PRODUCT MONOGRAPH

PrINVOKANA®

canagliflozin tablets

100 mg and 300 mg as anhydrous canagliflozin

ATC Code: A10BK02
Other blood glucose lowering drugs, excl. insulins

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 100 mg and 300 mg	Lactose *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

Monotherapy
INVOKANA® (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: INVOKANA® (canagliflozin) is indicated for use in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with:

- metformin
- sulfonylurea (with or without metformin)
- pioglitazone with metformin
- metformin and sitagliptin
- insulin (with or without metformin)

when the therapy listed above, along with diet and exercise, does not provide adequate glycemic control (see CLINICAL TRIALS).

Add-On Combination in Patients with Established Cardiovascular Disease:
INVOKANA® is indicated as an adjunct to diet, exercise, and standard of care therapy 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).

Patients with Diabetic Nephropathy:
INVOKANA® is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of end-stage kidney disease, doubling of serum creatinine, and cardiovascular (CV) death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (>33.9 mg/mmol).

Geriatrics (≥65 years of age): Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA®, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. Reactions were more common in patients over 75 years of age and with the 300 mg daily (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). Smaller reductions in HbA1C with INVOKANA® relative to placebo were seen in patients 65 years and older, compared to younger patients (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

Pediatrics (<18 years of age): The safety and efficacy of INVOKANA® in pediatric patients under 18 years of age have not been established. Therefore, INVOKANA® should not be used in this population.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

- Patients on dialysis (see **DOSAGE and ADMINISTRATION**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Diabetic Ketoacidosis** Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with INVOKANA® and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Some cases of DKA have been fatal. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see **ADVERSE REACTIONS**).
- Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur regardless of blood glucose level, and INVOKANA® should be **discontinued immediately**.
- INVOKANA® should not be used for the treatment of DKA or in patients with a history of DKA.
- Nephropathy may increase the risk of DKA during treatment with INVOKANA.
- INVOKANA® is not indicated, and should not be used, in patients with type 1 diabetes.
- See **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism.**

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 INVOKANA®, 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 INVOKANA® if these complications occur.
- See **WARNINGS AND PRECAUTIONS**, **Cardiovascular**.

Cardiovascular

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 evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. In CANVAS, INVOKANA®-treated patients and placebo-treated patients had 5.9 and 2.8 amputations per 1000 patients per year, respectively. In CANVAS-R, INVOKANA®-treated patients and placebo-treated patients had 7.5 and 4.2 amputations per 1000 patients per year, respectively. 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 10 and 11, respectively (see **ADVERSE REACTIONS**).

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 and adequate hydration. 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.

Reduced Intravascular Volume: Due to its mechanism of action, INVOKANA® increases urinary glucose excretion (UGE) and induces an osmotic diuresis, which may reduce intravascular volume.

Patients most susceptible to adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, hypotension or renal failure) include patients with moderate renal impairment, elderly patients, patients on loop diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), and patients with low systolic blood pressure (see **ADVERSE REACTIONS, DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**). Before initiating INVOKANA® in patients with one or more of these characteristics, volume status should be assessed and any volume depletion corrected. Caution should also be exercised in other patients for whom a drop in blood pressure could pose a risk, such as patients with known cardiovascular disease. Monitor for signs and symptoms after

initiating therapy. Patients should be advised to report symptoms of reduced intravascular volume.

In placebo-controlled clinical studies of INVOKANA®, increases in adverse reactions related to reduced intravascular volume were seen more commonly with the 300 mg dose and occurred most frequently in the first three months (see **ADVERSE REACTIONS**).

INVOKANA® is not recommended for use in patients receiving loop diuretics (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**) or who are volume depleted.

In case of intercurrent conditions that may lead to volume depletion (such as a gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including renal function tests), and serum electrolytes is recommended. In the case of volume depletion, temporary interruption of treatment with canagliflozin may be considered until the condition is corrected, and more frequent glucose monitoring may be considered.

Endocrine and Metabolism

Diabetic ketoacidosis: Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors, including INVOKANA®. Some cases of DKA have been fatal. In a number of reported cases, the presentation of the condition was atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see **ADVERSE REACTIONS**).

INVOKANA® is not indicated, and should not be used, in patients with type 1 diabetes. The diagnosis of T2DM should therefore be confirmed before initiating INVOKANA®.

INVOKANA® should not be used for the treatment of DKA or in patients with a history of DKA.

DKA must be considered in the event of non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, unusual fatigue or sleepiness.

If these symptoms occur, regardless of blood glucose level, patients should discontinue INVOKANA® treatment and be assessed for diabetic ketoacidosis immediately.

SGLT2 inhibitors have been shown to increase blood ketones in clinical trial subjects. Conditions that can precipitate DKA while taking INVOKANA® include a very low carbohydrate diet (as the combination may further increase ketone body production), dehydration, high alcohol consumption and a low beta-cell function reserve. Patients with nephropathy may be more susceptible to DKA during treatment with SGLT2 inhibitors. Patients with these risk factors should be monitored closely. Caution should also be taken when reducing the insulin dose in patients requiring insulin (see **DOSAGE AND ADMINISTRATION**).

Consider interrupting treatment with INVOKANA® in T2DM patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illnesses.

Hypoglycemia in Add-on Therapy with other Antihyperglycemic Agents: When INVOKANA® was used as add-on therapy with insulin or an insulin secretagogue (e.g., sulfonylurea), the incidence of hypoglycemia was increased over that of placebo. Therefore, to lower the risk of hypoglycemia, a dose reduction of insulin or an insulin secretagogue may be considered (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C are seen with INVOKANA® treatment (see **ADVERSE REACTIONS**). LDL-C levels should be monitored.

Genitourinary

Genital Mycotic Infections: INVOKANA® increases the risk of genital mycotic infections, consistent with the mechanism of increased urinary glucose excretion. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections (see **ADVERSE REACTIONS**).

Urinary tract infections (including urosepsis and pyelonephritis): Treatment with INVOKANA® increases the risk for urinary tract infections (see **ADVERSE REACTIONS**). There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients treated with INVOKANA®.

Necrotizing fasciitis of the perineum (Fournier's gangrene): Post-marketing cases of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and potentially life threatening necrotizing infection requiring urgent surgical intervention, have been reported in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries and death.

Patients treated with INVOKANA® who present with pain or tenderness, erythema, or swelling in the genital or perineal area, with or without fever, or malaise should be evaluated for necrotizing fasciitis. If suspected, INVOKANA® should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Hematologic

Elevated Hemoglobin and Hematocrit: Mean hemoglobin and hematocrit increased in patients administered INVOKANA®, as did the frequency of patients with abnormally elevated values for hemoglobin/hematocrit (see **ADVERSE REACTIONS**). INVOKANA® should be used with caution in patients with an elevated hematocrit.

Immune

Hypersensitivity: Serious hypersensitivity reactions, including angioedema and anaphylaxis, have been reported post-market in patients treated with canagliflozin. If a hypersensitivity reaction is suspected, discontinue INVOKANA®, assess for other potential causes and initiate alternative treatment for diabetes (see **ADVERSE REACTIONS – Post-Market Adverse Drug Reactions**).

Musculoskeletal

Bone fractures: An increased risk of bone fractures, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Consider factors that contribute to fracture risk prior to initiating INVOKANA®.

Renal

Impairment of renal function: INVOKANA® increases serum creatinine and decreases eGFR in a dose dependent fashion. In clinical trials, renal function abnormalities have occurred after initiating INVOKANA®. Post-marketing cases of acute kidney injury, including acute renal failure and a decline in eGFR, some requiring hospitalization and dialysis, have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. 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 (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS**).

Renal function should be assessed prior to initiation of INVOKANA® and regularly thereafter. In patients with eGFR less than 60 mL/min/1.73m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended especially if the eGFR is less than 45 mL/min/1.73m^2.

The glucose-lowering benefit of INVOKANA® decreases with declining renal function and has not been demonstrated for patients with eGFR <30 mL/min/1.73 m^2.

In patients with type 2 diabetes already initiated on treatment for diabetic nephropathy, the use of INVOKANA® 100 mg can be continued in patients with an eGFR <30 mL/min/1.73 m^2. INVOKANA® 100 mg should be discontinued if dialysis is initiated (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women: INVOKANA® should not be used during pregnancy. There are no adequate and well-controlled studies in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights

and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose (see **TOXICOLOGY**).

Nursing Women: INVOKANA® should not be used during nursing because of the potential for serious adverse reactions in nursing infants. It is not known if canagliflozin is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin in the milk of lactating rats reaching levels which are approximately 1.4 times higher than plasma systemic exposure. Data in juvenile rats directly exposed to INVOKANA® showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatrics (<18 years of age): Safety and effectiveness of INVOKANA® in pediatric patients under 18 years of age have not been established. Therefore, INVOKANA® should not be used in this population.

Geriatrics (≥65 years of age): Two thousand thirty-four (2,034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA® in nine clinical studies of INVOKANA® (see **CLINICAL TRIALS**).

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; more prominent increase in the incidence was seen in patients who were 75 years and older (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**). Smaller reductions in HbA1C with INVOKANA® relative to placebo were seen in older patients (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).

Hepatic Impairment: INVOKANA® has not been studied in patients with severe hepatic impairment and is therefore not recommended for use in this patient population. No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Monitoring and Laboratory Tests

Blood Glucose and Hb_{A1c}: Response to INVOKANA® treatment should be monitored by periodic measurements of blood glucose and Hb_{A1c} levels. Due to its mechanism of action, patients taking INVOKANA® will test positive for glucose in their urine.

Renal function: Renal function should be assessed prior to initiation of INVOKANA® and regularly thereafter, with more frequent renal function monitoring in patients whose eGFR is <60 mL/min/1.73 m^2. Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Reduced intravascular volume: INVOKANA® is not recommended for use in patients who are volume depleted. Before initiating INVOKANA®, assess volume status, particularly in patients at risk (e.g., moderate renal impairment, the elderly, in patients with low systolic blood pressure,

or if on a loop diuretic, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker).

In patients with volume depletion, the condition should be corrected prior to initiation of INVOKANA® (see **DOSAGE AND ADMINISTRATION**).

For patients with risk factors for volume depletion or in case of intercurrent conditions that may lead to volume depletion (such as a gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including renal function tests), and serum electrolytes is recommended during treatment with INVOKANA®. Temporary interruption of treatment with INVOKANA® should be considered until volume depletion is corrected.

LDL-cholesterol: LDL-C levels should be measured at baseline and at regular intervals during treatment with INVOKANA® due to dose-dependent increases in LDL-C seen with therapy.

Digoxin levels: In patients taking digoxin and INVOKANA® 300 mg once daily for seven days, there was an increase in the total exposure (AUC) and peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively), therefore patients taking INVOKANA® concomitantly with digoxin should be monitored appropriately.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of INVOKANA® (canagliflozin) was evaluated in fifteen double-blind, controlled Phase 3 and Phase 4 clinical studies involving 22,645 patients with type 2 diabetes, including 13,278 patients treated with INVOKANA® 100 mg and 7,170 patients, treated with INVOKANA® 300 mg. Of the 22,645 patients with type 2 diabetes, a total of 10,134 patients were treated in two dedicated cardiovascular outcomes studies for a mean exposure duration of 149 weeks (223 weeks in CANVAS and 94 weeks in CANVAS-R), and 8,114 patients were treated in 12 double-blind, controlled Phase 3 and Phase 4 clinical studies, for a mean exposure duration of 49 weeks. In a dedicated renal outcomes study, a total of 4,397 patients with type 2 diabetes and diabetic nephropathy had a mean duration of drug exposure of 115 weeks.

The primary assessment of safety and tolerability was conducted in a pooled analysis (N=2313) of four 26-week placebo-controlled clinical studies (monotherapy and add-on therapy with metformin, metformin and sulfonylurea, and metformin and pioglitazone). The most commonly reported adverse reactions during treatment (≥5%) were vulvovaginal candidiasis, urinary tract infection (UTI), and polyuria or pollakiuria. Adverse reactions leading to discontinuation of ≥0.5% of all INVOKANA®-treated patients in these studies were vulvovaginal candidiasis (0.7% of females) and balanitis or balanoposthitis (0.5% of males).

A total of 8 serious adverse drug reactions were reported in the primary placebo-controlled safety population, including 5 reports from patients taking INVOKANA® 100 mg daily (2 urticaria, 2 UTI, and 1 nausea), 2 reports from patients taking INVOKANA® 300 mg daily (1 UTI, 1

constipation) and 1 report from a patient in the placebo group (reduced intravascular volume). Of these serious adverse reactions, 2 led to discontinuation in the INVOKANA® group (UTI and urticaria).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 to Table 8 include treatment-emergent adverse events (TEAEs) reported in ≥2% of INVOKANA®-treated patients.

Monotherapy (Study DIA3005)
The incidence of adverse events, reported regardless of causality in ≥2% of patients treated with INVOKANA® 100 mg or 300 mg and more frequently than in the placebo group, is provided in Table 1. The core assessment period was 26 weeks for this placebo-controlled study.

Table 1: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo group in a double-blind clinical trial (Study DIA3005) of INVOKANA® compared with placebo

System Organ Class / Preferred Term	**Placebo** **n=192** **n (%)**	**INVOKANA® 100 mg** **n=195** **n (%)**	**INVOKANA® 300 mg** **n=197** **n (%)**
Gastrointestinal Disorders			
Constipation	2 (1.0)	4 (2.1)	6 (3.0)
Nausea	3 (1.6)	5 (2.6)	4 (2.0)
General Disorders and Administration Site Conditions			
Thirst	1 (0.5)	3 (1.5)	6 (3.0)
Infections and Infestations			
Bronchitis	2 (1.0)	6 (3.1)	2 (1.0)
Gastroenteritis	3 (1.6)	2 (1.0)	4 (2.0)
Influenza	6 (3.1)	9 (4.6)	8 (4.1)
Nasopharyngitis	10 (5.2)	10 (5.1)	16 (8.1)
Pharyngitis	1 (0.5)	6 (3.1)	4 (2.0)
Urinary Tract Infection	8 (4.2)	14 (7.2)	9 (4.6)
Vulvovaginal Mycotic Infection	2 (1.0)	4 (2.1)	2 (1.0)
Investigations			
Blood Creatine Phosphokinase Increased	1 (0.5)	0	4 (2.0)
Musculoskeletal and Connective Tissue Disorders			
Back Pain	6 (3.1)	5 (2.6)	12 (6.1)
Musculoskeletal Pain	3 (1.6)	4 (2.1)	1 (0.5)
Nervous System Disorders			
Headache	7 (3.6)	14 (7.2)	12 (6.1)
Renal and Urinary Disorders			
Pollakiuria	1 (0.5)	5 (2.6)	6 (3.0)
Polyuria	0	0	6 (3.0)
Reproductive System and Breast Disorders			
Vulvovaginal Pruritus	0	1 (0.5)	4 (2.0)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	2 (1.0)	3 (1.5)	4 (2.0)

Combination with Metformin (Studies DIA3006 and DIA3009)

The incidence of adverse events, reported regardless of causality in ≥2% of patients treated with INVOKANA® 100 mg or 300 mg and more frequently than in the placebo groups, in studies of INVOKANA® as add-on combination therapy with metformin, is provided in Table 2. The core assessment period was 26 weeks for the placebo- and active-controlled study versus sitagliptin (DIA3006) and 52 weeks for the active-controlled study versus glimepiride (DIA3009).

