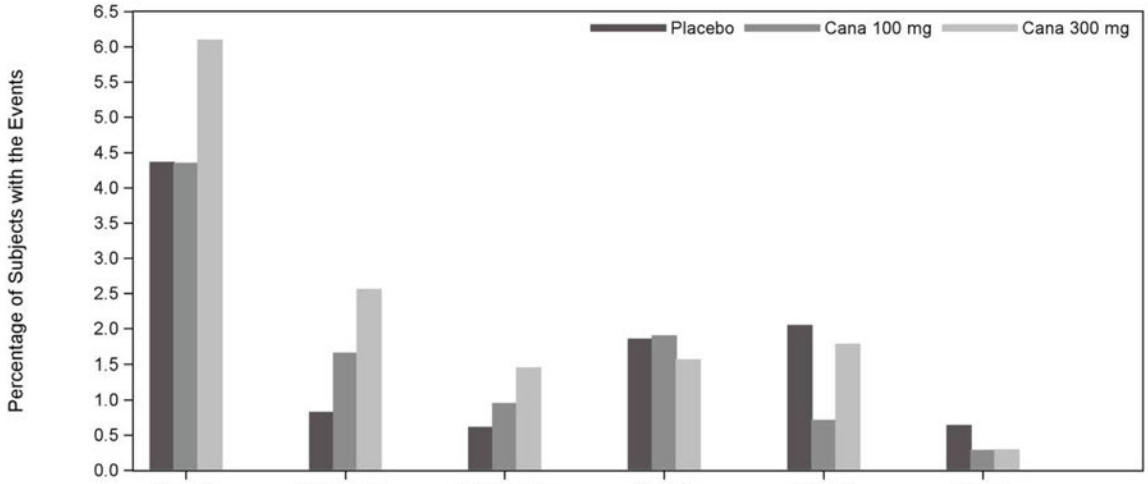
In DIA4003, during the on-treatment period with median follow-up of 2 years, the adjusted mean changes from baseline to last measurement during treatment were -2.36 $\pm$0.26 mL/min/1.73m^2 in the canagliflozin group and -1.69$\pm$0.26 mL/min/1.73m^2 in the placebo group. In the off-drug period measuring the last on-treatment measurement to last follow-up measurement (median follow-up of 30 days), the canagliflozin group had an increase of 2.78 $\pm$0.23 mL/min/1.73m^2 and the placebo group had an adjusted mean eGFR decrease of -0.53 $\pm$0.24 mL/min/1.73m^2.

Reviewer's comment: The off-treatment measurement of serum creatinine obtained about 30 days after discontinuation of study drug appears to suggest that the decrease in eGFR seen with canagliflozin group is reversed after discontinuation of study drug. This is reassuring and may indicate that decline in eGFR seen with canagliflozin may be hemodynamically related rather than a result of kidney injury.

Because it is known that renal-related changes with canagliflozin is dose-related, I will discuss results from DIA3008 here.

In DIA3008 up to INT-6, the incidence rate of renal AEs was higher in the canagliflozin 300 mg group (23.17/1000 PY) compared to placebo (17.42/1000 PY). Most of these were non-serious renal AEs, however, and most renal-related imbalance between treatment groups is apparent during the first year of treatment (Figure 26).

Figure 26: Summary of Subjects with Renal-Related AEs through January 7, 2014 (DIA3008 INT-6; On-treatment Analysis Set)

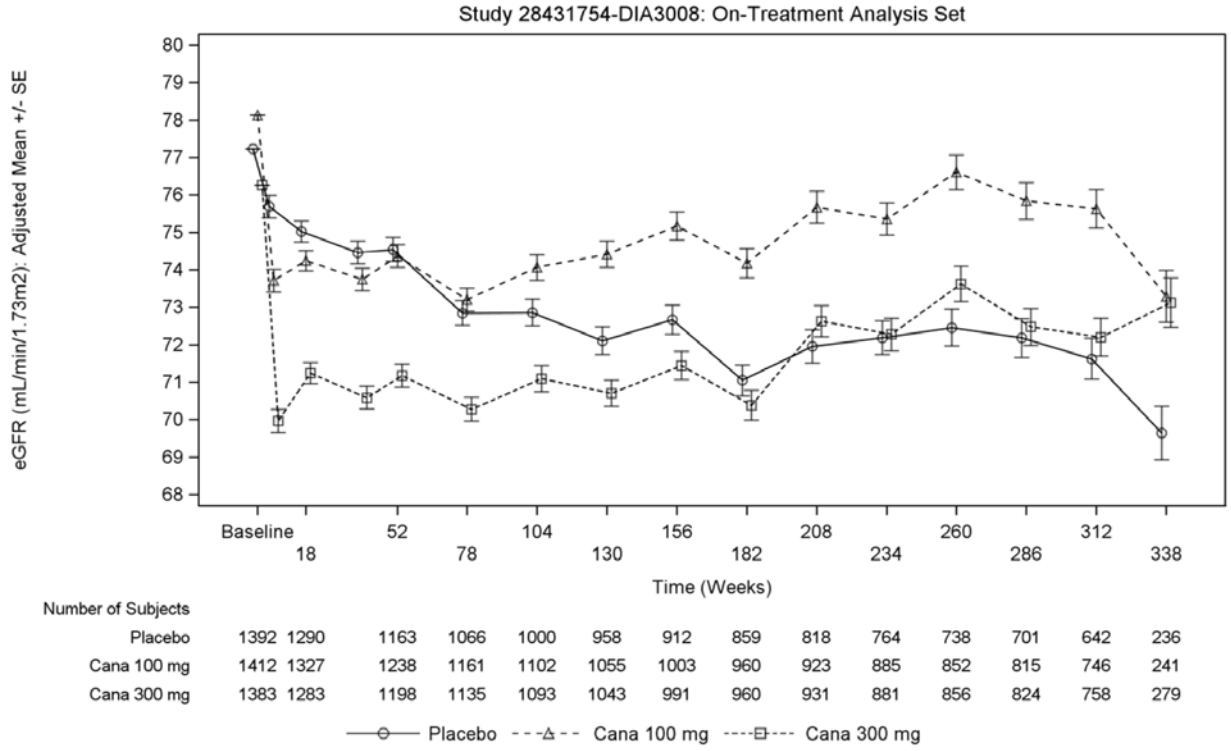


	Overall	0-6 months	>6-12 months	Year 2	Year 3	Year 4
Placebo	63/1441	12/1441	8/1295	22/1182	21/1021	6/928
Cana 100 mg	63/1445	24/1445	13/1351	24/1256	8/1116	3/1025
Cana 300 mg	88/1441	37/1441	19/1298	19/1210	20/1117	3/1007

Note: Percentages calculated with the number of subjects at risk for the AE at the start of each time interval as the denominator.
Note: A subject can be counted in more than one time interval if the subject had multiple AEs across the time intervals.
Source: DIA3008 CSR, Figure 33

As shown in Figure 27, an initial sharp dose-related decline in eGFR was seen mostly during the first year of treatment with canagliflozin and stabilized, whereas in the placebo group there was a progressive decline in eGFR over time.

Figure 27: Adjusted Mean eGFR Over Time in Each Treatment Group in DIA3008



Source: DIA3008 CSR, Figure 16

Table 69 summarizes renal-related SAEs by treatment group in DIA3008. Unlike the overall renal-related AEs, incidence of renal-related SAEs were not dose-related as canagliflozin 100 mg had the highest incidence of renal-related SAEs (3.55/1000 PY) compared to placebo (3.05/1000 PY) or canagliflozin 300 mg (1.71/1000 PY). The most common SAEs were acute kidney injury, followed by renal impairment.

Table 69: Serious Renal-Related Adverse Events in DIA3008 (On-Treatment Analysis Set)

Dictionary-Derived Term	Placebo (N=1441) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1441) n (%)	Cana Total (N=2886) n (%)
Total no. subjects with the AEs	18 (1.2)	23 (1.6)	11 (0.8)	34 (1.2)
Incidence rate per 1000 person-years	3.05	3.55	1.71	2.64
Acute kidney injury	13 (0.9)	15 (1.0)	8 (0.6)	23 (0.8)
Azotaemia	0	1 (0.1)	0	1 (<0.1)
Blood creatinine increased	1 (0.1)	1 (0.1)	0	1 (<0.1)
Glomerular filtration rate decreased	1 (0.1)	0	0	0
Oliguria	1 (0.1)	0	0	0
Renal failure	2 (0.1)	2 (0.1)	0	2 (0.1)
Renal impairment	1 (0.1)	6 (0.4)	3 (0.2)	9 (0.3)

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.
Source: DIA3008, Table 97

The incidence rate of renal-related AEs leading to discontinuation in DIA3008 was highest in the placebo group compared to canagliflozin group as shown in Table 70. The most common reason for discontinuation was renal impairment, followed by increased blood creatinine.

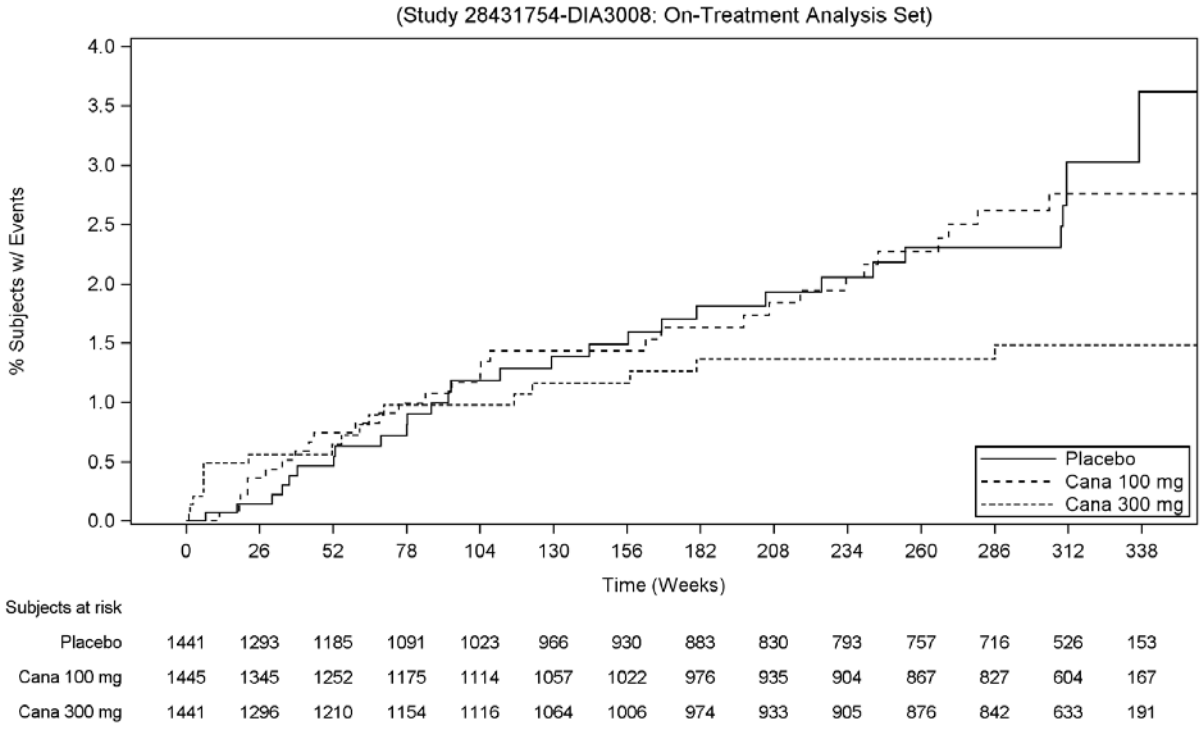
Table 70: Renal-Related Adverse Events Leading to Study Drug Discontinuation in DIA3008 (On-Treatment Analysis Set)

Dictionary-Derived Term	Placebo (N=1441) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1441) n (%)	Cana Total (N=2886) n (%)
Total no. subjects with the AEs	15 (1.0)	14 (1.0)	11 (0.8)	25 (0.9)
Incidence rate per 1000 person-years	2.54	2.16	1.71	1.94
Acute kidney injury	2 (0.1)	3 (0.2)	2 (0.1)	5 (0.2)
Azotaemia	0	1 (0.1)	0	1 (<0.1)
Blood creatinine increased	4 (0.3)	5 (0.3)	2 (0.1)	7 (0.2)
Blood urea increased	2 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Glomerular filtration rate decreased	1 (0.1)	0	1 (0.1)	1 (<0.1)
Prerenal failure	0	0	1 (0.1)	1 (<0.1)
Renal failure	4 (0.3)	2 (0.1)	0	2 (0.1)
Renal impairment	5 (0.3)	4 (0.3)	5 (0.3)	9 (0.3)

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.
Source: DIA3008, Table 98

Overall, renal related SAEs or AEs leading to study drug discontinuation were dose-related during the first 26 weeks, as shown in Figure 28.

Figure 28: Kaplan-Meier Plot of Time to the First Renal-Related Serious Adverse Events or Adverse Events Leading to Discontinuation of Study Drug in DIA3008



Source: DIA3008, Figure 36

In DIA4003, the incidence rate of renal-related SAEs were 2.17/1000 PY in the canagliflozin group compared to 3.51/1000 PY in the placebo group. The incidence of renal-related AEs leading to study drug discontinuation was 2.89/1000 PY in the canagliflozin group compared to 1.84/1000 PY in the placebo group.

Reviewer's comments: Acute kidney injury and impairment in renal function is a labeled event for canagliflozin. The renal adverse event data based on results of these two studies is consistent with labeled information.

Nephrolithiasis:

The AEs for nephrolithiasis were searched using the following MedDRA Preferred Terms: nephrocalcinosis, nephrolithiasis, stag horn calculus, calculus bladder, calculus prostatic, calculus ureteric, calculus urethral, and calculus urinary.

The incidence of nephrolithiasis in DIA3008 up to INT-6 are summarized in Table 71, which do not show an increased risk with canagliflozin treatment. Of these, 7 subjects (0.5%; 1.19/1000 PY) in placebo, 3 subjects (0.2%; 0.46/1000 PY) in canagliflozin 100 mg, and 3 subjects (0.2%; 0.47/1000 PY) in canagliflozin 300 mg had serious nephrolithiasis. No subject discontinued study drug due to nephrolithiasis.

Table 71: Nephrolithiasis Adverse Events by Preferred Term through January 7, 2014 (DIA 3008 INT-6, On-treatment Analysis Set)

Dictionary-Derived Term	Placebo (N=1441) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1441) n (%)	Cana Total (N=2886) n (%)
Total no. subjects with the AEs	22 (1.5)	21 (1.5)	11 (0.8)	32 (1.1)
Incidence rate per 1000 person-years	6.08	5.45	2.90	4.18
Calculus bladder	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Calculus urinary	2 (0.1)	3 (0.2)	0	3 (0.1)
Nephrolithiasis	19 (1.3)	17 (1.2)	9 (0.6)	26 (0.9)

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.
Source: DIA3008, Table 100

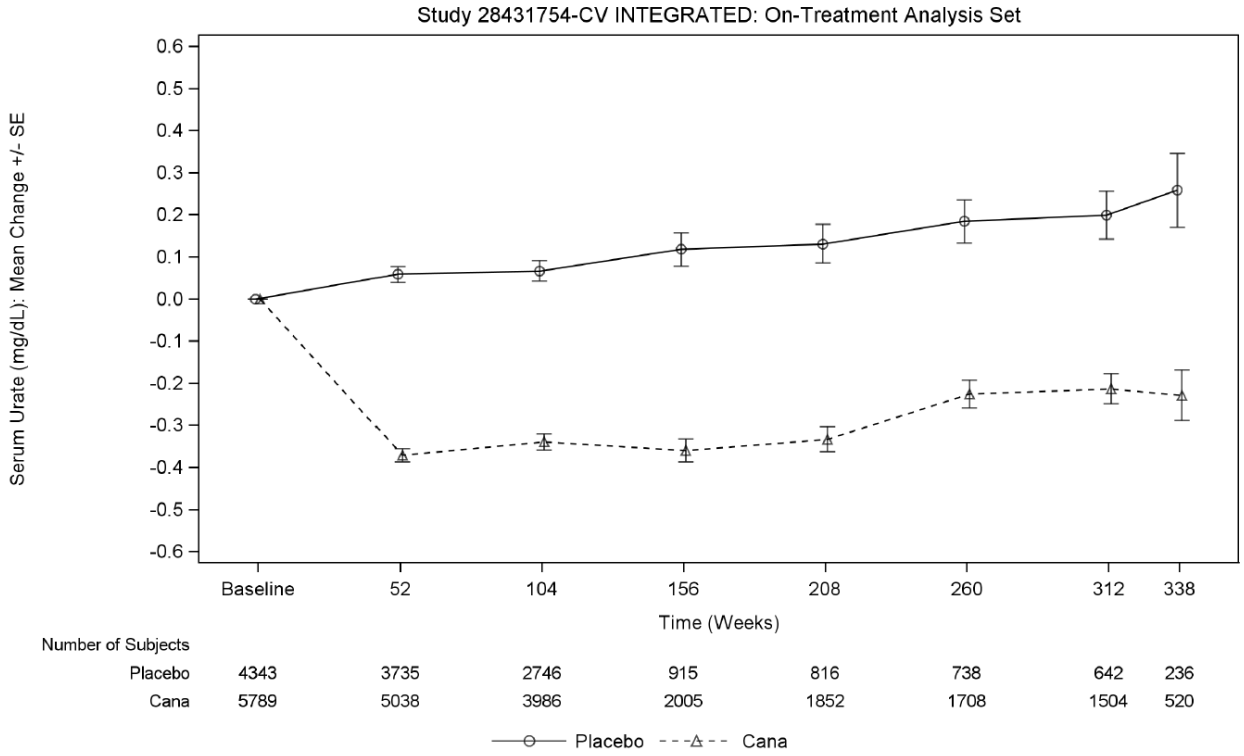
In DIA4003, the incidence rate of serious nephrolithiasis AEs were 1.45/1000 PY (8 subjects [0.3%]) in the canagliflozin group compared to 0.37/1000 PY (2 subjects [0.1%]) in the placebo group, with IRD of 1.08 (95% CI: -0.22, 2.37). One subject in the canagliflozin group discontinued the study drug due to nephrolithiasis (0.18/1000 PY).

In the pooled DIA3008 and DIA4003, the adjusted-incidence rate of serious nephrolithiasis AEs were 0.76/1000 PY in the combined canagliflozin and 0.79/1000 PY in the placebo groups.

Serum Urate:

As shown in Figure 29, most of the mean reduction in serum urate in the canagliflozin group occurred by Week 52 with gradual increase thereafter, whereas a very slow increase in serum urate was seen in the placebo group. The adjusted incidence rate of "any" post-baseline value of urate <LLN and >25% decrease from baseline was higher in the canagliflozin group compared to placebo (5.00 vs 3.09/1000 PY), but this was not seen for "last" post-baseline value. The mean percent changes from baseline to Week 104 in serum urate was -6.0% in the canagliflozin group and 1.2% in the placebo group.

Figure 29: Mean Change From Baseline in Serum Urate Over Time in Pooled DIA3008 and DIA4005



Source: ISS, GSFLABC09C

Reviewer's comment: Decreases in the serum urate levels have been observed with canagliflozin, which may lead to nephrolithiasis. However, DIA3008 did not show an imbalance in nephrolithiasis whereas DIA4003 showed a small imbalance in serious nephrolithiasis not favoring canagliflozin, but this imbalance in DIA4003 was based on small number of subjects.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As common AEs were identified during the original application review, and since the AE collection was streamlined after original NDA approval to collect only SAEs or AEs that led to study drug discontinuation except for certain AE of interest, the safety evaluation for this efficacy submission was mainly focused on SAEs (discussed in Section 7.3.2), AEs that led to study discontinuation (discussed in Section 7.3.3), and AEs of interest (discussed in Section 7.3.5).

7.4.2 Laboratory Findings

Laboratory values were evaluated with summary statistics for mean changes over time and by the incidence of laboratory values meeting the PDLC criteria.

Laboratory analytes were assessed using results obtained up to a maximum of 2 days of the last does of double-blind drug.

Laboratory evaluations of changes in renal function (i.e., eGFR) are discussed in section 7.3.5.2 under renal events, the changes in liver function are discussed in section 7.3.5.2 under hepatic events, changes in serum urate levels are discussed in section 7.5.3.2 under nephrolithiasis, and the changes in bicarbonate are discussed in section 7.3.5.1 under diabetic ketoacidosis.

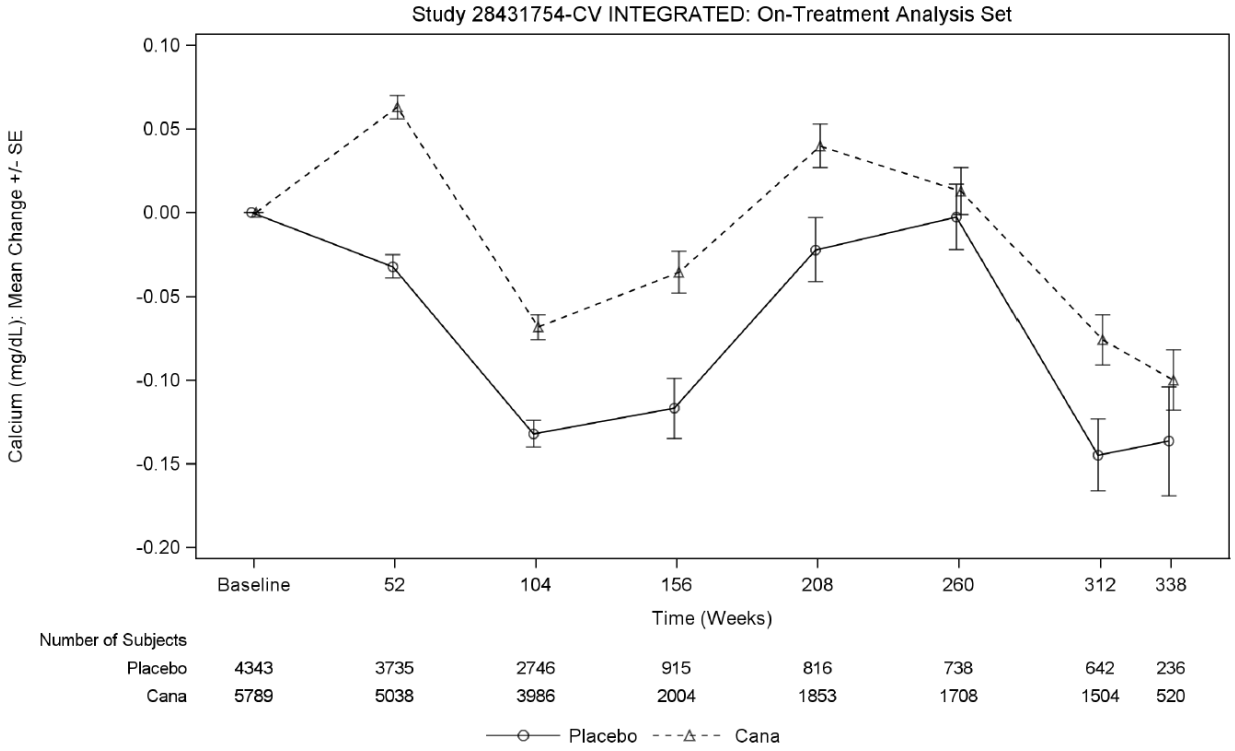
Changes from baseline in laboratory values were measured at Week 18 in DIA3008 and at Week 26 in DIA4003, and then every 26 weeks thereafter. Since measurements beyond Week 104 include mainly subjects from DIA3008, up to Week 104 are discussed for changes from baseline. For analyses of PDLC, all available data were included.

Serum Chemistry:

Calcium:

The adjusted-incidence rate of subjects meeting *any* post-baseline calcium >ULN and >10% increase from baseline was higher in the canagliflozin compared to placebo (6.17 vs 4.46/1000 PY), whereas the incidence of subjects meeting the *last* post-baseline value was similar between two groups (0.2% vs 0.1%). The median percent change of calcium from baseline to Week 104 was -0.8% in the canagliflozin group and -1.5% in the placebo group.

Figure 30: Mean Change From Baseline in Calcium Over Time in Pooled DIA3008 and DIA4003

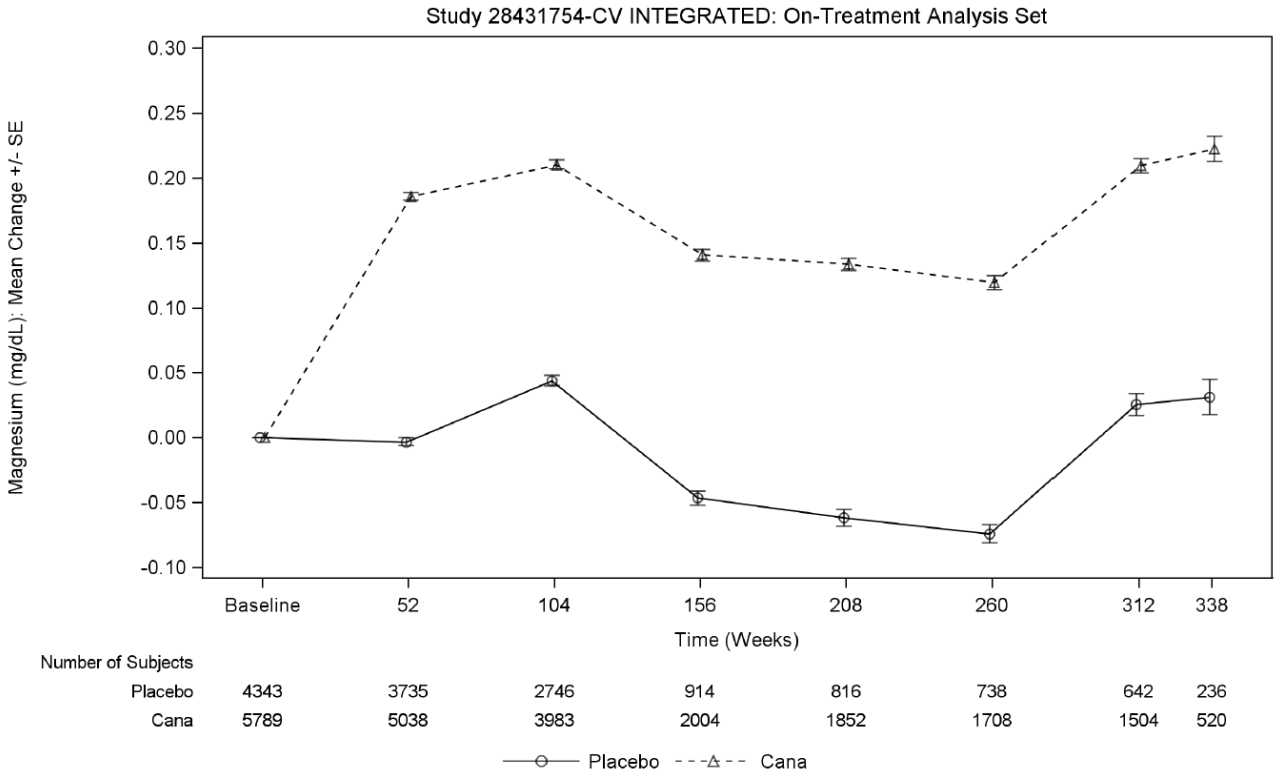


Source: ISS, GSFLAB09G

Magnesium:

The adjusted-incidence rate of subjects meeting *any* post-baseline magnesium <LLN and >25% decrease from baseline was lower in the canagliflozin compared to placebo (2.17 vs 7.55/1000 PY). And the adjusted-incidence rate of subjects meeting *any* post-baseline magnesium >ULN and >25% increase from baseline was higher in the canagliflozin compared to placebo (4.61 vs 1.45/1000 PY). The median percent change of magnesium from baseline to Week 104 was 10.5% in the canagliflozin group and 1.5% in the placebo group. As shown in Figure 31, the mean increase in magnesium in the canagliflozin occurred by Week 52.

Figure 31: Mean Change From Baseline in Magnesium (mg/dL) Over Time in Pooled DIA3008 and DIA4003



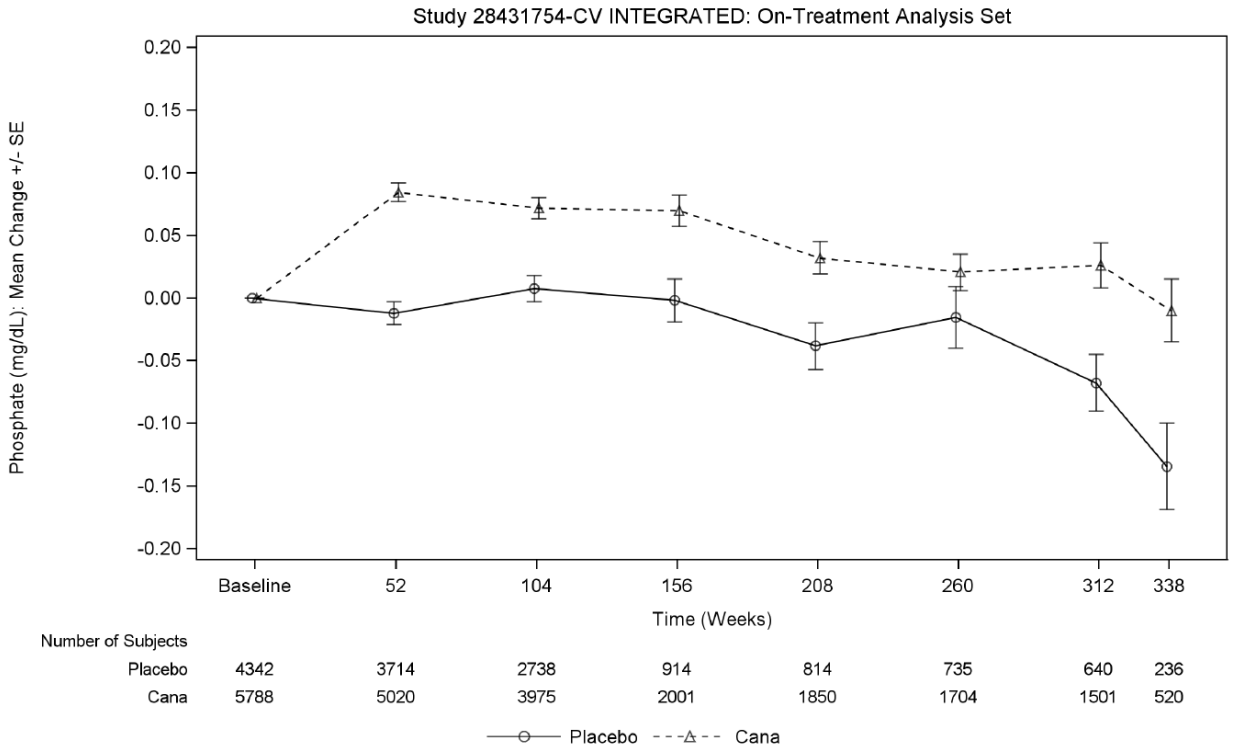
Source: ISS, Figure GSFLABC09D

Reviewer's comments: Increases in serum magnesium is described in the labeling for canagliflozin.

Phosphate:

The adjusted-incidence rate of subjects meeting *any* post-baseline phosphate >ULN and >25% increase from baseline was higher in the canagliflozin compared to placebo (9.56 vs 6.64/1000 PY). And the adjusted-incidence rate of subjects meeting *any* post-baseline phosphate <LLN and >25% decrease from baseline was lower in the canagliflozin compared to placebo (2.44 vs 5.27/1000 PY). These were not seen for the *last* post-baseline value however. The median percent change of phosphate from baseline to Week 104 was 2.4% in the canagliflozin group and 0% in the placebo group.

Figure 32: Mean Change From Baseline in Phosphate Over Time in Pooled DIA3008 and DIA4003



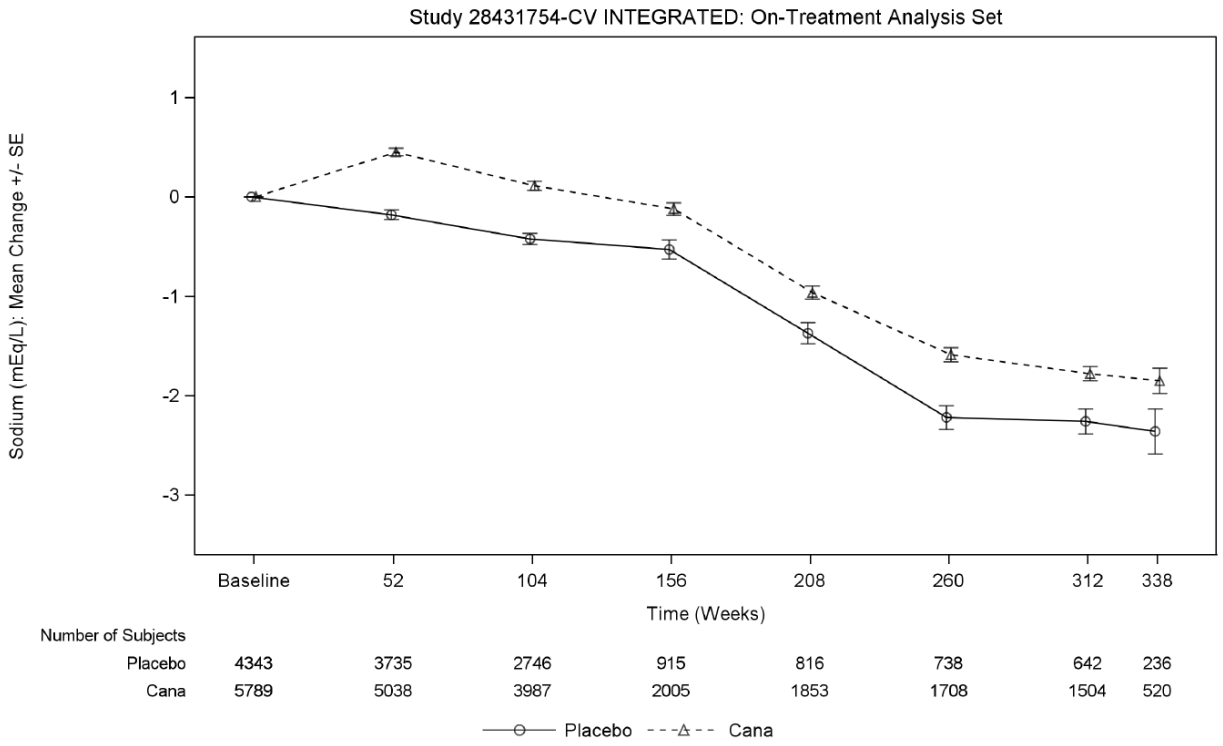
Source: ISS, GSFLABC09E

Reviewer's comments: Increases in serum phosphate is described in the labeling for canagliflozin.

Sodium:

The adjusted-incidence rate of subjects meeting *any* post-baseline sodium <LLN and a decrease of >5 mEq/L from baseline was lower in the canagliflozin compared to placebo (16.39 vs 26.37/1000 PY). And the adjusted-incidence rate of subjects meeting *any* post-baseline sodium >ULN and an increase of >5 mEq/L from baseline was higher in the canagliflozin compared to placebo (13.61 vs 8.46/1000 PY). These were not seen for the *last* post-baseline value however. The median percent change of sodium from baseline to Week 104 did not change in neither treatment groups.

Figure 33: Mean Change From Baseline in Sodium Over Time in Pooled DIA3008 and DIA4003



Source: ISS, GSFLAB09F

Potassium:

The incidence rate of treatment-emergent serum potassium values outside the PDLC at 'any' and 'last' post-baseline value is summarized in Table 72.

In the pooled dataset of DIA3008 and DIA4003, the adjusted-incidence rate of subjects meeting *any* post-baseline 'potassium >ULN and >15% increase from baseline' was not notably different between canagliflozin and placebo groups (23.78 vs 22.28/1000 PY). Imbalance between treatment groups was also not seen for the *last* post-baseline values. The mean baseline value of potassium was 4.4 mEq/L in both canagliflozin and placebo treatment groups, and the mean value in each treatment varied +0.1 mEq/L at few measured time points during the course of study but was not persistently elevated (not shown here; see TSFLAB01 in ISS). At Week 104, the mean change in potassium from baseline to Week 104 did not change in either canagliflozin or placebo group.