Table 2: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo groups* in double-blind clinical trials of INVOKANA® in add-on combination use with metformin, and compared to sitagliptin or placebo (Study DIA3006) or to glimepiride (Study DIA3009)

	Study DIA3006 (26 weeks)				**Study DIA3009 (52 weeks)**		
System Organ Class / Preferred Term	**Placebo + Metformin n=183 n (%)**	**INVOKANA® 100 mg + Metformin n=368 n (%)**	**INVOKANA® 300 mg + Metformin N=367 n (%)**	**Sitagliptin 100 mg + Metformin n=366 n (%)**	**INVOKANA® 100 mg + Metformin n=483 n (%)**	**INVOKANA® 300 mg + Metformin n=485 n (%)**	**Glimepiride + Metformin n=482 n (%)**
Gastrointestinal Disorders							
Diarrhea	12 (6.6)	12 (3.3)	18 (4.9)	16 (4.4)	24 (5.0)	33 (6.8)	29 (6.0)
Gastritis	3 (1.6)	3 (0.8)	8 (2.2)	3 (0.8)	2 (0.4)	5 (1.0)	7 (1.5)
Nausea	3 (1.6)	11 (3.0)	8 (2.2)	5 (1.4)	16 (3.3)	25 (5.2)	13 (2.7)
Toothache	2 (1.1)	3 (0.8)	8 (2.2)	4 (1.1)	8 (1.7)	7 (1.4)	6 (1.2)
Vomiting	1 (0.5)	8 (2.2)	1 (0.3)	3 (0.8)	9 (1.9)	7 (1.4)	8 (1.7)
General Disorders and Administration Site Conditions							
Fatigue	2 (1.1)	10 (2.7)	8 (2.2)	1 (0.3)	9 (1.9)	7 (1.4)	10 (2.1)
Pyrexia	3 (1.6)	4 (1.1)	5 (1.4)	3 (0.8)	11 (2.3)	9 (1.9)	7 (1.5)
Thirst	0	2 (0.5)	4 (1.1)	0	8 (1.7)	14 (2.9)	0
Infections and Infestations							
Bronchitis	2 (1.1)	2 (0.5)	5 (1.4)	9 (2.5)	11 (2.3)	9 (1.9)	10 (2.1)
Gastroenteritis	2 (1.1)	3 (0.8)	3 (0.8)	2 (0.5)	3 (0.6)	15 (3.1)	9 (1.9)
Influenza	5 (2.7)	6 (1.6)	4 (1.1)	8 (2.2)	17 (3.5)	17 (3.5)	8 (1.7)
Sinusitis	3 (1.6)	8 (2.2)	2 (0.5)	6 (1.6)	7 (1.4)	13 (2.7)	6 (1.2)
Urinary Tract Infection	4 (2.2)	19 (5.2)	13 (3.5)	12 (3.3)	27 (5.6)	24 (4.9)	18 (3.7)
Vaginal Infection	0	2 (0.5)	3 (0.8)	1 (0.3)	11 (2.3)	7 (1.4)	1 (0.2)
Vulvovaginal Mycotic Infection	0	10 (2.7)	7 (1.9)	1 (0.3)	6 (1.2)	14 (2.9)	4 (0.8)
Musculoskeletal and Connective Tissue Disorders							
Back Pain	6 (3.3)	8 (2.2)	12 (3.3)	4 (1.1)	29 (6.0)	18 (3.7)	20 (4.1)
Musculoskeletal Pain	1 (0.5)	3 (0.8)	6 (1.6)	5 (1.4)	9 (1.9)	10 (2.1)	9 (1.9)
Psychiatric Disorders							
Insomnia	0	3 (0.8)	0	1 (0.3)	7 (1.4)	10 (2.1)	6 (1.2)
Renal and Urinary Disorders							
Pollakiuria	1 (0.5)	21 (5.7)	10 (2.7)	2 (0.5)	12 (2.5)	12 (2.5)	1 (0.2)
Reproductive System and Breast Disorders							
Balanoposthitis	1 (0.5)	2 (0.5)	1 (0.3)	0	4 (0.8)	13 (2.7)	2 (0.4)
Vulvovaginal Pruritus	0	4 (1.1)	5 (1.4)	1 (0.3)	6 (1.2)	20 (4.1)	1 (0.2)

*In either study

Combination with a Sulfonylurea (Study DIA3008 SU Substudy)

The incidence of adverse events, reported regardless of causality in ≥2% of patients treated with INVOKANA® 100 mg or 300 mg and more frequently than in the placebo group, in a study of INVOKANA® as add-on combination therapy with a sulfonylurea, is shown in Table 3. The core assessment period was 18 weeks for this placebo-controlled study.

Table 3: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo group in a double-blind clinical trial of INVOKANA® in add-on combination use with a sulfonylurea, and compared to placebo (Study DIA3008 - sulfonylurea substudy)

System Organ Class / Preferred Term	**Placebo + Sulfonylurea n=69 n (%)**	**INVOKANA® 100 mg + Sulfonylurea n=74 n (%)**	**INVOKANA® 300 mg + Sulfonylurea n=72 n (%)**
Gastrointestinal Disorders			
Diarrhea	1 (1.4)	0	2 (2.8)
General Disorders and Administration Site Conditions			
Chest Pain	0	2 (2.7)	1 (1.4)
Thirst	0	1 (1.4)	2 (2.8)
Infections and Infestations			
Herpes Zoster	0	0	2 (2.8)
Vulvovaginal Candidiasis	0	2 (2.7)	0
Investigations			
Blood Creatinine Increased	1 (1.4)	2 (2.7)	1 (1.4)
Nervous System Disorders			
Dizziness	0	2 (2.7)	0
Headache	1 (1.4)	2 (2.7)	1 (1.4)
Renal and Urinary Disorders			
Pollakiuria	1 (1.4)	1 (1.4)	3 (4.2)
Renal Impairment	0	1 (1.4)	2 (2.8)
Vascular Disorders			
Peripheral Arterial Occlusive Disease	0	0	2 (2.8)

Combination with a Metformin and a Sulfonylurea (Studies DIA3002 and DIA3015)

The incidence of adverse events, reported regardless of causality in ≥2% of patients treated with INVOKANA® 100 mg or 300 mg and more frequently than in the placebo groups, in studies of INVOKANA® as add-on combination therapy with metformin and a sulfonylurea, is provided in Table 4. The core assessment period was 26 weeks for the placebo-controlled study (DIA3002) and 52 weeks for the active-controlled study with sitagliptin (DIA3015).

Table 4: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo groups* in double-blind clinical trials of INVOKANA® in add-on combination use with metformin and a sulfonylurea, and compared to placebo (Study DIA3002) or sitagliptin (Study DIA3015)

	Study DIA3002 (26 weeks)			Study DIA3015 (52 weeks)	
System Organ Class / Preferred Term	**Placebo+ Metformin + Sulfonylurea n=156 n (%)**	**INVOKANA® 100 mg + Metformin + Sulfonylurea n=157 n (%)**	**INVOKANA® 300 mg + Metformin + Sulfonylurea N=156 n (%)**	**INVOKANA® 300 mg + Metformin + Sulfonylurea n=377 n (%)**	**Sitagliptin 100 mg+ Metformin + Sulfonylurea n=378 n (%)**
Ear and Labyrinth Disorders					
Vertigo	1 (0.6)	1 (0.6)	1 (0.6)	14 (3.7)	11 (2.9)
Gastrointestinal Disorders					
Abdominal Pain	1 (0.6)	2 (1.3)	1 (0.6)	8 (2.1)	6 (1.6)
Abdominal Pain Upper	2 (1.3)	1 (0.6)	1 (0.6)	10 (2.7)	2 (0.5)
Constipation	0	4 (2.5)	5 (3.2)	9 (2.4)	3 (0.8)
Diarrhea	5 (3.2)	5 (3.2)	10 (6.4)	17 (4.5)	26 (6.9)
Nausea	1 (0.6)	2 (1.3)	4 (2.6)	9 (2.4)	11 (2.9)
Infections and Infestations					
Bronchitis	3 (1.9)	4 (2.5)	3 (1.9)	1 (0.3)	11 (2.9)
Influenza	7 (4.5)	2 (1.3)	3 (1.9)	22 (5.8)	15 (4.0)
Nasopharyngitis	4 (2.6)	6 (3.8)	8 (5.1)	33 (8.8)	38 (10.1)
Sinusitis	3 (1.9)	4 (2.5)	2 (1.3)	8 (2.1)	8 (2.1)
Tooth Abscess	0	4 (2.5)	1 (0.6)	0	2 (0.5)
Upper Respiratory Tract Infection	10 (6.4)	17 (10.8)	6 (3.8)	33 (8.8)	21 (5.6)
Urinary Tract Infection	8 (5.1)	9 (5.7)	8 (5.1)	15 (4.0)	19 (5.0)
Vulvovaginal Mycotic Infection	2 (1.3)	8 (5.1)	8 (5.1)	12 (3.2)	5 (1.3)
Metabolism and Nutrition Disorders					
Decreased Appetite	1 (0.6)	0	4 (2.6)	4 (1.1)	5 (1.3)
Hypoglycemia	6 (3.8)	11 (7.0)	9 (5.8)	66 (17.5)	75 (19.8)
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	4 (2.6)	7 (4.5)	7 (4.5)	17 (4.5)	8 (2.1)
Back Pain	4 (2.6)	2 (1.3)	5 (3.2)	8 (2.1)	15 (4.0)
Musculoskeletal Pain	1 (0.6)	0	3 (1.9)	8 (2.1)	6 (1.6)
Nervous System Disorders					
Headache	4 (2.6)	5 (3.2)	2 (1.3)	29 (7.7)	27 (7.1)
Renal and Urinary Disorders					
Pollakiuria	1 (0.6)	4 (2.5)	3 (1.9)	6 (1.6)	5 (1.3)
Reproductive System and Breast Disorders					
Vulvovaginal Pruritus	0	1 (0.6)	3 (1.9)	15 (4.0)	1 (0.3)

*In either study

Combination with Metformin and Pioglitazone (Study DIA3012)

The incidence of adverse events, reported regardless of causality in ≥2% of patients treated with INVOKANA® 100 mg or 300 mg and more frequently than in the placebo group, in a study of INVOKANA® as add-on combination therapy with metformin and pioglitazone, is provided in Table 5. The core assessment period was 26 weeks for this placebo-controlled study.

Table 5: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo group in a double-blind clinical trial of INVOKANA® in add-on combination use with metformin and pioglitazone, and compared to placebo (Study DIA3012)

System Organ Class / Preferred Term	**Placebo + Metformin+ Pioglitazone n=115 n (%)**	**INVOKANA® 100 mg + Metformin + Pioglitazone n=113 n (%)**	**INVOKANA® 300 mg + Metformin + Pioglitazone n=114 n (%)**
Gastrointestinal Disorders			
Gastritis	2 (1.7)	4 (3.5)	0
General Disorders and Administration Site Conditions			
Fatigue	2 (1.7)	1 (0.9)	4 (3.5)
Edema Peripheral	2 (1.7)	2 (1.8)	4 (3.5)
Thirst	0	5 (4.4)	4 (3.5)
Infections and Infestations			
Nasopharyngitis	6 (5.2)	6 (5.3)	11 (9.6)
Sinusitis	2 (1.7)	1 (0.9)	3 (2.6)
Upper Respiratory Tract Infection	7 (6.1)	9 (8.0)	5 (4.4)
Vulvovaginal Candidiasis	0	1 (0.9)	3 (2.6)
Vulvovaginal Mycotic Infection	0	3 (2.7)	6 (5.3)
Investigations			
Weight Decreased	1 (0.9)	1 (0.9)	3 (2.6)
Metabolism and Nutrition Disorders			
Hypoglycemia	2 (1.7)	1 (0.9)	6 (5.3)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	2 (1.7)	1 (0.9)	6 (5.3)
Back Pain	3 (2.6)	8 (7.1)	5 (4.4)
Pain in Extremity	1 (0.9)	4 (3.5)	3 (2.6)
Nervous System Disorders			
Dizziness	1 (0.9)	4 (3.5)	3 (2.6)
Headache	4 (3.5)	3 (2.7)	5 (4.4)
Renal and Urinary Disorders			
Pollakiuria	1 (0.9)	5 (4.4)	7 (6.1)
Reproductive System and Breast Disorders			
Balanitis	0	3 (2.7)	0
Respiratory, Thoracic and Mediastinal Disorders			
Oropharyngeal Pain	2 (1.7)	3 (2.7)	0
Vascular Disorders			
Hypotension	3 (2.6)	3 (2.7)	0

Combination with Metformin and Sitagliptin (Study DIA4004)

The incidence of adverse events, reported regardless of causality in ≥ 2% of patients treated with INVOKANA® and more frequently than in the placebo group, is provided in Table 6 below. The assessment period was 26 weeks for this placebo-controlled study.

Table 6. Adverse events (regardless of causality) reported in ≥ 2% of patients treated with INVOKANA® and more frequently than in the placebo group in a double-blind clinical trial of INVOKANA® in add-on combination use with metformin and sitagliptin, and compared to placebo (Study DIA4004)

System Organ Class / Preferred Term	**Placebo + Metformin+ Sitagliptin n=108 n (%)**	**INVOKANA®[1] + Metformin + Sitagliptin n=108[2] n (%)**
Musculoskeletal and Connective Tissue Disorders		
Back pain	1 (0.9)	3 (2.8)
Pain in Extremity	1 (0.9)	3 (2.8)
Psychiatric Disorders		
Depression	0	3 (2.8)

[1] 100 mg to 300 mg up-titration at Week 6

[2] 10 subjects did not up-titrate to canagliflozin 300 mg, 3 of whom completed Week 26

Combination with Insulin with or without Metformin (Study DIA3008 Insulin Substudy)

The incidence of adverse events, reported regardless of causality in ≥2% of patients treated with INVOKANA® 100 mg or 300 mg and more frequently than in the placebo group, in a study of INVOKANA® as add-on combination therapy with insulin is provided in Table 7,and as add-on combination therapy with insulin and metformin from the same study is provided in Table 8. The core assessment period was 18 weeks for this placebo-controlled study.