Table 72: Subjects with Serum Potassium (mEq/L) Values Outside Pre-Defined Limit with Risk Difference and 95% CI in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)

Potassium	Placebo (N=4207)	Cana (N=5616)
	N (%)	N
Any post-baseline value, n (%); /1000 patient-years		
Potassium <LLN & >15% Decrease from Baseline	70 (1.7); 6.36	107 (1.9); 5.94
Potassium >ULN & >15% Increase from Baseline	245 (5.8); 22.28	428 (7.6); 23.78
Potassium ≥6.5 mEq/L	23 (0.5); 2.09	37 (0.7); 2.06
Last post-baseline value, n (%)		
Potassium <LLN & >15% Decrease from Baseline	21 (0.5)	21 (0.4)
Potassium >ULN & >15% Increase from Baseline	49 (1.2)	65 (1.2)
Potassium ≥6.5 mEq/L	3 (0.1)	4 (0.1)

Note: Percentage is calculated with the number of subjects per time interval as denominator.
*Rate=exposure-adjusted incidence rate per 1000 patient-years (total number of subjects with an elevation or reduction divided by the total person-year exposure for all treated subjects who have a post baseline lab value); IRD=incidence rate difference
Source: ISS, TSFLABC04E

Reviewer's comment: During the original review of canagliflozin, changes in serum potassium levels were observed to occur early with canagliflozin treatment and imbalances appear to attenuate during the course of treatment. Therefore, PDLC of 'any' is more likely to capture potassium changes that may occur during the course of treatment rather than 'last' value. Therefore, following will mostly discuss 'any' PDLC changes.

The PDLC criteria for serum potassium levels were evaluated in subgroup analyses based on eGFR category and are shown in Table 73 for pooled DIA3008 and DIA4003 safety dataset. For PDLC of any 'potassium >ULN and >15% increase from baseline' there was a trend for imbalances not favoring canagliflozin compared to placebo in the subgroup of subjects with baseline eGFR of <60 mL/min/1.72m^2 (i.e, in both subgroups of 45 to <60 and 30 to <45 mL/min/1.72m^2). For PDLC of any 'potassium ≥6.5 mEq/L', the imbalance not favoring canagliflozin vs placebo was notable only in subgroup of subjects with baseline eGFR of 30 to <45 mL/min/1.72m^2. However, the overall observed imbalances were small.

Table 73: Subjects with Post-Baseline Serum Potassium Values Outside Pre-Defined Limit with Risk Difference and 95% CI by Baseline eGFR Category in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)

Any post-baseline potassium value	Placebo	Cana	Cana vs Placebo
Baseline eGFR Group: ≥60, N	**3317**	**4544**	**IRD (95% CI)**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	57 (1.7%); 6.42	81 (1.8%); 5.38	-1.04 (-3.09, 1.01)
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	188 (5.7%); 21.16	328 (7.2%); 21.79	0.63 (-3.21, 4.47)
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	15 (0.5%); 1.69	22 (0.5); 1.46	-0.23 (-1.31, 0.85)
Baseline eGFR Group: 45 to <60, N	**649**	**787**	
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	10 (1.5%); 6.19	16 (2.0%); 7.18	0.99 (-4.45, 6.43)
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	39 (6.0%); 24.12	70 (8.9%); 31.42	7.30 (-3.37, 17.97)
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	4 (0.6%); 2.47	7 (0.9%) 3.14	0.67 (-3.09, 4.43)
Baseline eGFR Group: 30 to <45, N	**224**	**273**	
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	3 (1.3); 6.47	9 (3.3); 13.01	6.54 (-6.18, 19.26)
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	17 (7.6%); 36.65	30 (11.0%); 43.38	6.73 (-17.18, 30.64)
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	4 (1.8%); 8.62	8 (2.9%); 11.57	2.95 (-10.04, 15.94)

IRD=incidence rate difference in /1000 patient-years
Source: ISS, Table 81

Reviewer's comments: In the pooled dataset of DIA3008 and DIA4003, all canagliflozin doses were combined regardless of dose and compared to combined placebo group. In the original review of canagliflozin, imbalance in the incidence of increases in potassium levels appeared to be dose-dependent and was observed mostly in 300 mg group compared to placebo and not always with 100 mg group. Since only DIA3008 had separate canagliflozin treatment groups by dose (i.e.,100 mg and 300 mg), DIA3008 results are described further below to show comparison of each dose group of canagliflozin against the placebo group.

In DIA3008, there was no notable imbalance in the incidence of subjects with PDLC of any 'potassium >ULN and >15% increase from baseline', and a small imbalance in the incidence of subjects with PDLC of any 'potassium ≥6.5 mEq/L' with canagliflozin 300 mg group vs placebo and not with canagliflozin 100 mg (Table 75).

Table 74: Subjects with Post-Baseline Serum Potassium Values Outside Pre-Defined Limit with Risk Difference and 95% CI by Baseline eGFR Category in DIA3008 (On-Treatment Analysis Set)

	Placebo	Cana 100 mg	Cana 300 mg
Any post-baseline value, N	**1394**	**1413**	**1382**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	31 (2.2%); 5.35	32 (2.3%); 5.02	37 (2.7%); 5.86
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	161 (11.5%); 27.77	150 (10.6%); 23.55	168 (12.2%); 26.59
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	17 (1.2%); 2.93	10 (0.7); 1.57	22 (1.6%); 3.48

Source: CSR DIA3008, Table 102

Because changes in potassium levels have shown to be dose-dependent, subgroup analyses based on baseline eGFR category for 3 PDLC criteria related to potassium levels by treatment groups in DIA3008 are shown in Table 75. Overall, the incidence between treatment groups were comparable in each eGFR category, except for the incidence of subjects with any 'potassium ≥6.5 mEq/L', where the incidence was higher with canagliflozin 300 mg compared to placebo in subjects with baseline eGFR 30 to <45 mL/min/1.72m^2, but the overall number of subjects was small (Table 75).

Table 75: Subjects With 'Any' Post-Baseline Serum Potassium Values Outside Pre-Defined Limit by Baseline eGFR Category in DIA3008 (On-Treatment Analysis Set)

Any post-baseline potassium value	Placebo	Cana 100	Cana 300
Baseline eGFR Group: ≥60, N	**1148**	**1205**	**1147**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	24 (2.1%); 4.93	23 (1.9%); 4.17	29 (2.5%); 5.42
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	127 (11.1%); 26.08	119 (9.9%); 21.57	133 (11.6); 24.83
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	11 (1.0%); 2.26	8 (0.7); 1.45	13 (1.1%); 2.43
Baseline eGFR Group: 45 to <60, N	**197**	**159**	**174**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	7 (3.6%); 9.10	5 (3.2%); 7.38	5 (2.9%); 7.00
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	24 (12.2%); 31.21	23 (14.6%); 33.93	22 (12.6%); 30.79
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	4 (2%); 5.20	1 (0.6%) 1.48	3 (1.7%); 4.20
Baseline eGFR Group: 30 to <45, N	**47**	**48**	**59**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	0	4 (8.3%); 24.08	2 (3.4%); 8.31
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	10 (21.3%); 65.90	8 (16.7%); 48.16	12 (22%); 54.03
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	2 (4.3%) 13.18	1 (2.1%) 6.02	6 (10.2%); 24.94

Source: DIA3008, TSFLAB04EEM

In subjects with baseline eGFR 30 to <45 mL/min/1.72m^2, similar trend of imbalance with canagliflozin vs placebo in the incidence of subjects with any post-baseline

potassium ≥6.5 mEq/L was seen only in the 300 mg group in those who were using RAAS inhibitor and/or with potassium sparing diuretics at baseline, as shown in table below. In fact, it appears that most subjects in this eGFR subgroup were on RAAS inhibitor with or without potassium sparing diuretics at baseline. However, the imbalance between treatment groups is based on small number of subjects. Of note, this imbalance was not seen in subjects with baseline eGFR 45 to <60 or ≥60 mL/min/1.72m^2 (data not shown; see Clinical Overview Tables 16 and 17).

Any post-baseline potassium value	Placebo	Cana 100	Cana 300
Baseline eGFR Group: 30 to <45 and on RAAS inhibitor at Baseline	**44**	**41**	**48**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	0	3 (7.3%); 20.83	1 (2.1%); 5.02
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	10 (22.7%); 72.70	7 (17.1%); 48.60	12 (25%); 60.28
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	2 (4.5%) 14.54	1 (2.4%) 6.94	5 (10.4%); 25.12
Baseline eGFR Group: 30 to <45 and on RAAS inhibitor and/or Potassium Sparing Diuretics at Baseline	**44**	**42**	**50**
Potassium <LLN & >15% Decrease from Baseline – n (%); rate/1000 PY	0	3 (7.1%); 20.64	1 (2.0%); 4.98
Potassium >ULN & >15% Increase from Baseline – n (%); rate/1000 PY	10 (22.7%); 72.70	7 (16.7%); 48.17	12 (24%); 59.77
Potassium ≥6.5 mEq/L – n (%); rate/1000 PY	2 (4.5%) 14.54	1 (2.4%) 6.88	5 (10.0%); 24.91

Source: Clinical Overview Table 16, Table 17

Hyperkalemia as Adverse Events:

In DIA3008, potassium elevations in 4 of 7 subjects (3 subjects receiving 300 mg and 1 subject receiving 100 mg) in the canagliflozin group meeting the PDLC criterion of any post-baseline potassium level ≥6.5 mEq/L with baseline eGFR of 30-45 mL/min/1.73m^2 (Table 75) were reported as adverse events. Two subjects reported 'hyperkalemia' and 2 subjects reported 'increased blood potassium'. Three subjects were receiving concomitant ACE inhibitor and one subjects was also receiving concomitant ARB, and the fourth subject was receiving a diuretic concomitantly. One of these events was a SAE of 'hyperkalemia'. None of events led to cardiac AEs due to elevated potassium values.

In DIA3008 up to Amendment INT-6, the incidence of hyperkalemia captured either as 'blood potassium increased' and 'hyperkalemia' was numerically higher with the canagliflozin 300 mg group (2.4%) compared to placebo (1.1%). No notable imbalance in SAEs of hyperkalemia in DIA3008 was seen between treatment groups, and the overall number of events was small in each treatment group for comparison. In DIA4003, there was no imbalance in SAEs related to hyperkalemia. These data are shown in Table 76.

Table 76: Hyperkalemia-related Adverse Events inDIA3008 and DIA4003

Preferred Terms			
DIA3008 INT-6	**Placebo (N=1441)**	**Cana 100 (N=1445)**	**Cana 300 (N=1441)**
All hyperkalemia AEs	16 (1.1%)	20 (1.4%)	34 (2.4%)
Blood potassium increased	3 (0.2%); 0.83/1000 PY	6 (0.4%); 1.56/1000 PY	11 (0.8%); 2.90/1000 PY
Hyperkalema	13 (0.9%); 3.59/1000 PY	14 (1.0%); 3.63/1000 PY	23 (1.6%); 6.05/1000 PY
DIA3008 SAEs	**Placebo (N=1441)**	**Cana 100 (N=1445)**	**Cana 300 (N=1441)**
Hyperkalemia	2 (0.1%)	3 (0.2%)	3 (0.2%)
DIA4003 SAEs	**Placebo (N=2903)**	**Cana (N=2904)**	
Hyperkalema	5 (0.2%)	2 (0.1%)	

Source: DIA3008 CSR TSFAE00_S1_A, TSFAE01_OS; DIA4003 CSR TSFAE00_SAE_A

Hyperkalemia data at the original NDA review (copied from the original NDA Clinical Review; please note that DIA3004 was a moderate renal impairment study that enrolled subjects with baseline eGFR 30 to <50 mL/min/1.73m^2; DS1 was pool of four 26-week placebo-controlled studies dataset; DS2 was pool of moderate renal impairment subjects with baseline eGFR 30 to <60 mL/min/1.73m^2 across studies; and that DS3 was a broad pool of <u>all</u> eight active- and placebo-controlled studies dataset):

The mean changes in potassium in DIA3004 and DIA3008 are summarized in Table 77. The changes in potassium levels in DIA3004 over 26 weeks were inconsistent between two canagliflozin groups. Compared to DS1, there was a slight higher mean change in potassium with canagliflozin at the end of Week 26 among subjects enrolled in DIA3008.

Table 77: Changes in Potassium (mEq/L) in DIA3004 and DIA3008

	Placebo	Cana 100 mg	Cana 300 mg
DIA3004	77	72	79
Mean baseline	4.69	4.63	4.56
Mean change from baseline at Week 26	0.02	-0.03	0
Mean % change	*0.4%*	*-0.6%*	*0*
DIA3008	456	488	474
Mean baseline	4.42	4.36	4.39
Mean change from baseline at Week 26	0	0.02	0.03
Mean % change	*0*	*0.5%*	*0.7%*

Source: DIA3008 CSR, DLAB51R_CNV; DIA3004 CSR, DLAB01RM_CORE_CNV

As previously noted, the maximal increase for potassium occurs early post dose, so PDLC analysis would be more relevant to evaluate any clinically significant changes that may occur with potassium levels during canagliflozin therapy. Summary of subjects who met PDLC criteria for serum potassium in DS1, DS2, and DS3 is presented in Table 78. Although there a higher incidence of subjects with serum potassium elevations meeting PDLC criteria with canagliflozin 300 mg compared to the other groups, the incidence was comparable between canagliflozin 100 mg and placebo.

Table 78: Subjects (N [%]) with Serum Potassium Outside Pre-Defined Limits - Regardless of Rescue

	Placebo/ Non-cana	Cana 100 mg	Cana 300 mg
DS1, N	624	809	805
Subjects with 'any' post-baseline >ULN and >15% from baseline	30 (4.8)	36 (4.4)	56 (7.0)
Subjects with 'last' post-baseline >ULN and >15% from baseline	2 (0.3)	7 (0.9)	10 (1.2)
DS2, N	366	332	351
Subjects with 'any' post-baseline >ULN and >15% from baseline	29 (7.9)	24 (7.2)	42 (12.0)
Subjects with 'last' post-baseline >ULN and >15% from baseline	11 (3.0)	6 (1.8)	11 (3.1)
DS3, N	3159	3016	2969
Subjects with 'any' post-baseline >ULN and >15% from baseline	174 (5.5)	165 (5.5)	211 (7.1)
Subjects with 'last' post-baseline >ULN and >15% from baseline	36 (1.1)	35 (1.2)	42 (1.4)

Source: ISS, DLAB02B_01, DLAB02BCNV_02, DLAB02BCNV_03

Adverse events related to elevated potassium levels (event terms of hyperkalemia and blood potassium increased) in DS1, DS2, DS3, and DS4 are presented in Table 79. The incidence of adverse events related to high potassium levels were overall low, with a higher incidence in subjects with moderate renal impairment (e.g., DS2). Similar to PDLC changes, a slightly higher incidence of adverse events related to hyperkalemia was observed with canagliflozin 300 mg compared to canagliflozin 100 mg or placebo.

In DS1, no hyperkalemia was serious, and two events in canagliflozin 300 mg led to treatment discontinuation. In DS2, three hyperkalemia events (one in 100 mg and two in 300 mg) were serious and two hyperkalemia events led to discontinuation, both with canagliflozin 300 mg. None of blood potassium increased were serious or led to discontinuation.

In DS3, a higher incidence of hyperkalemia occurred in canagliflozin 300 mg group compared to non-canagliflozin group, although the difference between treatment groups was not large. Three hyperkalemia events were serious (one in 100 mg and two in 300 mg). All three had baseline moderate renal impairment. Two of these subjects were also on diuretics and renin-angiotensin agents, and experienced severe hyperkalemia (>7 mEq/L). Third subject also had mild renal function (eGFR 55 mL/min/17.3m2) and was on ACE inhibitor, and developed worsening renal insufficiency with potassium of 5.8 mEq/L. Two events of hyperkalemia also led to discontinuation, both with canagliflozin 300 mg. A significantly higher incidence of blood potassium increased also occurred in DS3; three events led to discontinuation (two with canagliflozin 300 mg and one with non-canagliflozin).

The incidence of hyperkalemia were slightly higher in DS4 compared to DS3, and showed similar trend with DS3. The imbalance in the incidence of blood potassium increased remained not favoring canagliflozin. There were no additional subjects who discontinued in DS4.

Table 79: Hyperkalemia-related Adverse Events - Regardless of Rescue

	Placebo/ Non-cana	Cana 100 mg	Cana 300 mg	All-cana
DS1	N=646	N=833	N=834	N=1667
Hyperkalemia, n (%)	0	5 (0.6)	2 (0.2)	7 (0.4)
Blood potassium increased, n (%)	1 (0.2)	1 (0.1)	4 (0.5)	5 (0.3)
DS2	N=382	N=338	N=365	N=703
Hyperkalemia, n (%)	6 (1.6)	5 (1.5)	8 (2.2)	13 (1.8)
Blood potassium increased, n (%)	0	3 (0.9)	4 (1.1)	7 (1.0)
DS3, N	3262	3092	3085	6177
Hyperkalemia, n (%)	15 (0.5)	17 (0.5)	22 (0.7)	39 (0.6)
Blood potassium increased, n (%)	1 (<0.1)	11 (0.4)	10 (0.3)	21 (0.3)
DS4, N	3262	3092	3085	6177
Hyperkalemia, n (%)	21 (0.6)	20 (0.6)	25 (0.8)	45 (0.7)
Blood potassium increased, n (%)	2 (0.1)	12 (0.4)	13 (0.4)	25 (0.4)

Source: ISS, DAE01R_01, DAE01RB_02, DAE01RC_03, DAE01R_04

Overall, the incidence of adverse events related to elevated potassium levels occurred more often in subjects with baseline renal impairment and/or subjects who are receiving concomitant medications that may also precipitate hyperkalemia. The incidence of increased potassium levels appear to occur more often with canagliflozin 300 mg compared to 100 mg dose.

Reviewer's comment: Increases in serum potassium with canagliflozin is known to occur.

There were no notable treatment group differences in PDLC criteria for serum potassium values in the pooled DIA3008 and DIA4003 dataset. In subgroup analyses based on eGFR for pooled dataset, a trend for an increase in any 'potassium >ULN and >15% increase from baseline' was seen in the combined canagliflozin group compared to placebo in subgroup of subjects with baseline eGFR of 30 to <45 and 45 to <60 mL/min/1.73m^2, and a trend for an increased incidence of subjects with any post-baseline value ≥6.5 mEq/L was seen with canagliflozin compared to placebo in subgroup of subjects with baseline eGFR of 30 to <45 mL/min/1.73m^2 (11.57 vs 8.62/1000 PY). These trends were based on small treatment group differences however.

During the original review of canagliflozin, increase in potassium was noted to be dose-dependent. DIA3008 evaluated separate two canagliflozin treatment groups by dose whereas DIA4003 did not. In review of potassium changes from DIA3008, notable imbalance was mostly seen in subjects with PDLC criteria of any potassium ≥6.5 mEq/L in subgroup analysis by eGFR, where the incidence was higher with canagliflozin 300 mg compared to placebo in eGFR 30 to 45 mL/min/1.73m^2, but the overall number contributing to this imbalance was small (6 vs 2 subjects; 24.94 vs 13.18/1000 PY). This similar trend was seen in subjects who were using RAAS inhibitor with or without potassium sparing diuretics.

In DIA3008 up to Amendment INT-6, the incidence of hyperkalemia as adverse events was numerically higher with the canagliflozin 300 mg group compared to placebo; the overall frequency was low. No imbalance in SAEs of hyperkalemia was observed in either DIA3008 or DIA4003.

The Applicant proposes to remove hyperkalemia from the Warnings and Precautions section, based on these data that showed that significant changes in potassium levels were not seen and hyperkalemia events were infrequent and did not lead to serious sequelae.

As presented above, the Warnings and Precautions during the original review was based on higher incidence of elevated potassium levels in subjects with moderate renal impairment (DS2), imbalance in the incidence of hyperkalemia-related AEs with canagliflozin compared to placebo, as well as increased incidence of SAEs related to hyperkalemia events and hyperkalemia events leading to study discontinuation, particularly with canagliflozin 300 mg dose.

Since most of the incidence of elevations in potassium appear to be related to the higher dose of canagliflozin 300 mg and with lower eGFR (30-45 mL/min/1.73m^2) and the overall incidence was low, and given that canagliflozin is not recommended in patients with eGFR <45 mL/min/1.73m^2 and only 100 mg is recommended in patients with moderate renal impairment with an eGFR of 45 to <60 mL/min/1.73m^2, I agree that the hyperkalemia in the Warnings and Precautions section can be removed from the labeling. Increases in serum potassium is still described in Laboratory Tests section of Adverse Reactions 6.1 to alert health care professionals that canagliflozin can lead to increase in potassium levels.

Of note, canagliflozin is the only product among the currently approved SGLT inhibitors (i.e., empagliflozin, dapagliflozin) with hyperkalemia in the Warnings and Precautions section.

Serum Hematology:

As summarized in Table 80, the adjusted-incidence rate of 'any' post-baseline hemoglobin value ≥20 g/L increase from baseline was higher in the canagliflozin group compared to placebo (50.81 vs 11.62/1000 PY. A similar pattern was also seen for the 'last' post-baseline value with incidence of 8.8% with canagliflozin compared to 1.8% with placebo. As shown in Figure 34, the increase in hemoglobin in the canagliflozin group was seen during the first 52 weeks and subsequently remained stable, compared to slight decrease in the placebo group during the study with some fluctuations. At Week 104, the mean percent change in hemoglobin was 4.1% in the canagliflozin group and -1.6% in the placebo group.

No differences in platelet and leukocyte PDLC criteria were seen between canagliflozin and placebo group (Table 80).

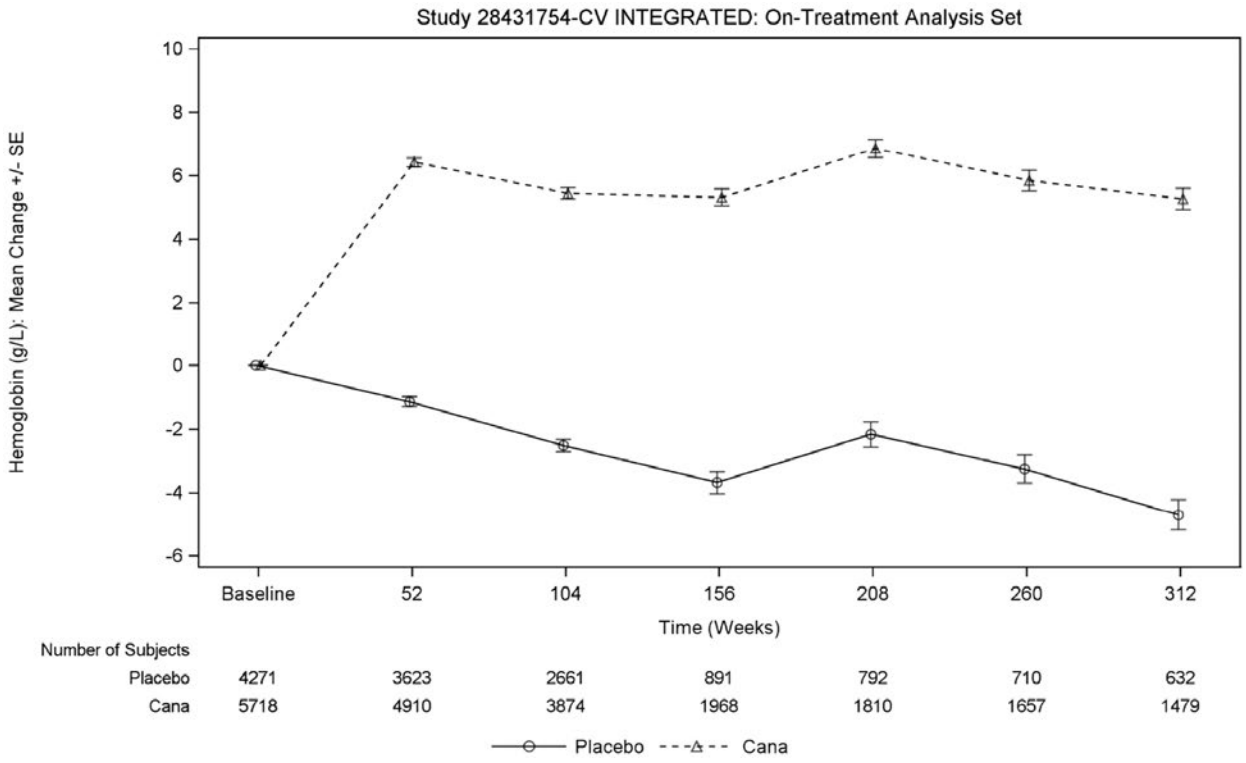
Reviewer's comment: Increases in hemoglobin is labeled in canagliflozin labeling.

Table 80: Subjects with 'Any' Hematology Values Outside Pre-Defined Limit with Risk Difference and 95% CI in Pooled DIA3008 and DIA4003 (On-Treatment Analysis Set)

Parameter Category 2: Hemogram	--------- Placebo ---------		---------- Cana ----------		------- Cana vs. Placebo -------	
	n(%)	Rate(/1000 subject-years)	n(%)	Rate(/1000 subject-years)	IRD(/1000 subject-years)	95%CI
Hemoglobin (g/L)						
Any post-baseline value	3936		5333			
HGB ≥ 20 g/L Decrease from Baseline	350 (8.9)	32.28	291 (5.5)	16.30	-15.98	(-19.85, -12.11)
HGB ≥ 20 g/L Increase from Baseline	126 (3.2)	11.62	907 (17.0)	50.81	39.19	(35.30, 43.08)
Leukocytes (x10E9/L)						
Any post-baseline value	3936		5333			
WBC < LLN and > 25% Decrease from Baseline	65 (1.7)	5.99	94 (1.8)	5.27	-0.72	(-2.54, 1.10)
WBC > ULN and > 50% Increase from Baseline	100 (2.5)	9.22	140 (2.6)	7.84	-1.38	(-3.62, 0.86)
Platelets (x10E9/L)						
Any post-baseline value	3926		5323			
Platelets < LLN and > 25% Decrease from Baseline	70 (1.8)	6.47	146 (2.7)	8.19	1.72	(-0.31, 3.75)
Platelets > ULN and > 25% Increase from Baseline	86 (2.2)	7.95	132 (2.5)	7.40	-0.55	(-2.66, 1.56)

Note: Percentages calculated with the number of subjects per time interval as the denominator.
Note: Incidence, IRD and 95% CI are only generated for any post-baseline value outside pre-defined limit.
Note: Exposure-adjusted incidence rates are per 1000 person-years and calculated as 1000*(the total number of subjects with an elevation or reduction divided by the total person-year exposure for all treated subjects who have a post baseline lab value.)
Note: 95% CI is based on the Normal approximation for the incidence rate difference (IRD).
Note: If no subject met a specific PDLC criterion, that specific criterion is not listed in this table.
Source, ISS, Table 85

Figure 34: Mean Change from Baseline in Hemoglobin Over Time in Pooled DIA3008 and DIA4003



Source: ISS, Figure 20

7.4.3 Vital Signs

Changes in blood pressure are discussed in Section 6.1.3.

Pulse rate measures after Week 104 include mainly subjects from DIA3008, and therefore changes up to Week 104 are discussed for pooled DIA3008 and DIA4003 data.

In the On-Treatment Analysis Set, the pulse rate in the canagliflozin showed a slight decrease (-0.5 bmp) from baseline at Week 26 and remained stable at lower than baseline for the remainder of this study. The pulse rate in the placebo group generally remained similar to baseline. At Week 104, the changes in pulse rate from baseline in combined canagliflozin group was -0.5 bmp (SE 0.15) and was -0.2 bpm (SE 0.19) in the placebo group.

Table 81 summarizes the incidence of treatment-emergent vital signs outside PDLC at any post-baseline measurement. The incidence of treatment-emergent vital signs

outside PDLC within 2 days of the last post-baseline measurement is summarized in Attachment TSFVIT03B in ISS (not shown here).

For any post-baseline measurement, the adjusted-incidence rate of PDLC criteria for a *decrease* in systolic and diastolic blood pressure was higher in the canagliflozin group compared to placebo (Table 81). For the last post-baseline measurement, the incidence of PDLC criteria for a decrease in systolic (0.2% vs <0.1%) or diastolic (0.4% vs 0.2%) blood pressure was similar in the combined canagliflozin and placebo groups.

For any post-baseline measurement, the adjusted-incidence rate of PDLC criteria for an *increase* in systolic and diastolic blood pressure was lower in the canagliflozin group compared to placebo (Table 81). For the last post-baseline measurement, the incidence of PDLC criterion for an increase in systolic blood pressure was lower in the combined canagliflozin group (1.7%) compared to placebo (2.8%), and the incidence of PDLC criterion for an increase in diastolic blood pressure was similar in the combined canagliflozin and placebo groups (0.2% vs 0.3%).

For any post-baseline measurement, the adjusted-incidence rate of PDLC criteria for pulse ≤50 bpm or ≥100 bpm was similar between combined canagliflozin group and placebo (Table 81). For the last post-baseline measurement, the incidence rate of PDLC criteria for pulse ≤50 bpm (1.3% vs 1.2%) or ≥100 bpm (1.2% vs 1.1%) was also similar between combined canagliflozin group and placebo.

Table 81: Subjects with Vital Signs Outside Pre-Defined Limit with Risk Difference and 95% CI (Pooled DIA3008 and DIA4003: On-Treatment Analysis Set)

	Placebo (N=4344)		Cana (N=5790)		Cana vs. Placebo	
	n(%)	Rate(/1000 subject-years)	n(%)	Rate(/1000 subject-years)	IRD(/1000 subject-years)	95%CI
Systolic Blood Pressure (mmHg)						
Any post-baseline value	4212		5630			
Average SBP Decrease from Baseline ≥ 20 mmHg and ≤ 90 mmHg	23 (0.5)	2.09	85 (1.5)	4.72	2.63	(1.30, 3.96)
Average SBP Increase from Baseline ≥ 20 mmHg and ≥ 160 mmHg	525 (12.5)	47.73	466 (8.3)	25.89	-21.84	(-26.56, -17.12)
Diastolic Blood Pressure (mmHg)						
Any post-baseline value	4212		5630			
Average DBP Decrease from Baseline ≥ 15 mmHg and ≤ 50 mmHg	44 (1.0)	4.00	128 (2.3)	7.11	3.11	(1.39, 4.83)
Average DBP Increase from Baseline ≥ 15 mmHg and ≥ 100 mmHg	87 (2.1)	7.91	92 (1.6)	5.11	-2.80	(-4.77, -0.83)
Pulse Rate (BEATS/MIN)						
Any post-baseline value	4212		5630			
Pulse ≤ 50 bpm	190 (4.5)	17.27	330 (5.9)	18.33	1.06	(-2.10, 4.22)
Pulse ≥ 100 bpm	219 (5.2)	19.91	337 (6.0)	18.72	-1.19	(-4.51, 2.13)

Note: Percentages calculated with the number of subjects per time interval as the denominator.
Note: If no subject met a specific PDLC criterion, that specific criterion is not listed in this table.
Note: 95% CI is based on the Normal approximation for the incidence rate difference (IRD).

Source: ISS, Table 86

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

None.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency for AEs are not relevant in this submission as all subjects in DIA3008 started 100 mg dose of canagliflozin and subsequently titrated to 300 mg if needed for additional glycemic control and tolerating the lower dose. All canagliflozin treatment groups were combined and compared to all placebo groups.

7.5.2 Time Dependency for Adverse Events

Time-related onset and course over time are discussed in each relevant section throughout as needed.

7.5.3 Drug-Demographic Interactions

No new analysis was done.

7.5.4 Drug-Disease Interactions

No new analysis was done.

7.5.5 Drug-Drug Interactions

No new analysis was done.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to section 7.3.5.1 for discussion of malignancies identified during the CANVAS Program.

7.6.2 Human Reproduction and Pregnancy Data

No subject became pregnant during the CANVAS Program.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable as no pediatric patients were enrolled in the CANVAS Program.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information is available. No adverse event reports of study drug overdose were reported in DIA3008 or DIA4003.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

During the review of this application, the Applicant submitted a 4-Month Safety Update for this supplement on January 24, 2018. The safety update included relevant postmarketing data from the last Periodic Safety Update Report (PSUR) covering Mary 29, 2017 to September 28, 2017, and relevant information from medical literature from July 1, 2017 through November 30, 2017. Review of the latest PSUR did not show new safety concerns related to canagliflozin.

The cutoff dates for information included in this 4MSU are September 15, 2017 for clinical studies. No new clinical studies have been completed since submission of this efficacy supplement as of September 15, 2017 cutoff.

Literature search for publications from July 1, 2017 through November 30, 2017 showed 23 unique citations, and none of these showed new safety concerns related to canagliflozin.

Canagliflozin is currently registered in more than 80 countries, and canagliflozin/metformin fixed dose combination tablets are registered in more than 50 countries. The estimated cumulative exposure to canagliflozin is 2,717,109 person-years, and 226,485 person-years for canagliflozin/metformin fixed dose combination products.

9 Appendices

9.1 Literature Review/References

Literature or references were discussed in relevant sections throughout the review as appropriate.

9.2 Labeling Recommendations

Labeling recommendations are contained within this review as appropriate. Labeling is not finalized at the time of this review.

9.3 Advisory Committee Meeting

No advisory committee meeting was convened for this application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYON J KWON
10/25/2018

LISA B YANOFF
10/26/2018

Consult from DMEP to DOP1
Medical Officer: Sundeep Agrawal, M.D.
Date: 8/8/18
Name of Drug: Invokana (canagliflozin)
Reason for consult: Safety

Summary of Consult Request:

The Division of Oncology Products 1 (DOP1) was consulted by DMEP to provide input regarding the increased incidence of renal cell carcinoma (RCC) noted in patients receiving Invokana (canagliflozin) versus patients receiving placebo on two trials, CANVAS (DIA3008) and CANVAS-R (DIA4003). These 2 trials were cardiovascular outcome trials that the sponsor undertook to fulfill PMR 2027-5, and both studies were pooled for efficacy and safety evaluation. Out of the 4344 patients who received placebo and the 5790 patients who received canagliflozin (noted as Cana below), 3 patients (0.1%) and 14 patients (0.2%), respectively, were noted to have renal cell carcinoma (RCC) reported as an adverse event.

Background:

Safety Signal in Pre-Clinical Program

Canaglifozin (trade name Invokana) is an SGLT2 inhibitor approved in 2013 for patients with type 2 diabetes. Increased renal neoplasms of the renal tubules were noted in rodent carcinogenicity studies, and this signal in the non-clinical program prompted a post-marketing requirement to assess the development of renal tumors in patients receiving canaglifozin. These renal tubular tumors were seen in Sprague-Dawley rats but not in CD-1 mice, and the sponsor notes that the exposure at the highest approved clinical dose (300 mg daily) is 5 to 7-fold lower than the lowest exposure which caused tumors in rats. Specifically, pheochromocytoma, Leydig cell tumors, and renal cell carcinoma are being monitored for 10 years from the date of approval. No imbalance in renal cell tumors were observed in the original clinical development program. The mechanism of action for the development of these tumors is still unclear, but one hypothesis presented by DMEP is that a diuretic effect via SGLT2i is required in combination with the SGLT1 inhibitor for the signal to manifest.

Reviewer's Comments: *The exact mechanism of action that may pre-dispose to these tumors is unclear. There are a number of retrospective review papers that note increased cases of cancer, including breast, bladder, and renal cell carcinoma, in patients receiving SGLT2 inhibitors, but these do not achieve statistical significance. The relationship between SGLT2 inhibition and cancer development is still inconclusive.*

CANVAS and CANVAS-R Studies and Finding of Increased RCC in Human Subjects

In regards to canagliflozin, the sponsor was also required to satisfy a PMR monitor for cardiovascular outcomes that included the conduct of a randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. The sponsor conducted the CANVAS and CANVAS-R trials to satisfy this PMR, and as noted above, both studies were pooled for efficacy and safety. Baseline demographics between treatment groups were similar and appeared well balanced. The median age was 63 years, 64% were men, and 78% were white. Median GFR, baseline BMI, and patients with a history of hypertension were

balanced between the arms. The median duration of exposure was 223 weeks (approximately 4.3 years) in CANVAS and 94 weeks (approximately 1.8 years) in CANVAS-R. An imbalance was noted in the incidence of renal cell carcinoma, with more cases noted in patients receiving canagliflozin compared to those receiving placebo. Table 1 summarizes these findings.