Table 7: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo group in a double-blind clinical trial of INVOKANA® in add-on combination use with insulin and compared to placebo (Study DIA3008 - Insulin Substudy)

System Organ Class / Preferred Term	Placebo + Insulin n=187 n (%)	INVOKANA® 100 mg + Insulin n=183 n (%)	INVOKANA® 300 mg + Insulin n=184 n (%)
Ear and labyrinth disorders			
Vertigo	2 (1.1)	2 (1.1)	5 (2.7)
Gastrointestinal disorders			
Abdominal pain upper	4 (2.1)	4 (2.2)	1 (0.5)
Constipation	3 (1.6)	4 (2.2)	2 (1.1)
Dry mouth	1 (0.5)	4 (2.2)	1 (0.5)
Nausea	2 (1.1)	5 (2.7)	3 (1.6)
General disorders and administration site conditions			
Asthenia	1 (0.5)	0	4 (2.2)
Fatigue	1 (0.5)	8 (4.4)	3 (1.6)
Infections and infestations			
Bronchitis	4 (2.1)	2 (1.1)	5 (2.7)
Influenza	1 (0.5)	4 (2.2)	2 (1.1)
Upper respiratory tract infection	6 (3.2)	8 (4.4)	5 (2.7)
Urinary tract infection	3 (1.6)	3 (1.6)	4 (2.2)
Investigations			
Blood creatinine increased	3 (1.6)	7 (3.8)	3 (1.6)
Blood urea increased	1 (0.5)	4 (2.2)	3 (1.6)
Metabolism and nutrition disorders			
Hypoglycemia	12 (6.4)	15 (8.2)	20 (10.9)
Musculoskeletal and connective tissue disorders			
Back pain	4 (2.1)	5 (2.7)	6 (3.3)
Osteoarthritis	3 (1.6)	4 (2.2)	0
Pain in extremity	1 (0.5)	0	5 (2.7)
Nervous system disorders			
Dizziness	2 (1.1)	0	4 (2.2)
Headache	4 (2.1)	6 (3.3)	4 (2.2)
Renal and urinary disorders			
Pollakiuria	0	7 (3.8)	7 (3.8)
Reproductive system and breast disorders			
Balanitis	0	3 (1.6)	4 (2.2)
Vulvovaginal pruritus	0	5 (2.7)	0
Skin and subcutaneous tissue disorders			
Rash	2 (1.1)	5 (2.7)	2 (1.1)
Vascular disorders			
Hypotension	0	5 (2.7)	8 (4.3)

Table 8: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA® and more frequently than in the placebo group in a double-blind clinical trial of INVOKANA® in add-on combination use with insulin and metformin, and compared to placebo (Study DIA3008 - Insulin Substudy)

System Organ Class / Preferred Term	Placebo + Insulin + Metformin n=244 n (%)	INVOKANA® 100 mg + Insulin + Metformin n=241 n (%)	INVOKANA® 300 mg + Insulin + Metformin n=246 n (%)
Gastrointestinal disorders			
Constipation	2 (0.8)	1 (0.4)	8 (3.3)
Diarrhea	7 (2.9)	4 (1.7)	14 (5.7)
Dyspepsia	0	2 (0.8)	5 (2.0)
Nausea	5 (2.0)	5 (2.1)	8 (3.3)
General disorders and administration site conditions			
Fatigue	4 (1.6)	6 (2.5)	8 (3.3)
Thirst	0	2 (0.8)	10 (4.1)
Infections and infestations			
Bronchitis	5 (2.0)	7 (2.9)	3 (1.2)
Nasopharyngitis	22 (9.0)	22 (9.1)	13 (5.3)
Urinary tract infection	4 (1.6)	3 (1.2)	10 (4.1)
Vulvovaginal mycotic infection	2 (0.8)	4 (1.7)	5 (2.0)
Metabolism and nutrition disorders			
Hypoglycemia	21 (8.6)	23 (9.5)	23 (9.3)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (1.2)	8 (3.3)	4 (1.6)
Back pain	5 (2.0)	3 (1.2)	13 (5.3)
Pain in extremity	4 (1.6)	7 (2.9)	6 (2.4)
Nervous system disorders			
Dizziness	0	1 (0.4)	6 (2.4)
Headache	7 (2.9)	8 (3.3)	7 (2.8)
Renal and urinary disorders			
Pollakiuria	1 (0.4)	7 (2.9)	18 (7.3)
Reproductive system and breast disorders			
Balanitis	1 (0.4)	7 (2.9)	9 (3.7)
Vascular disorders			
Hypertension	3 (1.2)	8 (3.3)	1 (0.4)

Less Common Clinical Trial Adverse Drug Reactions (<2%)[1]

Metabolism and nutrition disorders: dehydration[2]
Nervous system disorders: dizziness postural[2], syncope[2]
Skin and subcutaneous tissue disorders: rash[3], urticaria
Vascular disorders: hypotension[2], orthostatic hypotension[2]

Description of Selected Adverse Reactions

Diabetic ketoacidosis: Cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors, including INVOKANA®. In the on-treatment analysis of the CANVAS/CANVAS-R integrated dataset, the adjusted incidence rates of adjudicated diabetic ketoacidosis were 0.08 (0.2%, 14/5,790) and 0.01 (<0.1%, 1/4,344) per 100 subject-years, for the combined canagliflozin and the placebo groups, respectively. Some cases of DKA have been fatal. The risk of DKA during INVOKANA® treatment was greater in patients with eGFR <60 mL/min/1.73 m^2 than in patients with normal renal function or mild renal impairment. INVOKANA® is not indicated and should not be used in patients with type 1 diabetes. In a number of reported cases, the presentation of the condition was atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic nephropathy , on-treatment incidence rates of adjudicated events of DKA were 0.22 (0.5%, 11/2,200) and 0.02 (<0.1%, 1/2,197) per 100 patient-years with INVOKANA® 100 mg and placebo, respectively; of the 12 patients with DKA, 7 (6 on canagliflozin 100 mg and 1 on placebo) had an eGFR before treatment of 30 to < 45 mL/min/1.73m^2. Cases of DKA in the canagliflozin group occurred in the setting of an intercurrent illness requiring hospitalization (8 of 11 subjects), or with low beta cell function reserve (3 of 11 subjects).

Reduced intravascular volume: In the pooled analysis of the four 26-week, placebo-controlled studies, the incidence of all adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) was 1.2% for INVOKANA® 100 mg, 1.3% for INVOKANA® 300 mg, and 1.1% for placebo. The incidence of these adverse reactions with INVOKANA® treatment in the two active-controlled studies was similar to comparators.

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[1] Adverse drug reactions (ADRs) were identified based on a comprehensive assessment of biological plausibility, mechanism of action, dose dependence in incidence rate, time of onset, seriousness and consistency of findings across four, 26-week placebo-controlled Phase 3 clinical studies. Additional supportive safety analyses were conducted on a large pooled dataset from eight active- and placebo-controlled Phase 3 clinical studies.
[2] Related to reduced intravascular volume (see Adverse reactions related to reduced intravascular volume).
[3] Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular

In one of the dedicated long-term cardiovascular studies (CANVAS), where patients were generally older with a higher prevalence of comorbidities, the incidence rate of adverse reactions related to reduced intravascular volume were 2.34 with INVOKANA® 100 mg, 2.87 with INVOKANA® 300 mg, and 1.85 with placebo, events per 100 patient-years of exposure.

In the long-term renal outcomes trial, the incidence of hypotension was 2.8% in the INVOKANA 100 mg group and 1.5% in the placebo group.

To assess risk factors for these adverse reactions, a larger pooled analysis (N=12,441) of patients from 13 controlled Phase 3 and Phase 4 studies including both doses of INVOKANA® was conducted. In this pooled analysis, patients on loop diuretics, patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2), and patients ≥75 years of age had higher incidences of these reactions. For patients on loop diuretics, the incidence rates were 4.98 on INVOKANA® 100 mg and 5.67 on INVOKANA® 300 mg compared to 4.15 events per 100 patient-years of exposure in the control group. For patients with a baseline eGFR 30 to <60 mL/min/1.73 m^2, the incidence rates were 5.24 on INVOKANA® 100 mg and 5.35 on INVOKANA® 300 mg compared to 3.11 events per 100 patient-years of exposure in the control group. In patients ≥75 years of age, the incidence rates were 5.27 on INVOKANA® 100 mg and 6.08 on INVOKANA® 300 mg compared to 2.41 events per 100 patient-years of exposure in the control group (see **WARNINGS AND PRECAUTIONS**, **DOSING AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Hypoglycemia: In individual clinical trials (see **CLINICAL TRIALS**), episodes of hypoglycemia occurred at a higher rate when INVOKANA® was co-administered with insulin or sulfonylurea (Table 9 see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Table 9: Incidence of Hypoglycemia[1] 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 (%)][2]	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 (%)][2]	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 (%)][2]	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 (%)][2]	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 Metformin + Sitagliptin (26 weeks)	**Placebo + Metformin + Sitagliptin (N=108)**	**INVOKANA® [3] + Metformin + Sitagliptin (N=108)[4]**	
Overall [N (%)]	2 (1.9)	4 (3.7)	
Severe [N (%)][2]	0	0	
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 (%)][2]	14 (2.5)	10 (1.8)	16 (2.7)

[1] Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes (any glucose value ≤3.89 mmol/L) or severe hypoglycemic events in the intent-to-treat population.

[2] 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).

[3] 100 mg to 300 mg up-titration at Week 6

[4] 10 subjects did not up-titrate to canagliflozin 300 mg, 3 of whom completed Week 26

Genital mycotic infections: Vulvovaginal candidiasis (including vulvovaginitis and vulvovaginal mycotic infection) was reported in 10.4% and 11.4% of female patients treated with INVOKANA® 100 mg and INVOKANA® 300 mg, respectively, compared to 3.2% in placebo-treated female patients. Most reports of vulvovaginal candidiasis occurred during the first four months of treatment with canagliflozin. Among female patients taking INVOKANA®, 2.3% experienced more than one infection. Overall, 0.7% of all female patients discontinued INVOKANA® due to vulvovaginal candidiasis (see **WARNINGS AND PRECAUTIONS**).

Candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with INVOKANA® 100 mg and INVOKANA® 300 mg, respectively, compared to 0.6% in placebo-treated male patients. Among male patients taking INVOKANA®, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued INVOKANA® due to candidial balanitis or balanoposthitis. In uncircumcised males in a pooled analysis of 10 controlled studies, the incidence rate of phimosis was 0.56 events per 100 patient-years of exposure in patients treated with canagliflozin and 0.05 events per 100 patient-years in patients treated with comparator. In this pooled analysis, the incidence rate of circumcision was 0.38 events per 100 patient-years of exposure in male patients treated with canagliflozin compared to 0.10 events per 100 patients-years in male patients treated with comparator (see **WARNINGS AND PRECAUTIONS**).

In the CANVAS integrated dataset, the adjusted-incidence rates of any male mycotic genital infection were 3.17 and 0.96 per 100 patient-years in the combined canagliflozin and placebo groups, respectively.

Urinary tract infections: Urinary tract infections were more frequently reported for INVOKANA® 100 mg and 300 mg (5.9% versus 4.3%, respectively) compared to 4.0% with placebo. Most infections were mild to moderate with no increase in the occurrence of serious adverse events (see **WARNINGS AND PRECAUTIONS**). Subjects responded to standard treatments while continuing canagliflozin treatment. The incidence of recurrent infections was not increased with canagliflozin.

Falls: In the pool of all Phase 3 studies, the incidence rate of AEs coded as related to a fall was 7.3, 8.0, and 11.8 per 1000 patient years of exposure to comparator, INVOKANA® 100 mg, and INVOKANA® 300 mg, respectively.

Bone fractures: In a cardiovascular study (CANVAS) of 4,327 patients with established or at least two risk factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.59, 1.79, and 1.09 per 100 patient-years of follow up to INVOKANA® 100 mg, INVOKANA® 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy.

In a second cardiovascular study (CANVAS-R) of 5,807 patients with established or at least two risk factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.14 and 1.32 events per 100 patient-years of follow up to INVOKANA® and placebo, respectively.

In a long-term renal outcomes study (CREDENCE) of 4,397 patients with type 2 diabetes and diabetic nephropathy, the incidence rates of all adjudicated bone fracture were 1.18 and 1.21 events per 100 patient-years of follow-up for INVOKANA® 100 mg and placebo, respectively. In other type 2 diabetes studies with INVOKANA®, which enrolled a general diabetes population of 7,729 patients, the incidence rates of all adjudicated bone fracture were 1.18 and 1.08 events per 100 patient-years of follow up to INVOKANA® and control, respectively.

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). 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. 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%.

Photosensitivity: In the CANVAS outcome trials integrated dataset, the adjusted-incidence rates of photosensitivity adverse events were 1.03 (0.3%, 19/5790) and 0.26 (0.1%, 3/4344) events per 1,000 subject-years in the combined canagliflozin and the placebo groups, respectively. In a dataset from 12 other phase 3 or 4 trials (excluding the CANVAS outcome trials) that enrolled a diabetic population of 8114 patients, an imbalance in phototoxicity adverse events was not seen with INVOKANA® relative to control.

Skin ulcers and peripheral ischemia: In the pool of 8 clinical studies with 78 weeks of mean duration of exposure, skin ulcers occurred in 0.7%, 1.1%, and 1.5% of patients and peripheral ischemia occurred in 0.1%, 0.4%, and 0.2% of patients receiving comparator, INVOKANA® 100 mg, and INVOKANA® 300 mg, respectively. An imbalance in these events generally were seen within the first 24 weeks of treatment and occurred in patients with known or at high risk for atherosclerotic disease, longer duration of diabetes, presence of diabetic complications, and diuretic use. In the on-treatment analysis set of the CREDENCE renal outcomes trial, there was a higher incidence rate of adverse events of diabetic foot reported in the canagliflozin group compared with the placebo group: 8.47 (43 subjects) and 4.89 (24 subjects) per 1,000 subject-years, respectively.

Renal Cell Carcinoma: In the CANVAS outcome trials integrated dataset, the adjusted-incidence rates of any renal cell carcinoma adverse event were 0.62 (0.2%, 14/5790) and 0.21 (0.1%, 3/4344) per 1,000 subject-years in the canagliflozin and the placebo groups, respectively. Whether this numerical imbalance is related to INVOKANA® treatment is unknown.
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 evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The imbalance occurred as early as the first 26 weeks of therapy. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. The amputation data for CANVAS and CANVAS-R are shown in Table 10 and Table 11, respectively. See **WARNINGS AND PRECAUTIONS**, **Cardiovascular**.

Table 10: **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 11: 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.

In a datapool of patients from 12 other phase 3 or 4 trials (excluding CANVAS program) that enrolled a diabetic population of 8114 patients, the majority of which were without cardiovascular disease, no difference in lower limb amputation risk was observed on INVOKANA® relative to control.

The risk of lower limb amputations associated with the use of INVOKANA® 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively in CREDENCE, a long-term renal outcomes study of 4,397 patients with type 2 diabetes and diabetic nephropathy, with a mean follow-up duration of 136 weeks (see Table 12 and **WARNINGS AND PRECAUTIONS**).

Table 12: Lower limb amputations CREDENCE (On-study analysis)

	Placebo (N=2197)	**INVOKANA® 100 mg (N=2200)**
Patients with an amputation, n (%)	63 (2.9)	70 (3.2)
Total amputations	96	87
Amputation incidence rate (per 1000 patient-years)	11.2	12.3
Hazard Ratio (95% CI)	--	1.11 (0.79, 1.56)

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.

Adverse reactions in specific populations

Elderly patients: Compared to younger patients, patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA®, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. In particular, in patients ≥75 years of age, adverse reactions related to reduced intravascular volume occurred with incidence rates of 5.27, 6.08, and 2.41 events per 100 patient-years of exposure for INVOKANA® 100 mg, INVOKANA® 300 mg, and the control group, respectively. Decreases in eGFR (-3.41 and -4.67 mL/min/1.73 m^2) were reported with INVOKANA® 100 mg and 300 mg, respectively, compared to the control group (-4.15 mL/min/1.73 m^2) (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Patients with Moderate Renal Impairment

Patients with Type 2 Diabetes Mellitus and an eGFR 45 to <60 mL/min/1.73 m^2 Treated for Glycemic Control or for the Reduction of MACE : In a pooled analysis of patients (N=1087) with a baseline eGFR 45 to <60 mL/min/1.73 m^2, the incidence rates of adverse reactions related to reduced intravascular volume were 4.61 for INVOKANA® 100 mg and 4.37 with INVOKANA® 300 mg relative to 3.00 events per 100 patient-years of exposure for placebo (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Serum creatinine levels increased from baseline to end of treatment by 5.92 and 6.98 µmol/L for INVOKANA® 100 mg and 300 mg, respectively, relative to 7.03 µmol/L with placebo. Blood urea nitrogen (BUN) levels increased from baseline to end of treatment by 0.92 and 0.77 µmol/L for INVOKANA® 100 mg and 300 mg, respectively, relative to 0.57 µmol/L with placebo. The incidence rates of decreases in eGFR (<80 mL/min/1.73 m^2 and >30% decrease from baseline) at any time during treatment were 5.17, 6.62, and 5.82 events per 100 patient-years of exposure for INVOKANA® 100 mg, INVOKANA® 300 mg, and placebo, respectively. At the last post-baseline value, incidence rates for such decreases were 2.52 for patients treated with INVOKANA® 100 mg, 1.91 for patients treated with INVOKANA® 300 mg, and 3.20 events per 100 patient-years of exposure for placebo (see **WARNINGS AND PRECAUTIONS**).

The incidences of elevated serum potassium (>5.4 mEq/L and 15% above baseline) at any post-baseline value were 4.11 for INVOKANA® 100 mg, 4.33 for INVOKANA® 300 mg, and 3.8 events per 100 patient-years of exposure for placebo. Rare, more severe elevations were seen in patients with moderate renal impairment who had prior elevated potassium concentrations

and/or who were on multiple medications that reduce potassium excretion, such as potassium-sparing diuretics and angiotensin-converting-enzyme (ACE) inhibitors.

Serum phosphate changes from baseline to end of treatment were 0.00 and 0.02 mmol/L for INVOKANA® 100 mg and 300 mg, respectively, compared to 0.00 mmol/L for placebo. The incidence rates of elevated serum phosphate (>1.65 mmol/L and 25% above baseline) at any post-baseline value were 0.93 for INVOKANA® 100 mg, 1.15 for INVOKANA® 300 mg and 0.71 events per 100 patient-years of exposure for placebo.

Patients with Type 2 Diabetes Mellitus and an eGFR 30 to <60 mL/min/1.73 m^2 Treated for Diabetic Nephropathy:

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic nephropathy, the incidence rate for renal-related adverse events was lower in the canagliflozin 100-mg group compared with the placebo group (7.23 and 10.55 per 100 patient-years in INVOKANA® 100mg and placebo, respectively).

For the subset of patients with an eGFR before treatment of 45 to <60 mL/min/1.73m^2, the incidence rates of adverse reactions related to volume depletion were similar: 2.3 events per 100 patient-years for INVOKANA® 100 mg and 2.6 events per 100 patient-years of exposure for placebo. In the same study, for patients with an eGFR 30 to <45mL/min/1.73m^2 the incidence rate was higher for INVOKANA® 100 mg (4.9 events per 100 patient-years) than for placebo (2.6 events per 100 patient-years).

Clinical Chemistry and Hematology Findings

Laboratory values, described below, are derived from the pooled analysis of 26-week, placebo-controlled clinical studies unless otherwise noted.

Increases in serum potassium: Mean percent changes from baseline in blood potassium were 0.5% and 1.0% for INVOKANA® 100 mg and 300 mg, respectively, compared to 0.6% for placebo. Episodes of elevated serum potassium (>5.4 mEq/L and 15% above baseline) were seen in 4.4% of patients treated with INVOKANA® 100 mg, 7.0% of patients treated with INVOKANA® 300 mg, and 4.8% of patients treated with placebo.

In a trial in patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2), increases in serum potassium to >5.4 mEq/L and 15% above baseline were seen in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA® 100 mg, and INVOKANA® 300 mg, respectively. Elevations 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.

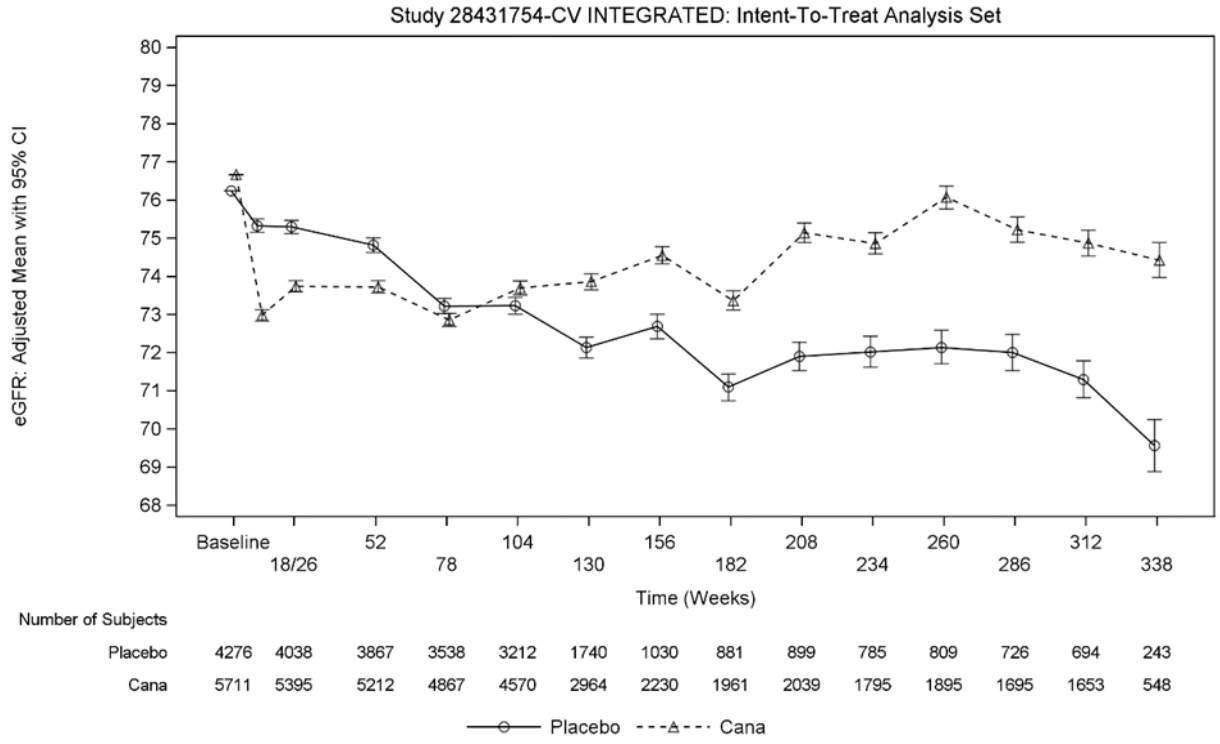
In a long-term renal outcomes study in patients with type 2 diabetes and diabetic nephropathy, no increase in adverse events of hyperkalemia, and no absolute (> 6.5mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with INVOKANA® 100 mg relative to placebo.

Increases in serum creatinine and blood urea nitrogen (BUN): Mean percent changes from baseline in creatinine, with commensurate decreases in eGFR, were 2.8% and 4.0% for INVOKANA® 100 mg and 300 mg, respectively, compared to 1.5% for placebo. Mean percent increases from baseline in BUN were 17.1% and 18.0% for INVOKANA® 100 mg and 300 mg, respectively, compared to 2.7% for placebo. These changes were generally observed within six weeks of treatment initiation. Subsequently, serum creatinine concentrations gradually trended toward baseline and BUN levels remained stable.

The proportion of patients with larger decreases in eGFR (>30%) from baseline, occurring at any time during treatment, was 2.0% with INVOKANA® 100 mg and 4.1% with INVOKANA® 300 mg relative to 2.1% with placebo. At study end, decreases of >30% from baseline were seen for 0.7% of subjects with INVOKANA® 100 mg, 1.4% with INVOKANA® 300 mg, and 0.5% with placebo (see **WARNINGS AND PRECAUTIONS**). After discontinuation of INVOKANA® therapy, these changes in laboratory values improved or returned to baseline.

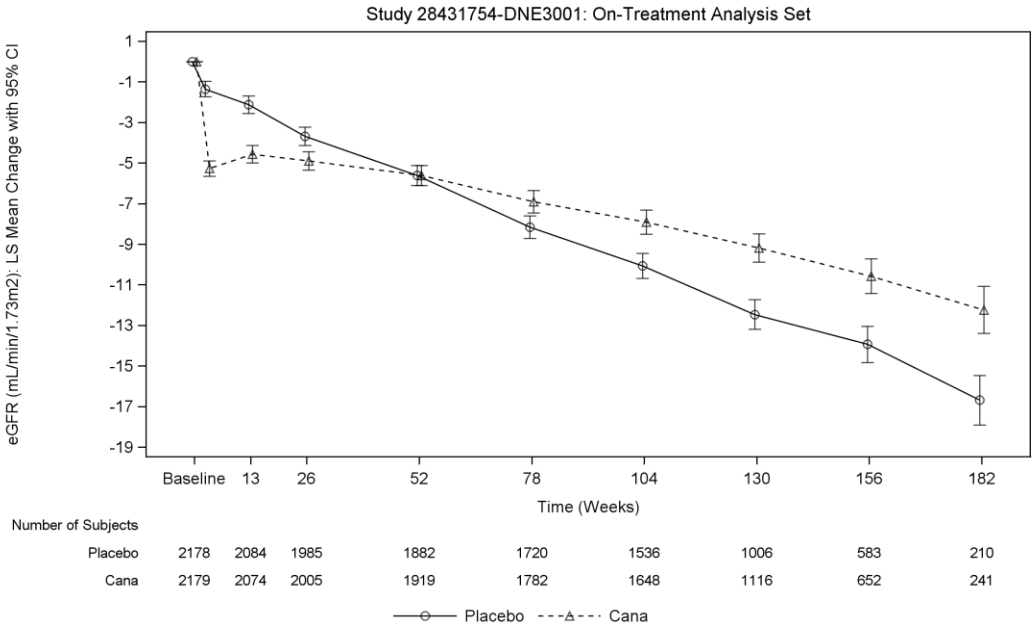
In an integrated analysis of data from two long-term cardiovascular outcome studies, patients treated with INVOKANA® experienced an initial fall in mean eGFR that thereafter stabilized (see Figure 1) whereas patients treated with placebo experienced a progressive decline in eGFR.

Figure 1: Adjusted mean eGFR over time



In a long-term renal outcomes trial, patients treated with INVOKANA® experienced an acute decrease in eGFR at Week 3, followed by an attenuated decline over time from week 3 to end of treatment. Placebo-treated patients demonstrated a progressive linear decline over time. After Week 52, the LS mean decrease in eGFR was smaller in the INVOKANA® 100 mg group than in the placebo group (Figure 2).

Figure 2: LS Mean Change From Baseline in eGFR Over Time (On-Treatment Analysis Set)



Lipid changes: Compared to placebo, mean increases from baseline in low density lipoprotein cholesterol (LDL-C) were 0.11 mmol/L (4.5%) and 0.21 mmol/L (8.0%) with INVOKANA® 100 mg and INVOKANA® 300 mg, respectively. Increases in total cholesterol of 0.12 mmol/L (2.5%) and 0.21 mmol/L (4.3%) were seen, relative to placebo, for INVOKANA® 100 mg and INVOKANA® 300 mg, respectively. Increases in non-HDL-C relative to placebo were 0.05 mmol/L (1.5%) and 0.13 mmol/L (3.6%) with INVOKANA® 100 mg and 300 mg, respectively. Increases in high-density lipoprotein cholesterol (HDL-C) were 0.06 mmol/L (5.4%), and 0.07 mmol/L (6.3%) relative to placebo for INVOKANA® 100 mg and INVOKANA® 300 mg, respectively. The LDL-C/HDL-C ratios did not change with either INVOKANA® dose compared to placebo.

Increases in hemoglobin: Mean hemoglobin concentration increased from baseline 4.7 g/L (3.5%) with INVOKANA® 100 mg and 5.1 g/L (3.8%) with INVOKANA® 300 mg, compared to a decrease of -1.8 g/L (-1.1%) with placebo. After 26 weeks of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA® 100 mg, and INVOKANA® 300 mg, respectively, had a hemoglobin level above the upper limit of normal.

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. Episodes of elevated serum phosphate (>1.65 mmol/L and 25% above baseline) were seen in 0.6% and 1.6% of patients treated with INVOKANA® 100 mg and 300 mg, respectively, compared to 1.3% of patients treated with placebo.

Decreases in serum urate: Moderate decreases in the mean percent change from baseline in serum urate were observed in the INVOKANA® 100 mg and 300 mg groups (-10.1% and -10.6%, respectively) compared with placebo, where a slight increase from baseline (1.9%) was observed. Decreases in serum urate in the INVOKANA® groups were maximal or near maximal by Week 6 and maintained with dosing. A transient increase in urinary uric acid excretion was seen, which was not persistent.

Electrolytes: The following changes from baseline to end of treatment in serum electrolytes were observed during INVOKANA® treatment in the CANVAS integrated database.

Table 13: Placebo-adjusted Mean Changes from Baseline in Electrolytes at Week 18 or 26[a] in the CANVAS program

Analyte [normal range, unit]	Baseline, mean (SE)	Placebo-corrected change from baseline at Week 18 or 26[a], mean (95%)	p-value
Sodium [135 – 145 mmol/L]			
INVOKANA®	139.3 (0.036)	0.40 (0.304; 0.496)	<0.001
Potassium [3.5 – 5.0 mmol/L]			
INVOKANA®	4.44 (0.006)	0.01 (-0.005; 0.028)	0.171
Magnesium [0.75 – 0.95 mmol/L]			
INVOKANA®	0.77 (0.001)	0.08 (0.074; 0.080)	<0.001
Bicarbonate [24 – 30 mmol/L]			
INVOKANA®	23.33 (0.036)	-0.41 (-0.504; -0.307)	<0.001
Phosphate [0.80-1.50 mmol/L]			
INVOKANA®	1.16 (0.002)	0.03 (0.028; 0.040)	<0.001
Calcium [2.07-2.64 mmol/L]			
INVOKANA®	2.41 (0.002)	0.02 (0.012, 0.020)	<0.001

[a] CANVAS study blood chemistries obtained at week 18, CANVAS-R study blood chemistries obtained at week 26
SE = standard error
ANCOVA for Week 18 or 26 includes the baseline electrolyte as a linear covariate, and treatment and study as fixed effects.

The following shifts from normal range at baseline to below or above the normal range at worst value on treatment were reported in the treated set in the CANVAS integrated database:

- Increases in serum sodium above the upper limit of normal occurred more frequently in patients receiving INVOKANA® than in those receiving placebo (2.63 per 100 subject years for INVOKANA® and 1.80 per 100 subject years for placebo).
- Decreases in serum magnesium below the lower limit of normal occurred more frequently in patients receiving placebo (0.65 per 100 subject years for INVOKANA® and 3.80 per 100

subject years for placebo), whilst increases in serum magnesium above the upper limit of normal occurred more frequently in patients receiving INVOKANA® than in those receiving placebo (1.25 per 100 subject years for INVOKANA® and 0.88 per 100 subject years for placebo).

- Decreases of serum bicarbonate below the lower limit of normal occurred more frequently in patients receiving INVOKANA® than in those receiving placebo (2.91 per 100 subject years for INVOKANA®, 2.39 per 100 subject years for placebo).
- Increases of serum phosphate above the upper limit of normal occurred more frequently in patients receiving INVOKANA® than in those receiving placebo (1.36 per 100 subject years for INVOKANA® and 1.00 per 100 subject years for placebo).

Post-Market Adverse Drug Reactions

Because these reactions were 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.

Gastrointestinal Disorders: pancreatitis acute

Metabolism and nutrition disorders: diabetic ketoacidosis

Immune system disorders: anaphylactic reaction

Skin and subcutaneous tissue disorders: angioedema

Renal and urinary disorders: acute kidney injury, including acute renal failure (with or without volume depletion)

Genitourinary: severe urinary tract infections; urosepsis and pyelonephritis

Musculoskeletal: bone fractures

Infections and Infestations: necrotizing fasciitis of the perineum (Fournier's gangrene)

DRUG INTERACTIONS

Overview

In vitro assessment of interactions
The metabolism of canagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 1A9 (UGT1A9) and 2B4 (UGT2B4).

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), Breast Cancer Resistance Protein (BCRP) and Multi-Drug Resistance-Associated Protein 2 (MRP2).

In vivo assessment of interactions
Specific clinical drug interaction studies were conducted to investigate the effects of co-administered drugs, inhibitors or inducers of the drug-metabolizing enzymes UGTs (1A9, 2B4), CYPs (3A4, 2C9) and transporters P-gp and MRP2 on canagliflozin pharmacokinetics. Clinical studies were also conducted to assess the inhibitory or induction effects of canagliflozin on the pharmacokinetics of the CYP (3A4, 2C9), P-gp, substrates and co-administered drugs (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug-Drug Interactions

Effects of other drugs on canagliflozin:
In clinical studies, the effects of other drugs on canagliflozin were assessed. Cyclosporin (P-gp inhibitor), hydrochlorothiazide, oral contraceptives (ethinyl estradiol and levonorgestrel), metformin, and probenecid (UGT, MRP2, OATP, OAT1 and OAT3 inhibitor) had no clinically relevant effect on the pharmacokinetics of canagliflozin.