Table 1: CANVAS Program, All Subjects with an RCC Event

CANVAS Program- All Subjects		
	Placebo (n=4344)	**Cana (n=5790)**
Renal Cancer, N (%)	3 (0.1%)	14 (0.2%)
Median onset for event	710 Days	1254 Days
Incidence rate per 1000 person-years	0.21	0.62
Clear cell renal cell carcinoma	1 (<0.1%)	2 (<0.1%)
Metastatic renal cell carcinoma	0	1 (<0.1%)
Renal cancer	0	6 (0.1%)
Renal cancer metastatic	1 (<0.1%)	0
Renal cancer stage 1	0	1 (<0.1%)
Renal cell carcinoma	1 (<0.1%)	4 (0.1%)
Renal cell carcinoma stage 2	0	1 (<0.1%)

Reviewer's Comments: *In reviewing the documentation provided, there are the following important factors to consider in the evaluation of this data:*

- *Statistical analysis was only done for the CANVAS trial, which included 13 of the 14 cases noted in the Cana arm, and all 3 of the placebo cases noted. There were 13 events out of 2886 patients on Cana vs. 3 out of 1441 on placebo, HR (95% CI): 1.97 (0.56, 6.91). Of note, the confidence intervals include 1, so insufficient evidence exists to conclude that the groups are statistically significantly different.*
- *The imbalance of renal cell cancer noted was mostly due to reported cases from the CANVAS study. This study had a much longer duration of follow-up than the CANVAS-R study, which is the likely reason why more RCC cases were noted in CANVAS.*
- *Two renal cell cancer cases were reported less than 180 days after study drug initiation, which suggests that they are unlikely to be related to the study drug due to the latency period for malignancy.*
- *One patient in each arm, on study for less than 90 days, reported renal cancer; this also suggests that these cases are unlikely to be related to the study drug for the reason mentioned above.*
- *Most patients had underlying risk factors that may have pre-disposed them to the development of a renal cell cancer malignancy, including hypertension (13 out of 14 patients), obesity (12 out of 14 patients), and smoking (5 out of 14 patients). Type 2 diabetes itself has been shown to be a risk factor for cancer development in some retrospective analyses and meta-analyses.*
- *Two patients receiving study drug who developed RCC had pre-existing conditions related to renal cancer. One had a renal cyst and another had a prior history of renal cancer*.

Summary and Review of Events

The sponsor provided the following table that summarizes each patient with an event, which arm they were assigned to, the dose of Cana, risk factors, and other notes.

Table 2: Subjects with Renal Carcinoma in the CANVAS Program

Subject	Treatment	Age at dx	Sex	Race	Country	BMI	Risk factors	Day of Dx	Exposure at Dx	Largest dimension of tumor	Relationship	Other notes
(b) (6)	Cana	59	F	W	DEU	38.2	HTN, Tobacco use, Obesity	40	40	4.5 cm	Not related	Onset < 180 days
	Cana 100 mg	63	M	W	USA	36.1	HTN, Tobacco use, Obesity	1254	664	Not indicated	Doubtful	History of bilateral renal cancer
	Cana 100 mg	75	M	W	NLD	29.6	HTN	705	705	12 cm	Not related	
	Cana 300 mg	65	M	W	NLD	31.3	HTN, Obesity	1356	1356	25 cm	Possible	
	Cana 100 mg	70	F	W	DEU	43.9	HTN, Obesity	1614	1614	Not indicated	Doubtful	History of renal cyst in same kidney
	Cana 100 mg	72	M	W	NLD	31.1	HTN, Tobacco use, Obesity	1099	77	6 cm	Doubtful	Exposure < 180 days
	Cana 300 mg	60	M	W	UKR	41.5	HTN, Obesity	32	32	4.7 cm	Not related	Onset < 180 days
	Cana 300 mg	87	M	W	AUS	26.1	HTN	722	722	3.2 cm	Doubtful	Reported 2 simultaneous primary tumors
	Cana 300 mg	50	M	W	AUS	36	HTN, Obesity	1806	1806	3 cm	Not related	
	Cana 100 mg	62	M	W	AUS	33.1	Obesity	849	849	10 cm	Possible	
	Cana 100 mg	69	M	W	RUS	30.3	HTN, Tobacco use, Obesity	451	451	2 cm	Not related	
	Cana 300 mg	66	F	W	EST	37.5	HTN, Obesity	1767	1767	7 cm	Not related	
	Cana 300 mg	55	M	AA/AI	USA	40	HTN, Tobacco use, Obesity	1808	1808	4.9 cm	Not related	
	Cana 100 mg	78	M	W	ISR	35.2	HTN, Tobacco use, Obesity	1767	1767	Not indicated	Doubtful	
	Placebo	60	M	W	RUS	29.1	HTN, Tobacco use	710	710	8.2 cm	Doubtful	
	Placebo	63	M	W	RUS	30.1	HTN, Tobacco use, Obesity	1343	1343	4 cm	Not related	
	Placebo	71	F	W	ARG	28.9	HTN	241	42	6.4 cm	Doubtful	Exposure < 180 days

Reviewer's Comments: *I have reviewed the adverse event reports as well as the case narratives provided by the sponsor. Table 2 appears to be an accurate representation of the important aspects of each case of RCC. In review of the case narratives, I have summarized cases where histology confirmed the diagnosis, and cases where no histology was available to confirm RCC.*

Table 3: Per Case Evaluation of Method of Diagnosis of RCC

Patient ID	Treatment Arm	Notes
(b) (6)	Cana	Histology confirmed
	Cana	Reported at RCC but no diagnostic testing or histology available
	Cana	No biopsy performed but clinical scenario highly suggestive of RCC, large mass, with metastatic lesions
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed

(b) (6)		
	Cana	No histology confirms RCC, but patient did have papillary urothelial carcinoma with renal lesion; not necessarily RCC[1]
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Cana	Histology confirmed
	Placebo	No biopsy but large renal mass and metastatic lesions, likely RCC
	Placebo	Histology confirmed
	Placebo	Histology confirmed

[1]Urothelial cancer does not typically metastasize to the kidney.

Incidence of RCC and Sponsor's Standardized Incidence Ratio (SIR) Compared to SEER

The sponsor calculated the incidence rate for renal cell carcinoma in the canagliflozin group to be 0.62 per 1000 person-years and 0.21 per 1000 person-years in the placebo group. The incidence rate difference was 0.41 (95% CI: -0.04, 0.86) with 14 and 3 patients, respectively, developing renal cell carcinomas. The sponsor also used the Surveillance, Epidemiology, and End Results (SEER) database to estimate expected cases of each treatment group and a standardized incidence ratio (SIR) and 95% confidence intervals. This is copied below.

Table 4: Standardized Incidence Ratio (SIR) Compared with SEER from Sponsor Analysis

Standardized Incidence Ratio (SIR) Compared with SEER

Treatment	Renal Malignancy			
	Observed	Expected*	SIR (95% CI) **	P-value**
Cana	14	14.24	0.983 (0.54-1.65)	0.91
Placebo	3	8.84	0.339 (0.070-0.99)	0.0475
All	17	23.08	0.737 (0.43-1.18)	0.239

95% CI=95% confidence interval
† Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (2000-2014) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2015 Counties, NCI, DCCPS, Surveillance Research Program, released April 2017. SEER*stat Version 8.3.4.
* Estimated based on SEER incidence rate, prevalence of diabetes in general US population, and relative risk of renal cancer comparing type 2 diabetes vs. non-diabetes (Larsson et al. 2011)
** Two-sided p-values and 95 % CI from exact test based on Poisson distribution (Rosner 2000) and Fisher's exact test (Rothman and Boice 1979) http://www.openepi.com/PDFDocs/SMRDoc.pdf accessed 6/27/2018

Reviewer's Comments: *The sponsor notes that while the expected number of cases were seen in the canagliflozin group, a significantly lower number of cases were observed in the placebo group, and with*

95% CIs for the SIRs for the canagliflozin and comparator groups overlapping. The sponsor's analysis was not confirmed by DOP1 and it is not clear how accurate these analyses are to draw conclusions from.

Consult Questions

DEMP is requesting your interpretation of the imbalance in cases of renal cell carcinoma (RCC) including your opinion on issues such as (but not limited to):

1.) Causality (drug-relatedness) assessment

DOP1 Answer: Surveillance studies of enhancing renal masses have reported mean tumor growth rates of 0.3 cm to 0.5 cm per year, but the populations studied vary and the actual rate of growth of renal tumors is heterogenous and highly variable. The 3 cases of renal tumors in the Cana arm that were diagnosed in patients with less than 180 days of exposure to study therapy are highly unlikely to be related to study treatment. These tumors, as well as the one case in the placebo arm with <180 days of exposure, were very likely present prior to the patient receiving study drug, but were only identified after they had enrolled onto the trial. In the other 10 cases reviewed, when taking into account the timing of diagnosis in relation to Cana exposure and size of the tumors, Cana contributing to the development of these tumors cannot be excluded.

2.) Whether the event rates of RCC observed in the trial are generally what you would expect in this patient population (i.e. older diabetes patients). Alternatively, is the placebo group rate unusually low?

DOP1 Answer: The event rates in the placebo group do appear to be low. This may be explained by the following: Patients receiving placebo were less likely to have adverse events caused by the active drug. Patients on the active drug likely developed more adverse events related to its use, which in turn prompted more diagnostic evaluations, resulting in more diagnoses of RCC. Upon review of the case narratives, some of these tumors were found incidentally when evaluating another adverse event. It is possible that the actual incidence of RCC is higher in the placebo group, and are yet to be diagnosed due to lack of symptoms prompting further evaluation.

Event rates in this specific patient population are not well elucidated, but DOP1 conducted a literature search and case narrative review and wanted to provide supplemental information based on this search.

A.) Approximately 1.7% of men and women will be diagnosed with kidney and renal pelvis cancer at some point during their lifetime, and the median age of diagnosis is 64 years, based on 2013-2015 data from the SEER database.

B.) The incidence of renal cell carcinoma in diabetic patients is not well elucidated, but two large prospective cohort studies have examined type 2 diabetes in relation to the risk of RCC among men and women. Following women from the Nurses' Health Study (NHS) with over 28 years of follow up, women with type 2 diabetes had a significantly increased risk of RCC compared with women without type 2 diabetes (multivariable HR 1.53; 95% CI: 1.14-2.04). Among men followed in the Health Professionals Follow-up Study (HPFS) for up to 38 years, type 2 diabetes was not associated with total RCC (HR 0.89; 95% CI 0.56-1.41). It is important to note that many of the same risk factors for diabetes (poor diet, sedentary lifestyle, etc.) are also risk factors for

development of malignancy, and as such, identifying a causal relationship between the two is difficult.

C.) Upon review of cases in CANVAS and CANVAS-R, one patient on study was 50 years old when diagnosed with RCC, and another was 45 years old. Both had extended exposure >1700 days, and were much younger than the expected age of diagnosis. Other than these 2 patients, the other 12 patients were in the expected age range of patients diagnosed with RCC.

3.) Data quality issues/reliability of MedDRA searches for malignancy signal detection (i.e. no pathology confirmation available for all patients)

DOP1 Answer: Histologic confirmation was not available for all patients, as noted in Table 3. Overall, only 3 patients on Cana diagnosed with RCC did not have histologic confirmation. It is unclear if Patient (b) (6) had true RCC. The other 2 cases (Patients (b) (6) and (b) (6) had narratives that were highly suggestive of RCC in the absence of histologic confirmation. Overall, 13 out of 14 cases were either histologically confirmed or highly suggestive of the RCC diagnosis so the reliability of the diagnoses appears adequate. Of note, it may be of value to confirm with the sponsor that other terms such as neoplasm, carcinoma, and cancer were searched along with the term "kidney," in addition to "renal," to evaluate for other cases noted but not reported by the sponsor.

4.) Clinical implications of the various reported pathological diagnoses, i.e. renal cell carcinoma vs. clear cell and how this may impact data interpretation or labeling language if the RCC risk were to be added to the product's prescribing information.

DOP1 Answer: The current WHO classification has many RCC histologic subtypes with diverse tumor biology, and many different terms may be used to describe a malignancy originating in the kidney and renal collecting system. All the terms included in the 14 cases provided appear consistent with renal cell carcinoma. Given the lack of histologic confirmation in some of these cases and the lack of information regarding pathologic features of each case, using a histologic descriptor may not be ideal for labeling language. Instead, a broader term such as kidney cancer may be more appropriate to consider.

5.) Except for 3 subjects, the size of tumor was available in case narratives; please provide your assessment as to whether the reported renal cancer in these subjects may have been present and undetected before their entry into the study, based on the reported tumor size when the renal cancer was detected during their participation in the study.

DOP1 Answer: Please see answer to Question 1.

Summary of DOP1 Impression: The statistical analysis comparing Cana vs. placebo has confidence intervals that include 1, therefore insufficient evidence exists to conclude that the groups are statistically significantly different. There are also a number of confounding factors when interpreting this data, including lack of histology in some cases, and variability in imaging or screening procedures that led to diagnosis between patients and arms of the study that could introduce bias, including lead-time bias. Longer follow up and more information is needed to make a more informed decision on whether Cana is truly contributing to or causing an increased incidence of RCC compared to placebo.

The incidence of renal cancer with canagliflozin on the CANVAS trial should be compared to both the incidence in the general population and to the placebo arm. While patients entering the CANVAS trial were not screened, they did undergo a general medical examination that may have detected gross abnormalities. The incidence on the placebo arm may, therefore, be a better comparator to the incidence with canagliflozin. However, as noted above, the incidence of renal cancers with canagliflozin could have been influenced by evaluation of adverse events on canagliflozin with an increase in adverse events on canagliflozin versus placebo.

Product Labeling

DMEP will determine the labeling of canagliflozin. Note that several oncology drugs contain Boxed Warnings or Warnings for the development of malignancy. Examples include:

Doxorubicin

Boxed Warning
Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE REACTIONS). The occurrence of refractory secondary AML or MDS is more common when anthracyclines are given in combination with DNA-damaging anti-neoplastic agents or radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The rate of developing secondary AML or MDS has been estimated in an analysis of 8563 patients with early breast cancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including NSABP B-15. Patients in these studies received standard doses of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years (95% CI, 0.16 to 0.57) and a cumulative incidence at 5 years of 0.21% (95% CI, 0.11 to 0.41%). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin-containing regimens in clinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older had an increased risk of secondary AML or MDS. Pediatric patients are also at risk of developing secondary AML.

Cyclophosphamide

Warning
Cyclophosphamide is genotoxic [see Nonclinical Toxicology (13.1)]. Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens. The risk of bladder cancer may be reduced by prevention of hemorrhagic cystitis.

Rucaparib

Warning

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

In addition, AML was reported in 2 (< 1%) patients with ovarian cancer enrolled in a blinded, random ized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents. …

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/s/

SUNDEEP AGRAWAL
08/08/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

PHARMACOLOGY REVIEW(S)

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Supervisory Memorandum
Division of Metabolic and Endocrine Products

11 Oct 2018

Re: Canagliflozin
Clinical relevance of rat carcinogenicity study
NDA 204042 s027
Submissions eCTD 212 (SDN 1173) and eCTD 255 (SDN 1357)

Executive Summary
A numerical imbalance of clinical renal cell carcinoma (RCC) was uncovered in the CANVAS clinical trials with canagliflozin, approximating 2:1 not favoring drug. Validity of this clinical signal for RCC appears bolstered by the occurrence of renal tubule tumors reported in the rat carcinogenicity study for canagliflozin. An understanding of the probable tumorigenic mode of action (MOA) is necessary to best address the clinical relevance of the rat study and its value in interpreting the validity of the clinical signal.

Carbohydrate malabsorption secondary to intestinal SLGT1 inhibition was put forward as a key event in the tumorigenic MOA for renal and adrenal tumors in rats exposed to canagliflozin. The literature and multiple experimental studies with canagliflozin strongly supported a key role for this pathway. As there was no evidence of carbohydrate malabsorption in clinical trials, tumorigenic risk related to this pathway in humans was considered minimal. However, more recent data from others in the drug class, particularly compounds with greater selectivity for SGLT1, raised concern that the carbohydrate malabsorption explanation is either incorrect or substantially deficient. Greater uncertainty regarding the tumorigenic MOA of canagliflozin in rats would bolster the validity of the clinical RCC signal, as one could not discount the human relevance of the renal tumor signal in rats on that basis.

This prompted a comparative evaluation of key events in the carbohydrate malabsorption pathway between canagliflozin and other class members, including two compounds with selective SGLT1 inhibitory activity. Differences in drug exposure and the degree of carbohydrate malabsorption likely achieved in the 2yr carcinogenicity studies provide a plausible explanation for the apparent discrepancy in renal tumor outcomes among the compounds. When considered with the strength of the prior weight-of-evidence, it is concluded that the currently accepted tumorigenic MOA remains valid for the drug class and is the most probable path by which canagliflozin induces renal tumors in rats.

Evaluation of clinical data from phase I and II studies re-affirmed that canagliflozin did not result in carbohydrate malabsorption to any notable degree in human subjects, which minimizes the clinical relevance of the renal tumor signal in rats. The clinical RCC signal with canagliflozin, therefore, is very unlikely to reflect same renal tumorigenic pathway that occurs in rats.

Regulatory Recommendations

The tumorigenic MOA leading to renal tumors in rats administered canagliflozin is well-characterized and remains consistent with carcinogenicity results with other compounds in the class. Additional nonclinical studies could refine and strengthen the MOA in rats, such as identifying the nearest event that injures renal tubules and causes them to proliferate, but this will not further inform the validity of the clinical RCC signal, or lack thereof.

Introduction

Prior to NDA approval for canagliflozin, Janssen provided a weight-of-evidence (WOE) evaluation that implicated inhibition of SGLT1 and subsequent carbohydrate malabsorption as necessary *proximal* key events that led to renal tubular tumors in SD rats. In conjunction with corroborative findings with the drug class, pharm/tox concurred with Janssen's proposed MOA, which was later published in the literature[1,2]. Subsequent to drug approval, Janssen submitted an additional long-term mechanistic study demonstrating that prevention of carbohydrate malabsorption with a fructose diet also prevented canagliflozin-induced renal tumors and other sequalae in SD rats[3], strongly supporting the prior dataset. As the therapeutic dose of canagliflozin did not result in carbohydrate malabsorption in the clinical program, the relevance of the rat finding to human risk was considered minimal and is described in the drug label as such.

Since that time, data emerged from the nonclinical programs of more recent class members that appeared at odds with the SGLT1-based MOA established with canagliflozin. Most notably, renal tumors in rodents were not observed with 6 of 8 other class members (Appendix 1), although mineralization and hyperplastic changes to renal tissue were variably reported. Particularly problematic was the apparent absence of renal tumors in the carcinogenicity studies conducted with sotagliflozin and mizagliflozin, variants in the drug class that intentionally target SGLT1. The apparent lack of rodent RCC in response to SGLT1/2 mixed inhibitors, in addition to other inconsistent findings, raised concern that the carbohydrate malabsorption MOA was incorrect or substantially deficient.

The nature of the nonclinical risk assessment differs depending on the validity of the carbohydrate malabsorption MOA for drug-induced renal tumors in rodents.

If valid, then clinical relevance is gauged by the occurrence of key events of the MOA in human subjects, as was done originally for canagliflozin. In this case, the discrepancies in the renal tumor outcome in rodents (i.e., Cana vs Sota, Miza) must stem from a difference not identified in the data, which required further analyses, and determining the impact of that difference on risk assessment.

If not valid or its key events critically flawed, then an alternative MOA or a substantial revision to the MOA is necessary. Such is absent at the present moment, which necessitates an empirical approach to risk assessment based on safety margins to the nonclinical cancer signal.

To re-evaluate the validity of the carbohydrate malabsorption MOA, select key events were compared from the nonclinical data available for canagliflozin and other class members with completed carcinogenicity studies. This analysis, presented below, identified differences in drug exposure and the degree of calcium disruption as a plausible explanation for the apparent

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[1] Mamidi RNVS, et al. (2014) Carbohydrate malabsorption mechanism for tumor formation in rats treated with the SGLT2 inhibitor canagliflozin. Chemico-Biol Inter 221; 109-118.
[2] Ways K, et al. (2015) Successful integration of nonclinical and clinical findings in interpreting the clinical relevance of rodent neoplasia with a new chemical entity. Toxicol Path 43; 48-56.
[3] IND 76479, 31 March 2014 Submission

discrepancy in renal tumor outcomes across the class. The weight of evidence remains plausibly consistent with SGLT1-based carbohydrate malabsorption as the likely tumorigenic MOA for renal tumors in rodents administered canagliflozin.

As this analysis reaffirms the probable tumorigenic MOA in rodents, clinical relevance was re-examined by reviewing evidence of carbohydrate malabsorption in the clinical trial data available for canagliflozin.

Review

Carbohydrate malabsorption MOA and biomarkers evaluated

Details of the carbohydrate malabsorption MOA are described extensively in prior FDA reviews and in the public literature[1,2,4,5]. In brief, inhibition of SGLT1 results in a higher content of intestinal sugars that undergo fermentation by the resident microbial flora. The ensuing local acidosis increases the solubility and intestinal absorption of calcium, resulting in transient periods of relative hypercalcemia. The excess calcium is deposited in bone and soft tissues and is excreted in the urine. Electrolyte loss, including inorganic phosphate, accompanies calcium excretion but this appears due to glucose-induced diuresis secondary to SGLT2 inhibition. Counter-regulatory mechanisms largely keep plasma calcium within the normal range, but the compensatory changes can be dramatic; for example, levels of vitamin D and parathyroid hormone can reach very low levels, stifle joints experience hyperostosis, and soft tissues, including the kidney, can become highly mineralized.

Interventional studies in rodents administered glucose-free fructose diets, which bypasses SGLT1 blockade, identified carbohydrate malabsorption and subsequent disruption in calcium homeostasis as key events preceding pre-neoplastic and neoplastic changes in the kidney induced by canagliflozin[1, 2, 3]. It is important to emphasize that key events distal to calcium homeostasis that result in renal tubule neoplasia were not identified[5], though histochemical evidence suggests the involvement of renal tubule injury and regeneration as preneoplastic events.

Biomarkers for maintaining calcium homeostasis are readily monitorable both in animals and in humans, and several were measured in nonclinical and clinical programs for SGLT2 inhibitors, including canagliflozin. Therefore, this analysis focuses on markers indicative of calcium disruption in the nonclinical programs for canagliflozin and other class members. These markers include urinary calcium excretion, parathyroid hormone, and 1,25 dihydroxy vitamin D3 (calcitriol). While many other markers were investigated, these were consistently measured and showed reproducible directional changes across nonclinical programs.

Importantly, urinary calcium, PTH, and calcitriol are also largely available in the clinical trial data, which provides a critical link for extrapolating from the animal data.

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[4] Tirmenstein M, et al. (2013) Nonclinical toxicology assessments support the chronic safety of dapagliflozin, a first-in-class sodium glucose cotransporter 2 inhibitor. Int J Toxicol 32(5);336-50.
[5] NDA 204042, F. Alavi 2/21/2013; T. Bourcier 2/7/2013

Calcium homeostasis markers in rats administered SGLT inhibitors

Urinary calcium excretion- Figure 1 depicts urinary calcium excretion in response to SGLT inhibitors at the highest dose tested in each compound's rat carcinogenicity study. As urinary calcium is not commonly measured in 2yr studies, these values were obtained from week 13 of either 3m or 6m toxicology studies in rats for each compound.

The comparison shows that urinary calcium excretion is greatest for canagliflozin at the highest dose evaluated in the 2yr rat study. Note that only Cana at the high dose of 100mg/kg yielded an unequivocal increase in renal tubule adenoma/carcinoma. No renal tumors were observed in rats for the other class members (Appendix 1).

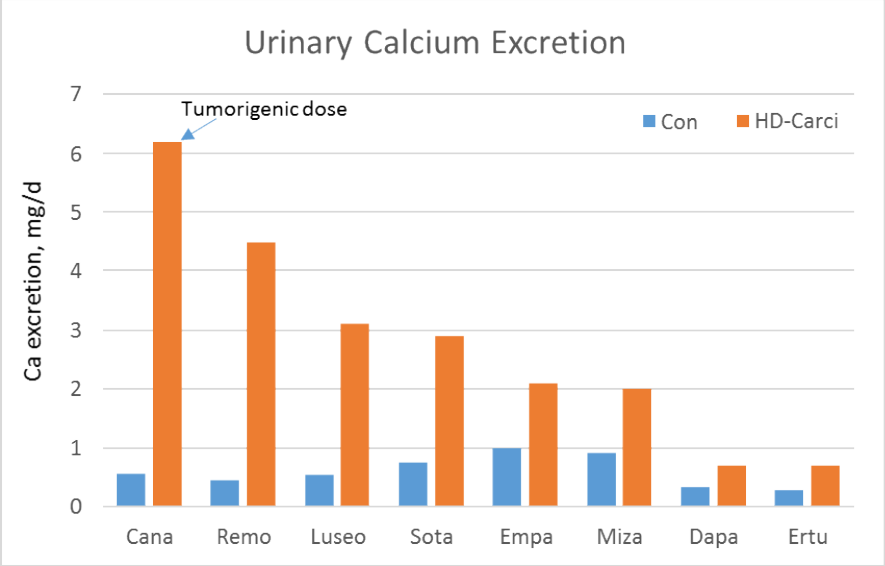

Figure 1: Urinary calcium excretion in rats at week 13 in response to SGLT inhibitors. 'HD-Carci' represents the highest dose of each compound evaluated in the 2yr carcinogenicity study. 'Tumorigenic dose' denotes the only compound (Cana) and dose associated with an unequivocal increase in RCC.

The data in Fig 1 suggests that the apparent discrepancy in tumor outcome, particularly between Cana, Sota, and Miza, might be due to the degree of calcium disruption achieved by the highest dose evaluated in the 2yr rat studies. Based on their selectivity for SGLT1, Sota and Miza should be more efficacious in disrupting calcium homeostasis than Cana. To explore this further, calcium excretion was plotted as a function of exposure to Cana, Sota, and Miza at all doses evaluated at week 13. Figure 2 indeed shows that Sota and Miza can result in more calcium excretion than Cana at any given exposure in rats. However, as indicated by the superimposed stars in Figure 2, Cana was tested at a higher AUC exposure than the other compounds, and therefore likely resulted in a higher degree of calcium excretion for a longer duration in the rat carcinogenicity studies.

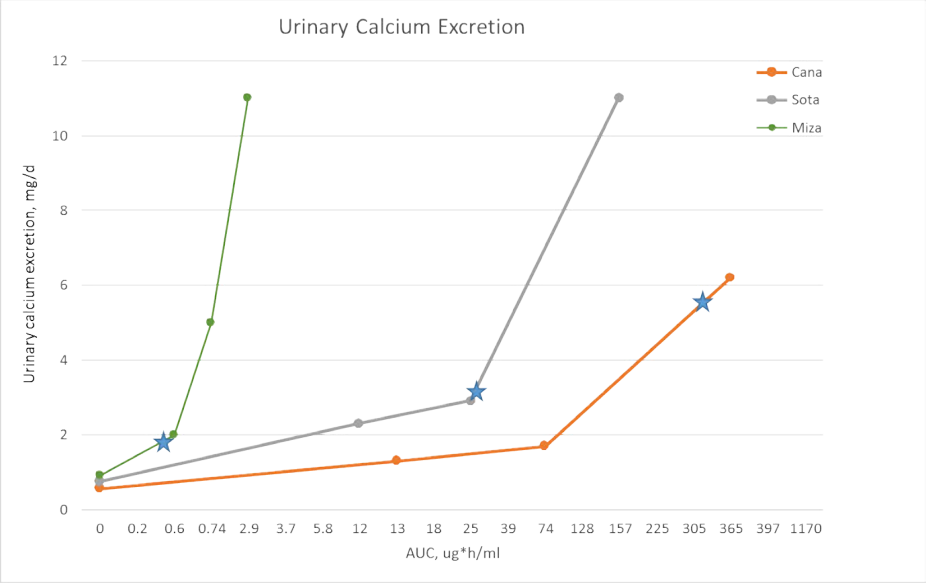

Figure 2: Urinary calcium excretion as a function of AUC at week 13 in rats administered Cana, Sota, or Miza. The superimposed stars indicate the highest exposure evaluated in the 2yr rat study for each compound.

Parathyroid Hormone and 1,25 (OH)$_2$ Vit D3: Plasma levels of PTH and calcitriol are available for Cana and Sota but were not collected in the Miza program. These values were derived from wk 13 of either 3m or 6m toxicology studies in SD rats. Both compounds dose-dependently reduced calcitriol and PTH relative to control (Fig 3). The superimposed stars indicate the highest exposure of Cana and Sota tested in the 2yr study. The higher exposure of Cana more robustly reduced both biomarkers than the lower exposure of Sota, again indicating that Cana was associated with a greater disruption of calcium balance in the 2yr rat study than achieved with Sota.

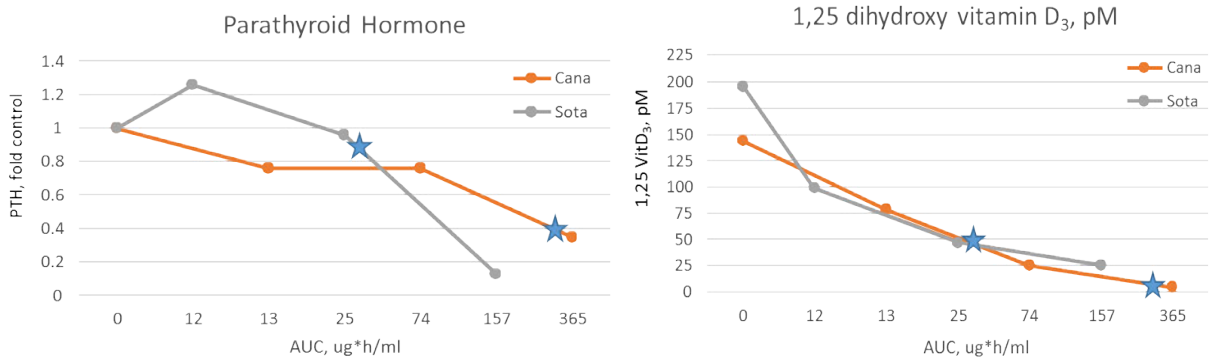

Fig 3: Plasma PTH (left) and calcitriol (right) in SD rats at week 13. The superimposed stars indicate the highest exposure evaluated in the 2yr rat study for each compound.

Renal tubular mineralization and tumor incidence

Events distal to calcium disruption that result in renal tubule neoplasia remain unidentified. Jansen produced histological evidence in NDA 204042 that markers of cell injury and proliferation co-localize in the proximal epithelium, pointing to renal cell injury as an inciting preneoplastic event. One potential source of proximal cell injury is tubular mineralization which can occur in rats administered SGLT2 inhibitors. The incidence of renal tubule mineralization

was plotted against the incidence of renal cell tubule neoplasia in the 2yr rat study for Cana, Sota, and Miza (Fig 4). The incidence of tubule mineralization and neoplasia appears to track in unison in response to Cana; however, Miza and Sota produced at least as much renal mineralization without resulting in renal tumors. It is recognized that a pathologist's call of mineralization can be subjective, so a quantitative comparison across studies is not definitive; nonetheless, tubule mineralization is clearly present and increases with dose for all three compounds, but renal tumors were only observed with canagliflozin. While this data cannot exclude a role for renal calcium deposition in the tumorigenic MOA, it does argue that mineralization alone is not sufficient to induce renal neoplasia.

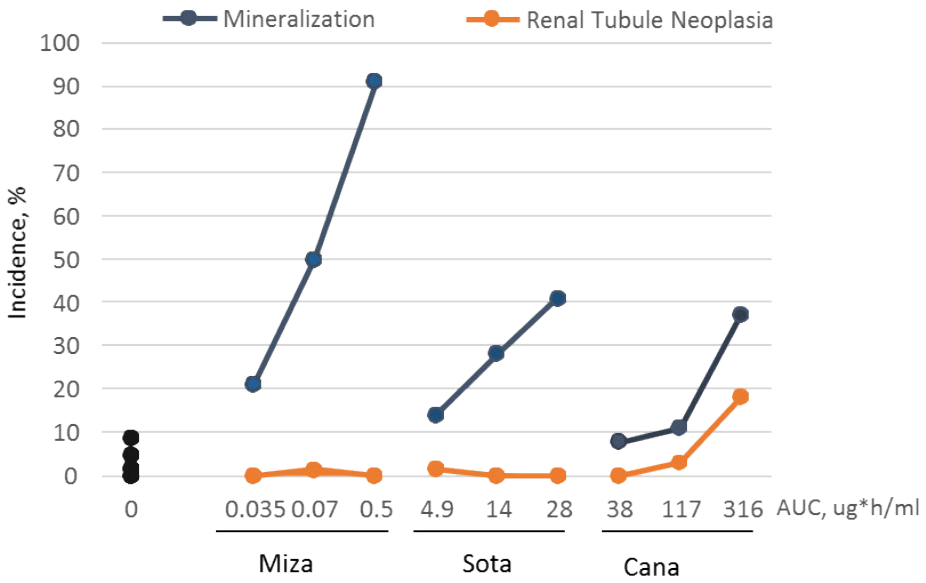

Figure 4: The incidences of renal tubule mineralization and renal tubule neoplasia in the 2yr rat carcinogenicity studies for Miza, Sota, and Cana.

Comments: The central nonclinical question was the validity of the carbohydrate malabsorption MOA resulting in renal tumors in rodents administered Cana. The interventional studies from Jansen persuasively support this MOA. It is the apparent conflicting lack of renal tumors with recent SGLT1-selective compounds that has primarily challenged the tumorigenic MOA. The discrepancy in renal tumor outcome between Cana and the more selective SGLT1 inhibitors Sota and Miza is plausibly due to an exposure difference between the highest doses tested in the 2yr rat study. For example, exposure at 100mg/kg Cana is ~10-fold higher than exposure at 75mg/kg Sota; this is key because the degree of carbohydrate malabsorption, as indicated by urinary calcium excretion and decreases in calcitriol and PTH, becomes more severe as exposure to each drug increases (Figs 2 & 3). The data in Fig 1 suggests that a threshold of calciuria, not its presence or absence, likely exists below which tubular neoplasms do not emerge. The higher exposure and greater degree of carbohydrate malabsorption likely achieved by Cana in the 2yr rat study is thus a plausible explanation for an absence of renal tumors in rats administered Sota or Miza.

Markers of carbohydrate malabsorption in the clinical program for canagliflozin

Recognition of one or more key events in an adverse outcome pathway enables an assessment of clinical relevance by measuring that key event in human subjects, to the extent feasible. In a response to the Division's request (9/22/2018), Jansen provided a summary for calcium excretion data and other indicators of carbohydrate malabsorption monitored during the clinical program for canagliflozin. The data suggest that canagliflozin inhibits intestinal SGLT1 to a limited extent, but does not result in a malabsorptive state sufficient to disrupt calcium balance, as observed in rats.

Urinary calcium excretion

Twenty-four-hour urines were collected from clinical studies NAP1001 (SAD, healthy volunteers), NAP1002 and DIA1007 (MAD, T2DM). Cumulative measures of calcium and other electrolytes were obtained. The sponsor reports and the reviewer verified that no change in urinary calcium was observed whether presented as mmol or mg/d or as fractional excretion relative to creatinine in Study NAP1001 (2wk dosing, healthy volunteers) and Study DIA1007 (28d dosing, T2DM). Figure 5 illustrates the percent change from baseline of 24h cumulative urinary calcium (mmol, raw values) from Study NAP1002, which was a 2wk repeat-dose study in T2DM at doses up to 400mg QD or 300mg BID canagliflozin. While variable, no overall trend is observed for a treatment-related change in urinary calcium.

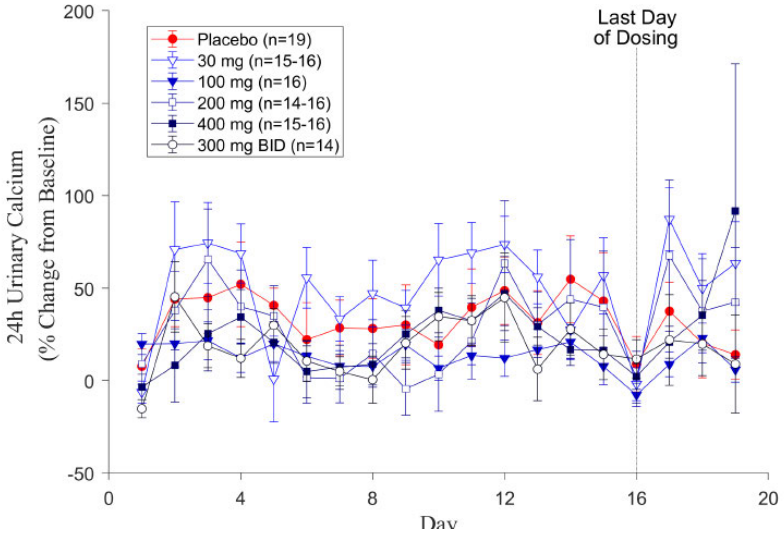

Figure 5: Percent change from baseline in 24h cumulative urinary calcium (Study NAP1002; Sponsor's figure).

Overnight urines were collected in Study DIA2001, a 12week phase 2 study conducted in T2DM. Urinary calcium expressed in mM concentrations is not increased but is arguably decreased slightly during the first few weeks of dosing with canagliflozin (Fig 6). Urinary calcium was also calculated as a calcium:creatinine ratio and as fractional calcium excretion (Fig 7); for both measures, the changes are small in degree and not dose related.

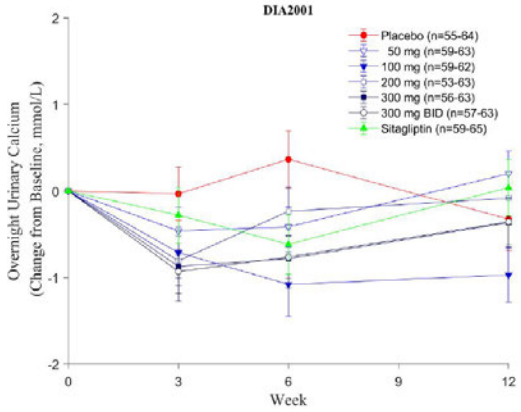

Figure 6: Change from baseline in overnight millimolar urinary calcium (Study DIA2001; Sponsor's figure)

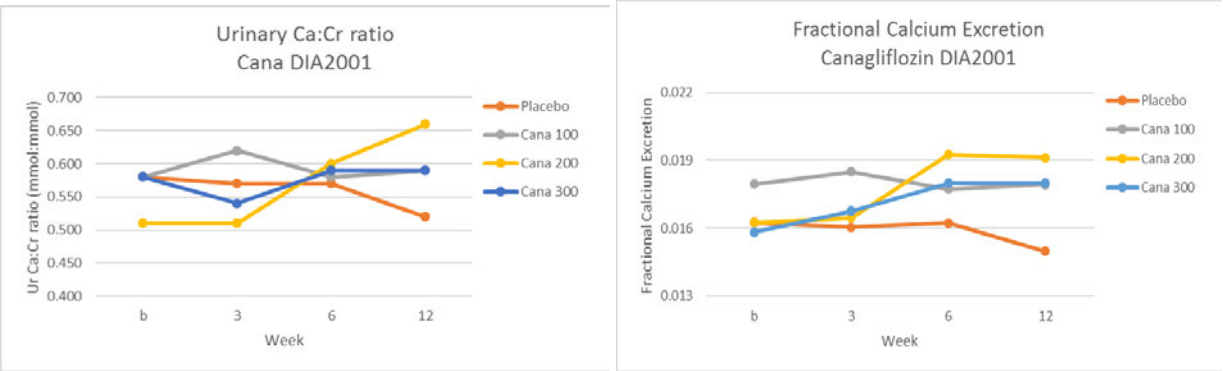

Figure 7: Overnight urinary calcium:creatinine ratio (mmol:mmol, left) and fractional calcium excretion (right) at baseline (b) and weeks 3, 6, and 12 of dosing with canagliflozin (Study DIA2001; Means).

Parathyroid Hormone and Vitamin D

PTH and 1,25 dihydroxy vitamin D were among the panel of bone biomarkers collected in DIA2001. Figure 8 illustrates that neither biomarker showed changes on the scale observed in rats administered canagliflozin.

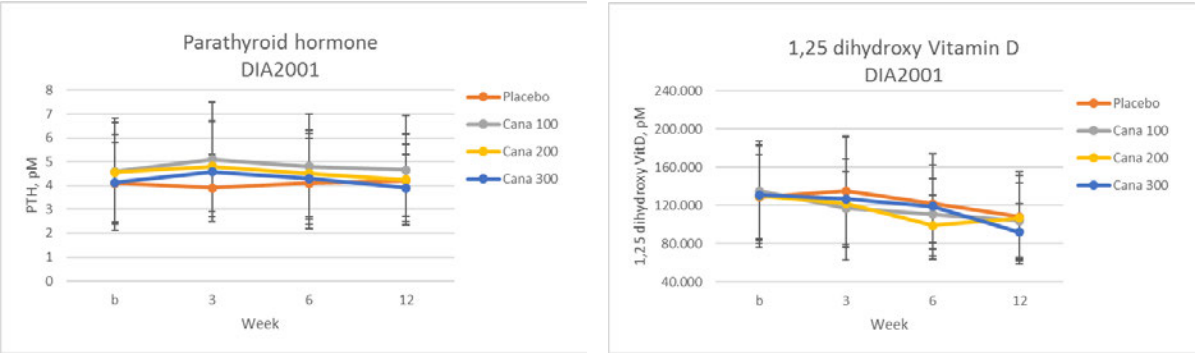

Figure 8: Parathyroid hormone (left) and 1, 25 dihydroxy Vitamin D (right) at baseline (b) and weeks 3, 6, and 12 of dosing with canagliflozin (Study DIA2001; Means±SD)

Hydrogen/methane breath test and oral glucose absorption

Evidence that canagliflozin indeed inhibits intestinal SGLT1 by some degree was obtained in clinical study DIA1022, which monitored the absorption of radiolabeled glucose in the absence and presence of 300mg canagliflozin. Sponsor's Figure 9 indicates that canagliflozin delayed glucose absorption, as would be anticipated if intestinal SGLT1 were blocked. However, this delay in glucose absorption was not associated with a positive hydrogen/methane breath test evaluated over a 2hr period following a glucose challenge in clinical study DIA1007 (Sponsor's Table 1). This suggests that the quantity of glucose reaching the distal intestine and colon is insufficient to result in local acidosis as would occur in a sugar malabsorption state.

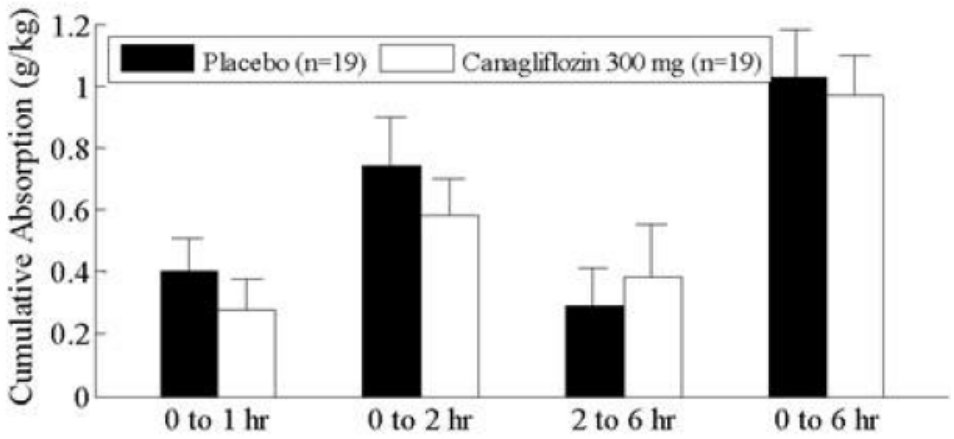

Figure 9: Rate of oral glucose appearance during MMTT, means±SE. (Study DIA1022; Sponsor's figure)

Analysis Set: SAFETY
Parameter: HYDROGEN BREATH TEST, ppm

Visit - Timepoint	--- JNJ-28431754 100 MG Q.D. versus Placebo -- Mean	SE	90% CI	-- JNJ-28431754 300 MG B.I.D. versus Placebo - Mean	SE	90% CI
DAY 26 Predose	11.84	21.538	(-25.915; 49.601)	14.04	14.260	(-10.956; 39.041)
DAY 26 5 min	-0.29	9.778	(-17.427; 16.856)	6.81	5.188	(-2.280; 15.909)
DAY 26 10 min	8.00	15.057	(-18.395; 34.395)	18.50	10.961	(-0.715; 37.715)
DAY 26 15 min	6.10	14.927	(-20.069; 32.269)	12.20	11.332	(-7.666; 32.066)
DAY 26 20 min	-1.31	15.256	(-28.059; 25.431)	9.89	9.154	(-6.162; 25.933)
DAY 26 0.5 h	-3.47	18.422	(-35.766; 28.823)	11.83	10.170	(-6.000; 29.657)
DAY 26 40 min	3.64	15.359	(-23.281; 30.567)	20.94	11.287	(1.156; 40.729)
DAY 26 50 min	10.19	14.454	(-15.153; 35.525)	20.09	12.287	(-1.454; 41.626)
DAY 26 1 h	1.89	14.878	(-24.196; 27.968)	8.49	14.418	(-16.789; 33.761)
DAY 26 70 min	20.87	13.583	(-2.941; 44.683)	28.07	13.726	(4.010; 52.133)
DAY 26 80 min	23.49	13.409	(-0.021; 46.992)	24.19	13.812	(-0.027; 48.398)
DAY 26 1.5 h	2.06	11.141	(-17.474; 21.588)	2.86	11.356	(-17.050; 22.764)
DAY 26 100 min	-10.07	16.388	(-38.801; 18.658)	-10.67	16.512	(-39.618; 18.276)
DAY 26 110 min	-0.49	9.760	(-17.595; 16.623)	1.41	9.195	(-14.704; 17.533)
DAY 26 2 h	-8.19	10.256	(-26.164; 9.793)	-5.79	9.300	(-22.089; 10.518)

Table 1: Results of hydrogen/methane breath test; mean differences in change from baseline between canagliflozin and placebo (Study DIA1007, Sponsor's table).

Appendix 1 Neoplasms with SGLT2 inhibitors in rodents				
Drug	Renal Tubules	Adrenal PC	Testicular Leydig	Other
Canagliflozin	X	X	X	
Dapagliflozin	atypical hyperplasia	-	-	
Empagliflozin	X (mice)	-	X	hemangioma
Remogliflozin	X (mice)	X (mice & rats)	X	bladder papilloma
Ipragliflozin	atypical hyperplasia	X	-	bladder hyperplasia
Luseogliflozin	-	X	X	
Sotagliflozin	-	-	-	Thyroid FC Bladder hyperplasia
Ertugliflozin	-	X	-	Bladder hyperplasia
Mizagliflozin	-	X	X	

'-' = not observed; 'X' denotes positive finding in rats unless otherwise noted

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TODD M BOURCIER
10/11/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW

CLINICAL STUDIES

NDA / Sequence Number:	204042 / S027 204353 / S025 205879 / S007
Drug Name:	Invokana (canagliflozin) tablets
Proposed Indications:	To reduce the risk of major adverse cardiovascular events (b) (4) in adults with type 2 diabetes mellitus who have established cardiovascular disease (b) (4)
Applicant:	Janssen Research & Development, L.L.C.
Date(s):	Submission Date: 9/29/2017 PDUFA Date: 7/27/2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II Division of Biometrics VII
Statistical Reviewers:	Roberto Crackel, Ph.D., Mathematical Statistician (DB2) Changming (Sherman) Xia, Ph.D., Mathematical Statistician (DB7)
Concurring Reviewers:	Yun Wang, Ph.D., Team Leader (DB2) Mark Rothmann, Ph.D. Acting Division Director (DB2) Eugenio Andraca-Carrera, Ph.D., Team Leader (DB7) Mark Levenson, Ph.D., Division Director (DB7)
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Medical Officer: Hyon Kwon Medical Team Leader: Lisa Yanoff
Project Manager:	Elizabeth Godwin
Keywords:	NDA review, Clinical Studies, Cardiovascular Outcomes Trial, Amputations

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1 Executive Summary

Janssen submitted a supplemental new drug application (sNDA) to obtain a superiority claim on major adverse cardiovascular events (MACE) for the already approved canagliflozin (marketed as INVOKANA), which is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. To support the claim and update the product label, the submission included the meta-analysis results for two large cardiovascular outcomes trials (CVOT's): CANagliflozin cardioVascular Assessment Study (CANVAS, also referred to as DIA 3008) and CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R, also referred to as DIA 4003). Studies CANVAS and CANVAS-R together are referred to as the CANVAS program.

The CANVAS study was originally intended to support initial marketing applications for canagliflozin in 2012 by demonstrating that there was not an unacceptable CV risk by ruling out an 80% risk increase. The intention was to enroll a first cohort and pool the data with other phase 2/3 trials to achieve this goal at an interim analysis. If results at the interim analysis trended toward a future favorable outcome, a second cohort would be enrolled. However, at the time of the filing application, results from the interim analysis were unblinded to the sponsor and the Steering Committee determined that the second cohort should not be recruited and that a new CVOT study CANVAS-R be initiated to further evaluate CV risk. The CANVAS trial stopped enrolling additional subjects but investigators and patients remained blinded to randomized treatment and the trial was allowed to continue follow-up for patients who had already enrolled.

With the initiation of CANVAS-R, to meet post-marketing requirements by ruling out a 30% increase in risk, data from the final analyses of CANVAS and CANVAS-R would be integrated into one analysis. The primary endpoint was time to first occurrence of MACE, a 3-component composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Results from the integrated analysis showed that the hazard ratio and 95% C.I. for time to first occurrence of MACE are 0.86 and (0.77, 0.97). Since the upper bound of the confidence interval is less than 1, superiority in MACE of canagliflozin to placebo was demonstrated. Therefore, although superiority in MACE was not part of the pre-specified testing strategy, Janssen is seeking a superiority claim for canagliflozin in the reduction of MACE risk.

A safety signal for atraumatic lower extremity amputation associated with canagliflozin was identified in the CANVAS program. An integrated time-to-event analysis showed that canagliflozin was associated with an approximately 2-fold increase in the risk of amputation compared to placebo, with a hazard ratio (HR) estimate of 1.97 and a 95% confidence interval (CI) [1.41, 2.75]. The exposure-adjusted annualized incidence rates for canagliflozin and placebo were 6.30 and 3.37, respectively, based on these two trials.

1.1 Background

The CANVAS study, a large long term CVOT was intended to assess the risk of MACE in patients with T2DM and to achieve other goals such as to evaluate overall safety and tolerability, glycemic efficacy, and long-term effects on renal functions. At an interim analysis in January 2012, data

from the CANVAS study were integrated with data from other phase 2/3 studies in a pre-approved meta-analysis to evaluate CV safety by showing that there is not a greater than 80% increase in CV risk. In May 2012, Janssen submitted a new NDA to market canagliflozin in patients with T2DM as an adjunct to diet and exercise.

Janssen originally intended to possibly enroll a second cohort depending on the results at the interim analysis. However, at a second interim analysis in November 2012, due to an increase in low-density lipoprotein-cholesterol (LDL-C) seen on the canagliflozin arm, which could have an adverse effect in CV risk, Janssen elected to unblind the results of the interim analysis. No unblinding of MACE data from CANVAS occurred post November 2012. The Steering Committee determined that there would be no enrollment of a second cohort. To satisfy post-marketing requirements by ruling out a 30% increase in CV risk, and to accrue sufficient MACE data within an appropriate time, a new study CANVAS-R was initiated, where the intent would be to pool data from both studies. To facilitate the pooling of CANVAS and CANVAS-R, design characteristics such as inclusion/exclusion criteria and event definitions were identical.

1.2 Findings and Recommendations

Findings and recommendations regarding cardiovascular endpoints:

From a statistical perspective, we believe the CANVAS program demonstrated that canagliflozin is superior to placebo in reducing the risk for MACE and recommend approval for the following reasons:

- In the integrated analysis, the hazard ratio and 95% C.I. for time to first occurrence of MACE is 0.86 and (0.75, 0.97)

- Though none of studies showed a significant result, there was a positive trend for CV risk reduction in both CANVAS and CANVAS-R

However, we note there are issues that needed to be taken into consideration. One issue was that the impact of missing values on the primary efficacy results. Another issue was the appropriateness of integrating two separate studies, CANVAS and CANVAS-R into one analysis. Please refer to Section 5.1 for further details.

Findings and recommendations regarding the risk of amputations:

An approximately 2-fold increase in the risk of atraumatic lower extremity amputation was observed in subjects randomized to canagliflozin compared to placebo, with incidence rates 6.30 for canagliflozin and 3.37 for placebo (per 1000 patient-years). The HR estimate was 1.97 with a 95% CI [1.41, 2.75], which excluded 1. Some limitations of this safety analysis included: (1)

CANVAS and CANVAS-R were not designed to evaluate the amputation safety signal; (2) the definition, event identification and adjudication methods were not pre-specified; (3) amputation data collection had changed over the course of these two trials, and was different between these two trials.

2 INTRODUCTION

2.1 Overview

CANVAS and CANVAS-R were event-driven, multinational, randomized, double-blind, placebo-controlled studies. The CANVAS study was originally designed to include 2 sequential cohorts, with up to 18,500 subjects and a duration for individual subjects of up to approximately 8 years. However, due to unblinding at the sponsor level because of a safety concern after an interim analysis, the study only included the initial cohort of 4,330 subjects. To help fulfill post-marketing requirements, a new and similar CVOT study (CANVAS-R) was initiated. Approximately 5,700 patients in CANVAS-R were to be randomized and the studies were pooled in the analysis.

In total, 10,142 patients were enrolled in CANVAS and CANVAS-R. The studies would terminate when 688 patients experienced an adjudicated MACE and the last subject randomized had approximately 78 weeks of follow-up. The sponsor estimated that this would provide approximately 90% power to rule out the 1.3 post-marketing margin for CV risk. For the CANVAS study, patients were enrolled in a 1:1:1 fashion to placebo, canagliflozin 100mg, or canagliflozin 300mg. For the CANVAS-R study, patients were randomized in a 1:1 fashion to either placebo or canagliflozin 100mg. The canagliflozin/placebo dosage were up-titrated from 100mg to 300mg only if better glycemic control was necessary. After pooling the studies, there were 5,795 patients randomized to canagliflozin and 4,347 patients to placebo.

For the primary analysis population, all canagliflozin patients were pooled and tested against placebo. The primary analysis model was a Cox proportional hazards model which included treatment as the explanatory variable, and study (CANVAS or CANVAS-R), and prior CV disease subgroup (secondary or primary prevention) as stratification factors. The first step in the testing hierarchy was to demonstrate non-inferiority. Key secondary endpoints included all-cause mortality, CV death, and albuminuria progression. While not part of the testing strategy, the statistical analysis plan stated that if the upper bound of the confidence interval excluded 1, and a study by treatment interaction was not significant, superiority would be claimed.

2.2 Regulatory History of Cardiovascular Safety and Efficacy

In May 2012, a new NDA was submitted by Janssen to support the registration of canagliflozin. The submission included data from one phase 2 study and eight phase 3 clinical studies, including a long-term CV outcome study (CANVAS). To fulfill regulatory requirements, an 80% increase in CV risk need to be ruled out, i.e. the upper bound of the 2-sided 95% confidence interval of the

hazard ratio for time to first occurrence of MACE should be less than 1.8. Partial results of the CANVAS study were integrated with the other phase 3 studies and confirmed the requirement.

Canagliflozin was approved for two dose levels (100mg and 300mg) on March 29th 2013 in the U.S. under the trade name INVOKANA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. INVOKAMET (combination of INVOKANA and metformin) was approved on August 8th 2014 for the treatment of T2DM.

2.3 Regulatory History of Amputations

After canagliflozin was approved in 2013, the CANVAS trial stopped enrolling additional subjects but investigators and patients remained blinded to randomized treatment and the trial was allowed to continue follow-up for patients who had already enrolled. The sponsor received an initial notification on 2/18/2016 from the Independent Data Monitoring Committee (IDMC) following a regularly scheduled IDMC meeting held on 1/11/2016 regarding an observed increase in the rate of lower extremity amputations in subjects randomized to canagliflozin compared to placebo in CANVAS. The IDMC analyses were based on a data cut-off date of 10/7/2015. At that time, CANVAS was ongoing with a mean on-trial follow-up time of approximately 4.5 years. The analysis was based on a total of 101 subjects with atraumatic lower extremity amputations in CANVAS. The annualized incidence was 3.0, 7.3, and 5.4 events per 1000 subject-years in the placebo, canagliflozin 100mg, and canagliflozin 300 mg treatment groups respectively. At that time, trial CANVAS-R had a mean follow-up of 0.75 year, and a total of 28 subjects had experienced an event, with a corresponding annualized incidence rate of 5.3 and 7.0 per 1000 subject-years in the placebo group and the pooled canagliflozin group respectively. CANVAS and CANVAS-R shared the same IDMC. The IDMC recommended the trials to continue. Both trials were fully enrolled and ongoing at the time of this finding.

On 3/16/2016, the sponsor sent a letter to investigators notifying them of the potential lower extremity amputation risk and submitted a safety update report to health authorities, including FDA, regarding this safety signal. On 5/18/2016 the FDA issued a Drug Safety Communication (DSC) to notify the public of this risk. On 5/16/2017 the FDA added a Boxed Warning to the product label for products containing canagliflozin (INVOKANA, INVOKAMET) and updated the language of the DSC based on the final results of CANVAS and CANVAS-R:

> *Final results from two clinical trials – the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) – showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs.*

This review evaluates the risk of atraumatic lower extremity amputations associated with canagliflozin based on the final results of CANVAS and CANVAS-R.

2.4 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission can be accessed at the following link: \\CDSESUB1\evsprod\NDA204042\0212

The following documents were used to support this review.

Document
Integrated Summary of Efficacy
CSR for study DIA3008
CSR for study DIA4003
Statistical Analysis Plan for Integrated Database of Canvas and Canvas-R
Pre-sNDA Meeting Briefing Document
Request for Health Authority Feedback on the Methodology for the Multiple Imputation Analysis and on the Definition of the Retreived Drop-Outs
Integrated Summary of Safety
INVOKANA (Canagliflozin) Update to Health Authorities on Aggregate Analysis of Safety Data from CANVAS (DIA3008)

All results presented in this review were based on data derived from the submitted datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

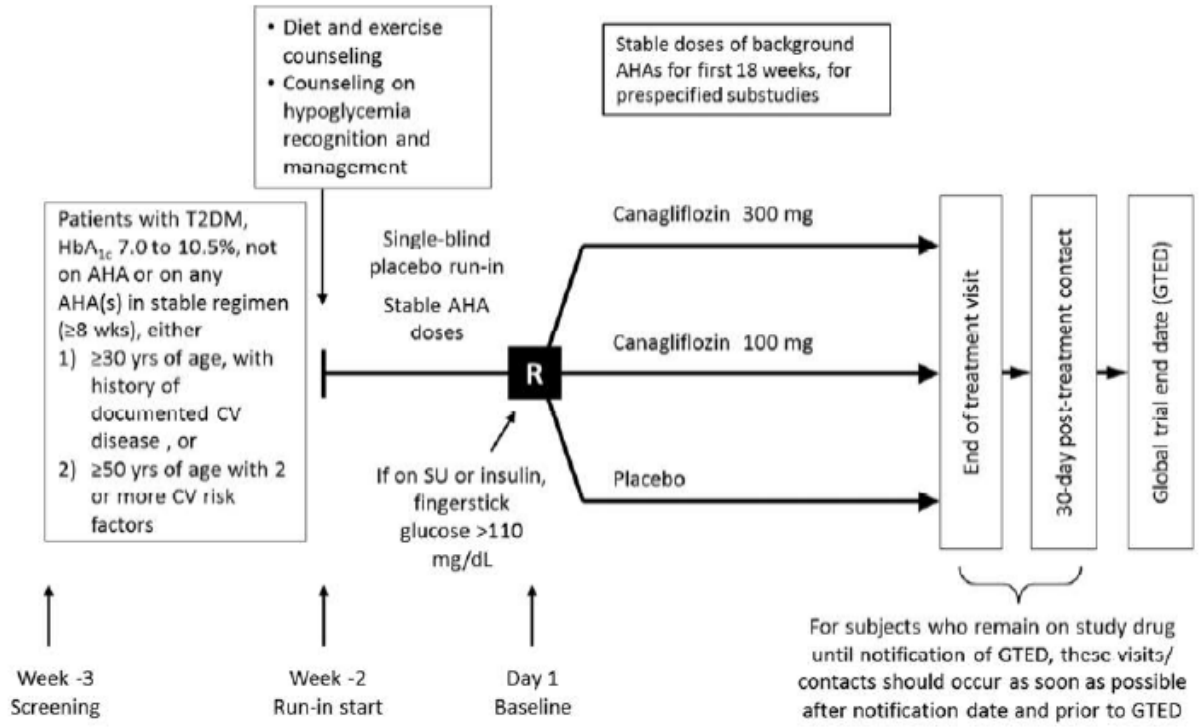
There were no issues concerning the submission of data sets and files.

3.2 Study Design and Endpoints

3.2.1 Trial Design

To justify the integrated analysis, both studies were similar in design, eligibility criteria, and study population. Study 3008 (CANVAS) was a randomized, double-blind, placebo-controlled, 3 parallel-group, multi-center study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM. A total of 4,330 patients were enrolled in a 1:1:1 fashion to placebo, canagliflozin 100mg, or canagliflozin 300mg. Figure 1 below displays the study design:

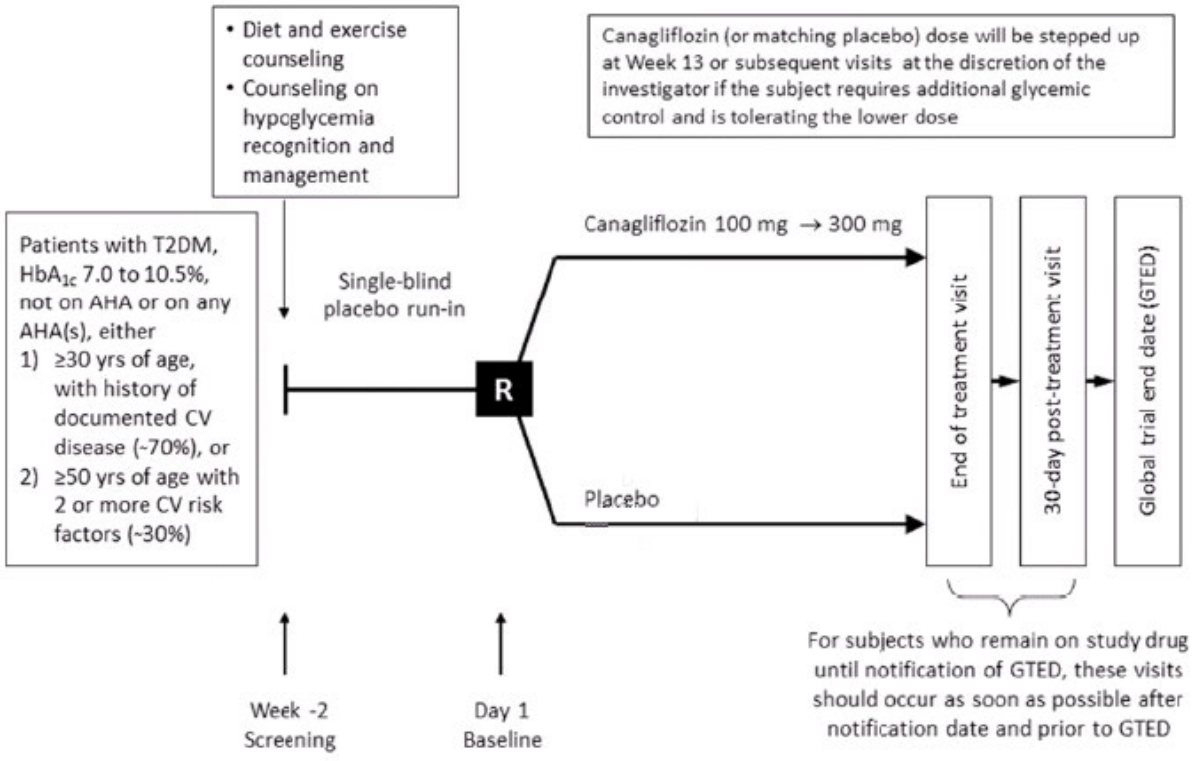
Figure 1: Study design of the CANVAS trial



[Source: CSR: The CANVAS Trial Page 36]

CANVAS-R was a randomized, double-blind, placebo-controlled study, parallel-group, multi-center study to evaluate the effects of canagliflozin compared to placebo in subjects with T2DM. A total of 5,812 patients were randomized in a 1:1 fashion to placebo or canagliflozin. Figure 2 below displays the study design:

Figure 2: Study design of the CANVAS-R trial



[Source: CSR: The CANVAS-R Trial Page 28]

The patient population for both studies consisted of men and women diagnosed with T2DM with HbA1c ≥ 7.0% to ≤ 10.5% at screening who were either: 1) not currently on AHA therapy or 2) on AHA monotherapy or combination therapy with any approved agent and:

- At least 30 years of age with documented CV disease (a target of 70%)
- At least 50 years of age with 2 or more CV risk factors (a target of 30%)

For the CANVAS study, the first and last subjects randomized were on December 9th 2009 and February 22nd 2011. For the CANVAS-R study, the first and last subjects randomized were on January 27th 2014 and May 29th 2015. The median and maximum follow-up times for the CANVAS study were approximately 6 and 7 years, respectively while the median and maximum follow-up times for the CANVAS-R study were approximately 2 and 3 years, respectively. Both studies were scheduled to end when 688 patients experienced an adjudicated MACE and the last subject randomized had approximately 78 weeks of follow-up. Both studies were overseen by a single Steering Committee and Independent Data Monitoring Committee (IDMC) and cardiovascular endpoints were adjudicated by a single Endpoint Adjudication Committee (EAC).

3.2.2 Primary Efficacy Endpoint

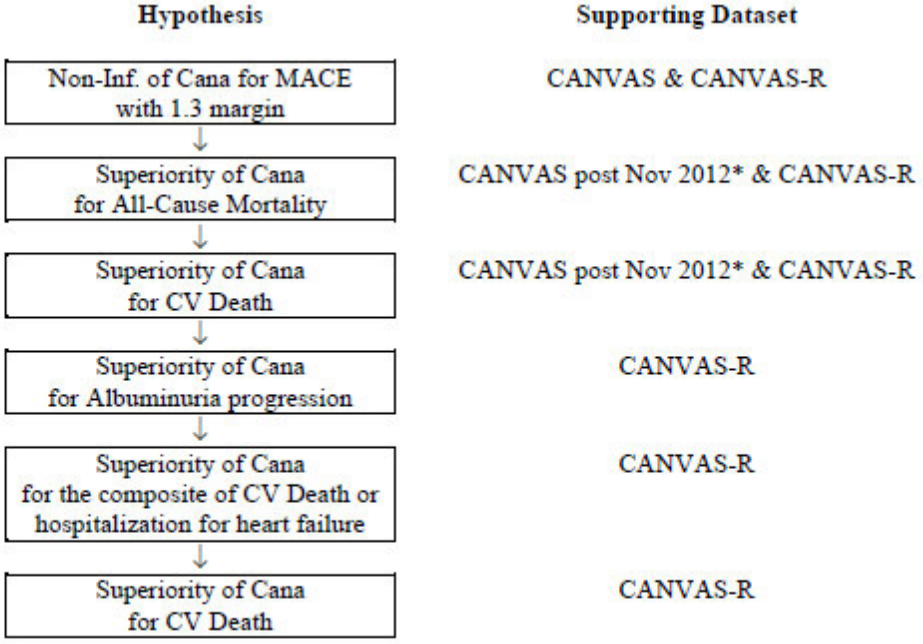
The primary endpoint was time to first occurrence of MACE, which is a 3-point composite of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction.

3.2.3 Secondary Efficacy Endpoints

When CANVAS was first initiated, a formal testing procedure for secondary endpoints was specified. However, due to the unblinding of the data at an interim analysis on November 19th 2012, and the available results of the empagliflozin CVOT (EMPA-REG), when the CANVAS-R study was initiated, a new testing sequence was specified. The first two secondary endpoints to be tested is the superiority of canagliflozin over placebo in reducing all-cause mortality and CV death. To remove any bias due to the unblinding, data from the CANVAS study was left truncated, i.e., only deaths accrued after November 19th 2012 was included in the analyses.

Further testing included albuminuria progression, the composite of CV death or hospitalization for heart failure, and CV death alone. These endpoints would be tested using only the CANVAS-R dataset. Figure 3 below displays the testing sequence:

Figure 3: Hypothesis Testing Sequence of the CANVAS program



* Only subjects who were at risk for mortality after 19-Nov-2012 are included.

[Source: Pre-sNDA Meeting Briefing Document: Page 14]

3.2.4 Primary Safety Endpoint

3.2.4.1 Description of the Safety Endpoint

The primary safety endpoint evaluated in this review is atraumatic lower extremity amputation, which contributed to the majority of amputation events observed in these two trials (187 out of 206). Unless otherwise noted, hereafter the term "amputation" refers to only atraumatic lower extremity amputation. Traumatic and/or upper extremity amputations are not discussed in this review.

3.2.4.2 Identification of Amputation Events

The sponsor identified amputation events using four sources:

- A dedicated electronic case report form (eCRF) for amputation. This eCRF was introduced after the IDMC initially identified the amputation safety signal while the two trials were ongoing (see Section 2.3). After introduction of the amputation-specific eCRF, the investigators were asked to complete the amputation CRFs prospectively for every new event of amputation, as well as retroactively for every amputation event that occurred from Day 1 post-randomization and prior to the introduction of the CRF.
- Adverse Event eCRF. This eCRF was used in both CANVAS and CANVAS-R.
- Diagnostic or Therapeutic Procedures (DTP) eCRF. This was only used in CANVAS. Investigators were instructed to record procedures in the verbatim description in the Adverse Event eCRF for CANVAS-R.
- Sponsor's pharmacovigilance database (CIOMS reports).

For the last three sources listed above, the sponsor searched the available text descriptions using terms 'ampu', 'remov', 'resection', 'necrosectomy', 'disarticulation', 'exarticulation', 'BKA', and 'AKA' to identify any additional events of amputation not already entered by the investigators in the dedicated eCRF. Subjects with traumatic amputations were excluded from all analyses. The revised number of subjects with an on-study non-traumatic amputation was confirmed by the IDMC.

Prior to the conclusion of CANVAS and CANVAS-R, the sponsor and Steering Committee were firewalled from the unblinded safety reviews by the IDMC. The sponsor's medical monitoring team for CANVAS and CANVAS-R, the sponsor's site monitors, and the Endpoint Adjudication Committee, were firewalled from access to any subject level unblinded information (e.g., listings or narratives).

Reviwer's Comment: *Because amputation was an unexpected safety signal, the collection and adjudication of amputation were not pre-specified for either CANVAS or CANVAS-R. After the signal was identified by IDMC, a dedicated eCRF for amputation was introduced to record amputations in a more systematic way. Investigators were also asked to fill out the same eCRF retrospectively for previously identified amputation events. The Kaplan-Meier plots for CANVAS and CANVAS-R in Section 3.6 did not show an obvious difference in howevents accumulated between the two trials.*

3.3 Statistical Methodologies

3.3.1 Methods Related to the Analysis of Efficacy

Pooling: Patients on the canagliflozin 100mg and 300mg arms from the CANVAS study were pooled together with patients from the canagliflozin arm from the CANVAS-R study. Likewise, placebo patients were pooled together.

Analysis Set: The analysis population was the intention-to-treat (ITT) defined as all randomized subjects dating from day 1 to the last trial contact date up to the global trial end date (GTED).

Primary Analysis Model: A Cox proportional hazards model which included treatment as the explanatory variable, and study (CANVAS or CANVAS-R), and prior CV disease subgroup (secondary or primary prevention) as stratification factors.

3.3.2 Methods Related to the Analysis of Safety

3.3.2.1 Safety Analysis Populations

The following populations for safety analysis were defined in the sponsor's clinical study reports for CANVAS and CANVAS-R:

On-study population: defined as all subjects who were randomized and received at least one dose of randomized treatment. The on-study population serves as the primary population for the analysis of amputation.

On-treatment population: A supportive analysis for the risk of amputation was performed by censoring the information collected up to 30 days after the last dose of blinded study medication. This analysis was conducted to reduce the potential impact from off-treatment events on parameter estimates.

3.3.2.2 Primary Safety Analysis

The primary analysis of time to the first atraumatic lower extremity amputation was evaluated through a stratified Cox proportional hazards model with planned treatment (a 2-level categorical variable) as the single covariate, with baseline hazards stratified by trial (a 2-level categorical variable). The primary analysis was conducted on the on-study population. Since amputation was an unexpected safety signal observed while the trials were ongoing, this was a post-hoc analysis not pre-specified prior to the initiation of the trials.

3.3.2.3 Sensitivity Analysis of the Primary Safety Endpoint

A sensitivity analysis was performed on the on-treatment population, using the same model as described in Section 3.3.2.2. Analysis by trial on the on-study population was also performed.

3.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1 below describes the completion and vital status of the integrated studies. We see that a total of 10,142 patients were randomized and that 96.0% of patients completed the study. Through public records searches, the final vital status of 99.6% of patients were captured.