Table 14: Effect of Co-administered Drugs on Systemic Exposure of Canagliflozin

Co-administered Drug	Dose of Co-administered Drug[1]	Dose of Canagliflozin[1]	Geometric Mean Ratio (Ratio With/Without Co-administered Drug) No Effect = 1.0		Clinical Comment
			AUC[2] (90% CI)	C_{max} (90% CI)	
Cyclosporin	400 mg	300 mg once daily for 8 days	1.23 (1.19; 1.27)	1.01 (0.91; 1.11)	No dosage adjustment for INVOKANA® required
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)	No dosage adjustment for INVOKANA® required
Hydrochlorothiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)	No dosage adjustment for INVOKANA® required
Metformin	2000 mg	300 mg once daily for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)	No dosage adjustment for INVOKANA® required
Probenecid	500 mg twice daily for 3 days	300 mg once daily for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)	No dosage adjustment for INVOKANA® required
Inducers of UGT enzymes / drug transporters					
Rifampin	600 mg once daily for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)	Consider increasing the INVOKANA® dose to 300 mg once daily if patients are currently tolerating INVOKANA® 100 mg once daily (refer to **DOSAGE AND ADMINISTRATION**).
Phenytoin, phenobarbital, barbiturates, carbamazepine, ritonavir, efavirenz, or St. John's Wort	N/A[3]				Consider increasing the INVOKANA® dose to 300 mg once daily if patients are currently tolerating INVOKANA® 100 mg once daily (refer to **DOSAGE AND ADMINISTRATION**).

[1] Single dose unless otherwise noted
[2] AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
[3] N/A = Not applicable

Effects of canagliflozin on other drugs:
Canagliflozin at steady-state had no clinically relevant effect on the pharmacokinetics of metformin, oral contraceptives (ethinyl estradiol and levonorgestrel-CYP3A4 substrates), glyburide (CYP2C9 substrate), simvastatin (CYP3A4 substrate), acetaminophen, hydrochlorothiazide, or warfarin (CYP2C9 substrate), in healthy subjects.

Inhibition of BCRP by canagliflozin cannot be excluded at an intestinal level and increased exposure may therefore occur for drugs transported by BCRP, e.g., certain statins like rosuvastatin and some anti-cancer agents.

Table 15: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	Dose of Co-Administered Drug[1]	Dose of Canagliflozin[1]	Geometric Mean Ratio (Ratio With/Without Co-Administered Drugs) No Effect = 1.0			Clinical Comment
				AUC[2] (90% CI)	C_{max} (90% CI)	
Digoxin	0.5 mg once daily first day followed by 0.25 mg once daily for 6 days	300 mg once daily for 7 days	Digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)	Patients taking INVOKANA® with concomitant digoxin should be monitored appropriately
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)	No dosage adjustment required for ethinyl estradiol and levonorgestrel
			Levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)	
Glyburide	1.25 mg	200 mg once daily for 6 days	Glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)	No dosage adjustment required for glyburide
			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)	
Hydrochloro-thiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)	No dosage adjustment required for hydrochlorothiazide
Metformin	2000 mg	300 mg once daily for 8 days	Metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)	No dosage adjustment required for metformin
Acetaminophen	1000 mg	300 mg twice daily for 25 days	Acetaminophen	1.06[3] (0.98; 1.14)	1.00 (0.92; 1.09)	No dosage adjustment required for acetaminophen

Table 15: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	Dose of Co-Administered Drug[1]	Dose of Canagliflozin[1]	Geometric Mean Ratio (Ratio With/Without Co-Administered Drugs) No Effect = 1.0			Clinical Comment
				AUC[2] (90% CI)	C_{max} (90% CI)	
Simvastatin	40 mg	300 mg once daily for 7 days	Simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)	No dosage adjustment required for simvastatin
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)	
Warfarin	30 mg	300 mg once daily for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)	No dosage adjustment required for warfarin
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)	

[1] Single dose unless otherwise noted
[2] AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses.
[3] AUC_{0-12h}

Pharmacodynamic Interactions

Diuretics: INVOKANA® is not recommended for use in patients receiving loop diuretics. INVOKANA® may add to the effect of diuretics and may increase the risk of hypovolemia and hypotension (see **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

St John's Wort (*Hypericum perforatum*) is a CYP3A4 inducer and co-administration with INVOKANA® may result in loss of efficacy or reduced clinical response. Dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION**).

Drug-Laboratory Interactions

Due to its mechanism of action, patients taking INVOKANA® will test positive for glucose in their urine.

Increases in urinary glucose excretion with INVOKANA® can falsely lower 1,5-anhydroglucitol (1,5 AG) levels and make measurements of 1,5 AG unreliable in assessing glycemic control. Therefore, 1,5-AG assays should not be used for assessment of glycemic control in patients on

canagliflozin. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

Drug-Lifestyle Interactions

Effects on Ability to Drive and Use Machines: The effect of canagliflozin on the ability to drive and use machines has not been examined. However, patients should be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness, and to the risk of hypoglycemia when INVOKANA® is used as add-on therapy with insulin or an insulin secretagogue (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Prior to Initiation of INVOKANA

Assess renal function before initiating INVOKANA® and periodically thereafter (see **WARNINGS AND PRECAUTIONS**). In patients with volume depletion not previously treated with canagliflozin, normalize volume status before initiating INVOKANA® (see **WARNINGS AND PRECAUTIONS**).

Recommended Dosage and Dose Adjustments

See Table 16 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 16 Recommended Dosage

Estimated glomerular filtration rate eGFR (mL/min/1.73 m^2)	**Recommended Dosage**
eGFR ≥ 60	100 mg orally once daily, taken before the first meal of the day. Dose can be increased to 300 mg once daily for additional glycemic control
eGFR 30 to < 60	100 mg once daily
On dialysis	Contraindicated (see **CONTRAINDICATIONS**)

There are insufficient data to support dosing recommendations for initiation of therapy in patients with an eGFR < 30 mL/min/1.73 m^2. In patients already initiated on therapy who meet the criterion of an eGFR < 30 mL/min/1.73 m^2 with albuminuria greater than >33.9 mg/mmol, therapy can be continued at 100 mg once daily.

Dosing Considerations

Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea): When INVOKANA® is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia (see **WARNINGS AND PRECAUTIONS** and **ADVERSE**

REACTIONS).

Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers: If an inducer of UGTs and drug transport systems (e.g., rifampin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz, St John's wort [*Hypericum perforatum*]) is co-administered with INVOKANA®, monitor A1C in patients receiving INVOKANA® 100 mg once daily and consider increasing the dose to 300 mg once daily in patients currently tolerating INVOKANA® 100 mg once daily with an eGFR ≥60 mL/min/1.73 m^2 or CrCl ≥60 mL/min and require additional glycemic control. 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.

Diuretics: INVOKANA® is not recommended for use in patients on loop diuretics.

Geriatrics (≥65 years of age): Renal function and risk of volume depletion should be taken into account. For those patients who are tolerating INVOKANA® 100 mg and who need more glycemic control, the dose can be increased to INVOKANA® 300 mg (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**) See **Renal Impairment**.

Pediatrics (<18 years of age): The safety and efficacy of INVOKANA® have not been established in pediatric patients. Therefore, INVOKANA® should not be used in this population.

Hepatic Impairment: INVOKANA® has not been studied in patients with severe hepatic impairment and is therefore not recommended for use in this patient population. No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

INVOKANA® (canagliflozin) should be taken orally once a day, preferably before the first meal of the day, due to the potential to reduce postprandial plasma glucose excursions through delayed intestinal glucose absorption. However, INVOKANA® may be taken with or without food. Tablets are to be swallowed whole.

Missed Dose

If a dose of INVOKANA® is missed, the patient should be advised to take one dose as soon as they remember and the next dose at the usual time. A double dose of INVOKANA® should not be taken on the same day.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of an overdose, contact the Poison Control Centre. 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.

ACTION AND CLINICAL PHARMACOLOGY

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. Patients with diabetes have been shown to have elevated renal glucose reabsorption which may contribute to persistent elevated glucose concentrations. Canagliflozin is an orally-active 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, which decreases elevated plasma glucose concentrations by an insulin-independent mechanism in patients with type 2 diabetes. The increased urinary glucose excretion with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in urinary glucose excretion results in a loss of calories and therefore a reduction in body weight, as demonstrated in studies of patients with type 2 diabetes.

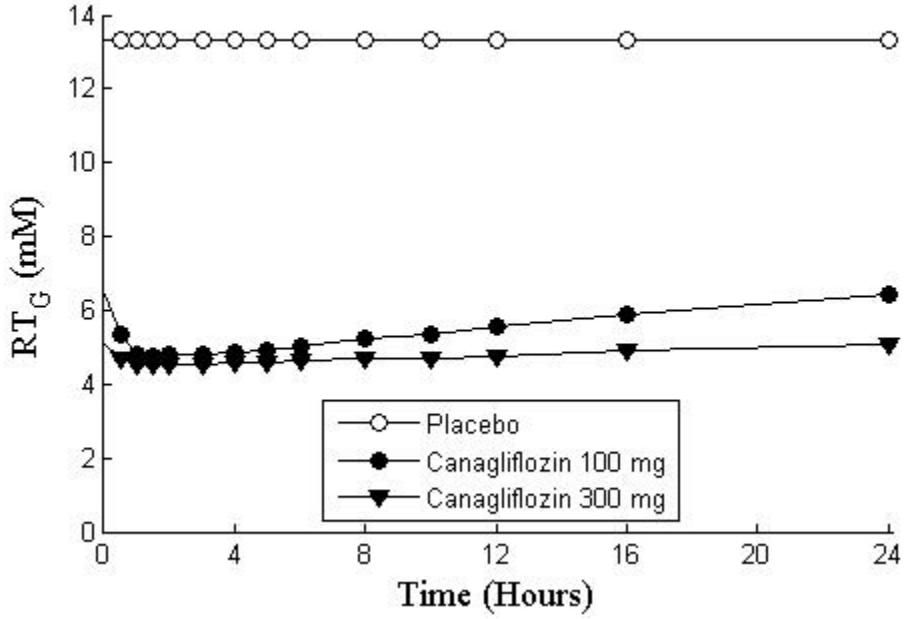
Canagliflozin's action to increase UGE directly lowering plasma glucose is independent of insulin. Improvement in homeostasis model assessment for beta-cell function (HOMA beta-cell) and improved beta-cell insulin secretion response to a mixed-meal challenge has been observed in clinical studies with INVOKANA®.

In Phase 3 studies, pre-meal administration of canagliflozin 300 mg provided a greater reduction in post-meal glucose excursion than observed with the 100 mg dose. This effect at the 300 mg dose of canagliflozin may, in part, be due to local inhibition of intestinal SGLT1 (an important intestinal glucose co-transporter) related to transient high concentrations of canagliflozin in the intestinal lumen prior to drug absorption (canagliflozin is a low potency inhibitor of SGLT1). Studies have shown no glucose malabsorption with canagliflozin.

Pharmacodynamics

Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in urinary glucose excretion were observed. From a starting value of RT_G of approximately 13 mmol/L, maximal suppression of 24-hour mean RT_G was seen with the 300 mg daily dose to approximately 4 to 5 mmol/L in patients with type 2 diabetes in Phase 1 studies (see model in Figure 3, suggesting a low risk for treatment-induced hypoglycemia. The reductions in RTG led to increased UGE in subjects with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin ranging from 77 to 119 g/day across the Phase 1 studies; the UGE observed translates to a loss of 308 to 476 kcal/day. The reductions in RT_G and increases in UGE were sustained over a 26-week dosing period in patients with type 2 diabetes. Moderate increases (generally <400-500 mL) in daily urine volume were seen that attenuated over several days of dosing. Urinary uric acid excretion was transiently increased by canagliflozin (increased by 19% compared to baseline on day 1 and then attenuating to 6% on day 2 and 1% on day 13). This was accompanied by a sustained reduction in serum uric acid concentration of approximately 20%.

Figure 3: Predicted (PK/PD Modelled) 24-Hour Profile for RT_G in Subjects with Type 2 Diabetes Treated with Canagliflozin 100 mg and 300 mg



In a single-dose study in patients with type 2 diabetes, treatment with 300 mg before a mixed meal delayed intestinal glucose absorption and reduced postprandial glucose through both renal and non-renal mechanisms.

Cardiac electrophysiology

In a randomized, double-blind, placebo-controlled, active-comparator, 4-way crossover study, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QT_c interval were observed with either the recommended dose of 300 mg or the 1200 mg dose. At the 1200 mg dose, peak canagliflozin plasma concentrations were approximately 1.4 times the steady-state peak concentrations following a 300 mg once-daily dose.

Pharmacokinetics

Pharmacokinetics of INVOKANA® were comparable between healthy volunteers and type 2 diabetic patients based on clinical trials and population pharmacokinetic data. After single-dose oral administration of 100 mg and 300 mg in healthy subjects, canagliflozin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 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 ($t_{1/2}$) (expressed as mean ± standard deviation) was 10.6 ± 2.13 hours to 13.1 ± 3.28 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.

Table 17: Summary of Canagliflozin's Pharmacokinetic Parameters in Healthy Subjects and T2DM Patients at Steady State

	N	C_{max} (SD) (ng/mL)	$t_{1/2}$ (h)	AUC_{24h} (SD) (ng.h/mL)	Cl/F	Vd/F
	Healthy Volunteers[a]					
100 mg multiple oral doses qd	9	1,118 (143)	13.3 (4.8)	6,056 (959)	16.4 (2.16)	304 (79.7)
300 mg multiple oral doses qd	9	3,379 (728)	13.5 (3.2)	19,252 (5,348)	16.4 (3.60)	319 (104)
	T2DM Patients[b]					
100 mg multiple oral doses qd	8	1,227 (481)	13.7 (2.1)	8,225 (1,947)	13.0 (4.43)	250 (50.7)
300 mg multiple oral doses qd	10	4,678 (1,685)	14.9 (4.8)	30,995 (11,146)	11.3 (5.21)	226 (89.4)

[a] From Study DIA1030
[b] From Study DIA1023

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® preferably be taken before the first meal of the day (see **DOSAGE AND ADMINISTRATION**).

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 faeces 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 for the 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min.

Canagliflozin is a low-clearance drug, with a mean systemic clearance of approximately 192 mL/min in healthy subjects following intravenous administration.

Special Populations and Conditions

Pediatrics: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of canagliflozin in pediatric patients <18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see **WARNING AND PRECAUTIONS**, Pediatrics).

An open-label, sequential, multiple-dose, multicentre pediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥11 to < 18 years of age (mean age 14.6 years) with type 2 diabetes mellitus who were on a stable dose of metformin. The mean body weight was 107.15 kg (range: 48.5 to 168.6 kg).

The patients were treated with canagliflozin once-daily 100 mg or 300 mg for 14 days.

Table 18 Mean (SD) Plasma Canagliflozin Pharmacokinetic Parameters on Day 14

Parameters	**Canagliflozin 100 mg QD (N=8) Mean (Std. Dev.)**	**Canagliflozin 300 mg QD (N=9) Mean (Std. Dev.)**
C_{max} (ng/mL)	951 (429)	3,260 (1,330)
AUC (h*ng/mL)	6,190 (1,770)	28,392 (12,412)
$t_{1/2}$ (h)	11.3 (2.5)	15.2 (6.9)
CLss/F (L/h)	17.5 (5.78)	12.3 (6.90)

Geriatrics (≥65 years of age): Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis. However, patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA® (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Body weight: For subjects with body weight <78.2 kg, the dose normalized exposures of INVOKANA® increased by 33%, based on population pharmacokinetic analysis. These increases in exposures are not clinically meaningful and hence no dosage adjustment of INVOKANA® is necessary based on body weight.

Gender: Dose normalized exposures of INVOKANA® in females were 22% higher than males, based on population pharmacokinetic analysis. These increases in exposures are not clinically meaningful and hence no dosage adjustment of INVOKANA® is necessary based on gender.

Race: Dose normalized exposures of INVOKANA® were comparable in white and non-white subjects, Blacks, Asians, and other races. A population PK analysis of canagliflozin in 942 white subjects and 674 non-white subjects showed no significant impact of race on canagliflozin PK and hence no dosage adjustment of INVOKANA® is necessary based on race.

Hepatic Insufficiency: 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. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment and, therefore, INVOKANA® is not recommended for use in this patient population.

Renal Insufficiency: A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment, classified using the Modification of Diet in Renal Disease (MDRD)-eGFR formula, compared to healthy subjects. The study included 3 subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2), 10 subjects with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2), 9 subjects with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2), and 10 subjects with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2) as well as 8 subjects with end stage renal disease (ESRD) on hemodialysis.

The C_{max} of canagliflozin was moderately increased by 13%, 29%, and 29% in subjects with mild, moderate, and severe renal failure, respectively, but not in subjects on hemodialysis. Compared to healthy subjects, plasma AUC of canagliflozin was increased by approximately 17%, 63%, and 50% in subjects with mild, moderate, and severe renal impairment, respectively, but was similar for ESRD subjects and healthy subjects. Increases in canagliflozin AUC of this magnitude are not considered clinically relevant, however, the pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). Canagliflozin was negligibly removed by hemodialysis.

Genetic polymorphism: Both UGT1A9 and UGT2B4 are subject to genetic polymorphism. In a pooled analysis of clinical data, increases in canagliflozin AUC of 26% were observed in UGT1A9*1/*3 carriers and 18% in UGT2B4*2/*2 carriers. These increases in canagliflozin exposure are not expected to be clinically relevant and no dosage adjustment is necessary based on UGT1A9 and UGT2B4 genetic polymorphisms. The effect of being homozygote (UGT1A9*3/*3, frequency <0.1%) is probably more marked, but has not been investigated.

STORAGE AND STABILITY

INVOKANA® tablets should be stored at 15-30°C.

SPECIAL HANDLING INSTRUCTIONS

Keep INVOKANA® out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INVOKANA® is supplied as film-coated, immediate-release tablets for oral administration. Each tablet strength contains canagliflozin drug substance as the hemihydrate equivalent to 100- and 300-mg doses of anhydrous canagliflozin, respectively. Both tablet strengths are supplied as blisters in cartons of 30 or 90.

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

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

Composition

Each tablet contains the following non-medicinal ingredients:

Core Tablet: croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose.

Film Coat: iron oxide yellow (100 mg tablet only), Macrogol (polyethylene glycol), polyvinyl alcohol, talc, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: canagliflozin

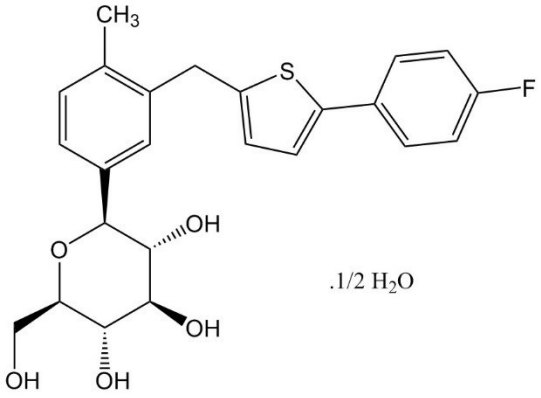
Chemical name: (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

Molecular formula: $C_{24}H_{25}FO_5S \bullet 1/2\ H_2O$

Molecular mass:

- Hemihydrate: 453.53
- Anhydrous: 444.52

Structural formula:



Physicochemical properties: Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9. There is no detectable pK_a value for this substance.

CLINICAL TRIALS

INVOKANA® was studied as monotherapy in one placebo-controlled study of 26 weeks duration, which included an active-treatment substudy in patients with more severe hyperglycemia (HbA1C [A1C] >10 and ≤12%). Six placebo- or active-controlled studies investigated INVOKANA® as add-on therapy with other antihyperglycemic agents: two studies with metformin (26 and 52 weeks); two studies with metformin and sulfonylurea (26 and 52 weeks), one study with metformin and pioglitazone (26 weeks) and one study with metformin and sitagliptin (26 weeks). Two placebo-controlled studies investigated the use of INVOKANA®, added onto the current diabetes treatment regimen, one in older patients, and one in patients with moderate renal impairment. A cardiovascular study has been conducted in patients with type 2 diabetes; safety analyses were conducted that investigated INVOKANA® as add-on therapy with a sulfonylurea and with insulin. A long-term renal outcomes study has been conducted in patients with type 2 diabetes and diabetic nephropathy on a background of standard of care including maximally tolerated labelled ACEi and ARB treatments.

Study Demographics and Trial Design

Table 19: Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
Monotherapy					
DIA3005	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Placebo 26-week	Total: 584 INVOKANA® 100 mg: 195 INVOKANA® 300 mg: 197 Placebo: 192	55.4 (24-79)	55.8/44.2
Add-on Therapy with Metformin (≥ 1500 mg/day)					
DIA3006	Randomized, double-blind, active-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Sitagliptin 100 mg/day or Placebo 26-week	Total: 1284 INVOKANA® 100 mg: 368 INVOKANA® 300 mg: 367 Sitagliptin 100 mg: 366 Placebo: 183	55.4 (21-79)	52.9/47.1
DIA3009	Randomized, double-blind, active-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Glimepiride 1- 8 mg (titration protocol) 52-week	Total: 1450 INVOKANA® 100 mg: 483 INVOKANA® 300 mg: 485 Glimepiride: 482	56.2 (22-80)	47.9/52.1

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
Add-on Therapy with a Sulfonylurea (stable dose)					
DIA3008 SU Substudy	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Placebo 18-week	Total: 127 INVOKANA® 100 mg: 42 INVOKANA® 300 mg: 40 Placebo: 45	64.8 (44-82)	43.3/56.7
Add-on Therapy with Metformin (≥ 1500 mg/day) and a Sulfonylurea (stable dose)					
DIA3002	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Placebo 26-week	Total: 469 INVOKANA® 100 mg: 157 INVOKANA® 300 mg: 156 Placebo: 156	56.8 (27-79)	49.0/51.0
DIA3015	Randomized, double-blind, active-controlled, parallel-group, multicentre	INVOKANA® 300 mg/day or Sitagliptin 100 mg/day or Placebo 52-week	Total: 755 INVOKANA® 300 mg: 377 Sitagliptin 100 mg: 378	56.7 (21-91)	44.1/55.9
Add-on Therapy with Metformin (≥ 1500 mg/day) and Pioglitazone (30 or 45 mg/day)					
DIA3012	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Placebo 26-week	Total: 342 INVOKANA® 100 mg: 113 INVOKANA® 300 mg: 114 Placebo: 115	57.4 (27-78)	36.8/63.2
Add-on with Insulin (≥20 units/day) as monotherapy or in combination with other AHA(s)[1]					
DIA3008 Insulin Substudy	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA® 100 or 300 mg/day or Placebo 18-week	Total: 1718 INVOKANA® 100 mg: 566 INVOKANA® 300 mg: 587 Placebo: 565	62.8 (32-85)	33.5/66.5
Add-on Therapy with Metformin (≥ 1500 mg/day) and Sitagliptin (100 mg/day)					
DIA4004	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA® 100 up-titrated to 300 mg/day at Week 6 or Placebo 26-week	Total: 213 INVOKANA®:107[2] Placebo: 106	57.4 (23-76)	43.2/56.8

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
Cardiovascular					
DIA3008	Randomized, double-blind, placebo-controlled, parallel-group, Multicentre	INVOKANA® 100 or 300 mg/day or Placebo mean 223 weeks exposure to study drug	Total: 4330 INVOKANA® 100 mg: 1445 INVOKANA® 300 mg: 1443 Placebo: 1442	62.4 (32-87)	33.9/66.1
DIA4003	Randomized, double-blind, placebo-controlled, parallel-group, Multicentre	INVOKANA® 100 up-titrated to 300 mg/day at week 13 or later at investigators' discretion mean 94 weeks exposure to study drug	Total: 5813 INVOKANA® 100 mg up titrated: 2907 Placebo: 2906	64 (30-90)	37.2/62.8
Renal					
DNE3001	Randomized, double-blind, placebo-controlled, parallel-group, Multicentre	INVOKANA® 100 or Placebo mean 115 weeks exposure to study drug	Total: 4401 INVOKANA® 100 mg: 2202 Placebo: 2199	63 (30-89)	33.9/66.1
Special Populations					
DIA3010 (Older Adults)	Randomized, double-blind, placebo-controlled, parallel-group, Multicentre	INVOKANA® 100 or 300 mg/day + any AHA[1] or Placebo + any AHA[1] 26-week	Total: 714 INVOKANA® 100 mg: 241 INVOKANA® 300 mg: 236 Placebo: 237	63.6 (55-80)	44.5/55.5
DIA3004 (Renal Impairment)	Randomized, double-blind, placebo-controlled, parallel-group, Multicentre	INVOKANA® 100 or 300 mg/day + any AHA[1] or Placebo + any AHA[1] 26-week	Total: 269 INVOKANA® 100 mg: 90 INVOKANA® 300 mg: 89 Placebo: 90	68.5 (39-96)	39.4/60.6

[1] AHA = antihyperglycemic agent

[2] 10 subjects did not up-titrate to canagliflozin 300 mg at Week 6, 3 of whom completed Week 26

A total of 10,285 patients with type 2 diabetes were randomized in nine double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of INVOKANA® on glycemic control. The racial distribution was 72% White, 16% Asian, 4% Black, and 8% other

groups. Approximately 16% of patients were Hispanic. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 to 96 years), with 3082 patients 65 years of age and older and 510 patients 75 years of age and older. One study was conducted in patients with moderate renal impairment with an eGFR 30 to <50 mL/min/1.73 m^2 (N=269) and three other studies included patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) (N=816).

Study Results

In patients with type 2 diabetes, treatment with INVOKANA® produced statistically significant improvements in A1C, fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG), and body weight, compared to placebo. INVOKANA® was effective in reducing A1C in a broad range of patients regardless of disease duration and concomitant use of antihyperglycemic agents. The durability of these reductions in A1C was demonstrated in two Phase 3 studies, with minimal attenuation of the glycemic response to INVOKANA® over 52 weeks, in contrast to the deterioration of the glycemic response observed with comparators.

Statistically significant improvements in glycemic control relative to placebo were observed with INVOKANA® when given as monotherapy, as-add on therapy with metformin or a sulfonylurea, metformin and a sulfonylurea, metformin and pioglitazone, metformin and sitagliptin or as add-on therapy with insulin (with or without other antihyperglycemic agents).

In addition, significant improvements in A1C were observed with INVOKANA® in subjects with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) and in older patients. Reductions in A1C were observed across subgroups including age, gender, race, baseline body mass index (BMI), and baseline beta-cell function. Greater reductions in A1C relative to placebo were observed in patients with higher baseline A1C or eGFR values.

Monotherapy (Study DIA3005)

A total of 584 patients with inadequate glycemic control (A1C of ≥7% to ≤10%) on diet and exercise participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA® over 26 weeks. 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 a drug washout period of approximately 8 weeks immediately followed by a 2-week, single-blind, placebo run-in period. Patients not taking an oral antihyperglycemic agent (off therapy for at least 8 weeks) (N=303) with inadequate glycemic control entered a 2-week, single-blind, placebo run-in period. Patients were randomized to take INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo, administered once daily. As shown in Table 20, statistically significant ($p<0.001$) reductions in A1C, FPG, PPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an A1C <7.0% compared to placebo. Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -3.7 mmHg and -5.4 mmHg, respectively.

Patients who were not eligible for inclusion in the main placebo-controlled study due to more severe hyperglycemia (A1C >10 and ≤ 12%) participated in a separate active-treatment substudy (N=91) and were treated with either INVOKANA® 100 mg or INVOKANA® 300 mg (see Table 20).

Table 20: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA® as Monotherapy[1]

Efficacy Parameter	INVOKANA® 100 mg (N=195)	INVOKANA® 300 mg (N=197)	Placebo (N=192)
A1C (%)			
Baseline (mean)	8.06	8.01	7.97
Change from baseline (adjusted mean)	-0.77	-1.03	0.14
Difference from placebo (adjusted mean) (95% CI)	-0.91[2] (-1.09; -0.73)	-1.16[2] (-1.34; -0.99)	N/A[3]
Percent of Patients Achieving A1C <7%	44.5[2]	62.4[2]	20.6
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.57	9.57	9.20
Change from baseline (adjusted mean)	-1.51	-1.94	0.46
Difference from placebo (adjusted mean) (95% CI)	-1.97[2] (-2.34; -1.60)	-2.41[2] (-2.78; -2.03)	N/A[3]
2-hour Postprandial Glucose (mmol/L)			
Baseline (mean)	13.87	14.10	12.74
Change from baseline (adjusted mean)	-2.38	-3.27	0.29
Difference from placebo (adjusted mean) (95% CI)	-2.67[2] (-3.28; -2.05)	-3.55[2] (-4.17; -2.94)	N/A[3]
Body Weight			
Baseline (mean) in kg	85.9	86.9	87.5
% change from baseline (adjusted mean)	-2.8	-3.9	-0.6
Difference from placebo (adjusted mean) (95% CI)	-2.2[2] (-2.9; -1.6)	-3.3[2] (-4.0; -2.6)	N/A[3]
	Separate Active-Treatment Substudy of Patients with High Baseline A1C Levels (>10 to ≤12%)		
Efficacy Parameter	**INVOKANA® 100 mg (N=47)**	**INVOKANA® 300 mg (N=44)**	
A1C (%)			
Baseline (mean)	10.59	10.62	
Change from baseline (adjusted mean)	-2.13	-2.56	
Percent of Patients Achieving A1C <7%	17.4	11.6	
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	13.18	13.50	
Change from baseline (adjusted mean)	-4.54	-4.79	
2-hour Postprandial Glucose (mmol/L)			
Baseline (mean)	18.34	19.68	
Change from baseline (adjusted mean)	-6.58	-6.98	
Body Weight			
Baseline (mean) in kg	83.2	81.6	
% change from baseline (adjusted mean)	-3.0	-3.8	

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] p<0.001 compared to placebo
[3] N/A = Not applicable

Add-on Therapy
Add-on Therapy with Metformin (Study DIA3006)

A total of 1284 patients with inadequate glycemic control (A1C of ≥7% to ≤10.5%) on metformin monotherapy (2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a randomized, double-blind, placebo- and active-controlled, parallel-group, 4-arm, multicentre clinical study to evaluate the efficacy of INVOKANA® as add-on therapy with metformin over 26 weeks. 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 metformin (N=1009) at screening with inadequate glycemic control completed a 2-week, single-blind, placebo run-in period. Other patients on metformin and another oral agent or a lower than required dose of metformin (N=275) were switched to a regimen of metformin monotherapy. After at least 8 weeks on a stable dose of metformin monotherapy, patients entered a 2-week, single-blind, placebo run-in period. Patients were randomized to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, sitagliptin 100 mg, or placebo, administered once daily.

As shown in Table 21, statistically significant ($p<0.001$) reductions in A1C, FPG, PPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an A1C <7.0% compared to placebo. Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -5.4 mmHg and -6.6 mmHg, respectively.