Table 1: Study Completion and Vital Status for the Integrated study

	Placebo (N=4348*) n (%)	Cana (N=5795) n (%)	Total (N=10143*) n (%)
Study in ITT analysis set	4347 (>99.9)	5795 (100)	10142 (>99.9)
Completed Study	4163 (95.7)	5571 (96.1)	9734 (96.0)
Final vital status known	4327 (99.5)	5773 (99.6)	10100 (99.6)
Alive	4046 (93.1)	5371 (92.7)	9417 (92.8)
Died	281 (6.5)	402 (6.9)	683 (6.7)
Final vital status Unknown	20 (0.5)	22 (0.4)	42 (0.4)

[Source: Integrated Summary of Efficacy Page 28]
***: One subject was randomized at 2 different sites and only the first randomization was included in the ITT**

From Table 2 below, we see that the most common reason for discontinuation from study medication was withdrawal from study medication (14.0% and 10.9% for placebo and canagliflozin, respectively) while the second most common reason was due to adverse event (6.9% and 9.7% for placebo and canagliflozin, respectively).

Table 2: Reasons for Discontinuation from Study Medication for the Integrated study

	Placebo (N=4344) n (%)	Cana (N=5790) n (%)	Total (N=10134*) n (%)
Primary reason for discontinuation	1297 (29.9)	1693 (29.2)	2990 (29.5)
Adverse event	301 (6.9)	559 (9.7)	860 (8.5)
Lost to follow-up	8 (0.2)	19 (0.3)	27 (0.3)
Noncompliance with study drug	45 (1.0)	60 (1.0)	105 (1.0)
Physician decision	75 (1.7)	100 (1.7)	175 (1.7)
Product quality complaint	1 (<0.1)	1 (<0.1)	2 (<0.1)
Product violation	14 (0.3)	20 (0.3)	34 (0.3)
Study terminated by sponsor	3 (0.1)	5 (0.1)	8 (0.1)
Withdrawn from study medication	606 (14.0)	630 (10.9)	1236 (12.2)
Withdrew consent	61 (1.4)	79 (1.4)	140 (1.4)
eGFR withdrawal criteria	4 (0.1)	6 (0.1)	10 (0.1)
Other	179 (4.1)	214 (3.7)	393 (3.9)

[Source: Integrated Summary of Efficacy Page 29]
***: On treatment analysis set**

Table 3 below describes demographic characteristics at baseline. We see that 64.2% of the patients were male, 78.3% were white, and that the average age was 63.3 years. Further, the region with the most patients was Europe (35.6%). Characteristics were evenly balanced between treatment groups.

Table 3: Baseline Demographic Characteristics for the Integrated study

	Placebo (N=4347)	Cana (N=5795)	Total (N=10142)
Sex [n(%)]			
Male	2750 (63.3)	3759 (64.9)	6509 (64.2)
Female	1597 (36.7)	2036 (35.1)	3633 (35.8)
Age (years)			
Mean (SD)	63.4 (8.21)	63.2 (8.27)	63.3 (8.25)
Age group [n(%)]			
< 65	2369 (54.5)	3209 (55.4)	5578 (55.0)
≥ 65	1978 (45.5)	2586 (44.6)	4564 (45.0)
Race [n(%)]			
White	3436 (79.0)	4508 (77.8)	7944 (78.3)
Black or African American	160 (3.7)	176 (3.0)	336 (3.3)
Asian	507 (11.7)	777 (13.4)	1284 (12.7)
American Indian or Alaska Native	22 (0.5)	16 (0.3)	38 (0.4)
Native Hawaiian or Other Pacific Islander	10 (0.2)	13 (0.2)	23 (0.2)
Multiple	20 (0.5)	30 (0.5)	50 (0.5)
Other	191 (4.4)	272 (4.7)	463 (4.6)
Unknown	1 (<0.1)	3 (0.1)	4 (<0.1)
Region [n(%)]			
North America	1005 (23.1)	1425 (24.6)	2430 (24.0)
Central / South America	484 (11.1)	537 (9.3)	1021 (10.1)
Europe	1566 (36.0)	2043 (35.3)	3609 (35.6)
Rest of the World	1292 (29.7)	1790 (30.9)	3082 (30.4)
Baseline HbA1c (%)			
Mean (SD)	8.2 (0.93)	8.2 (0.94)	8.2 (0.94)
Diabetes duration (years)			
Mean (SD)	13.7 (7.82)	13.5 (7.71)	13.5 (7.76)

[Source: Integrated Summary of Efficacy Page 31-33]

3.5 Evaluation of Efficacy

3.5.1 Results and Conclusions

Primary Endpoint

Table 4 below shows the MACE results for the CANVAS study. When comparing canagliflozin 100mg to placebo, the hazard ratio for time to first occurrence of MACE is 0.93 with a 95% C.I. of (0.78, 1.12), hence, there was not a significant reduction in CV risk since the upper bound of the confidence interval excludes 1. However, when comparing canagliflozin 300mg to placebo, there was a significant finding in time to first occurrence of MACE (nominal p-value=0.0467), where the hazard ratio is 0.83 with a 95% C.I. of (0.68, 1.00) (upper bound of the confidence interval is rounded up). After pooling the canagliflozin arms together, the hazard ratio and 95% C.I. is 0.88 and (0.75, 1.03), hence, the CANVAS study alone did not demonstrate that canagliflozin offers a CV risk benefit. However, we note that the hazard ratio is in a positive direction and that the study was underpowered to demonstrate a CV risk benefit.

Table 4: Time to the First Occurrence of MACE (Including Components) for the CANVAS study

	Placebo: n/N (%)	Cana 100mg: n/N (%)	Cana 300mg: n/N (%)	Cana Total: n/N (%)	Cana 100mg vs. Placebo	Cana 300mg vs. Placebo	Cana Total vs. Placebo
Endpoint							
MACE	233/1442 (16.2)	224/1445 (15.5)	201/1443 (13.9)	425/2888 (14.7)	0.93 (0.78, 1.12)	0.83 (0.68, 1.00)	0.88 (0.75, 1.03)
CV Death	115/1442 (8.0)	104/1445 (7.2)	103/1443 (7.1)	207/2888 (7.2)	0.89 (0.68, 1.16)	0.87 (0.67, 1.14)	0.88 (0.70, 1.10)
Non-Fatal MI	86/1442 (6.0)	80/1445 (5.5)	72/1443 (5.0)	152/2888 (5.3)	0.90 (0.66, 1.22)	0.80 (0.58, 1.09)	0.85 (0.65, 1.11)
Non-Fatal Stroke	53/1442 (3.7)	61/1445 (4.2)	45/1443 (3.1)	106/2888 (3.7)	1.12 (0.78, 1.62)	0.82 (0.55, 1.22)	0.97 (0.70, 1.35)
All MI	97/1442 (6.7)	94/1445 (6.5)	83/1443 (5.8)	177/2888 (6.1)	0.94 (0.70, 1.24)	0.82 (0.61, 1.09)	0.88 (0.68, 1.12)
All Stroke	62/1442 (4.3)	67/1445 (4.6)	52/1443 (3.6)	119/2888 (4.1)	1.05 (0.75, 1.49)	0.81 (0.56, 1.18)	0.93 (0.69, 1.27)

[Source: CSR: The CANVAS Trial Page 79, 88 and Statistical Reviewer's Analysis]

Table 5 below characterizes the follow-up and missing follow-up for the CANVAS study. The percentage of patients enrolled in the study who experienced a MACE is 15.2%, while 76.1% of patients were followed through the global trial end date (GTED) who did not experience a MACE. The percentage of patients who were censored for a non-CV death while in the study was 2.6%, and 6.1% of patients were lost-to-follow up before experiencing a MACE (i.e., censored before the GTED).

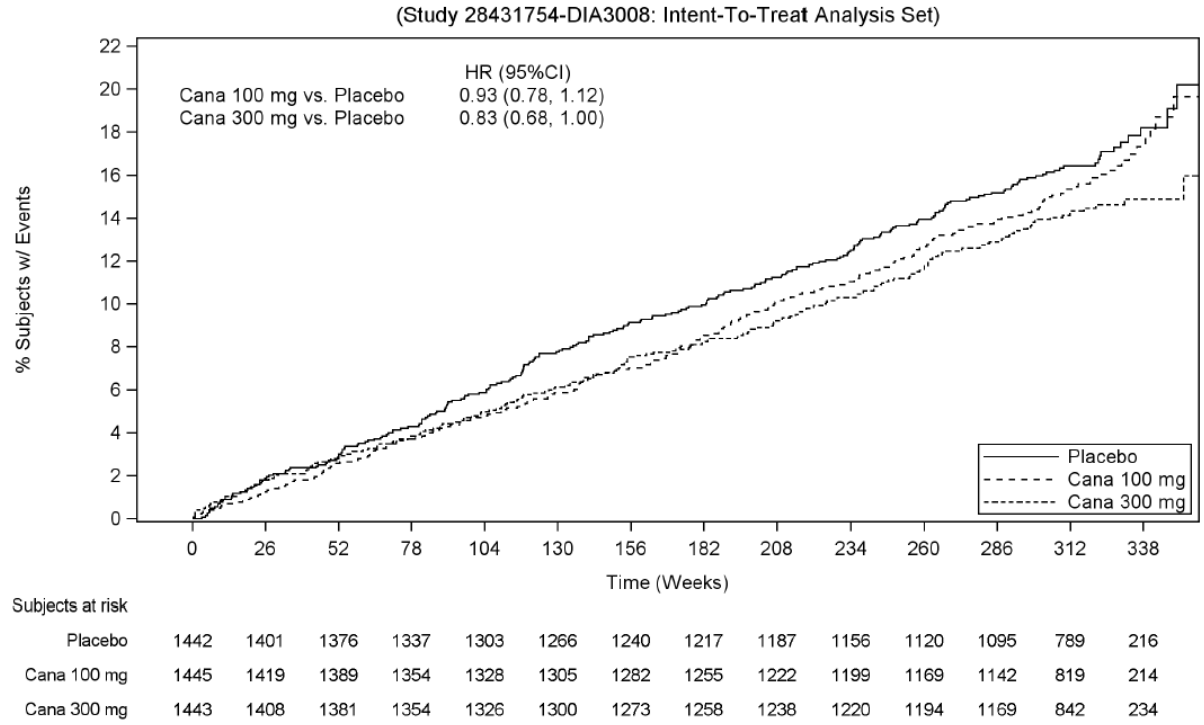
Table 5: Characterization of follow-up for the CANVAS study

Follow-up for MACE	Placebo (N=1442)	Cana 100mg (N=1445)	Cana 300mg (N=1443)	Cana Total (N=2888)	Total (N=4330)
Event [n(%)]	233 (16.2%)	224 (15.5%)	201 (13.9%)	425 (14.7%)	658 (15.2%)
Censored at GTED [n(%)]	1057 (73.3%)	1097 (75.9%)	1140 (79.0%)	2237 (77.5%)	3294 (76.1%)
Censored for non-CV death [n(%)]	42 (2.9%)	40 (2.8%)	32 (2.2%)	72 (2.5%)	114 (2.6%)
Censored before GTED (Missing Flag) [n(%)]	91 (6.3%)	66 (4.6%)	56 (3.9%)	122 (4.2%)	213 (4.9%)
Censored before GTED (No Missing Flag) [n(%)]	19 (1.3%)	18 (1.2%)	14 (1.0%)	32 (1.1%)	51 (1.2%)

[Source: Statistical Reviewer's Analysis]

Figure 4 below displays the Kaplan-Meier estimates for time to first occurrence of MACE by treatment groups in the CANVAS study:

Figure 4: Kaplan-Meier Estimate of First Occurrence of MACE for the CANVAS study



[Source: CSR: The CANVAS Trial Page 73]

Table 6 below shows the MACE results for the CANVAS-R study. The hazard ratio for time to first occurrence of MACE is 0.82 with a 95% C.I. of (0.66, 1.01), hence the study did not demonstrate that canagliflozin offers a CV risk benefit. However, as with the CANVAS study we note that the hazard ratio is in a positive direction and that the study was underpowered to demonstrate a CV risk benefit.

Table 6: Time to the First Occurrence of MACE (Including Components) for the CANVAS-R study

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo
Endpoint			HR (95% C.I.)
MACE	193/2905 (6.6)	160/2907 (5.5)	0.82 (0.66, 1.01)
CV Death	70/2905 (2.4)	61/2907 (2.1)	0.86 (0.61, 1.22)
Non-Fatal MI	73/2905 (2.5)	63/2907 (2.2)	0.85 (0.61, 1.19)
Non-Fatal Stroke	63/2905 (2.2)	52/2907 (1.8)	0.82 (0.57, 1.18)
All MI	76/2905 (2.6)	71/2907 (2.4)	0.92 (0.67, 1.27)
All Stroke	71/2905 (2.4)	57/2907 (2.0)	0.80 (0.56, 1.13)

[Source: CSR: The CANVAS-R Trial Page 19, 8953 and Statistical Reviewer's Analysis]

Table 7 below characterizes the follow-up and missing follow-up for the CANVAS-R study. There were 6.1% of patients enrolled in the study who experienced a MACE, while 91.7% of patients did not experience a MACE and who were followed through the GTED. The percentage of patients who were censored for a non-CV death while in the study was 1.0%, and 1.2% of patients were lost-to-follow up before experiencing a MACE.

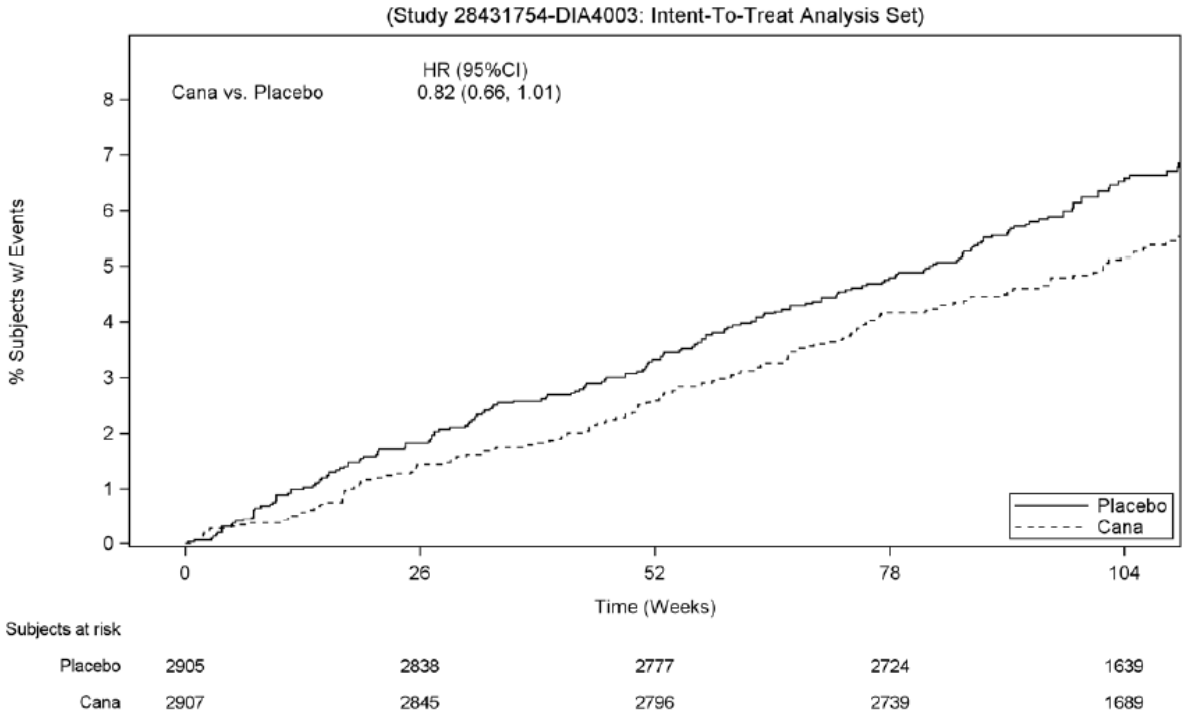
Table 7: Characterization of follow-up for the CANVAS-R study

Follow-up for MACE	Placebo (N=2905)	Cana (N=2907)	Total (N=5812)
Event [n(%)]	193 (6.6%)	160 (5.5%)	353 (6.1%)
Censored at GTED [n(%)]	2649 (91.2%)	2683 (92.3%)	5332 (91.7%)
Censored for non-CV death [n(%)]	27 (0.9%)	33 (1.1%)	60 (1.0%)
Censored before GTED (Missing Flag) [n(%)]	35 (1.2%)	31 (1.1%)	66 (1.1%)
Censored before GTED (No Missing Flag) [n(%)]	1 (0.03%)	0 (0%)	1 (0.02%)

[Source: Statistical Reviewer's Analysis]

Figure 5 below displays the Kaplan-Meier estimates for time to first occurrence of MACE by treatment groups in the CANVAS study:

Figure 5: Kaplan-Meier Estimate of First Occurrence of MACE for the CANVAS-R study



[Source: CSR: The CANVAS-R Trial Page 97]

Table 8 below display the results of the primary analysis of CANVAS and CANVAS-R pooled together. The hazard ratio for time to first occurrence of MACE is 0.86 with a 95% C.I. of (0.75, 0.97). Since the upper bound is less than 1, the evidence supports the claim that canagliflozin is superior to placebo in reducing CV risk. We note that while overall MACE is statistically significant, none of the individual components were.

Table 8: Time to the First Occurrence of MACE (Including Components) for the Integrated study

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo	
Endpoint			**HR (95% C.I.)**	**P-value**
MACE	426/4347 (9.8)	585/5795 (10.1)	0.86 (0.75, 0.97)	0.0158
CV Death	185/4347 (4.3)	268/5795 (4.6)	0.87 (0.72, 1.06)	0.1658
Non-Fatal MI	159/4347 (3.7)	215/5795 (3.7)	0.85 (0.69, 1.05)	0.1257
Non-Fatal Stroke	116/4347 (2.7)	158/5795 (2.7)	0.90 (0.71, 1.15)	0.3967
All MI	173/4347 (4.0)	248/5795 (4.3)	0.89 (0.73, 1.09)	0.2588
All Stroke	133/4347 (3.1)	176/5795 (3.0)	0.87 (0.69, 1.09)	0.2343

[Source: Integrated Summary of Efficacy Page 44, 93 and Statistical Reviewer's Analysis]

We take note that in the CANVAS study, the percentage of patients who experienced a MACE is 16.2%, 15.5%, and 13.9%, for the placebo, canagliflozin 100mg, and canagliflozin 300mg arms, respectively and in the CANVAS-R study, the percentage of patients who experienced a MACE on placebo is 6.6% and 5.5% for the canagliflozin arm. However, after pooling the studies together, the percentage is now lower in placebo arm (9.8%) than in the canagliflozin arm (10.1%). This phenomenon is known as Simpson's paradox and occurs when studies with unequal randomization rates are pooled as in our case where the CANVAS study had a 2:1 ratio of canagliflozin patients to placebo along with a much greater percent of patients having a MACE due to longer follow-up than the CANVAS-R study (which had an even randomization). By including study as a stratification factor, the MACE analysis in Table 8 accounts for differences between studies in both the randomization ratios and the percent of patients having a MACE.

Table 9 below characterizes the follow-up and missing follow-up for the combined CANVAS and CANVAS-R studies. The percentage of patients who experienced a MACE was 10.0%, while 85.0% of patients were followed through the GTED and did not experience a MACE. The percentage of patients who were censored for a non-CV death while in either study was 1.7%, and 3.3% of patients were lost-to-follow up before experiencing a MACE.

Table 9: Characterization of follow-up for the Integrated study

Follow-up for MACE	**Placebo (N=4347)**	**Cana (N=5795)**	**Total (N=10142)**
Event [n(%)]	426 (9.8%)	585 (10.1%)	1011 (10.0%)
Censored at GTED [n(%)]	3706 (85.3%)	4920 (84.9%)	8626 (85.1%)
Censored for non-CV death [n(%)]	69 (1.6%)	105 (1.8%)	174 (1.7%)
Censored before GTED (Missing Flag) [n(%)]	126 (2.9%)	153 (2.6%)	279 (2.8%)
Censored before GTED (No Missing Flag) [n(%)]	20 (0.5%)	32 (0.6%)	52 (0.5%)

[Source: Statistical Reviewer's Analysis]

As an additional analysis, since MACE censors non-CV deaths and inference can only be applied to a hypothetical situation, we looked at MACE+, which considers all deaths as an event. Table 10 below displays the results of the integrated study. We see that the upper bound of the confidence interval excludes 1, so we conclude that canagliflozin is superior to placebo in reducing CV risk when all deaths are considered as an event. It should be noted that the events tabulated do not include deaths confirmed through a public records search, since we don't know if the patient experienced a non-fatal MI or non-fatal stroke between the time they were lost to follow-up and known death.

Table 10: Time to the First Occurrence of MACE+ (Including Components) for the Integrated study

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo	
Endpoint			**HR (95% C.I.)**	**P-value**
MACE+*	494/4347 (11.4)	690/5795 (11.9)	0.87 (0.77, 0.98)	0.0192

[Source: Statistical Reviewer's Analysis]

*** Does not include deaths confirmed from a public records search**

Secondary Endpoints

Table 11 below displays the event rates and hazard ratios for all-cause mortality using the intention-to-treat population in the CANVAS study. Pooling the canagliflozin 100mg and 300mg arms did not yield a statistically significant result.

Table 11: Time to All-Cause Mortality (ITT) for the CANVAS study

	Placebo: n/N (%)	Cana 100mg: n/N (%)	Cana 300mg: n/N (%)	Cana Total: n/N (%)	Cana 100mg vs. Placebo	Cana 300mg vs. Placebo	Cana Total vs. Placebo
					HR (95% C.I.)	HR (95% C.I.)	HR (95% C.I.)
All-Cause Mortality (ITT)	175/1442 (12.1)	157/1445 (10.9)	146/1443 (10.1)	303/2888 (10.5)	0.88 (0.71, 1.09)	0.82 (0.65, 1.02)	0.85 (0.70, 1.02)

[Source: Statistical Reviewer's Analysis]

Table 12 below characterizes the follow-up and missing follow-up with respect to all-cause mortality for the CANVAS study. In total, 11.0% patients died from any cause in the study; 9.2% while enrolled in the study and 1.8% of deaths were confirmed through a publics records search.

Table 12: Characterization of follow-up for the CANVAS study

Follow-up for All-Cause Mortality	**Placebo (N=1442)**	**Cana 100mg (N=1445)**	**Cana 300 mg (N=1443)**	**Cana Total (N=2888)**	**Total (N=4330)**
All-Cause Mortality [n(%)]	175 (12.1%)	157 (10.9%)	146 (10.1%)	303 (10.5%)	478 (11.0%)
Death while in study [n]	137	133	130	263	400
Death confirmed through public record search [n]	38	24	16	40	78
Alive [n(%)]	1254 (87.0%)	1280 (88.6%)	1289 (89.3%)	2569 (89.0%)	3823 (88.3%)
Alive while in study [n]	1160	1211	1223	2434	3594
Alive confirmed through public record search [n]	94	69	66	135	229
Unknown [n(%)]	13 (0.9%)	8 (0.6%)	8 (0.6%)	16 (0.6%)	29 (0.7%)

[Source: Statistical Reviewer's Analysis]

Table 13 below displays the event rates and hazard ratios for all-cause mortality using the intention-to-treat population in the CANVAS-R study. We can see that there was not a statistically significant result.

Table 13: Time to All-Cause Mortality (ITT) for the CANVAS-R study

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo HR (95% C.I.)
All-Cause Mortality (ITT)	106/2905 (3.6)	99/2907 (3.4)	0.92 (0.70, 1.21)

[Source: CSR: The CANVAS-R Trial Page 8953 and Statistical Reviewer's Analysis]

Table 14 below characterizes the follow-up and missing follow-up with respect to all-cause mortality for the CANVAS study. In total, 3.5% patients died from any cause in the study; 3.4% while enrolled in the study and 0.1% of deaths were confirmed through a publics records search.

Table 14: Characterization of follow-up for CANVAS-R study

Follow-up for All-Cause Mortality	Placebo (N=2905)	Cana (N=2907)	Total (N=5812)
All-Cause Mortality [n(%)]	106 (3.6%)	99 (3.4%)	205 (3.5%)
Death while in study [n]	102	95	197
Death confirmed through public record search [n]	4	4	8
Alive [n(%)]	2792 (96.1%)	2802 (96.4%)	5594 (96.2%)
Alive while in study [n]	2761	2773	5534
Alive confirmed through public record search [n]	31	29	60
Unknown [n(%)]	7 (0.2%)	6 (0.2%)	13 (0.2%)

[Source: Statistical Reviewer's Analysis]

Table 15 below displays the event rates and hazard ratios for all-cause mortality using the intention-to-treat population in the pooled CANVAS and CANVAS-R studies. We can see that there was not a statistically significant result.

Table 15: Time to All-Cause Mortality (ITT) for the Integrated study

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo HR (95% C.I.)
All-Cause Mortality (ITT)	281/4347 (6.5)	402/5795 (6.9)	0.87 (0.75, 1.02)

[Source: Statistical Reviewer's Analysis]

Table 16 below characterizes the follow-up and missing follow-up with respect to all-cause mortality for the pooled CANVAS and CANVAS-R studies. In total, 6.7% patients died from any cause in the study; 5.9% while enrolled in the study and 0.8% of deaths were confirmed through a publics records search.

Table 16: Characterization of follow-up for the Integrated study

Follow-up for All-Cause Mortality	Placebo (N=4347)	Cana (N=5795)	Total (N=10142)
All-Cause Mortality [n(%)]	281 (6.5%)	402 (6.9%)	683 (6.7%)
Death while in study [n]	239	358	597
Death confirmed through public record search [n]	42	44	86
Alive [n(%)]	4046 (93.1%)	5371 (92.7%)	9417 (92.9%)
Alive while in study [n]	3921	5207	9128
Alive confirmed through public record search [n]	125	164	289
Unknown [n(%)]	20 (0.5%)	22 (0.4%)	42 (0.4%)

[Source: Statistical Reviewer's Analysis]

As with time to first occurrence of MACE, we see the effect of pooling studies with unequal randomization rates. In the CANVAS study, the percentage of deaths were 12.0%, 10.9%, and 10.0%, for the placebo, canagliflozin 100mg, and canagliflozin 300mg arms, respectively and in the CANVAS-R study, the percentage of deaths on placebo is 3.6% and 3.4% for canagliflozin. However, after pooling the studies together, the percentage is now lower in placebo arm (6.5%) than in the canagliflozin arm (6.9%). Again, we note that the analysis model adjusted for this when study was included as a stratification factor.

With respect to formal hypothesis testing for all-cause mortality, due to the unblinding at the interim analysis, the population set only included deaths accrued after November 19th 2012 for the CANVAS study and all deaths in the CANVAS-R study. Table 17 displays these results, where we see that the upper bound of the 95% C.I. for the HR includes 1, therefore the result is not statistically significant. Since the testing scheme was sequential, all of alpha is burned and subsequent endpoints are not tested.

Table 17: Time to All-Cause Mortality for the Integrated study (truncated ITT)

	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo HR (95% C.I.)
All-Cause Mortality (Truncated ITT)	229/4288 (5.3)	324/5711 (5.7)	0.90 (0.76, 1.07)

[Source: Integrated Summary of Efficacy Page 68 and Statistical Reviewer's Analysis]

Sensitivity Analysis (Addressing Missing Data)

A multiple imputation analysis was performed to address missing follow-up time using data from retrieved drop-outs. Retrieved drop-out data was defined as the follow-up data between treatment discontinuation and the GTED (and who did not develop a MACE prior to treatment discontinuation). Table 18 below shows the event rates by year:

Table 18: Event rates by year (per 100 patient years) for the Integrated study

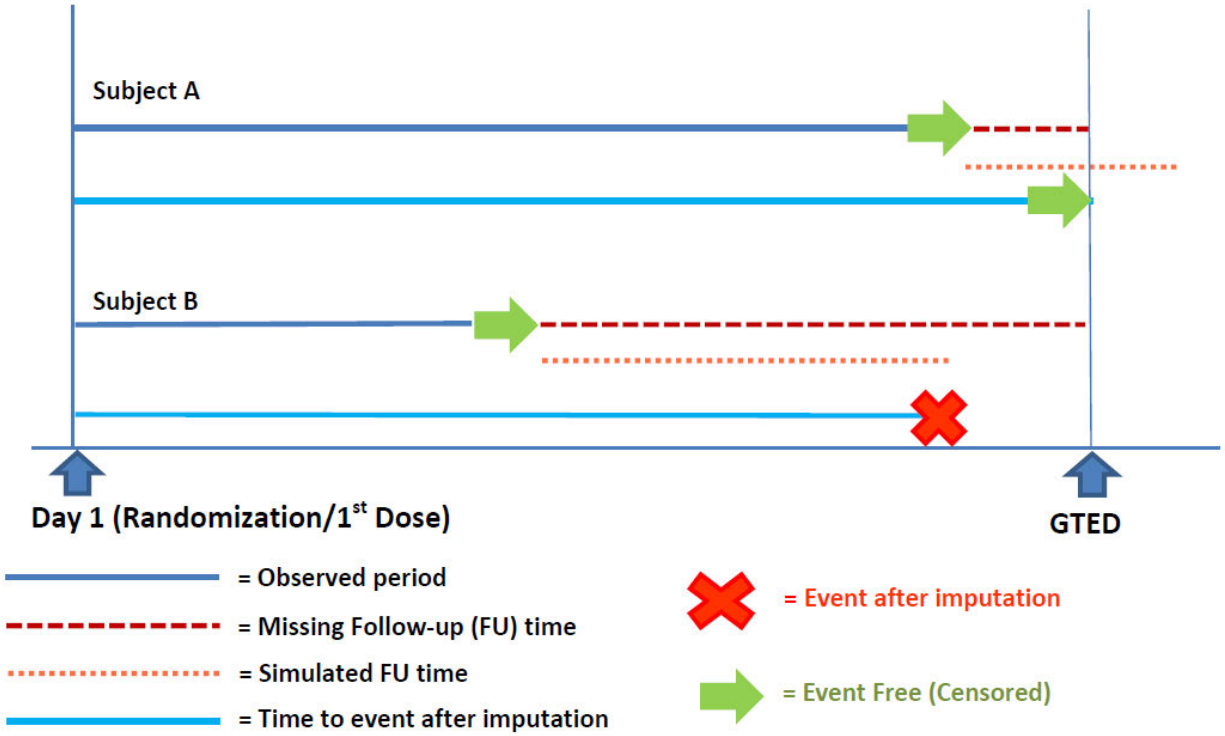
	0-1	1-2	2-3	3-4	4-5	5-6	> 7
Cana	2.70	2.44	2.70	2.63	2.86	3.02	3.37
Placebo	3.28	3.24	3.23	2.31	3.12	2.95	3.97

[Source: Statistical Reviewer's Analysis]

Since the event rates were relatively constant across years, this justifies imputing remaining time to an event at a constant rate. The imputation model was an Exponential time model which utilized the observed time to MACE data from the retrieve drop-out population. The model was stratified by study and prior CV disease (yes/no).

Figure 6 below depicts the time to event imputation for subjects with missing data:

Figure 6: Schematic of time to event imputation for subjects with missing data



[Source: Request for Health Authority Feedback on the Methodology for the Multiple Imputation Analysis and on the Definition of the Retreived Drop-Outs: Page 4]

The imputed remaining time to an event were integrated with the observed data to generate 1,000 datasets. The primary efficacy model for each imputed dataset was ran and inference for the HR and 95% C.I. was made using Rubin's rule. Table 19 below displays the number of patients with missing follow up and Table 20 shows the number of retrieved drop-outs used in the imputation model.

Table 19: Proportion of Missing Data for MACE for the Integrated study

	Placebo: n	Cana: n	Total: n
Total expected follow-up	4347	5795	10142
Total missing follow-up	126	153	279

[Source: Integrated Summary of Efficacy Page 55 and Statistical Reviewer's Analysis]

Table 20: Number of retrieved drop-outs for the Integrated study

	Placebo: n	Cana: n	Total: n
Retrieved Drop outs	1113	1450	2563

[Source: Statistical Reviewer's Analysis]

Table 21 below displays the results of the analysis. We see that the HR and 95% C.I. is 0.86 and (0.76, 0.97). Hence, the results were near identical to the primary analysis and the impact of missing data is negligible.

Table 21: Multiple Imputation Analysis of MACE for the Integrated study

	Placebo		Cana		Cana vs. Placebo
	Total Event	Event Imputed	Total Event	Event Imputed	HR (95% C.I.)
Observed	426		585		0.86 (0.75, 0.97)
Imputed	434	8	595	10	0.86 (0.76, 0.97)

[Source: Statistical Reviewer's Analysis]

Shrinkage Analysis

During the review process, there was some discussion as to how many study worth of evidence CANVAS and CANVAS-R provided. Since the result of the integrated studies were significant but neither of the individual studies was, there is one study worth of evidence. To see if there was more than one study worth of evidence, a shrinkage analysis was performed (see appendix for details) for the two studies. A shrinkage analysis allows for different treatment effects and obtains more precise estimates of those effects by removing variability and obtaining more narrow confidence / credible intervals. The treatment effects for both studies would have to be significant to conclude that there is between 1 and 2 studies worth of evidence. The results of the analysis are displayed in Table 22 below:

Table 22: Shrinkage Analysis

Study	HR (95% C.I.)
Canvas	0.868 (0.749, 1.006)
Canvas-R	0.834 (0.697, 0.999)

[Source: Statistical Reviewer's Analysis]

We see that only the HR for the CANVAS-R study was significant so we still have only one study worth of evidence.

3.6 Evaluation of Safety

This section discusses the analyses of amputations associated with canagliflozin observed in CANVAS and CANVAS-R.

3.6.1 Results and Conclusions

Table 23 and Table 24 show a descriptive summary of amputations observed in CANVAS and CANVAS-R. In both trials, subjects randomized to canagliflozin were more likely to experience an amputation than patients randomized to placebo.

Table 23 Amputation Summary, CANVAS

	Placebo (N=1441)	Canagliflozin 100 mg (N=1445)	Canagliflozin 300 mg (N=1441)
CANVAS			
Mean on-study follow-up (years)	5.53	5.61	5.64
Mean on-treatment time (years)	4.07	4.40	4.39
Subjects with an event (%) (on-study)	22 (1.5%)	50 (3.5%)	45 (3.1%)
IR per 1000 PY (on-study)	2.76	6.17	5.54

Note: Exposure time was calculated up to first amputation event.

Table 24 Amputation Summary, CANVAS-R

	Placebo (N=2903)	Canagliflozin * (N=2904)
CANVAS-R		
Mean on-study follow-up (years)	2.06	2.06
Mean on-treatment time (years)	1.86	1.89
Subjects with an event (%) (on-study)	25 (0.9)	45 (1.6)
IR per 1000 PY (on-study)	4.18	7.52

Note: Exposure time was calculated up to first amputation event.

*All subjects randomized to canagliflozin in CANVAS-R were initially on 100 mg with possible dose change to 300 mg after 13 weeks. See Section 3.2.1 for more information on trial design.

As shown in Table 25, canagliflozin was associated with an approximately 2-fold risk of amputation compared to placebo. In the integrated dataset of CANVAS and CANVAS-R, 2.4% of canagliflozin subjects experienced at least 1 amputation event, compared to 1.1% in the placebo arm. A time-to-event analysis shows an estimated hazard ratio of 1.965 (canagliflozin to placebo) with a 95% confidence interval of [1.407, 2.745]. The Kaplan-Meier curves of cumulative incidence over time are shown in Figure 7 and Figure 8 by treatment arm and trial. Tests of the proportional hazards assumption and survival probability plots are available in the Appendix.

Table 25 Primary Analysis of Amputation Events, Integrated (On-Study)

	Canagliflozin*	Placebo*
Subjects with an event/N (%) *IR per 1000 PY*	140/5790 (2.4) *6.30*	47/4344 (1.1) *3.37*
HR‡ [95% CI]	**1.965 [1.407, 2.745]**	

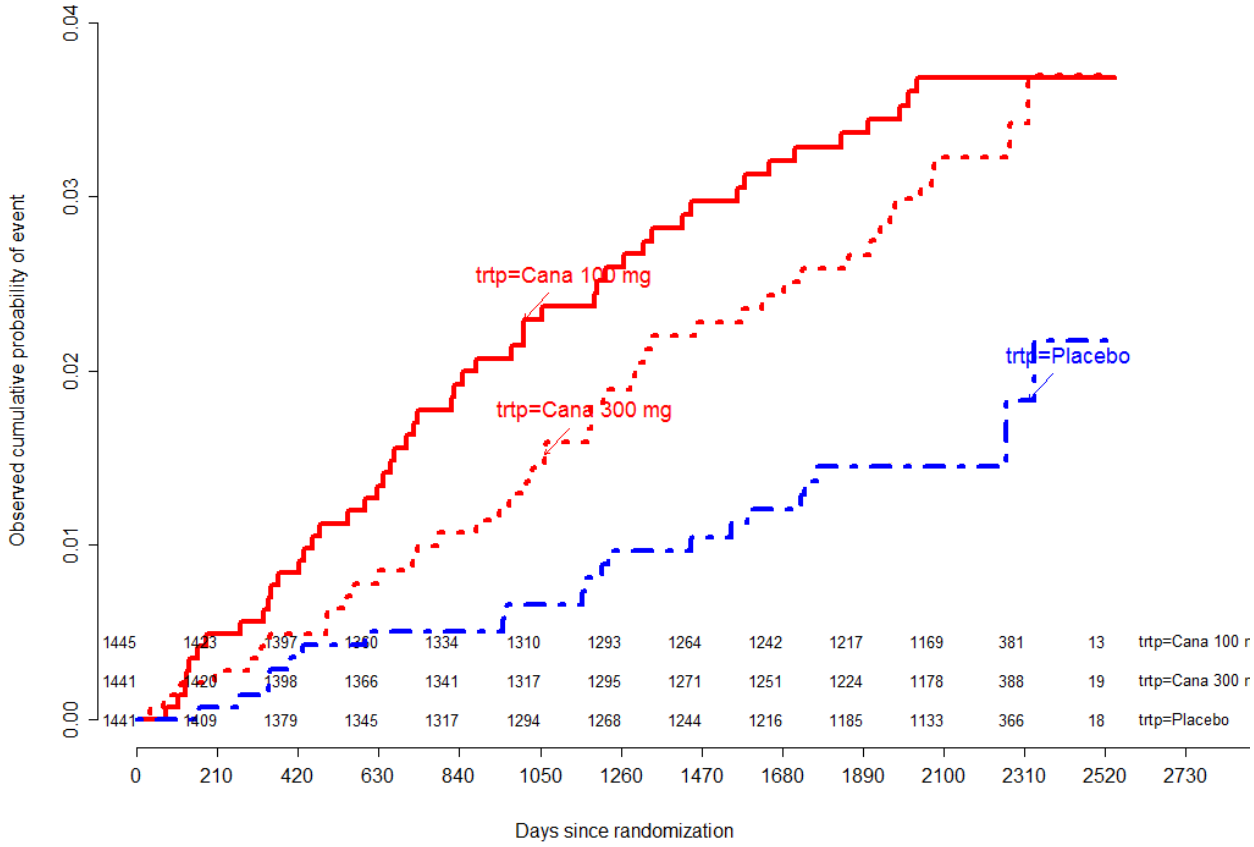
* Planned treatment. The canagliflozin arm included both 100mg and 300mg doses.

† On-study, censored by the date of first amputation event.

‡ Hazard ratio of canagliflozin to placebo based on a Cox proportional hazards model with baseline hazards stratified by trial and a single covariate of planned treatment, using the on-study analysis set.

Source: Created by FDA statistical reviewer using dataset adtteaep.xpt.

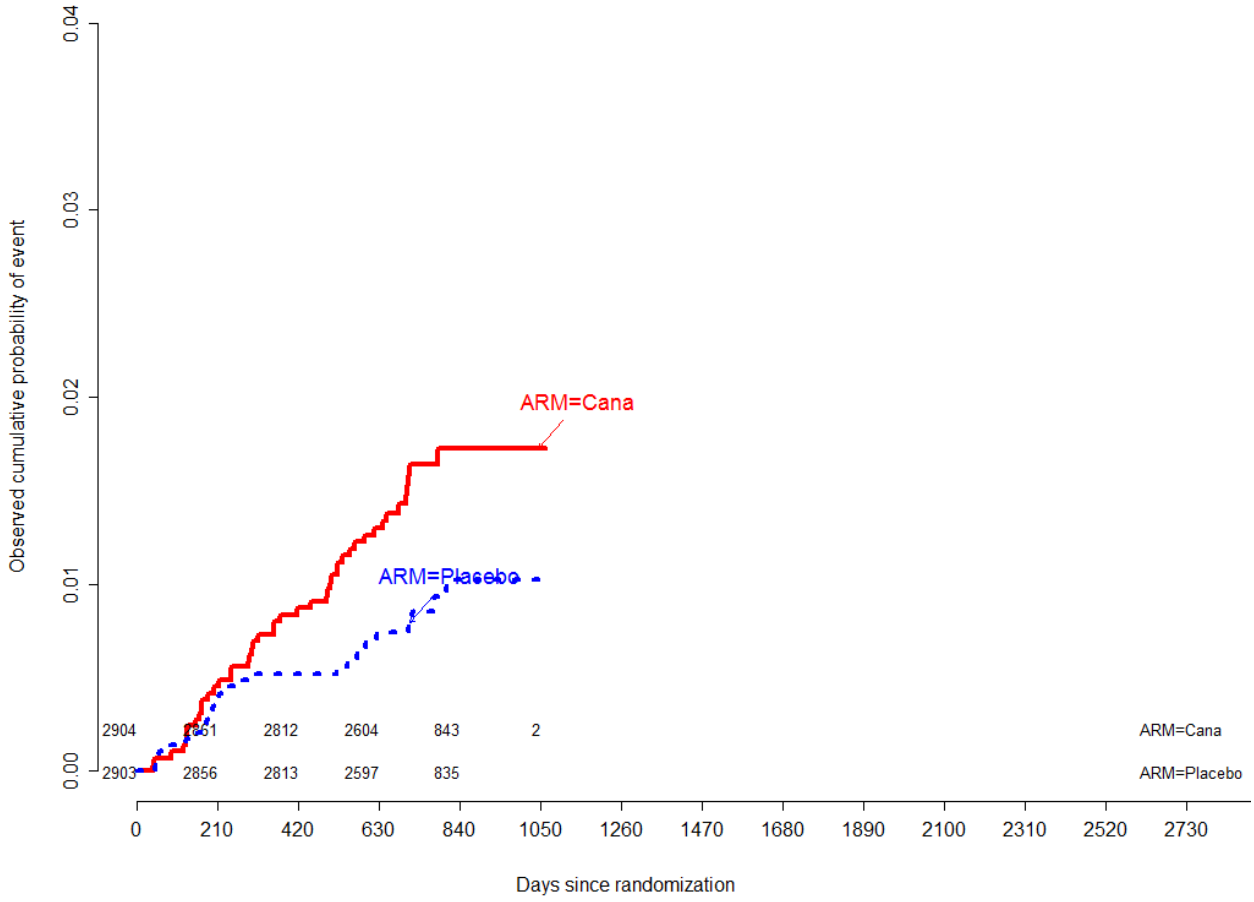
Figure 7 Cumulative Incidence Plot by Treatment, CANVAS



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The corresponding survival probability plot with confidence bars is available in the Appendix.

Source: Created by FDA statistical reviewer using dataset adtteaep.xpt

Figure 8 Cumulative Incidence Plot by Treatment, CANVAS-R



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The corresponding survival probability plot with confidence bars is available in the Appendix.

Source: Created by FDA statistical reviewer using dataset adtteaep.xpt

3.6.2 Sensitivity Analyses

3.6.2.1 On-Treatment Analysis

An on-treatment sensitivity analysis was conducted to explore the impact of treatment discontinuation on the risk of amputation associated with canagliflozin. In this analysis, data were truncated after 30 days post last dose of treatment. The estimated HR of amputations associated with canagliflozin relative to placebo was 1.995 with a 95% CI [1.384, 2.877], which is consistent with the primary on-study analysis results.

Table 26 Sensitivity Analysis of Amputation Events, Integrated (On-Treatment)

	Canagliflozin*	Placebo*
Subjects with any events/N (%) *IR per 1000 PY*	120/5790 (2.1) *6.60*	39/4344 (0.90) *3.46*
HR‡ [95% CI]	**1.995 [1.384, 2.877]**	

* Planned treatment. The canagliflozin arm included both 100mg and 300mg doses.
† On-treatment, censored at 30 days after last treatment (TRTEDT).
‡ Hazard ratio of canagliflozin to placebo was based on a Cox proportional hazards model with baseline hazards stratified by trial and a single covariate of planned treatment, using the on-treatment safety analysis set.
Source: Created by FDA statistical reviewer using dataset adtteaep.xpt.

3.6.2.2 Analysis by Trial and Dose

The primary on-study amputation analysis combined data from CANVAS and CANVAS-R through a stratified Cox model to account for potential differences in the baseline hazard functions. As shown in Table 23 and Table 24, CANVAS had longer follow-up than CANVAS-R, with mean on-study follow-up times of 5.59 years and 2.06 years, respectively. The estimated HR of amputations associated with canagliflozin was numerically higher in CANVAS (HR 2.123) than in CANVAS-R (HR 1.798). However, the wide confidence intervals do not suggest that these two HR estimates are statistically different. The estimated hazard ratio of amputations was consistent in the two canagliflozin dose groups in CANVAS relative to placebo; with an estimated HR and 95% CI of 2.239 (0.356, .3697) for canagliflozin 100 mg, and 2.006 (1.205, 3.340) for canagliflozin 300 mg. The Kaplan-Meier survival probability plots for the individual trials are available in the Appendix. Note that neither the percentages of subjects with any events nor the incidence rates should be compared directly between CANVAS and CANVAS-R, as the randomization ratios are different.

Table 27 Analysis of Amputation Events by Trial

	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg
CANVAS			
Subjects with an event/N (%)	22 / 1441 (1.5)	50 / 1445 (3.5)	45 / 1441 (3.1)
IR per 1000 PY*	2.76	6.17	5.53
HR† [95% CI]		2.239 [0.356, .3697]	2.006 [1.205, 3.340]
		2.123 [1.335, 3.376]	
CANVAS-R‡			
Subjects with an event/N (%)	25 / 2903 (0.9)	45 / 2904 (1.6)	
IR per 1000 PY*	4.19	7.53	
HR† [95% CI] †		**1.798 [1.103, 2.931]**	

* On-study, censored by the date of first amputation event.
† Hazard ratio comparing canagliflozin to placebo based on a Cox proportional hazards model with a single covariate for planned treatment, using the on-study analysis set.
‡ All subjects randomized to canagliflozin in CANVAS-R were initially on 100 mg with possible dose change to 300 mg after 13 weeks. See Section 3.2.1for more information on trial design.

4 Findings in Special/Subgroup Populations

4.1 Subgroup Analyses of Efficacy

Subgroup analyses for time to first occurrence of MACE were performed. Table 28 below displays the results of subgroups of primary interest. There were no other significant interactions among the reported subgroups. However, though not reported in this table, there were significant interactions among baseline use of beta blockers and baseline use of diuretics.

Table 28: Subgroup Analysis of time to first occurrence of MACE for integrated study

Group	Category	Placebo: n/N (%)	Cana: n/N (%)	HR (95% C.I.)	Interaction P-value
Study	Canvas	233/1442 (16.2)	425/2888 (14.7)	0.88 (0.75, 1.03)	0.598
	Canvas-R	193/2905 (6.6)	160/2907 (5.5)	0.82 (0.66, 1.01)	
Age	< 65	185/2369 (7.8)	276/3209 (8.6)	0.91 (0.76, 1.10)	0.2574
	≥ 65	241/1978 (12.2)	309/2586 (11.9)	0.80 (0.67, 0.95)	
Sex	Male	305/2750 (11.1)	421/3759 (11.2)	0.86 (0.74, 1.00)	0.7998
	Female	121/1597 (7.6)	164/2036 (8.1)	0.84 (0.66, 1.06)	
Race	White	357/3436 (10.4)	478/4508 (10.6)	0.84 (0.73, 0.96)	0.3976
	Black or African American	14/160 (8.8)	10/176 (5.7)	0.45 (0.19, 1.03)	
	Asian	36/507 (7.1)	65/777 (8.4)	1.08 (0.72, 1.64)	
	Other	19/244 (7.8)	32/334 (9.6)	1.01 (0.57, 1.80)	
History of CV disease	Yes	346/2900 (11.9)	450/3756 (12.0)	0.82 (0.72, 0.95)	0.1803
	No	80/1447 (5.5)	135/2039 (6.6)	0.98 (0.74, 1.30)	
Region	North America	100/1005 (10.0)	152/1425 (10.7)	0.84 (0.65, 1.09)	0.8867
	Central / South America	37/484 (7.6)	36/537 (6.7)	0.84 (0.53, 1.33)	
	Europe	162/1566 (10.3)	208/2043 (10.2)	0.80 (0.65, 0.99)	
	Rest of the World	127/1292 (9.8)	189/1790 (10.6)	0.94 (0.75, 1.18)	
Duration of Diabetes ≥ 10 years					0.3275
	Yes	312/3038 (10.3)	411/4007 (10.3)	0.81 (0.70, 0.95)	
	No	114/1303 (8.7)	173/1783 (9.7)	0.96 (0.76, 1.22)	
Baseline HbA1c (8%)					0.2853
	< 8	164/1880 (8.7)	241/2531 (9.5)	0.94 (0.77, 1.15)	
	≥ 8	262/2467 (10.6)	344/3264 (10.5)	0.80 (0.68, 0.94)	

[Source: Integrated Summary of Efficacy Page 262-266]

Since it is likely that the indicated population will be patients with established CV disease, we note that 65.6% of patients had established CV disease. Table 29 below displays the results of MACE. We see that the hazard ratio for time to first occurrence of MACE is 0.82 with a 95% C.I. of (0.72, 0.95).

Table 29: Time to the First Occurrence of MACE (Including Components) for the Integrated study for patients with established CV disease

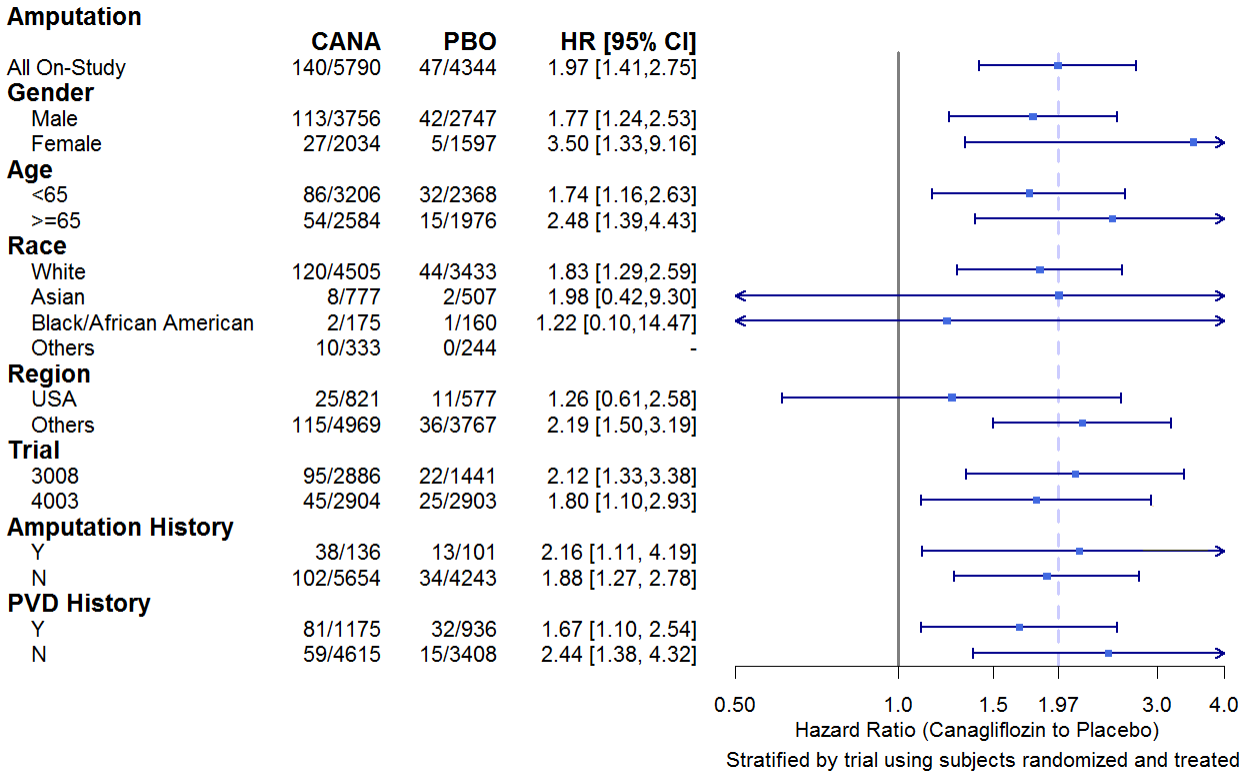
	Placebo: n/N (%)	Cana: n/N (%)	Cana vs. Placebo	
Endpoint			**HR (95% C.I.)**	**P-value**
MACE	346/2900 (11.9)	450/3756 (12.0)	0.82 (0.72, 0.95)	0.0079
CV Death	152/2900 (5.2)	210/3756 (5.6)	0.86 (0.70, 1.07)	0.1685
Non-Fatal MI	136/2900 (4.7)	168/3756 (4.5)	0.79 (0.63, 0.99)	0.0413
Non-Fatal Stroke	90/2900 (3.1)	119/3756 (3.2)	0.88 (0.67, 1.16)	0.3610
All MI	150/2900 (5.2)	194/3756 (5.2)	0.82 (0.66, 1.01)	0.0642
All Stroke	105/2900 (3.6)	129/3756 (3.4)	0.82 (0.63, 1.06)	0.1308

[Source: Statistical Reviewer's Analysis]

4.2 Subgroup Analyses of Safety

Similar to the primary amputation analysis, a proportional hazards model stratified by trial was used for subgroup analysis (except for the *Trial* subgroup). Subgroup analysis results for amputation by gender, age, race, region, trial, baseline amputation history, and peripheral vascular disease (PVD) history are shown in Figure 9. The estimated hazard ratio for the risk of amputations was undefined among subjects whose race was categorized as "Other": no amputation events were observed among 244 subjects in the placebo arm and 10 amputations were observed among 333 subjects in the canagliflozin arm. Among all subgroups with at least one event in both the placebo and canagliflozin treatment arms, females had the largest observed hazard ratio associated with canagliflozin with a HR estimate of 3.50 but a wide 95% CI of [1.33, 9.16] due to the small number of events. The subgroup of subjects age 65 or older had a numerically higher HR estimate than the subgroup of age younger than 65, with HR estimates and 95% CIs being 2.48 [1.39, 4.43] and 1.74 [1.24, 2.53], respectively. Subjects with no PVD history had a numerically higher HR estimate associated with canagliflozin (2.44 [1.38, 4.32]) than those with PVD history (1.67 [1.10, 2.54]). No clear difference in risk was observed in subgroups defined by trial or amputation history. All subgroups considered in this analysis observed an estimated hazard ratio of amputations associated with canagliflozin greater than 1.

Figure 9 Amputation Subgroup Analysis, Integrated (On-Study)



Source: Created by FDA statistical reviewer using datasets adtteaep.xpt and adsl.xpt.

5 Summary and Conclusions

5.1 Statistical Issues

Statistical issues related to cardiovascular endpoints:

Three statistical issues that were taken into consideration during this review for the assessment of cardiovascular endpoints. They are summarized as follows:

1. The intention was for there to be only one long term CV outcomes study, however due to unblinding at an interim analysis, a second CVOT was initiated. The studies were pooled together and results integrated as one analysis. Due to the high similarities in trial designs, patient population, and conduct, we did not consider this to be of significant concern.

2. While missing data was low (4%), the impact of missing data was assessed by conducting a multiple imputation analysis based on retrieved drop-outs. The results of the analysis were almost identical to the results of the primary analysis so the impact of missing data did not change our confidence in the primary analysis.

3. Unlike in the empagliflozin cardiovascular outcome study, where CV death was known to drive the MACE result, none of the individual components were significant in the integrated study. While this is not a requirement for a superiority claim, there should be a clear distinction in the writing of the product label for canagliflozin and empagliflozin.

Statistical issues related to amputations:

Trials CANVAS and CANVAS-R were designed to evaluate CV risk and the progression of albuminuria. Amputation was an unexpected safety signal first identified by the IDMC in early 2016. A post-hoc analysis was performed by the sponsor to evaluate the risk of amputations using the integrated dataset consisting of 10134 randomized and treated subjects from CANVAS and CANVAS-R The primary endpoint was atraumatic lower extremity amputation as identified by the sponsor from multiple eCRFs and the sponsor's pharmacovigilance database. A Cox proportional hazards model was used to conduct a time-to-event analysis to evaluate the amputation risk associated with canagliflozin compared to placebo.

Some limitations of the amputation safety analysis include:

- Trials CANVAS and CANVAS-R were not designed to evaluate the amputation safety signal.
- Amputation was a new safety signal that was identified while the trials were already fully enrolled and ongoing. Therefore, the definition, event identification and adjudication were not pre-specified prior to the initiation of the trials.
- Data collection of amputation events changed over the course of these two trials, and was different between these two trials.
-

5.2 Collective Evidence

The original objective of the CANVAS program was to rule out an 80% increase in CV risk to support the initial marketing application. To support post-marketing requirements, a second large CVOT was initiated (CANVAS-R) and the studies were pooled and integrated into one analysis. The primary objective of the integrated analysis was to demonstrate non-inferiority of MACE. Since the upper bound of the 95% C.I. for the HR excluded 1, the primary objective was achieved and in addition demonstrated that there is evidence that canagliflozin reduces CV risk. The assessment of the missing data revealed little to no impact on the results of the primary analysis which strengthens our confidence for the superiority claim. However, while overall MACE was significant, none of the individual components were.

As summarized in Table 30, canagliflozin was associated with an approximately 2-fold increase in the risk of amputation compared to placebo, with a HR estimate of 1.97 and 95% CI [1.41, 2.75]. The estimated exposure-adjusted annualized incidence rates for canagliflozin and placebo are 6.30 and 3.37, respectively, based on these two trials.

Table 30. Primary Safety Results of Amputations, Integrated (On-Study)

	Canagliflozin*	Placebo*
Subjects with any events/N (%)	140/5790 (2.4)	47/4344 (1.1)
IR per 1000 PY	*6.30*	*3.37*
HR† [95% CI]	**1.97 [1.41, 2.75]**	

* Planned treatment. The canagliflozin arm included both 100mg and 300mg doses.

† Hazard ratio of canagliflozin to placebo based on a Cox proportional hazards model with baseline hazards stratified by trial and a single covariate of planned treatment, using the on-study analysis set.

Source: Created by FDA statistical reviewer

5.3 Conclusions and Recommendations

The hazard ratio and 95% C.I. for time to first occurrence of MACE are 0.86 and (0.75, 0.97). Since the upper-bound of the 95% C.I. excluded 1, there is evidence that canagliflozin offers CV benefit in patients with T2DM who have a history of CV disease. In regards to the pooling of CANVAS and CANVAS-R, while it is not general practice to make regulatory decisions based on a meta-analysis, because the two studies were similar in design, patient population, and conduct we did not consider this to be a significant issue. While overall MACE was significant, none of the individual components were. This needs to be taken into consideration in product labelling. In addition, we recommend in future testing superiority should be included in a pre-specified hierarchical testing strategy if the sponsor intends to claim superiority after achieving non-inferiority for primary efficacy endpoint.

A 2-fold increased risk of atraumatic lower extremity amputations was observed among subjects randomized to canagliflozin compared to placebo, with an HR estimate of 1.97 with a 95% CI [1.41, 2.75]. The amputation safety signal is already included as a boxed warning in the current label. The integrated safety analyses in this review utilizing data from two completed trials, CANVAS and CANVAS-R, have confirmed this important safety signal.

6 Appendix

6.1 Bayesian Hierachical Model for Shrinkage Estimates

Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different and related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. Below is the model used in the analysis:

$$Y_i \sim N(\mu_i, \sigma_i^2)$$

$$\mu_i \sim N(\mu, \tau^2)$$

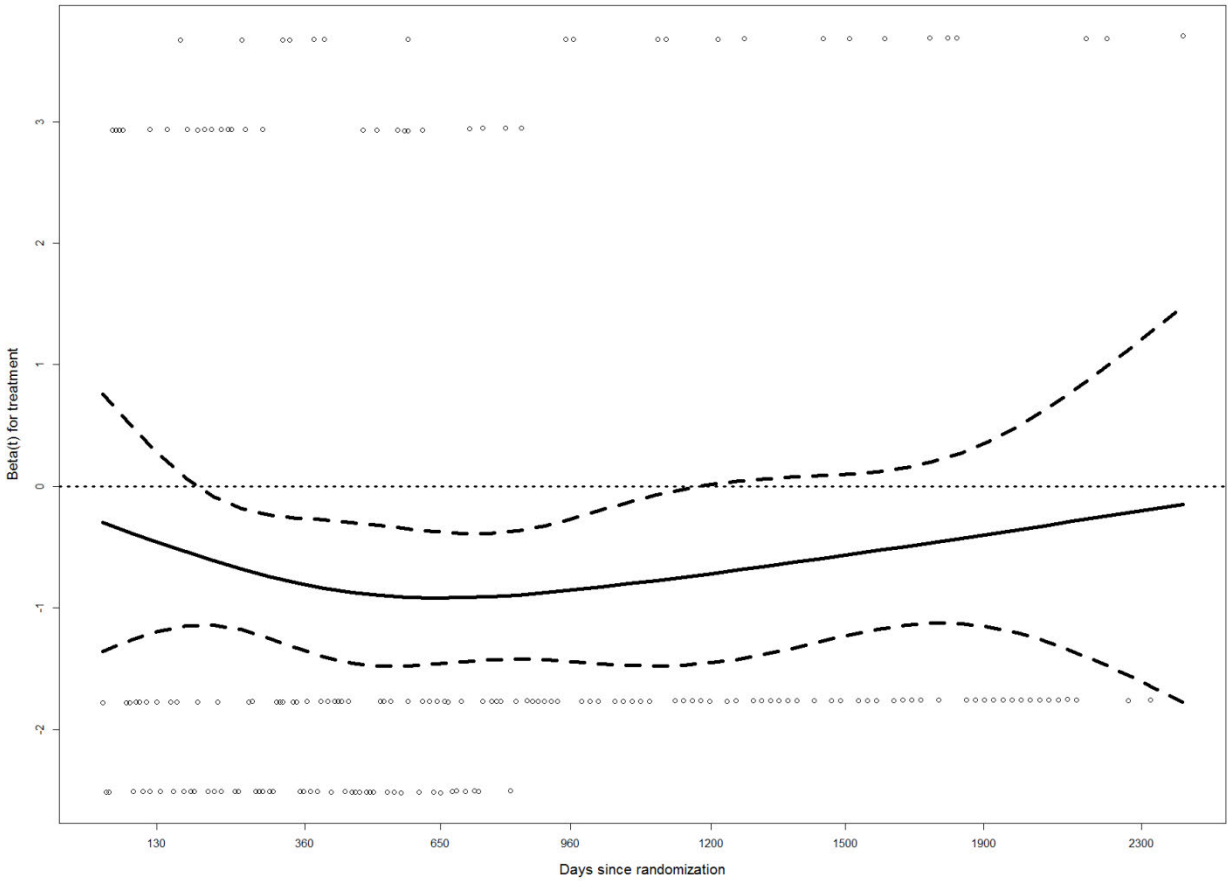
$$\mu \sim \mathrm{N}(0, 16), \quad \tau^{-2} \sim Gamma(0.001, 0.001)$$

Here Y_1 and Y_2 are the log HR for CANVAS and CANVAS-R, respectively and σ_1^2 and σ_2^2 are the variances of $Y_1$and Y_2. Hence, Y_1 = - 0.12957 is assumed to be the observed value drawn from a normal distribution with mean μ_1 and variance $\sigma_1^2 = 0.006647$ and likewise, Y_2 = - 0.20091 is assumed to be the observed value drawn from a normal distribution with mean μ_2 and variance $\sigma_2^2 = 0.011432$. The model assumes that the parameters μ_1 and μ_2 are independent and follows a normal distribution with parameters μ and τ^2, where μ and τ^{-2}independently follow a normal and gamma distribution, respectively.

6.2 Assessment of the Proportional Hazards Assumption for Amputation Safety Analysis

The safety analysis for amputation used a stratified Cox proportional hazards model to estimate the hazard ratio of lower-extremity amputation events and associated confidence intervals, with stratification of the baseline hazards by trial (CANVAS or CANVAS-R). The proportionality assumption is examined for planned treatment *TR01PG1* (Cana or Placebo). If the proportional hazard assumption holds, the scaled Schoenfeld residuals Beta(t) should approximately follow a horizontal line at 0 over time.

Figure 10 Scaled Schoenfeld Residual Plot with 95% CI for Treatment in Primary Amputation Analysis, Integrated (On-Study)

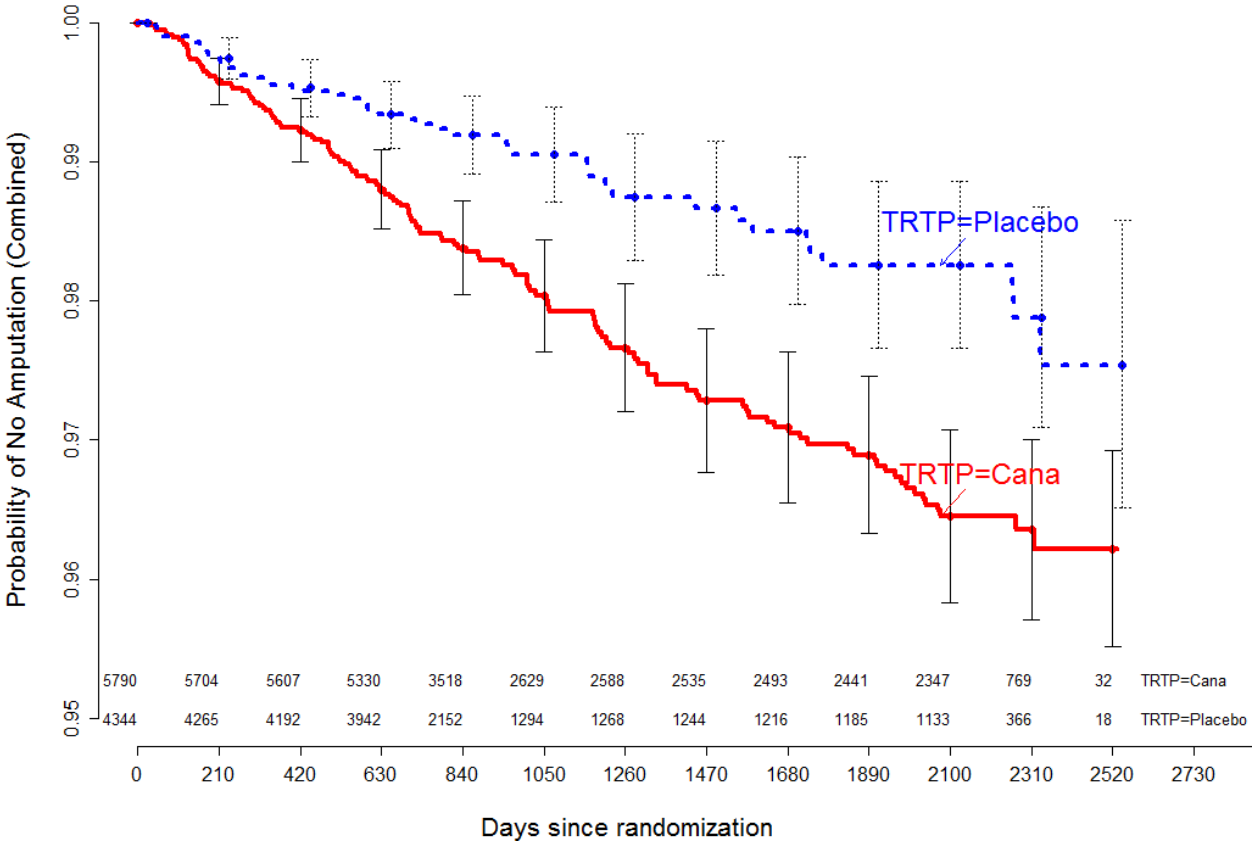


Source: Created by FDA statistical reviewer using dataset adtteaep.xpt

From the above scaled Schoefeld residual plot, there is no obvious violation of the proportional hazard assumption for the variable of planned treatment, when we compare the 95% confidence interval of the curve to the dotted zero line. The p-value is 0.729 against the null hypothesis of proportional hazards in the variable *TR01PG1* (planned treatment), and does not reject the proportionality assumption in the primary analysis model.

6.3 Survival Probability Plot with Confindence Intervals

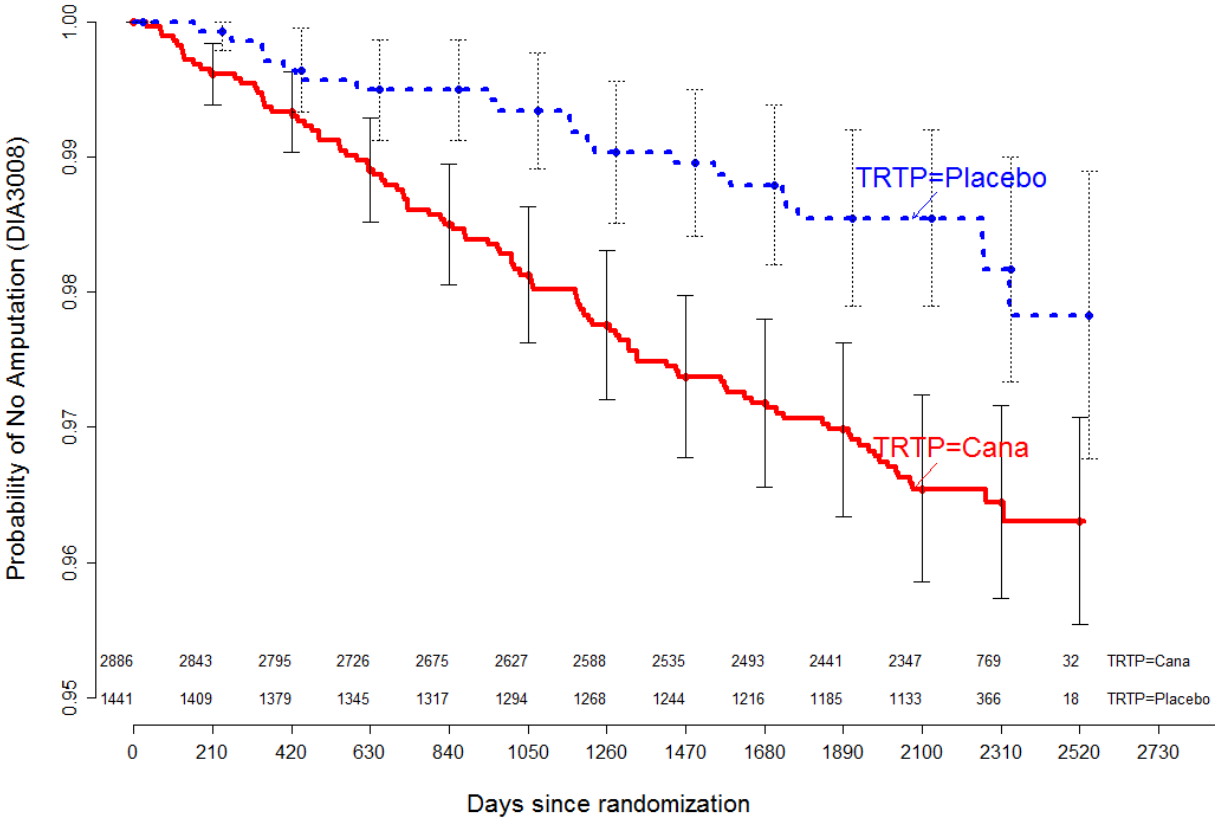
Figure 11 Kaplan-Meier (Survival Probability) Plot with Confidence Bars for Amputations, Integrated (On-Study)



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method (Therneau, 2000).