Table 21: Results from Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Metformin[1]

Efficacy Parameter	INVOKANA® + Metformin 26 weeks		Placebo + Metformin (N=183)
	100 mg (N=368)	300 mg (N=367)	
A1C (%)			
Baseline (mean)	7.94	7.95	7.96
Change from baseline (adjusted mean)	-0.79	-0.94	-0.17
Difference from placebo (adjusted mean) (95% CI)	-0.62[2] (-0.76; -0.48)	-0.77[2] (-0.91; -0.64)	N/A[3]
Percent of patients achieving A1C < 7%	45.5[2]	57.8[2]	29.8
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.36	9.59	9.12
Change from baseline (adjusted mean)	-1.52	-2.10	0.14
Difference from placebo (adjusted mean) (95% CI)	-1.65[2] (-1.99; -1.32)	-2.23[2] (-2.57; -1.90)	N/A[3]
2-hour Postprandial Glucose (mmol/L)			
Baseline (mean)	14.30	14.54	13.81
Change from baseline (adjusted mean)	-2.66	-3.17	-0.55
Difference from placebo (adjusted mean) (95% CI)	-2.12[2] (-2.73; -1.51)	-2.62[2] (-3.24; -2.01)	N/A[3]
Body Weight			
Baseline (mean) in kg	88.7	85.4	86.7
% change from baseline (adjusted mean)	-3.7	-4.2	-1.2
Difference from placebo (adjusted mean) (95% CI)	-2.5[2] (-3.1; -1.9)	-2.9[2] (-3.5; -2.3)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] $p<0.001$ compared to placebo
[3] N/A = Not applicable

Active-Controlled Study versus Glimepiride as add-on therapy with Metformin (Study DIA3009)

A total of 1450 patients with inadequate glycemic control (A1C level of ≥7% to ≤9.5%) on metformin monotherapy (≥2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a randomized, double-blind, active-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA® as add-on therapy with metformin over 52 weeks. 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 on metformin (N=928) at a stable protocol-specified dose entered a 2-week, single-blind, placebo run-in period. Other patients (N=522) entered a metformin dose titration and dose stabilization/antihyperglycemic agent washout period, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or glimepiride (titration allowed throughout the 52-week study to 6 to

8 mg), administered once daily.

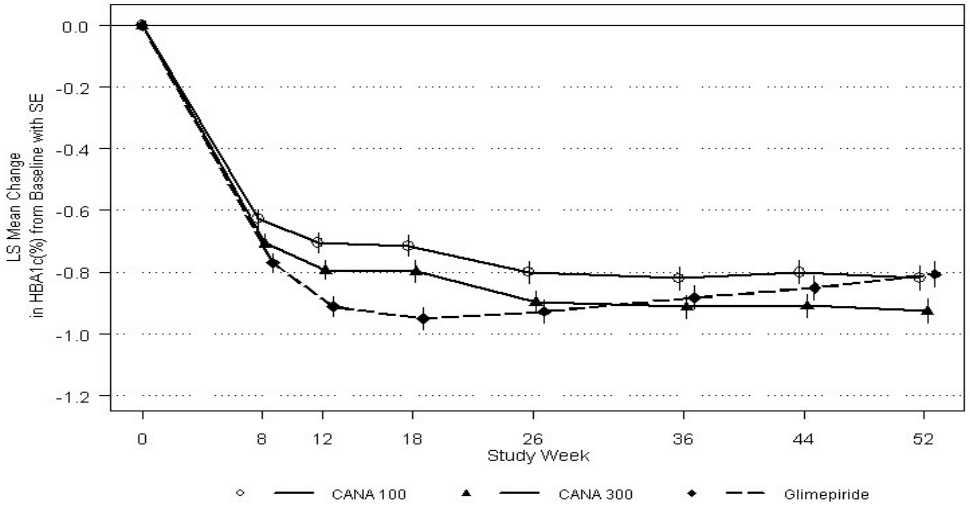
As shown in Table 22 and Figure 4, after 52 weeks, treatment with INVOKANA® 100 mg provided similar reductions in A1C from baseline compared to glimepiride (with the upper bound of the 95% confidence interval around the between-group difference less than the pre-specified non-inferiority margin of 0.3%); INVOKANA® 300 mg provided a superior ($p<0.05$) reduction from baseline in A1C compared to glimepiride (with the upper bound of the 95% confidence interval below 0). Statistically significant ($p<0.001$) reductions in body weight were observed with INVOKANA® compared to glimepiride. Reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to glimepiride of -3.5 mmHg and -4.8 mmHg, respectively. The incidence of hypoglycemia with INVOKANA® was significantly lower ($p<0.001$) compared to glimepiride.

Table 22: Results from 52-Week Clinical Study Comparing INVOKANA® to Glimepiride as Add-on Therapy with Metformin[1]

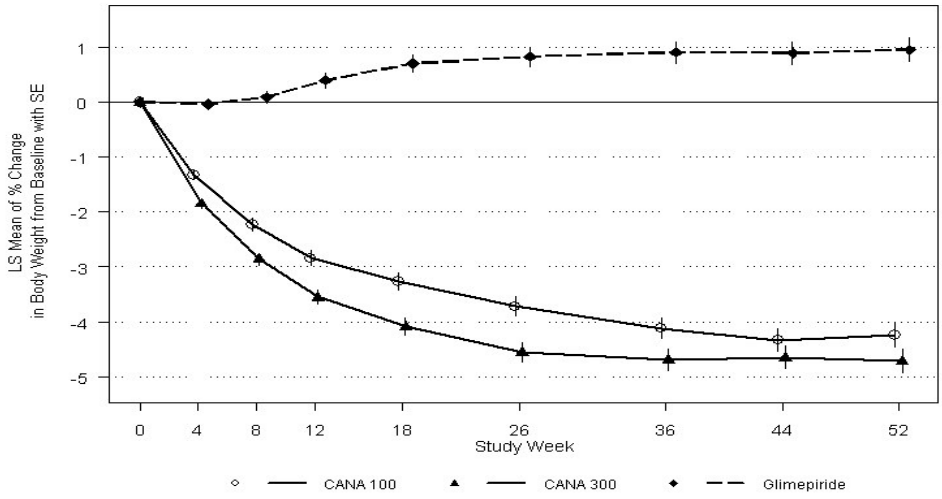
Efficacy Parameter	INVOKANA® + Metformin 52 Weeks		Glimepiride (titrated) + Metformin (N=482)
	100 mg (N=483)	300 mg (N=485)	
A1C (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)	-0.01[2] (-0.11; 0.09)	-0.12[2] (-0.22; -0.02)	N/A[3]
Percent of patients achieving A1C <7%	53.6	60.1	55.8
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.18	9.09	9.20
Change from baseline (adjusted mean)	-1.35	-1.52	-1.02
Difference from glimepiride (adjusted mean) (95% CI)	-0.33 (-0.56; -0.11)	-0.51 (-0.73; -0.28)	N/A[3]
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[4] (-5.7; -4.7)	-5.7[4] (-6.2; -5.1)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] Met pre-specified criteria for non-inferiority to glimepiride (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of <0.3%). In a pre-specified assessment, the upper bound of the 95% CI for INVOKANA® 300 mg, but not for INVOKANA® 100 mg was < 0, indicating a superior ($p<0.05$) reduction in A1C relative to glimepiride with INVOKANA® 300 mg.
[3] N/A = Not applicable
[4] $p<0.001$
[5] Includes only patients who had both baseline and post-baseline values

Figure 4: **Mean Changes from Baseline for A1C (%) and Body Weight Over 52 Weeks in a Study Comparing INVOKANA® to Glimepiride as Add-on Therapy with Metformin**



Note: LS Mean and SE in each post baseline visit are based on data with LOCF.



Note: LS Mean and SE in each post baseline visit are based on data with LOCF.

Add-on Therapy with Sulfonylurea (DIA3008 Substudy)

A total of 127 patients with inadequate glycemic control (A1C of ≥7% to ≤10.5%) on sulfonylurea monotherapy participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre substudy of a cardiovascular outcomes study to evaluate the efficacy of INVOKANA® as add-on therapy with sulfonylurea over 18 weeks. 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 on sulfonylurea monotherapy at a stable protocol-specified dose (≥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 the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo, administered once daily.

As shown in Table 23, statistically significant (p<0.001) reductions in A1C and FPG relative to placebo were observed at Week 18. In addition, a greater percentage of patients achieved an A1C <7.0% compared to placebo. Patients treated with INVOKANA® 300 mg exhibited reductions in body weight compared to placebo. Reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -0.1 mmHg and -1.8 mmHg, respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Table 23: Results from Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with a Sulfonylurea[1]

Efficacy Parameter	INVOKANA® + Sulfonylurea 18 weeks		Placebo + Sulfonylurea (N=45)
	100 mg (N=42)	300 mg (N=40)	
A1C (%)			
Baseline (mean)	8.29	8.28	8.49
Change from baseline (adjusted mean)	-0.70	-0.79	0.04
Difference from placebo (adjusted mean) (95% CI)	-0.74[2] (-1.15; -0.33)	-0.83[2] (-1.24; -0.41)	N/A[4]
Percent of patients achieving A1C <7 %	25.0	33.3[3]	5.0
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	10.29	9.84	10.27
Change from baseline (adjusted mean)	-1.41	-2.00	0.67
Difference from placebo (adjusted mean) (95% CI)	-2.07 (-2.99; -1.15)	-2.66[2] (-3.59; -1.74)	N/A[4]
Body Weight			
Baseline (mean) in kg	85.1	80.4	85.5
% change from baseline (adjusted mean)	-0.6	-2.0	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.4 (-1.8; 1.0)	-1.8[3] (-3.2; -0.4)	N/A[4]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] p<0.001 compared to placebo
[3] p<0.025 compared to placebo
[4] N/A = Not applicable

Add-on Therapy with Metformin and Sulfonylurea (Study DIA3002)

A total of 469 patients with inadequate glycemic control (A1C level of ≥7% to ≤10.5%) on the combination of metformin (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 randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA® as add-on therapy with metformin and sulfonylurea over 26 weeks. 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 on near-maximal or maximal effective doses of metformin and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) entered a metformin and sulfonylurea dose titration and dose stabilization/antihyperglycemic agent washout period of up to 12 weeks, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo administered once daily.

As shown in Table 24, statistically significant ($p<0.001$) reductions in A1C, FPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an A1C <7.0% compared to placebo. Reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -2.2 mmHg and -1.6 mmHg, respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Table 24: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Metformin and Sulfonylurea[1]

Efficacy Parameter	INVOKANA® + Metformin and Sulfonylurea 26 Weeks		Placebo + Metformin and Sulfonylurea (N=156)
	100 mg (N=157)	300 mg (N=156)	
A1C (%)			
Baseline (mean)	8.13	8.13	8.12
Change from baseline (adjusted mean)	-0.85	-1.06	-0.13
Difference from placebo (adjusted mean) (95% CI)	-0.71[2] (-0.90; -0.52)	-0.92[2] (-1.11; -0.73)	N/A[3]
Percent of patients achieving A1C < 7%	43.2[2]	56.6[2]	18.0
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.60	9.34	9.42
Change from baseline (adjusted mean)	-1.01	-1.69	0.23
Difference from placebo (adjusted mean) (95% CI)	-1.24[2] (-1.75; -0.73)	-1.92[2] (-2.43; -1.41)	N/A[3]
Body Weight			
Baseline (mean) in kg	93.5	93.5	90.8
% change from baseline (adjusted mean)	-2.1	-2.6	-0.7
Difference from placebo (adjusted mean) (95% CI)	-1.4[2] (-2.1; -0.7)	-2.0[2] (-2.7; -1.3)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] $p<0.001$ compared to placebo
[3] N/A = Not applicable or not measured in this study

Active-Controlled Study versus Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea (Study DIA3015)

A total of 755 patients with inadequate glycemic control (A1C level of ≥7.0% to ≤10.5%) on the combination of metformin (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 double-blind, active-controlled, parallel-group, 2-arm, multicentre clinical study to evaluate the efficacy of INVOKANA® 300 mg as add-on therapy with metformin and sulfonylurea versus sitagliptin 100 mg as add-on therapy with metformin and sulfonylurea over 52 weeks. 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 on near-maximal or maximal effective doses of metformin and sulfonylurea (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) entered a metformin and sulfonylurea dose titration and dose stabilization period of up to 12 weeks, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA® 300 mg or sitagliptin 100 mg.

As shown in Table 25 and

Figure 5 after 52 weeks, INVOKANA® 300 mg provided a superior ($p<0.05$) reduction in A1C compared to sitagliptin 100 mg (with the upper bound of the 95% confidence interval around the between-group difference below 0). In addition, a greater percent of patients achieved an A1C of <7.0% with INVOKANA® 300 mg relative to sitagliptin: 47.6% of patients receiving INVOKANA® 300 mg and 35.3% of patients receiving sitagliptin. Patients treated with INVOKANA® 300 mg exhibited a significant mean decrease in percent change from baseline body weight compared to patients administered sitagliptin 100 mg. A statistically significant ($p<0.001$) reduction in systolic blood pressure was observed with INVOKANA® 300 mg of -5.9 mmHg relative to sitagliptin. A similar increased incidence of hypoglycemia was observed with both INVOKANA® 300 mg and sitagliptin in this study, consistent with the expected increase of hypoglycemia when agents not associated with hypoglycemia are added to sulfonylurea (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**). The proportion of patients who met glycemic withdrawal criteria (based on FPG until Week 26 and A1C thereafter) was lower with INVOKANA® 300 mg (10.6%) compared with sitagliptin 100 mg (22.5%).

Table 25: Results from 52-Week Clinical Study Comparing INVOKANA® to Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea[1]

Efficacy Parameter	INVOKANA® 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
A1C (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)	-0.37[2] (-0.50; -0.25)	N/A[4]
Percent of patients achieving A1C <7%	47.6	35.3
Fasting Plasma Glucose (mmol/L)		
Baseline (mean)	9.42	9.09
Change from baseline (adjusted mean)	-1.66	-0.32
Difference from sitagliptin (adjusted mean) (95% CI)	-1.34 (-1.66; -1.01)	N/A[4]
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] (-3.3; -2.2)	N/A[4]

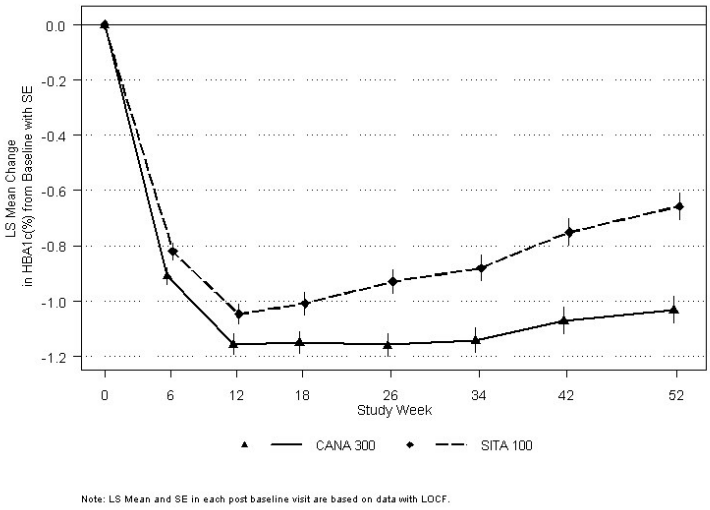
[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy

[2] Met pre-specified criteria for non-inferiority to sitagliptin (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of <0.3%); in a pre-specified assessment, the upper bound of the 95% CI for INVOKANA® 300 mg was <0, indicating a superior ($p<0.05$) reduction in A1C relative to sitagliptin with INVOKANA® 300 mg.

[3] $p<0.001$

[4] N/A = Not applicable

Figure 5: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study Comparing INVOKANA® to Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea



Note: LS Mean and SE in each post baseline visit are based on data with LOCF.

Add-on Therapy with Metformin and Pioglitazone (Study DIA3012)

A total of 342 patients with inadequate glycemic control (A1C level of ≥7.0% to ≤10.5%) on the combination of metformin (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 randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA® as add-on therapy with metformin and pioglitazone over 26 weeks. 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) entered a metformin and pioglitazone dose titration and dose stabilization period for up to 12 weeks with at least 8 weeks on stable doses of metformin and pioglitazone, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized (N=344) to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo, administered once daily.