Source: Created by FDA statistical reviewer using dataset adtte.xpt

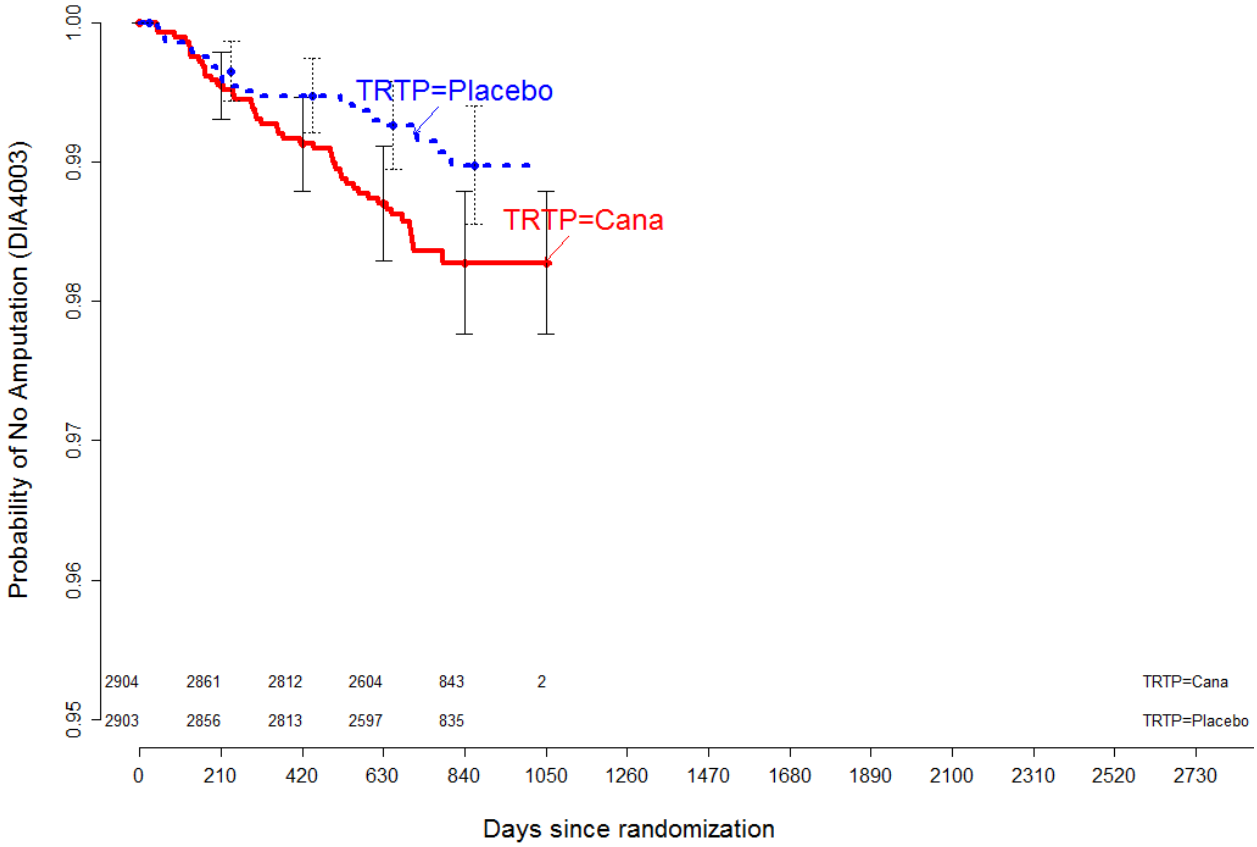
Figure 12 Kaplan-Meier (Survival Probability) Plot with Confidence Bars for Amputations, CANVAS (On-Study)



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method (Therneau, 2000).

Source: Created by FDA statistical reviewer using dataset adtte.xpt

Figure 13 Kaplan-Meier (Survival Probability) Plot with Confidence Bars for Amputations, CANVAS-R (On-Study)



Note: The numbers marked above the x-axis represent number of subjects at risk at annotated time points. The "at-risk" set includes the day noted on the x-axis. The 95% confidence bars on the K-M curves were calculated using the log-survival method (Therneau, 2000).

Source: Created by FDA statistical reviewer using dataset adtte.xpt

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/s/

ROBERTO C CRACKEL
06/23/2018

CHANGMING N XIA
06/24/2018

YUN WANG
06/24/2018

EUGENIO ANDRACA-CARRERA
06/25/2018

MARK S LEVENSON
06/25/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	204042/S-027
Submission Date	September 29, 2017
Brand Name	Invokana
Generic Name	Canagliflozin tablets
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Division of Metabolism and Endocrinology Products
Sponsor	Janssen Pharmaceuticals, Inc.
Formulation; Strength	Tablets, 100 mg, 300 mg
Indication	INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated: • as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus **(approved indication)** • *to reduce the risk of major adverse cardiovascular events* [redacted (b) (4)] *in adults with type 2 diabetes mellitus who have established cardiovascular disease (CVD)* [redacted (b) (4)]

Canagliflozin developed by Janssen Research & Development in collaboration with Mitsubishi Tanabe Pharma Corporation (MTPC), belongs to the sodium-glucose cotransporter-2 (SGLT2) inhibitor class of antidiabetic agents. Canagliflozin (tradename; Invokana) was approved for marketing on March 29, 2013.

The sponsor submitted a supplemental New Drug Application (sNDA) to the INVOKANA® (canagliflozin) NDA204042 to fulfil a post-marketing requirement (PMR) and to support inclusion of a new indication in the United States Package Insert (USPI). INVOKANA was originally approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The new indication that the Sponsor is seeking adds the following claim: "to reduce the risk of major adverse cardiovascular events [redacted (b) (4)] in adults with type 2 diabetes mellitus who have established cardiovascular disease (CVD) [redacted (b) (4)]

As part of the March 29, 2013, approval, the following PMR was included in the letter for NDA204042:

- 2027-5: A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients

with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

The Sponsor conducted 2 studies to fulfil the PMR: (a) Study 28431754DIA3008, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo- Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS), and (b) Study 28431754DIA4003, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS-R). There was a combined total of 10,142 subjects randomized in these 2 studies.

There is no new information relevant to biopharmaceutics of canagliflozin in this supplement. Additionally, pharmacokinetic evaluations were not conducted in the 2 studies.

Glycemic Efficacy - Changes in HbA1c:

An examination of the changes in HbA1c over time from Study 28431754DIA3008 indicated that relatively little change in HbA1c was observed in the placebo group, compared to reduction of HbA1c in both canagliflozin dose groups, starting at approximately Week 12 through Week 52., The HbA1c levels in both canagliflozin groups gradually rose after Week 52 (Figure 1). The 95% CI of both canagliflozin doses compared to placebo at all time points remained significant through Week 338, and excluded 0.

For additional details on the discussion of efficacy of canagliflozin in the CANVAS program, refer to the review by Dr. Hyon Kwon.

Cardiovascular Outcomes:

Studies CANVAS and CANVAS-R evaluated the comparison of the risk of experiencing a major adverse cardiovascular event (MACE) defined as the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, between canagliflozin and placebo on a background of standard of care treatments for diabetes and atherosclerotic cardiovascular disease. The primary endpoint in the CANVAS and CANVAS-R studies were the time to first occurrence of a MACE.

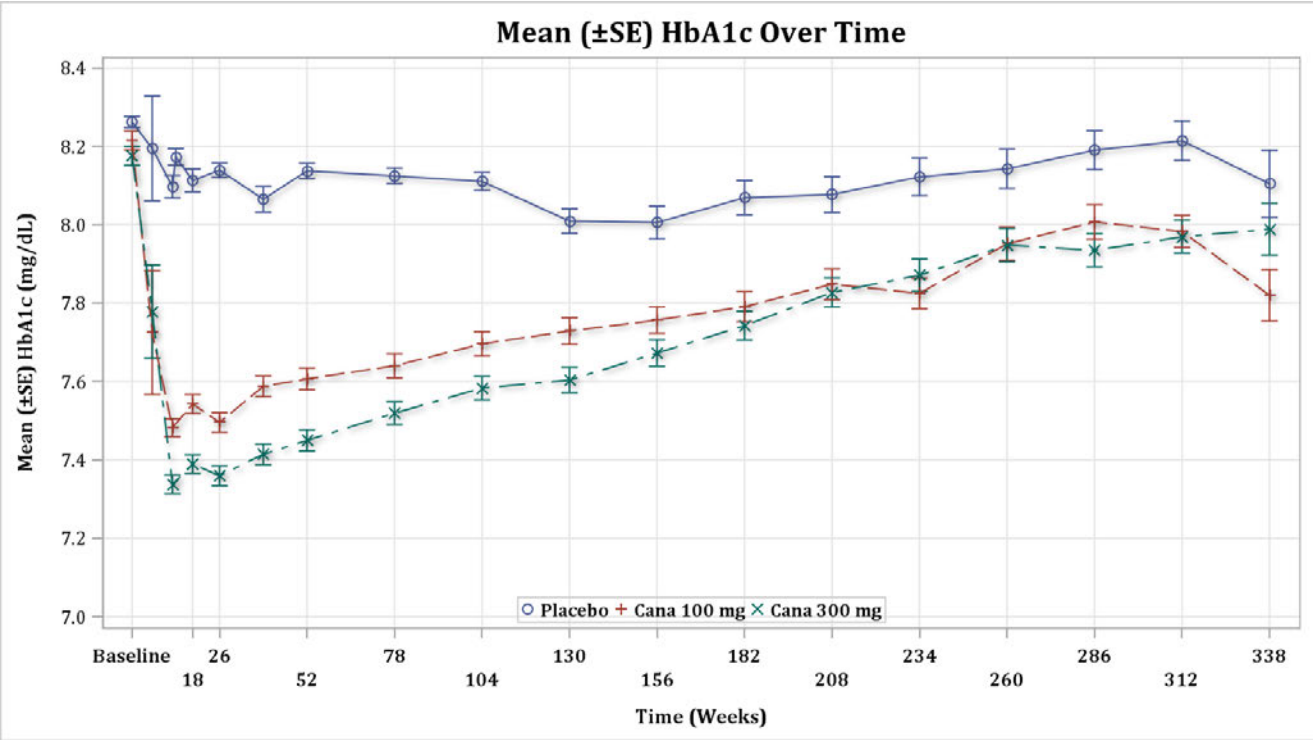
A stratified Cox proportional hazards regression model was used to estimate the MACE hazard ratio (HR) in patients treated with canagliflozin compared with placebo. The 95% CI of the HR was estimated using stratification by study and by established cardiovascular disease.

The time to first occurrence of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was reduced by canagliflozin (HR: 0.86; 95% CI 0.75, 0.97). Results for the 100 mg and 300 mg canagliflozin doses were consistent with results for the

combined dose groups. The efficacy of canagliflozin on MACE was generally consistent across major demographic and disease subgroups, including presence or absence of established cardiovascular disease.

For additional details on acceptability of the claims and discussion of cardiovascular safety of canagliflozin in the CANVAS program, refer to the safety stats review by Dr. Changming Xia.

Figure 1: Adjusted Mean HbA1c Over Time - Canagliflozin 100 mg and 300 mg Compared to Placebo



Reviewer Comments:

These HbA1c values observed in Study 28431754DIA3008, specifically Week 26, compare well with reported values for canagliflozin from the original NDA as shown in the table below

Table 9: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA as Monotherapy*

Efficacy Parameter	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
HbA_{1C} (%)			
Baseline (mean)	7.97	8.06	8.01
Change from baseline (adjusted mean)	0.14	-0.77	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.91‡ (-1.09; -0.73)	-1.16‡ (-1.34; -0.99)
Percent of Patients Achieving HbA_{1C} < 7%	21	45‡	62‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	166	172	173
Change from baseline (adjusted mean)	8	-27	-35
Difference from placebo (adjusted mean) (95% CI)†		-36‡ (-42; -29)	-43‡ (-50; -37)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	229	250	254
Change from baseline (adjusted mean)	5	-43	-59
Difference from placebo (adjusted mean) (95% CI)†		-48‡ (-59.1; -37.0)	-64‡ (-75.0; -52.9)
Body Weight			
Baseline (mean) in kg	87.5	85.9	86.9
% change from baseline (adjusted mean)	-0.6	-2.8	-3.9
Difference from placebo (adjusted mean) (95% CI)†		-2.2‡ (-2.9; -1.6)	-3.3‡ (-4.0; -2.6)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

(Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204042s026lbl.pdf)

Labeling Recommendations:

Deferred to acceptability of claims by clinical and statistical disciplines.

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/s/

SURYANARAYANA M SISTA
05/21/2018

MANOJ KHURANA
05/21/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 18, 2018

To: Liz Godwin, Regulatory Project Manager, Division of Metabolism & Endocrine Products (DMEP)

Monika Houstoun, Associate Director for Labeling, DMEP

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for INVOKAMET (canagliflozin and metformin hydrochloride) and INVOKAMET XR (canagliflozin and metformin hydrochloride)

NDA: 204353/ S-025
205879/S-007

In response to DMEP's consult request dated October 4th, 2017, OPDP has reviewed the proposed combined product labeling (PI) and Medication Guide for Invokamet and Invokamet XR. These supplements (S025 and S007) propose a new indication and revised labeling based on the results of the cardiovascular outcomes trials CANVAS and CANVAS-R.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP on October 11, 2018 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

71 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEENA R SAVANI
10/18/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	October 12, 2018
Reviewer:	Christian Hampp, PhD Division of Epidemiology I
Team Leader: (Acting)	Yandong Qiang, MD, PhD, MPH, MHS Division of Epidemiology I
Division Director:	Simone P. Pinheiro, ScD, MSc, ALM Division of Epidemiology I
Subject:	ARIA Sufficiency Memo: Canagliflozin and Renal Cell Carcinoma
Drug Name:	Invokana (canagliflozin)
Application Type/Number:	NDA 204042/S-027 (Invokana), 204353/S-025 (Invokamet), 205879/S-007 (Invokamet XR)
Applicant/sponsor:	Janssen Pharmaceuticals
OSE RCM #:	2018-970
TSI #:	1979

EXECUTIVE SUMMARY

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	
-Post-approval	X
Is ARIA sufficient to help characterize the safety concern?	
-Yes	X
-No	
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

Between September 18, 2018, and September 28, 2018, staff from the Division of Epidemiology-I in the Office of Surveillance and Epidemiology, staff from the Office of Pharmacovigilance and Epidemiology, and staff from the Division of Metabolism and Endocrinology Products in the Office of New Drugs conducted a virtual Signal Assessment Meeting (SAM), using email and phone calls. On September 28, 2018, SAM participants determined that the Active Risk Identification and Analysis (ARIA) System would be sufficient to evaluate the potential association between canagliflozin and renal cell carcinoma (RCC).

1. BACKGROUND INFORMATION

1.1. Medical Product

Canagliflozin (Invokana, Janssen Pharmaceuticals, NDA 204042) is an oral sodium-glucose-cotransporter-2 (SGLT-2) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. SGLT-2 inhibitors lower blood glucose by reducing renal glucose reabsorption and thus, increasing renal glucose excretion.

Table 1 lists all SGLT-2 inhibitors that are approved in the United States. Members of the class are also available in fixed-dose combination with other antidiabetic drugs (e.g., metformin, saxagliptin, linagliptin) or as extended release formulation. These are not listed in Table 1.

Table 1. FDA-approved SGLT-2 inhibitors, excluding fixed-dose combination products

Active ingredient	Trade name	Sponsor	NDA	Approval date
Canagliflozin	Invokana	Janssen Pharmaceuticals	204042	03/29/2013
Dapagliflozin	Farxiga	Astra Zeneca	202293	01/08/2014
Empagliflozin	Jardiance	Boehringer Ingelheim	204629	08/01/2014
Ertugliflozin	Steglatro	Merck Sharp Dohme	209803	12/19/2017

1.2. Describe the Safety Concern

An imbalance in RCC cases was newly observed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial program (14 events, 0.62 per 1000 person-years, canagliflozin, vs. 3 events, 0.21 per 1000 person-years, placebo). The CANVAS program (CANVAS and CANVAS R) included 4347 subjects in the placebo and 5795 subjects in the canagliflozin arms. The mean duration of exposure was 4.3 years in CANVAS and 1.8 years CANVAS R. In the CANVAS trial alone, there were 13 events in 2886 subjects randomized to canagliflozin vs. 3 events among 1441 patients randomized to placebo (HR, 1.97; 95% CI, 0.56 - 6.91). The median onset for renal cancer events was 1254 days from randomization in the canagliflozin arm compared to ~710 days in the placebo arm.

A signal for renal carcinogenicity related to canagliflozin was also observed in the nonclinical development program of canagliflozin and other SGLT-2 inhibitors. Dr. Fred Alavi reviewed (1) and Dr. Todd Bourcier summarized (2) animal data available at the initial NDA review for canagliflozin in 2013:

- Among five investigational SGLT-2 inhibitors that have filed final or interim findings from rodent carcinogenicity studies, four have reported neoplasms of the renal tubules, adrenal glands, or testicular Leydig cells. The agent without observed tumors in these tissues was associated with an increased incidence of atypical hyperplasia of the renal tubules.
- For canagliflozin, renal tubule adenoma/carcinoma increased "robustly and significantly in both male and female rats at 100mg/kg, or approximately 12-times clinical exposure from a 300mg maximal clinical dose." A small numerical increase in renal tumors (2 of 65 males) was seen at the next lower dose.

Dr. Bourcier noted that carbohydrate malabsorption is the most probable path by which canagliflozin induces renal tumors in rats. However, since then, further evaluation of clinical data from phase I and II studies re-affirmed that canagliflozin did not result in carbohydrate malabsorption to any notable degree in human subjects, which minimizes the clinical relevance of the renal tumor signal in rats.(3) Dr. Bourcier concluded that the clinical RCC signal with canagliflozin, therefore, is very unlikely to reflect the same renal tumorigenic pathway that occurs in rats.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Assess a known serious risk Assess signals of serious risk Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

The purpose of the inferential analysis is to evaluate the potential association between canagliflozin and RCC. Canagliflozin could be compared with dipeptidyl-peptidase-4 (DPP-4) inhibitors, which are used at a similar diabetes stage. If power is sufficient, SGLT-2 inhibitors could be compared with each other and, individually, with DPP-4 inhibitors. In this signal evaluation study, FDA desires a high level of precision and certainty. Results of the study may support regulatory action, including labeling.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

The Sentinel data partners comprise a large sample of patients who are susceptible to the exposures and outcomes of interest.

3 EXPOSURES

Sentinel currently includes the following exposure counts and duration of exposure episodes[1]:

- Canagliflozin: 345,000 initiators, mean duration of 1st episode, 171 days, median, 90 days, 75th percentile, 214 days. Currently, 46,000 patients have >1 year duration and 102,000 patients have >180 days' duration of their 1st treatment episode.
- Dapagliflozin: 95,000 initiators, mean duration of 1st episode, 142 days, median, 72 days, 75th percentile, 180 days. Currently, 9,400 patients have >1 year duration and 23,000 patients have >180 days' duration of their 1st treatment episode.
- Empagliflozin: 127,000 initiators, mean duration of 1st episode, 131 days, median, 78 days, 75th percentile, 175 days. Currently, 10,300 patients have >1 year duration and 29,000 patients have >180 days' duration of their 1st treatment episode.

In comparison: Sitagliptin: 1,630,000 initiators, mean duration of 1st episode, 207 days, median, 90 days, 75th percentile, 233 days. Currently, 266,000 patients have >1 year duration and 500,000 patients have >180 days' duration of their 1st treatment episode.

Regardless of the duration of exposure, Sentinel includes the following distribution of follow-up[2]:

- All SGLT-2 inhibitors: average duration of follow-up (includes new and prevalent users), 14.2 months, median, 11.3 months. Follow-up 24-36 months: 13.8%, 36-48 months: 4.6%, >48 months: 0.6%.

In comparison: DPP-4 inhibitors: average duration of follow-up, 29.6 months, median, 23.9 months. F/u 24-36 months: 16.5%, 36-48 months: 11.9%, >48 months: 21.7%.

Based on the preliminary analyses of exposure and follow-up time, we consider the total number of patients exposed to canagliflozin to be substantial, but for most patients, exposure duration may not be adequate to support a causal association (median, 90 days). Yet, with 46,000 patients with >1 year duration of the 1st episode, an analysis within these patients may be possible. Of note, stricter inclusion criteria may reduce these counts, and conducting the study in the future is expected to yield larger numbers.

However, the currently available follow-up time after SGLT-2 inhibitor initiation (not censored upon drug discontinuation) appears inadequate to ascertain a biologically plausible, causal effect between SGLT-2 inhibitors and RCC. For instance, only

[1] Sentinel data from 1/2008-6/2018 (includes CMS data 1/2010-12-2015), new users of antidiabetic drugs, with continuous drug coverage for 183-day baseline period, using a 10-days allowable gap between dispensings.
[2] Sentinel data from 2008- 06/2018 (includes CMS data 1/2010-12-2015). This analysis includes both prevalent and incident use.

approximately 5% of SGLT-2 inhibitor users had >3 years of follow-up, while this was the case for >33% of DPP-4 inhibitor users. The limited follow-up time after initiation is likely a consequence of the comparably recent approval of canagliflozin (2013). We expect that this will be a limiting factor in all available databases and that available follow-up time will be much improved for SGLT-2 inhibitor users with additional years of data accumulation, as can be seen with DPP-4 inhibitors, which were first approved in 2005. Therefore, we determined that ARIA would be sufficient to investigate the potential association between canagliflozin and RCC, once sufficient follow-up time has accumulated.

4 OUTCOME

We were unable to identify a published and validated algorithm to identify RCC in claims data. Arguably, RCC could be ascertained using ICD-9 and ICD-10 diagnostic codes, possibly in conjunction with evidence for treatment (nephrectomy, thermablation, others). Efforts are underway by OSE (David Graham) to develop and validate algorithms for cancer diagnoses using a SEER-Medicare linked database. Participants at the virtual SAM expressed that the absence of a validated endpoint algorithm at this time would not render ARIA insufficient.

5 COVARIATES

Smoking (current, past) and obesity/BMI are risk factors for RCC and are known to be widely missing from claims data. The impact of smoking may not be major, due to its modest association with RCC and because the rates of smoking are not expected to differ substantially between users of SGLT-2 inhibitors and DPP-4 inhibitors. However, average BMI may differ between users of SGLT-2 inhibitors and DPP-4 inhibitors. Presumably, BMI would likely be missing in most large claims-based databases. Thus, a quantitative bias analysis, or calibration based on external data, may be indicated.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

Parts of the analysis may require somewhat complex analytic tools, including a complex endpoint algorithm, lagging of exposure, analysis by time since initiation, and quantitative bias analysis. However, staff from the Sentinel Core Team advised that these analysis features would likely be within the ARIA framework.

7 NEXT STEPS

DEPI staff will draft a planning concept brief, which will outline a plan to monitor accumulation of canagliflozin exposure and follow-up time in Sentinel, to help determine when an ARIA study could feasibly detect a biologically plausible association, if present.

References

1. Fred Alavi. Pharmacology/Toxicology NDA Review and Evaluation, Canagliflozin, Feburary 1 , 2013, RefID: 3254315.

2. Todd Bourcier. NDA Secondary Pharmacology/Toxicology Review, Canagliflozin, February 5, 2013, RefID: 3257588.

3. Todd Bourcier. Supervisory Memorandum: Canagliflozin - Clinical relevance of rat carcinogencity study, October 11, 2018, RefID: 4333104.

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/s/

CHRISTIAN HAMPP
10/12/2018

YANDONG QIANG
10/14/2018

SIMONE P PINHEIRO
10/15/2018

MICHAEL D NGUYEN
10/15/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 10, 2018
To:	William Chong, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Lablieng Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Meena Savani, PharmD, RAC Regulatory Reviewer **Office of Prescription Drug Promotion (OPDP)** Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	INVOKANA (canagliflozin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 204042
Supplement Number:	S-27
Applicant:	Janssen Research & Development, LLC

1 INTRODUCTION

On September 29, 2017, Janssen Research & Development, LLC submitted for the Agency's review a supplemental New Drug Application (sNDA) to the INVOKANA (canagliflozin) to support inclusion of a new indication in the United States Package Insert. INVOKANA(canagliflozin) tablets, for oral use is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on October 6, 2017 and October 4, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INVOKANA(canagliflozin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft INVOKANA(canagliflozin) MG received on September 29, 2017, and received by DMPP and OPDP on September 28, 2018.
- Draft INVOKANA(canagliflozin) Prescribing Information (PI) received on September 29, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 28, 2018.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
10/10/2018

SHARON W WILLIAMS
10/10/2018

MEENA R SAVANI
10/10/2018

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 204042/S-027 Prior Approval Supplement

Name of Drug: Invokana (canagliflozin) tablets

Applicant: Janssen Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: September 29, 2017

Receipt Date: September 29, 2017

Background and Summary Description:

Invokana (canagliflozin) tablet is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The original New Drug Application (NDA) for Invokana (NDA 204042) was approved on March 29, 2013.

On September 29, 2017, Janssen submitted a Prior Approval Supplement (S-027) proposing to add a new indication for Invokana based on the results of the cardiovascular safety studies 28431754DIA3008, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS) and 28431754DIA4003, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS-R).

The new proposed indication was: *to reduce the risk of major adverse cardiovascular events* (b) (4) *in adults with type 2 diabetes mellitus who have established cardiovascular disease (CVD)* (b) (4)

Materials Review

Labeling Reviewed	Submission Date of Final Proposed Labeling	Currently Approved Labeling (Supplement and Date)
Prescribing Information	October 29, 2018	NDA 204042/S-031 October 26, 2018
Medication Guide	October 29, 2018	NDA 204042/S-031 October 26, 2018

Review

The currently approved prescribing information (PI) and medication guide (MG) for Invokana (canagliflozin) tablets (S-031) was approved on October 26, 2018. The proposed PI and MG for NDA 204042/S-027, submitted on October 29, 2018, was compared to the currently approved labels for Invokana (canagliflozin) tablets using the Microsoft Word compare documents function. A PDF copy of this comparison document is appended to this review.

The following significant changes were noted to the PI and MG. Underline is text added to currently proposed labeling; strikethrough is text deleted from currently proposed labeling.

(b) (4)

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Recommendations

The PI and MG were reviewed and agreed upon by the DMEP, DBII, DBVII, DMEPA, DMPP, and OPDP review teams. An approval letter should be drafted and issued for Invokana (canagliflozin) tablets, NDA 204042/S-027, based on the labeling submitted on October 29, 2018.

Elizabeth Godwin	October 29, 2018
Regulatory Project Manager	Date
Julie Van der Waag	October 29, 2018
Chief, Project Management Staff	Date

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/s/

ELIZABETH R GODWIN
10/29/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 19, 2018
To:	William Chong, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Lablieng Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Meena Savani, PharmD, RAC Regulatory Reviewer **Office of Prescription Drug Promotion (OPDP)** Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	INVOKAMET (canagliflozin and metformin hydrochloride) INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 204353/ S-025 NDA 205879/S-007
Applicant:	Janssen Research & Development, LLC

1 INTRODUCTION

On September 29, 2017, Janssen Research & Development, LLC submitted for the Agency's review a supplemental New Drug Application (sNDA) to the INVOKANA (canagliflozin) with cross reference to INVOKAMET (canagliflozin and metformin hydrochloride) and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) to support inclusion of a new indication in the United States Package Insert. INVOKAMET (canagliflozin and metformin hydrochloride) and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on October 6, 2017 and October 4, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INVOKAMET (canagliflozin and metformin hydrochloride) and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft INVOKAMET (canagliflozin and metformin hydrochloride) and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) MG received on September 29, 2017, and received by DMPP and OPDP on October 11, 2018.
- Draft INVOKAMET (canagliflozin and metformin hydrochloride) and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) Prescribing Information (PI) received on September 29, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 11, 2018.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
10/19/2018

SHARON W WILLIAMS
10/19/2018

MEENA R SAVANI
10/19/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 5, 2018

To: Liz Godwin, Regulatory Project Manager, Division of Metabolism & Endocrine Products (DMEP)

Monika Houstoun, Associate Director for Labeling, DMEP

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for Invokana (canagliflozin)

NDA: NDA 204042/S-027

In response to DMEP's consult request dated October 4th, 2017, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Invokana. This supplement (S027) proposes a new indication and revised labeling based on the results of the cardiovascular outcomes trials CANVAS and CANVAS-R.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP on September 28, 2018 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
10/05/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Response to Information Request

Date:	August 10, 2018
Reviewer:	Christian Hampp, PhD Division of Epidemiology I
Team Leader: (Acting)	Yandong Qiang, MD, PhD, MPH, MHS Division of Epidemiology I
Division Director:	Simone P. Pinheiro, ScD, MSc, ALM Division of Epidemiology I
Subject:	Review and replication of sponsor's analysis of renal cell carcinoma observed in the CANVAS program and comparison with expected rates in U.S. SEER
Drug Name:	Invokana (canagliflozin)
Application Type/Number:	NDA 204042 (Invokana), 204353 (Invokamet), 205879 (Invokamet XR)
Submission Number:	244, 247 (NDA 204042)
Applicant/sponsor:	Janssen Pharmaceuticals
OSE RCM #:	2018-1433

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Division of Epidemiology-I (DEPI-I) consult review replicates and critically evaluates the sponsor's calculation of observed rates of renal cell carcinoma (RCC) in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program compared with expected rates. This review is intended to help staff from the Division of Metabolism and Endocrinology (DMEP) recognize the appropriateness, utility, and limitations of comparing observed cancer rates in clinical trials with observed rates based on external data.

To help evaluate an observed imbalance in RCC cases in the CANVAS program (14 events, 0.62 per 1000 person-years, canagliflozin, vs. 3 events, 0.21 per 1000 person-years, placebo), the sponsor calculated standardized incidence ratios (SIRs). These compare observed events with expected events based on age-, and sex-specific cancer rates from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, adjusted for the effects of diabetes. Upon receiving DMEP's consult request, DEPI-I staff requested information from the sponsor that would enable replication of the analyses. In its response from July 16, 2018, the sponsor provided the requested information, in addition to a refined analysis. The original analysis showed that cancers of the "kidney and renal pelvis" observed in the canagliflozin arm of the CANVAS program were similar to rates expected based on U.S. SEER data (SIR, 0.98, 95% CI, 0.54-1.65). Rates observed in the placebo arm were statistically significantly lower than expected rates based on SEER (SIR, 0.34, 95% CI, 0.07-0.99). The SIRs for canagliflozin and placebo were numerically, but not statistically significantly, different form each other. The refined analysis, using a stricter definition of RCC, yielded slightly, but not decisively, higher SIRs for both arms. Based on replication of the sponsor's analysis, DEPI-I staff confirms these estimates.

The sponsor used generally accepted methods and appropriate databases to calculate SIRs. However, the comparison between expected RCC rates in an age- and sex-matched U.S. general population, adjusted for diabetes, and those observed in an international clinical trial, is subject to many limitations. Some of these limitations can lead to higher rates of RCC in clinical trials compared with U.S. SEER data (i.e., surveillance bias, detection bias, and different event definition and adjudication), lower rates in clinical trials compared with U.S. SEER data (i.e., healthier trial participants, lower rates in developing countries, which were part of CANVAS), or unclear directionality (i.e., imperfect adjustment for risk associated with diabetes, other risk factors for RCC that may differ between clinical trials and U.S. SEER data). Appropriately, the sponsor did not use the different SIRs observed for canagliflozin and placebo to explain the imbalance in RCC cases observed within the clinical trial program. Indeed, the reviewed analysis does not provide information about a possible causal role of the exposure of interest, beyond what is already known based on an observed within-trial imbalance.

The sponsor noted the ongoing CREDENCE trial, which is being conducted in a large sample of patients with renal impairment. To date, three blinded cases of RCC were detected in the trial. With additional follow-up (estimated study completion: June 2019), this trial may provide additional data regarding the potential risk for RCC with canagliflozin.

1 INTRODUCTION

This DEPI-I consult review replicates and critically evaluates the sponsor's calculation of observed rates of RCC in the CANVAS program compared with expected rates. This review is intended to help DMEP staff recognize the appropriateness, utility, and limitations of comparing observed cancer rates in clinical trials with observed rates based on external data.

On September 29, 2017, Janssen Pharmaceuticals submitted a supplemental New Drug Application (sNDA 204042/S-027) with results from the CANVAS and CANVAS–Renal (CANVAS-R) clinical trials, referred together as the CANVAS program. The Integrated Summary of Safety (ISS, Section 2.1.4.1.2.2.3) indicates an imbalance in the incidence rate for RCC across both trials in the CANVAS program, not favoring canagliflozin. The incidence of RCC in the canagliflozin arm was 0.62 per 1000 person-years (14 events) and 0.21 per 1000 person-years in the placebo group (3 events). The incidence rate difference was 0.41 per 1000 person-years (95% CI: -0.04, 0.86).

On June 21, 2018, DMEP staff sent the following information request to the sponsor:

> *We note a numerical imbalance in cases of renal cell carcinoma not favoring canagliflozin in the integrated CANVAS analysis. We are concerned about this numerical imbalance in light of findings from the nonclinical program for canagliflozin, which showed an increased incidence of renal tubule adenoma and carcinoma with canagliflozin.*
>
> *Although Section 2.1.4.1.2.2.3 in the Integrated Summary of Safety reports the numerical data regarding renal cell carcinoma, it does not include clinical interpretation of this imbalance (e.g., comparative analyses, causality assessment). We request that you submit additional analyses and/or additional information including your interpretation of the finding(s).*

The sponsor responded to FDA's information request on June 28, 2018. The sponsor's response included a section that presents the calculation of a SIR, whereby RCC events observed in each arm of the CANVAS program were compared with expected rates based on SEER data. On July 3, 2018, DEPI-I received a request for consultation from DMEP, to comment on the sponsor's analysis using SEER data as the reference. On July 6, 2018, DEPI-I staff requested that the sponsor provide a description of the methods used in its SIR calculation, age- and sex- specific follow-up times in each trial to allow for replication of the analysis, a comparison of case definitions and adjudication methods used in CANVAS and in SEER, and any information not specifically requested above, that is needed to replicate and interpret the analysis. The sponsor provided the requested information on July 16, 2018. The sponsor's response also included a refined analysis, as described in Section 3 of this review.

2 REVIEW METHODS AND MATERIALS

I reviewed the sponsor's initial SEER analysis from June 28, 2018, and the refined analysis included in the July 16, 2018, response to FDA's July 6, 2018, information request, which also included an explanation of the methods of the original analysis.

To replicate the sponsor's analysis, I followed the sponsor's methods described in Section 3 of this review. I extracted SEER data using the same query, database, and software (1) as the sponsor and replicated SIR and 95% CI calculations with OpenEpi,(2) which was used also used by the sponsor.

Finally, I critically evaluated the sponsor's approach to this analysis and its conclusions.

3 REVIEW RESULTS

3.1 SPONSOR'S ANALYSIS METHODS

The methods used in calculation of SIRs in the original analysis from June 28, 2018, and the refined analysis from July 16, 2018, are similar and differ only in the calculation of expected event counts based on SEER data. For the original analysis, the sponsor extracted age- and sex-specific incidence rates for the cancer site "kidney and renal pelvis" in the November 2016 SEER data collection that includes the years 2000 through 2014.[1] However, the sponsor recognized that diabetes is a risk factor for renal malignancy.(3) Because the SEER data arise from the general population but only diabetic patients were included in the CANVAS program, the sponsor calculated age- and sex-specific incidence rates for kidney and renal pelvis cancer separately for patients with and without diabetes, according to this formula:

> *R (rate in overall SEER population) = % of non-DM * R0 (rate in non-DM) + % of DM * R0 * RR (relative risk comparing DM vs. non-DM).*

In this calculation, the sponsor used age-specific diabetes prevalence rates provided by the Centers for Disease Control and Prevention (CDC).(4) The RR estimate was extracted from a meta-analysis of observational studies, conducted by Larsson et al., (3) which found that diabetes was associated with an increased risk for kidney cancer in males (RR=1.26) and females (RR=1.70).

In the next step, the sponsor applied the calculated age- and sex-specific incidence rates of cancers of the "kidney and renal pelvis" in SEER individuals, adjusted for the effects of diabetes, to the CANVAS program's age- and sex-specific person-years of follow-up (intent-to-treat, on-study) to calculate the expected number of cases with renal malignancy in the CANVAS program.

Using OpenEpi, the sponsor then calculated SIR and 95% CIs by dividing the number of observed events in the CANVAS program by the number of events that are expected in a general diabetic population of the same age-and sex distribution, followed for the same time as in the CANVAS program, based on SEER data.

In the refined analysis provided on July 16, 2018, the sponsor aimed to calculate expected counts of RCC, rather the more comprehensive "kidney and renal pelvis" cancer used in the original analysis. To extract these data from SEER, RCC cases were identified using

---

[1] Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (2000-2014) <Katrina/Rita Population Adjustment> - Linked to County Attributes - Total U.S., 1969-2015 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2017.

the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) primary site code C64.9 and histology codes 8010 to 8051 and 8131 to 8719. In addition to the 2016 SEER database used in the original analysis (with data from 2000 through 2014), this refined analysis was also conducted in the newly available SEER database collected in November 2017, released in April 2018, with data from 2000 through 2015.[2] Also, the Larsson meta-analysis provided separate estimates for the association between diabetes and "kidney cancer," used on the original analysis (RR=1.26, males; RR=1.70, females) and between diabetes and RCC (RR=1.12, regardless of sex).(3) The sponsor applied RR=1.12 to model the expected prevalence of RCC in a diabetic population. The remainder of the SIR calculation followed the same methods as used in the original analysis.

3.2 RESULTS

The original analysis from June 28, 2018, showed that cancers of the "kidney and renal pelvis" observed in the canagliflozin arm of the CANVAS program were close to rates expected based on SEER data (SIR, 0.98, 95% CI, 0.54-1.65, Table 1). Rates observed in the placebo arm were statistically significantly lower than expected rates based on SEER (SIR, 0.34, 95% CI, 0.07-0.99). The point estimate of the SIR for canagliflozin is close to the upper bound of the 95% CI of the SIR for the placebo arm, but because it falls inside the latter 95% CI, it can be inferred that the two SIRs are not statistically significantly different.

Table 1, Sponsor's Original Analysis from June 28, 2018. Standardized Incidence Ratio Compared with SEER (Table 1 in June 28, 2018, submission)

Treatment	Renal Malignancy			
	Observed	Expected*	SIR (95% CI) **	P-value**
Cana	14	14.24	0.983 (0.54-1.65)	0.91
Placebo	3	8.84	0.339 (0.070-0.99)	0.0475
All	17	23.08	0.737 (0.43-1.18)	0.239

[2] Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> - Linked to County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.

95% CI=95% confidence interval
† Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (2000-2014) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2015 Counties, NCI, DCCPS, Surveillance Research Program, released April 2017. SEER*stat Version 8.3.4.
* Estimated based on SEER incidence rate, prevalence of diabetes in general US population, and relative risk of renal cancer comparing type 2 diabetes vs. non-diabetes (Larsson et al. 2011)
** Two-sided p-values and 95 % CI from exact test based on Poisson distribution (Rosner 2000) and Fisher's exact test (Rothman and Boice 1979) http://www.openepi.com/PDFDocs/SMRDoc.pdf accessed 6/27/2018

In its revised analysis from July 16, 2018, the sponsor extracted SEER data for RCC instead of cancer of the "kidney or pelvis." Because the RCC definition selects a subset of the latter, expected events based on SEER were fewer than in the original analysis, but not decisively so (Table 2).[3] Consequently, observed rates of RCC among canagliflozin patients in the CANVAS program are somewhat higher than expected based on 2017 SEER data (with data from 2000 through 2015, SIR, 1.23, 95% CI, 0.67-2.06), but lower than expected among placebo patients (SIR, 0.43, 95% CI, 0.09-2.14). Neither SIR is statistically significantly different from the null and both 95% CIs cover the SIR estimate of the other trial arm, suggesting that they are not statistically significantly different from each other. In this analysis, the sponsor contrasted 2017 SEER data (covering 2000-2015) and the previously used 2016 SEER data (covering 2000-2014), with almost identical results.

Table 2. Sponsor's Revised Analysis from July 16, 2018. Standardized Incidence Ratio of Renal Cell Carcinoma in the CANVAS Program Compared with the SEER Database Using Relative Risk for Renal Cell Carcinoma Standardized Incidence Ratio Compared with SEER (Table 1 in July 16, 2018, submission)

Treatment	Observed	SEER Nov 2017 data collection†			SEER Nov 2016 data collection††		
		Expected* RCC	SIR (95% CI) **	P-value**	Expected* RCC	SIR (95% CI) **	P-value**
Cana	14	11.51	1.216 (0.67-2.04)	0.54	11.41	1.227 (0.67-2.06)	0.52
Placebo	3	7.12	0.421 (0.087-1.23)	0.15	7.06	0.425 (0.088-1.24)	0.16
All	17	18.63	0.913 (0.53-1.46)	0.82	18.47	0.920 (0.54-1.47)	0.85

RCC in SEER was identified by using ICD-O-3 primary site code C64.9 in combination with histology codes 8010-8051 and 8131-8719.
95% CI = 95% confidence interval
† Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015)
†† Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (2000-2014)
* Estimated based on SEER incidence rate, prevalence of diabetes in general US population, and relative risk of RCC comparing diabetes vs. non-diabetes (Larsson et al. 2011)
** Two-sided p-values and 95 % CI from exact test based on Poisson distribution (Rosner 2000) and Fisher's exact test (Rothman and Boice 1979) http://www.openepi.com/PDFDocs/SMRDoc.pdf accessed 7/12/2018

[3] Appendix, Attachments 1.1 and 1.2 provide age-and sex-specific RCC incidence rates from SEER, the sponsor's adjustment for the effects of diabetes, and their application to age- and sex-specific follow-up times in the CANVAS program, resulting in the expected RCC event counts shown in Table 2, for the SEER 2017 data collection.

The sponsor also compared the prevalence of selected baseline covariates between RCC cases and the overall trial population (Appendix, Table 3). Imbalances between RCC cases and all patients confirm that the following are risk factors for RCC: male sex, Caucasian race, hypertension and obesity. Looking at the overall trial population (regardless of RCC), the sponsor noted that baseline characteristics were balanced between treatment arms, due to randomization.

To address part of FDA's information request, the sponsor described and contrasted case definitions and adjudication methods used in CANVAS and in SEER. In CANVAS, RCC cases were identified based on investigator reported adverse events coded to the pre-specified list of preferred terms (PTs) shown below, which was derived from the high-level term of Renal Neoplasms Malignant:

Table 3. Preferred Terms Used to Identify Renal Cell Carcinoma (Table 2 in July 16, 2018, submission)

Clear cell renal cell carcinoma	Non−renal cell carcinoma of kidney	Renal cell carcinoma
Clear cell sarcoma of the kidney	Renal cancer	Renal cell carcinoma recurrent
Denys−Drash syndrome	Renal cancer metastatic	Renal cell carcinoma stage I
Hereditary leiomyomatosis renal cell carcinoma	Renal cancer recurrent	Renal cell carcinoma stage II
Hereditary papillary renal carcinoma	Renal cancer stage I	Renal cell carcinoma stage III
Metastatic renal cell carcinoma	Renal cancer stage II	Renal cell carcinoma stage IV
Papillary renal cell carcinoma	Renal cancer stage III	Rhabdoid tumour of the kidney
Nephroblastoma	Renal cancer stage IV	

The sponsor noted that non-RCC malignancies could have been captured from this list of PTs, (e.g., as a "non-renal cell carcinoma of kidney" or "renal cancer"); however, where possible histology results were obtained and when missing, cases were presumed to be RCCs. In addition, cases of RCC were not independently adjudicated to confirm the diagnosis of RCC in the CANVAS program. According to the sponsor, SEER cases are based on histologic classification, without additional adjudication of renal cancer cases. Renal cancers are coded using ICD-O-3 codes, which can be mapped to ICD-10 codes. Based on the ICD-10 code for the reported verbatim terms of the RCC cases in the CANVAS program (C64.9, Malignant neoplasm of unspecified kidney, except renal pelvis), the sponsor stated that the CANVAS cases would map (via the ICD-10 code) to relevant ICD-O-3 codes in the SEER database.

Finally, the sponsor mentioned the ongoing CREDENCE study, an international, multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial designed to assess whether canagliflozin has a renal and cardiovascular protective effect in reducing the progression of renal impairment relative to placebo in subjects with type 2 diabetes mellitus, Stage 2 or 3 chronic kidney disease, and macro albuminuria, who are receiving standard of care, including a maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. As of July 13, 2018, a total of 4,398 subjects were randomized and treated, with 10,203 subject-years of total follow-up. The methodology used for capture of RCC events in the CANVAS program is also being used in the CREDENCE study. Three blinded cases of RCC occurred so far in CREDENCDE, 2 of them within the first 6 months of the study. Histology was available

for 2 cases (PT: "renal cancer" reported on Day 603 and PT: "renal cell carcinoma stage 1" reported on Day 32), and the sponsor stated that queries for details regarding the histology for the third case are currently ongoing.

3.3 SPONSOR'S CONCLUSIONS

The sponsor concluded that the rate of RCC in subjects receiving canagliflozin in the CANVAS program was similar to that expected using the SEER database. The sponsor observed a numerical difference in the incidence of RCC between pooled canagliflozin and placebo in the CANVAS program, and noted that "the SIRs for RCC included "1"[4] with broad 95% CIs for both the pooled canagliflozin and placebo groups." Furthermore, the sponsor noted that the SIR for RCC in the placebo group was trending towards being statistically significant with a p-value of 0.15, suggesting that the incidence of RCC in the placebo group in the CANVAS program may be slightly lower than expected.

In addition, the sponsor concluded based on the clinical review of RCC cases, that all case subjects had risk factors, and characteristics of subjects with RCC are consistent with what would be expected for RCC occurring in the general population.

Finally, the sponsor restated its conclusion from the sponsor's June 28, 2018, response that no dose response was observed, and based on the size of tumors and duration of exposure, in most cases an undiagnosed tumor at study entry is biologically plausible.

3.4 DEPI-I REPLICATION OF SPONSOR'S ANALYSIS

My replication of the sponsor's SEER data extraction, adjustment for the effects of diabetes, and calculation of SIRs and 95% CIs confirm the sponsor's estimates provided in the original and the refined analysis.

4 DISCUSSION

The sponsor's analysis found that RCC cases in patients randomized to canagliflozin in the CANVAS program were close to expected kidney and pelvis cancer rates, based on age-, sex-specific SEER data that were adjusted for the effects of diabetes. Rates observed among placebo patients were lower than expected, even though the SIR for both arms were not statistically significantly different. Observations were similar in the sponsor's refined analysis, in which SEER rates were mainly based on a narrower RCC definition.

The sponsor relied on the following data sources: (i) RCC rates provided by U.S. SEER, (ii) age-specific diabetes prevalence rates provided by the CDC, (iii) an estimate for the association between diabetes and RCC provided in a meta-analysis of observational studies,(3) (iv) age- and sex-specific follow up times (intent-to-treat) and RCC event counts form the CANVAS program.

The following section provides a description and evaluation of each data source:

[4] Presumably, the sponsor is referring to the 95% CIs that include "1."

i. According to its description,(5) SEER collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34 percent of the U.S. population. These registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status (survival). These data are collected on every cancer case reported from 19 U.S. geographic areas. The use of SEER in this analysis is appropriate, but limitations, as described below, are important to consider.

ii. The CDC's diabetes prevalence rates (4) used by the sponsor describe broad age categories (30-44, 45-64, ≥ 65 years), which may not adequately describe age-specific diabetes prevalence. However, the degree of imprecision and its importance are unclear and the use of these estimates is likely appropriate.

iii. Larsson et al. conducted a systematic review and meta-analysis of observational studies that examined an association between diabetes and kidney cancer.(3) The overall association (RR=1.42) was based on 9 cohort studies. Restriction to studies that adjusted for cigarette smoking and obesity yielded lower RR estimates, suggesting that these factors partially explain the association between diabetes and kidney cancer. The estimate for RCC (RR=1.12) was only based on 3 included studies. Larsson et al. acknowledged that the association between diabetes and kidney cancer is not necessarily causal and could be related to confounding and/or detection bias. Despite these limitations, the use of its results to adjust the sponsor's SIR calculation is appropriate.

iv. The inclusion of the pooled intent-to-treat population of the CANVAS program is appropriate.

The sponsor's approach to calculating SIRs was appropriate and my replication yielded the same point estimates and 95% CIs.

The sponsor's interpretation of the SEER analysis is appropriate. The sponsor did not use the numerically (not statistically significant) different SIRs observed for canagliflozin and placebo to explain the imbalance in RCC cases observed within the clinical trial. Indeed, comparisons between the trial and external populations are subject to inherent limitations. Several factors can bias these comparisons either towards higher or lower rates in clinical trials compared with the external standard and some factors could impact clinical trial rates in either direction.

The following factors could potentially lead to higher rates of RCC in clinical trials compared with U.S. SEER data:

- **Surveillance bias due to regularly scheduled follow-up visits in clinical trials.** This would result in more diagnoses in both treatment arms, compared with SEER data.
- **Detection bias related to known side effects of SGLT-2 inhibitors related the urinary tract**. This bias could affect the clinical trial treatment arms differentially but may not impact the comparison between the placebo arm and SEER data.

- **Event definition and adjudication**: The sponsor noted that cases in the SEER database were identified based on histologic diagnosis, whereas cases in CANVAS were identified per investigator adverse event reporting. Although a histologic diagnosis was provided in most CANVAS cases (10 of 14 cases on canagliflozin and 2 of 3 cases on placebo), even those cases without histology were considered RCC cases to avoid underestimation of the rate of RCC.

The following factors could potentially lead to lower cancer rates in the clinical trials compared with U.S. SEER data:

- **Voluntary participation can result in the selection of healthier patients** (fewer cancer risk factors, incl. smoking) with higher socioeconomic status and better access to healthcare and prevention.
- **Lower RCC rates for international trial participants compared to U.S. population captured in SEER data could affect the comparison.** The sponsor cited epidemiologic studies that found regional differences in the incidence of RCC, with generally higher rates found in developed countries such as the United States and the European Union, relative to developing countries. While the SEER data are U.S.-based, the CANVAS program was conducted globally (58% of subjects were recruited from developed countries [US, Canada, EU, Australia]). Out of 17 RCC cases, 11 occurred in developed countries.

The following factors could impact comparisons between clinical trials and U.S. SEER data, but the directionality is unclear:

- **Potentially imperfect accounting for the association of the underlying disease (diabetes) with increased risk of RCC**.(6) The sponsor accounted for this association; however, the adequacy of adjustment is difficult to evaluate. For instance, the CDC's diabetes prevalence rates (4) used by the sponsor describe broad age categories, which may not adequately describe age-specific diabetes prevalence. In addition, the sponsor acknowledged that its underlying assumption was that the distribution of persons with and without diabetes in the SEER database was similar to the general U.S. population. However, because diabetes is a risk factor for RCC, the prevalence of diabetes in the population with RCC may be higher than in the general population.
- **Inclusion and exclusion criteria may result in a sample at lower or higher risk for renal cell carcinoma.** The sponsor only adjusted for the effects of age, sex, and diabetes. However, other risk factors for RCC (e.g., smoking history, Caucasian race, hypertension, and obesity) may differ between the CANVAS program and SEER data.

Although these factors can bias the results in opposite directions, their relative magnitude is difficult to predict and it would be imprudent to assume that they cancel each other out. As a consequence, SIRs resulting from comparisons with an external standard can be subject to systematic error and should be interpreted with caution.

5 CONCLUSION

The sponsor used generally accepted methods to calculate SIRs based on the number of observed RCC events in the CANVAS program and the number of RCC events that are expected in a general diabetic population of the same age-and sex distribution, followed for the same time as in the CANVAS program. DEPI-I replicated the sponsor's analysis, which suggests that using the SEER data as the reference, RCC rates in the canagliflozin arm of the CANVAS program were close to expected rates, while rates observed in the placebo arm were lower than expected, albeit not statistically significantly different.

The comparison between expected RCC rates in a U.S. general diabetic population and those observed in an international clinical trial, is subject to many limitations that were outlined in this review. I acknowledge that the sponsor did not use the different SIRs observed for canagliflozin and placebo to explain the imbalance in RCC cases observed within the clinical trial. Indeed, the reviewed analysis does not provide information about a possible causal role of the exposure of interest, beyond what is already known based on an observed within-trial imbalance.

The sponsor noted the ongoing CREDENCE trial, which is being conducted in a large sample of patients with renal impairment. To date, 3 blinded cases of RCC were detected in the trial. With additional follow-up (estimated study completion: June 2019), this trial may provide additional data regarding the potential risk for RCC with canagliflozin.

Christian Hampp, PhD

Cc: Chong W /Pippins J /Kwon H /Conrad A /Alavi F /Hanan E /Petrucelli M /Godwin E /DMEP
Qiang Y /Sandhu S /Pinheiro S /Calloway P /DEPI -I
Cao C /Chamberlain C /DPV
Thomas T /OSE

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APPENDICES

Attachment 1.1: Estimation of Incidence Rate of Renal Cell Carcinoma Among Diabetes Patients in SEER

Age	SEER RCC incidence rate *		Pop % of diabetes **	Estimated rate in non-diabetes (1)		Estimated rate in diabetes (2)	
	Male	Female		Male	Female	Male	Female
30-34 y	2.5	1.9	4%	2.49	1.89	2.79	2.12
35-39 y	5.3	3.3	4%	5.27	3.28	5.91	3.68
40-44 y	10.2	5.8	4%	10.15	5.77	11.37	6.46
45-49 y	17.4	9	17%	17.05	8.82	19.10	9.88
50-54 y	27.3	13.5	17%	26.75	13.23	29.96	14.82
55-59 y	40.6	19	17%	39.79	18.62	44.56	20.85
60-64 y	56.3	26	17%	55.17	25.48	61.80	28.54
65-69 y	72.6	34.5	25.2%	70.47	33.49	78.93	37.51
70-74 y	81.4	38.8	25.2%	79.01	37.66	88.49	42.18
75-79 y	84.7	40.1	25.2%	82.21	38.92	92.08	43.59
80-84 y	76.8	36.5	25.2%	74.55	35.43	83.49	39.68
85+ y	62.2	27.8	25.2%	60.37	26.98	67.62	30.22

* Rates are per 100,000 person-years and age-adjusted to the 2000 US std Population (19 age groups - Census P25-1130) standard.
Database: Incidence - SEER 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.

** Prevalence of diabetes in US population per CDC National Diabetes Statistics Report 2017 (data based on 2011-2014 National Health and Nutrition Examination Survey and 2015 US Census Bureau data).

(1) Calculated based on the equation: % of non-dm * R0 (rate in non-dm) + % of dm * R0 * RR (relative risk comparing dm vs. non-dm) = R (rate in overall SEER population)
(2) Calculated as R1 (rate in dm) = R0 * RR (Larsson 2011 Diabetologia RR of RCC comparing DM vs. non-DM: 1.12)

Attachment 1.2: Calculation of Expected Number of Renal Cell Carcinoma Cases in CANVAS Using Estimated Incidence Rates Among Diabetes Patients in SEER

Age	SEER		CANVAS									
			Cana					Placebo				
	Estimated rate in dm		person-years		Expected n of cases (1)			person-years		Expected n of cases (1)		
	Male	Female	Male	Female	Male	Female	Total	Male	Female	Male	Female	Total
30-34 y	2.79	2.12	12.7	0.0	0.00	0.00		4.0	6.4	0.00	0.00	
35-39 y	5.91	3.68	46.7	19.8	0.00	0.00		28.7	3.6	0.00	0.00	
40-44 y	11.37	6.46	188.9	70.0	0.02	0.00		96.7	27.5	0.01	0.00	
45-49 y	19.10	9.88	358.3	192.6	0.07	0.02		252.2	120.8	0.05	0.01	
50-54 y	29.96	14.82	1701.8	1019.8	0.51	0.15		1019.3	575.2	0.31	0.09	
55-59 y	44.56	20.85	2713.3	1260.5	1.21	0.26		1720.5	819.1	0.77	0.17	
60-64 y	61.80	28.54	3529.7	1940.6	2.18	0.55		2163.0	1217.9	1.34	0.35	
65-69 y	78.93	37.51	3201.6	1690.1	2.53	0.63		1869.5	1050.3	1.48	0.39	
70-74 y	88.49	42.18	1907.3	1002.4	1.69	0.42		1217.9	737.1	1.08	0.31	
75-79 y	92.08	43.59	887.1	438.9	0.82	0.19		496.9	339.3	0.46	0.15	
80-84 y	83.49	39.68	209.1	117.7	0.17	0.05		144.6	58.6	0.12	0.02	
85+ y	67.62	30.22	26.4	9.2	0.02	0.00		30.6	13.1	0.02	0.00	
Total			14783.0	7761.5	9.22	2.29	11.51	9043.9	4969.0	5.62	1.50	7.12

(1) Expected number of incident cases is calculated as estimated incidence rates from SEER * person-years follow-up in CANVAS.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTIAN HAMPP
08/10/2018

YANDONG QIANG
08/10/2018

SIMONE P PINHEIRO
08/10/2018

Clinical Inspection Summary

Date	6/11/2018
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Hyon J. Kwon, Pharm.D., M.P.H., Senior Clinical Analyst Lisa B. Yanoff, M.D., Clinical Team Leader Elizabeth Godwin, MSHS, CCRP, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	NDA 204042/s027; *cross reference to* NDA 204353/s025 and NDA 205879/s007
Applicant	Janssen Pharmaceuticals, Inc.
Drug	Canagliflozin (Invokana®)
NME	No
Therapeutic Classification	Antidiabetic
Proposed Indication	To reduce the risk of major adverse cardiovascular events (b) (4) in adults with type 2 diabetes mellitus who have established cardiovascular disease (CVD) (b) (4)
Consultation Request Date	11/3/2017
Summary Goal Date	6/20/2018
Action Goal Date	7/27/2018
PDUFA Date	7/29/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this sNDA consisted of three domestic and two foreign clinical sites (representing eight study sites). The inspection of two clinical investigators listed below revealed regulatory violations. The inspection of the remaining clinical investigators revealed no regulatory violations.

In general, based on the inspections of the five clinical sites (representing eight study sites), the inspectional findings support the validity of data as reported by the sponsor under this NDA.

The classification for Drs. Dumas and Trenche is Voluntary Action Indicated (VAI). Although

regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Data from these two investigators (representing three study sites) is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) for Dr. Dumas was submitted for review. The full EIR for Dr. Trenche was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The classification for Drs. Blouin, Claxton, and Wynne is No Action Indicated (NAI). Data from these sites is considered reliable based on the available information. The full Establishment Inspection Reports were submitted for review.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Reports.

II. BACKGROUND

Janssen Research & Development, LLC (JRD) on behalf of Janssen Pharmaceuticals Inc., submitted a supplemental new drug application (sNDA) to NDA 204042 to support inclusion of a new indication: "*to reduce the risk of major adverse cardiovascular events* (b) (4) *in adults with type 2 diabetes mellitus who have established cardiovascular disease* (b) (4)

INVOKANA® 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). This submission fulfills the postmarketing requirement (PMR) 2027-5 for NDA 204042 to evaluate the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus.

In order to satisfy the aforementioned PMR, JRD conducted the CANVAS program consisting of Study **28431754DIA3008**, entitled, "*A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus,*" (CANVAS) and Study **28431754DIA4003**, entitled, "*A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type 2 Diabetes Mellitus*," (CANVAS-R). Inspections were requested for both studies.

28431754DIA3008
The study began November 17, 2009 and completed on February 22, 2017. Database lock was March 28, 2017. The study was performed at 359 centers in 24 countries. A total of 7,693 subjects were screened, 4,330 subjects were randomized, 4327 subjects were dosed, and 4301 subjects were completers.

The primary measure of efficacy was the hazard ratio (HR) of the composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). The primary efficacy endpoint for CV benefit was time to MACE, which was calculated as the time from Day 1 to the first occurrence of MACE.

28431754DIA4003
The study began January 17, 2014 and completed February 23, 2017. Final database lock was March 28, 2017. Subjects were enrolled at 419 sites in 24 countries. A total of 7,801 subjects were screened, 5,813 subjects were randomized (one twice), 5,809 subjects were dosed, and 5799 were completers.

The primary efficacy endpoint was the time to the first occurrence of progression of albuminuria, defined as the development of micro-albuminuria or macro-albuminuria in a subject with baseline normo-albuminuria or the development of macro-albuminuria in a subject with baseline micro-albuminuria, accompanied by an albumin/creatinine ratio (ACR) value increase of greater than or equal to 30% from baseline.

III. RESULTS (by Site):

Name of CI/ Address Site#	**Protocol #/Site # and # of Subjects Randomized**	**Inspection Date**	**Classification**
Francois Blouin 1190 A Rue de Courchevel Lévis, Quebec G6W 0M6 Canada	3008 Site 11004 66 subjects 4003 Site CA00121 42 subjects	03/06 – 03/15/2018	No Action Indicated (NAI)
Richard Dumas 3030 Blvd de Carrefour Laval, Quebec H7T 2P5 Canada	3008 Site 11005 146 subjects	03/12 – 03/29/2018	Voluntary Action Indicated (VAI)
Richard Dumas Centre de Recherche Clinique de Laval Laval, QC H7T 2P5 Canada	4003 Site CA00120 20 subjects	03/12 – 03/29/2018	Voluntary Action Indicated (VAI)
Edmund Claxton 2 Great Falls Plaza Auburn, ME 04210-5966	3008 Site 1062 36 subjects	03/19 – 03/22/2018	No Action Indicated (NAI)
Samuel Mujica Trenche 3930 E. Patrick Lane Las Vegas, NV 89120	4003 Site US98044 66 subjects	04/16 – 04/20/2018	Voluntary Action Indicated (VAI)*
Alan Wynne 3520 SW 6th Avenue Topeka, KS 66606	3008 Site 1066 17 subject 4003 Site US10706 48 subjects	01/16 – 01/23/2018	No Action Indicated (NAI)

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Francois Blouin/ 3008 Site 11004/ 4003 Site CA00121

For Study 3008, there were 107 subjects screened and 66 subjects enrolled into the study; 43 subjects completed the study (six deaths, four lost to follow-up, 13 stopped drug). There were 62 subject records reviewed.

For Study 4003, there were 49 subjects screened and 42 subjects randomized (four re-screens); 32 subjects completed the study (two deaths, eight stopped drug). There were 24 subject records reviewed.

In 2006, Dr. Blouin started working for Pro-Research (which became Manna Research). In 2015, LMC Diabetes & Endocrinology merged with Manna Research. LMC Manna Research is the largest network of its kind in outpatient North American research.

There was a transfer of the ethics committee of record during the 3008 study. Trafalgar Ethics Board, Inc. was the initial ethics committee. Responsibilities were transferred to IRB Services.

The records were organized and available. Source records were in French and a translator was present. For both studies, there was no under-reporting of adverse events. The primary efficacy endpoints were verifiable.

Source data was compared to the sponsor data line listings and there were no discrepancies except with some screen failures. It was noted that the reason for screen failure differed for some subjects for Study 3008. Upon further investigation, a June 17, 2010 communication from the sponsor warned about a numbering error associated with the inclusion/exclusion form version dated September 2009 with the correct numbering being associated with the version dated November 30, 2009. Subjects (b) (6), and (b) (6) should be listed as screen failures due to renal (eGFR) exclusion criteria.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations was issued.

2. Richard Dumas/ 3008 Site 11005/ 4003 Site CA00120

Although two sites are listed in the application, it was confirmed during the inspection that Dr. Dumas enrolled all subjects for both studies at the Centre de Recherche Clinique de Laval. Dr. Dumas splits his clinic time between the private research clinic and Cite de la Sante de Laval as head of the Endocrinology Dept. for the Diabetes Education Center. Subjects were all current patients of Dr. Dumas.

For Study 3008, there were 208 subjects screened and 146 subjects enrolled into the study; 132 subjects completed the study. There were approximately 48 subject records reviewed.

There was a transfer of the ethics committee of record during the 3008 study. Trafalgar Ethics Board, Inc. was the initial ethics committee. Responsibilities were transferred to IRB Services.

The files were organized, legible, and available. Source data was compared to the data line listings. Adverse events were overall reported as appropriate to the sponsor and IRB. However, Subject (b) (6) had constipation from 9/18-23/11 noted at Week 78 (9/29/11) that was not reported as an adverse event to the sponsor. The primary efficacy endpoint was verifiable.

For Study 4003, there were 24 subjects screened and 20 subjects enrolled into the study; 17 subjects completed the study. There were 20 subject records reviewed.

The files were organized, legible and available. Source data was compared to the data line listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

- For Study 3008, 52 subjects did not sign version #2 (dated March 24, 2010) of the informed consent approved by the IRB on April 15, 2010.
  OSI Reviewer Comment: The changes concerned blood pressure procedures done at the screening visit and corrections of administrative mistakes made by the sponsor. All subjects were already enrolled into the trial and there was a misunderstanding at the site that all subjects needed to be re-consented. This error was discovered during the trial, reported to the IRB, and version #3 of the ICF was signed by all subjects.
- For Study 3008, 46 subjects did not sign the amended informed consent dated November 16, 2101 as soon as available.
  OSI Reviewer Comment: Since there were several updates, errors, and corrections in the previous ICFs, the study coordinator was waiting for

confirmation from the site manager before obtaining informed consent from subjects again. During the wait, the updated ICF was misplaced by the site. Once the error was discovered, all subjects signed informed consent at their next appointment. This error was reported to the IRB.

- For both studies, there were four subjects with laboratory specimens that were "hemolyzed" or with an insufficient quantity that were not repeated. *OSI Reviewer Comment: Redraws were not stipulated in the protocol. The investigator determined that previous results did not warrant bringing subjects back to the site for repeat testing.*

Dr. Dumas sent a response on April 16, 2018 to the 483 observations. His corrective and preventive actions were deemed acceptable.

3. Edmund Claxton/ 3008 Site 1062

There were 60 subjects screened and 36 subjects enrolled into the study; 30 subjects completed the study. There were 18 subject records reviewed.

Dr. Claxton has been employed with Maine Research Associates for 2 years and began on the study in October 2016 after the retirement of the original clinical investigator, Dr. Robert Weiss. Subjects were recruited from area cardiologists who would refer patients to the study.

A Central IRB, Sterling Institutional Review Board, was utilized for the study. The appropriate IRB-approved version of the informed consent document was used for 35 of the 36 subjects. Subject (b) (6) was given the wrong consent form version to sign.

Source documents were organized, legible and complete. Source records were compared to the data line listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Samuel Mujica Trenche/ 4003 Site US98044

There were 75 subjects screened and 66 subjects enrolled into the study; 66 subjects completed the study. There were 26 subject records reviewed.

Subject files were organized and complete. Source records were compared to data line listings and there were no discrepancies. A significant protocol deviation occurred on 3/13/14, where a screen-failure was enrolled (Subject (b) (6)). The study PI at the time was Rubin H. Saavedra, M.D. Re-training was conducted by the sponsor in response to the

deviation. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to obtain a signed ICF for every ICF revision for Subjects (b) (6)

OSI Reviewer Comment: All but one of these related to a revision due to change in site address or change in PI (there were four different PIs on this study). The initial informed consents were adequately obtained and verified for all 66 subjects. Although regulatory violations were noted as described above, they do not impact primary safety and efficacy.

5. Alan Wynne/ 3008 Site 1066/ 4003 Site US10706

Dr. Wynne has been at the Cotton-O'Neill Diabetes Center since 2002. He also has a private practice.

Sterling IRB was the central IRB of record for both studies.

For Study 3008, there were 20 subjects screened and 17 subjects enrolled into the study (including five subjects that were transferred from another site); seven subjects completed the study. There were 20 subject records reviewed.

Source records were compared to the data line listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

For Study 4003, there were 54 subjects screened and 48 subjects enrolled into the study; 38 subjects completed the study. There were 21 subject records reviewed.

Source records were compared to the data line listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Susan Thompson, M.D. for
Janice Pohlman, M.D., M.P.H, Team Leader and
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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cc:

Central Doc. Rm./ NDA 204042s027; NDA 204353/s025; NDA 205879/s007
DMEP/Division Director/ Mary Thanh-Hai
DMEP /Deputy Director/Jim P. Smith
DMEP/Team Lead/Lisa B. Yanoff
DMEP/Clinical Reviewer/ Hyon J. Kwon
DMEP /Regulatory Project Manager/Elizabeth Godwin
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Janice Pohlman
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OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

CYNTHIA F KLEPPINGER
06/11/2018

SUSAN D THOMPSON
06/11/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 5, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	204042/S-027 204353/ S-025 205879/S-007
Product Name and Strength:	Invokana (canagliflozin), tablet, 100 mg and 300 mg Invokamet (canagliflozin and metformin), tablet, 50 mg/500 mg, 50 mg/1,000 mg, and 150 mg/1,000 mg Invokamet XR (canagliflozin and metformin extended release), tablet, 50 mg/500 mg, 50 mg/1,000 mg, and 150 mg/1,000 mg
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
Submission Date:	September 29, 2017
OSE RCM #:	2017-2035
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised prescribing information (PI) and medication guides for Invokana (canagliflozin), Invokamet (canagliflozin and metformin), and Invokamet XR (canagliflozin and metformin extended release) to determine if they are acceptable from a medication error perspective.

Janssen submitted an efficacy supplement for a new indication and revised labeling for Invokana, Invokamet, and Invokamet XR on September 29, 2017. They propose to add the following as the new indication: to reduce the risk of major adverse cardiovascular events (b) (4) in adults with type 2 diabetes mellitus who have established cardiovascular disease (b) (4)

Thus, they have proposed changes to the prescribing information (Highlights of Prescribing Information-Indications and Usage and Warnings and Precautions sections; Full Prescribing Information- Section 1 Indications and Usage, Section 5 Warnings and Precautions, Section 6 Adverse Reactions, Section 8 Use in Specific Populations, Section 12 Clinical Pharmacology, and Section 14 Clinical Studies) and the Medication Guide.

2 CONCLUSION

We defer to the review team for analysis of the proposed changes to the various sections of the prescribing information. The revised prescribing information and medication guide for Invokana, Invokamet, and Invokamet XR are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. PRESCRIBING INFORMATION AND MEDICATION GUIDES REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Invokana, Invokamet, and Invokamet XR labeling submitted by Janssen on September 29, 2017.

- Invokana (NDA 204042)
  \\cdsesub1\evsprod\nda204042\0212\m1\us\draft-labeling-text-cvd.docx

- Invokamet (NDA 204353)
  \\cdsesub1\evsprod\nda204353\0149\m1\us\draft-labeling-text-cvd.docx

- Invokamet XR (NDA 205879)
  \\cdsesub1\evsprod\nda205879\0046\m1\us\draft-labeling-text-cvd.docx

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARIANE O CONRAD
02/05/2018

HINA S MEHTA
02/07/2018

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 204042/S- 027

Application Type: Efficacy Supplement

Drug Name/Dosage Form: Invokana (canagliflozin) tablets

Applicant: Janssen Pharmaceutical

Receipt Date: September 29, 2017

Goal Date: July 29, 2018

1. Regulatory History and Applicant's Main Proposals

Invokana (canagliflozin) tablet is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The original New Drug Application (NDA) for Invokana (NDA 204042) was approved on March 29, 2013.

On September 29, 2017, Janssen submitted a new efficacy (SE-1) supplement application to NDA 204042 (Invokana) to propose a new indication based on the results of the cardiovascular safety (CANVAS program) studies 28431754DIA3008, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo- Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus," (CANVAS) and 28431754DIA4003, entitled, "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type2 Diabetes Mellitus," (CANVAS-R).

The proposed indication is to reduce the risk of major adverse cardiovascular events (b) (4) in adults with type 2 diabetes mellitus who have established cardiovascular disease (b) (4)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

N/A 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *A waiver has been granted previously for the length of the HL section.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment: *Contraindications are listed*

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH R GODWIN
11/29/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204042 SUPPL # 27 HFD # 510

Trade Name Invokana

Generic Name canagliflozin

Applicant Name Janssen Pharmaceuticals, Inc.

Approval Date, If Known October 29, 2018

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 204042 Invokana (canagliflozin)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to

clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. Protocol 28431754DIA3008, “A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus” The CANVAS Trial (CANagliflozin cardioVascular Assessment Study)

2. Protocol 28431754DIA4003, “A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus” The “CANVAS-R” Trial (CANagliflozin cardioVascular Assessment Study-Renal)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (DIA3008) YES ☐ NO ☒

Investigation #2 (DIA4003) YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such

investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	(DIA3008)	YES ☐	NO ☒
Investigation #2	(DIA4003)	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Protocol 28431754DIA3008, “A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus” The CANVAS Trial (CANagliflozin cardioVascular Assessment Study)

2. Protocol 28431754DIA4003, “A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus” The “CANVAS-R” Trial (CANagliflozin cardioVascular Assessment Study-Renal)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (DIA3008)		!
		!
IND # 076479	YES ☒	! NO ☐
		! Explain:

Investigation #2 (DIA4003)		!
		!
IND # 076479	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

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Name of person completing form: Elizabeth Godwin
Title: Regulatory Project Manager
Date: 10/29/2018

Name of Division Director signing form: William Chong, MD
Title: Director (Acting)
Signed by Lisa Yanoff MD, Deputy Director (Acting), on behalf of Dr. Chong

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELIZABETH R GODWIN
10/29/2018

LISA B YANOFF
10/29/2018
signing on behalf of Dr. William Chong