As shown in Table 26, statistically significant ($p<0.001$) reductions in A1C, baseline FPG, and body weight relative to placebo were observed for INVOKANA® at Week 26. In addition, a greater percent of patients achieved an A1C of <7.0% compared to placebo. Statistically significant reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -4.1 mmHg ($p=0.005$) and -3.5 mmHg ($p=0.016$), respectively.

Table 26: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Metformin and Pioglitazone[1]

Efficacy Parameter	INVOKANA® + Metformin and Pioglitazone 26 Weeks		Placebo + Metformin and Pioglitazone (N=115)
	100 mg (N=113)	300 mg (N=114)	
A1C (%)			
Baseline (mean)	7.99	7.84	8.00
Change from baseline (adjusted mean)	-0.89	-1.03	-0.26
Difference from placebo (adjusted mean) (95% CI)	-0.62[2] (-0.81; -0.44)	-0.76[2] (-0.95; -0.58)	N/A[3]
Percent of patients achieving A1C <7%	46.9[2]	64.3[2]	32.5
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.38	9.11	9.13
Change from baseline (adjusted mean)	-1.49	-1.84	0.14
Difference from placebo (adjusted mean) (95% CI)	-1.63[2] (-2.05; -1.21)	-1.98[2] (-2.41; -1.56)	N/A[3]
Body Weight			
Baseline (mean) in kg	94.2	94.4	94
% change from baseline (adjusted mean)	-2.8	-3.8	-0.1
Difference from placebo (adjusted mean) (95% CI)	-2.7[2] (-3.6; -1.8)	-3.7[2] (-4.6; -2.8)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] $p<0.001$ compared to placebo
[3] N/A = Not applicable or not measured in this study

Add-on Therapy with Metformin and Sitagliptin (Study DIA4004)

A total of 213 patients with inadequate glycemic control (A1C level of ≥ 7.5% to ≤ 10.5%) 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 study to evaluate the efficacy and safety of INVOKANA® in combination with metformin and sitagliptin. The mean age was 57 years, 57% of patients were men, and the mean baseline eGFR was 90.5 mL/min/1.73 m^2. Following the 2-week single-blind placebo run-in period, patients were randomized to INVOKANA® 100 mg or placebo, administered once daily as add-on to metformin and sitagliptin.

At Week 6, canagliflozin was up-titrated to 300 mg in patients with an eGFR greater than or equal to 70 mL/min/1.73 m^2, and had a fasting self-monitoring blood glucose greater than or equal to 5.6 mmol/L, and who had not experienced reduced intravascular volume related adverse events (e.g., hypotension, postural dizziness or orthostatic hypotension). A total of 90.7% subjects were dose up-titrated to canagliflozin 300 mg in the INVOKANA® treatment group. Ten subjects were not dose up-titrated to canagliflozin 300 mg, 7 of them due to early discontinuation and the other 3 did not meet the baseline eGFR criteria and remained on canagliflozin 100 mg dose.

As shown in Table 27, statistically significant reductions in A1C, FPG, and body weight relative to placebo were observed for the INVOKANA® treatment group at Week 26. In addition, a

greater percent of patients achieved an A1C of <7.0% compared to placebo. A statistically significant mean change from baseline in systolic blood pressure relative to placebo of -5.85 mmHg was observed with the INVOKANA® treatment group.

Table 27: Results from 26−Week Placebo-Controlled Clinical Study of INVOKANA® in Combination with Metformin and Sitagliptin*

Efficacy Parameter	Placebo + Metformin and Sitagliptin (N=106)	INVOKANA®[1] + Metformin and Sitagliptin (N=107)[2]
A1C (%)		
Baseline (mean)	8.38	8.53
Change from baseline (adjusted mean)	-0.01	-0.91
Difference from placebo (adjusted mean) (95% CI)†		-0.89‡ (-1.19; -0.59)
Percent of patients achieving A1C < 7%	12	32
Fasting Plasma Glucose (mmol/L)		
Baseline (mean)	10.01	10.33
Change from baseline (adjusted mean)	-0.14	-1.65
Difference from placebo (adjusted mean) (95% CI)†		-1.50‡ (-2.24; -0.77)
Body Weight		
Baseline (mean) in kg	89.9	93.8
% change from baseline (adjusted mean)	-1.6	-3.4
Difference from placebo (adjusted mean) (95% CI)†		-1.8‡ (-2.7; -0.9)

* Modified Intent-to-treat population
† Adjusted mean and CI are derived from a mixed model for repeated measures
‡ p<0.001
[1] 100 mg to 300 mg up-titration at Week 6
[2] 10 subjects did not up-titrate to canagliflozin 300 mg, 3 of whom completed Week 26

Add-on Therapy with Insulin (with or without Metformin) (Derived from DIA3008 substudy)

A total of 1718 patients with inadequate glycemic control (A1C level of ≥7.0 to ≤10.5%) on insulin ≥30 units/day or insulin add-on therapy with other antihyperglycemic agents participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre substudy of a cardiovascular outcomes study; this substudy evaluated the efficacy of INVOKANA® as add-on therapy with insulin over 18 weeks. 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, with the majority on a background basal/bolus insulin regimen, for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. After the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo, administered once daily. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups.

Patients were stratified by (a) insulin monotherapy, (b) insulin and metformin only therapy, and (c) insulin and other antihyperglycemic agent therapy. Corresponding to approved indications,

Table 28 and Table 29 show statistically significant (p<0.001) reductions in A1C, FPG, and body weight relative to placebo were observed for INVOKANA® at Week 18 in patients both on an insulin monotherapy and insulin+metformin background. In addition, a greater percentage of patients achieved an A1C <7.0% compared to placebo. In the insulin monotherapy stratum, reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -2.9 mmHg (p=0.027) and -4.2 mmHg (p=0.001), respectively. In the insulin and metformin only stratum, reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -2.9 mmHg (p=0.011) and -4.8 mmHg (p<0.001), respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**).

Table 28: Results from 18-Week Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Insulin ≥30 Units/Day (With Insulin Only)[1]

Efficacy Parameter	INVOKANA® + Insulin 18 Weeks		Placebo + Insulin (N=187)
	100 mg (N=183)	300 mg (N=184)	
A1C (%)			
Baseline (mean)	8.28	8.32	8.16
Change from baseline (adjusted mean)	-0.61	-0.70	-0.06
Difference from placebo (adjusted mean) (95% CI)	-0.54[2] (-0.70; -0.39)	-0.63[2] (-0.79; -0.48)	N/A[3]
Percent of patients achieving A1C <7%	24.7[2]	24.0[2]	9.3
Fasting Plasma Glucose (mmol/L)			
Baseline	9.62	9.49	9.65
Change from baseline (adjusted mean)	-1.10	-1.33	0.32
Difference from placebo (adjusted mean) (95% CI)	-1.43[2] (-1.98; -0.88)	-1.65[2] (-2.20; -1.09)	N/A[3]
Body Weight			
Baseline (mean) in kg	95.8	93.5	94.5
% change from baseline (adjusted mean)	-1.9	-1.9	0.3
Difference from placebo (adjusted mean) (95% CI)	-2.2[2] (-2.7; -1.6)	-2.1[2] (-2.7; -1.6)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] p<0.001 compared to placebo
[3] N/A = Not applicable

Table 29: Results from 18-Week Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Insulin ≥30 Units/Day (With Insulin and Metformin)[1]

Efficacy Parameter	INVOKANA® + Insulin + Metformin 18 Weeks		Placebo + Insulin + Metformin (N=244)
	100 mg (N=241)	300 mg (N=246)	
A1C (%)			
Baseline (mean)	8.28	8.21	8.21
Change from baseline (adjusted mean)	-0.66	-0.77	0.01
Difference from placebo (adjusted mean) (95% CI)	-0.67[2] (-0.79; -0.55)	-0.78[2] (-0.90; -0.66)	N/A[3]
Percent of patients achieving A1C <7%	19.6[2]	26.7[2]	7.1
Fasting Plasma Glucose (mmol/L)			
Baseline	9.38	9.35	9.34
Change from baseline (adjusted mean)	-1.06	-1.48	0.09
Difference from placebo (adjusted mean) (95% CI)	-1.15[2] (-1.56; -0.73)	-1.57[2] (-1.98; -1.16)	N/A[3]
Body Weight			
Baseline (mean) in kg	97.4	98.4	99.9
% change from baseline (adjusted mean)	-1.9	-2.7	0.0
Difference from placebo (adjusted mean) (95% CI)	-1.9[2] (-2.4; -1.5)	-2.7[2] (-3.2; -2.3)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] $p < 0.001$ compared to placebo
[3] N/A = Not applicable

Cardiovascular Outcomes (CANVAS (DIA3008) and CANVAS-R (DIA4003))

The effect of INVOKANA® on cardiovascular risk in adults with type 2 diabetes who had established cardiovascular (CV) disease or were at risk for CVD (two or more CV risk factors), was evaluated in the CANVAS Program (CANVAS and CANVAS-R studies). These studies were multicenter, multi-national, randomized, double-blind, placebo-controlled parallel group, time- and event-driven, with similar inclusion and exclusion criteria and patient populations. The studies compared the risk of experiencing a Major Adverse Cardiovascular Event (MACE) defined as the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, between INVOKANA® and placebo on a background of standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Additional pre-specified, adjudicated endpoints included CV death, fatal/non-fatal myocardial infarction, fatal/non-fatal stroke, hospitalization for heart failure, and all-cause mortality.

In CANVAS, subjects were randomly assigned 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. In CANVAS-R, subjects 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) at Week 13 or later visits. 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.

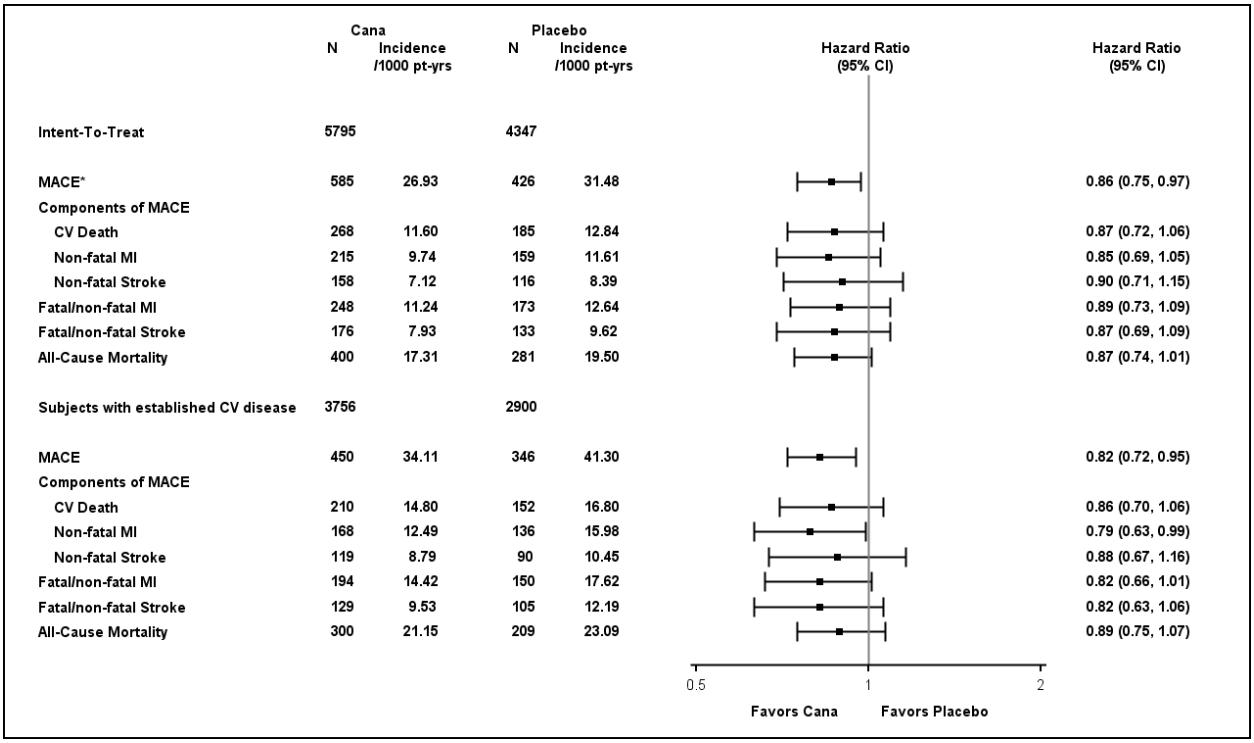
A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin). For the integrated CANVAS

trials, the mean duration of treatment was 149.2 weeks (mean of 222.8 weeks for CANVAS and 94.4 weeks for CANVAS-R) and the mean duration of study follow-up was 188.2 weeks (mean of 295.9 for CANVAS and 108.0 weeks for CANVAS-R). Vital status was obtained for 99.6% of the subjects. The proportion of subjects who completed the study was 96.0%. Approximately 78% of the study population was Caucasian, 13% was Asian, and 3% was Black. The mean age was 63 years and approximately 64% were male. All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA_{1c} ≥7.0% to ≤10.5%). The mean HbA_{1c} at baseline was 8.2% and mean duration of diabetes was 13.5 years. Baseline renal function was normal or mildly impaired in 80% of patients and moderately impaired in 20% of patients (mean eGFR 77 mL/min/1.73 m^2). There were 526 patients with eGFR 30-<45 mL/min/1.73 m^2, 1485 patients with eGFR 45-<60 mL/min/1.73 m^2, and 5625 with eGFR 60-<90 mL/min/1.73 m^2. At baseline, 99% of patients were treated with one or more antidiabetic medications including metformin (77%), insulin (50%), and sulfonylurea (43%).

Sixty-six percent of subjects had a history of established cardiovascular disease, with 56% having a history of coronary disease, 19% with cerebrovascular disease, and 21% with peripheral vascular disease; 14% had a history of heart failure. At baseline, the mean systolic blood pressure was 137 mmHg, the mean diastolic blood pressure was 78 mmHg, the mean LDL was 2.29 mmol/L, the mean HDL was 1.2 mmol/L, 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, 54% with beta-blockers, 13% with loop diuretics, 36% with non-loop diuretics, 75% with statins, and 74% with antiplatelet agents (including aspirin).

The primary endpoint in the CANVAS Program was the time to first occurrence of a composite MACE endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, considering all events up to individual trial completion. The MACE hazard ratio (HR) in patients treated with canagliflozin compared with placebo and its 95% CI was estimated using a stratified Cox proportional hazards regression model with stratification by study and by established cardiovascular disease (HR: 0.86; 95% CI 0.75, 0.97, p<0.0001 for non-inferiority; p=0.0158 for superiority). According to the primary hypothesis, the integrated canagliflozin treatment (CANVAS and CANVAS-R) was found to be non-inferior to placebo, since the upper bound of the 95% CI was below 1.3 and superior to placebo, since the upper bound of the 95% CI was also below 1.0. Each of the components of the MACE composite endpoint showed a similar reduction when assessed as independent endpoints (see Figure 6). Results for the 100 mg and 300 mg canagliflozin doses were consistent with results for the combined dose groups. The reduction in MACE was accounted for by the subgroup of patients with established cardiovascular disease (HR 0.82; 95% CI 0.72, 0.95) (see Figure 6), whilst the subgroup of patients with only risk factors for cardiovascular disease at baseline had a hazard ratio whose 95% confidence interval included one (HR 0.98; 95% CI 0.74, 1.30).

Figure 6: Treatment Effect for Cardiovascular Events (CANVAS Integrated and Subjects with Established CV Disease



* P value for superiority (2-sided) = 0.0158.

Based on the Kaplan-Meier plot for the first occurrence of MACE, shown below, the reduction in MACE in the canagliflozin group was observed as early as Week 26 and was maintained throughout the remainder of the study (Figure 7 and Figure 8).

Figure 7: Time to First Occurrence of MACE (CANVAS Integrated)

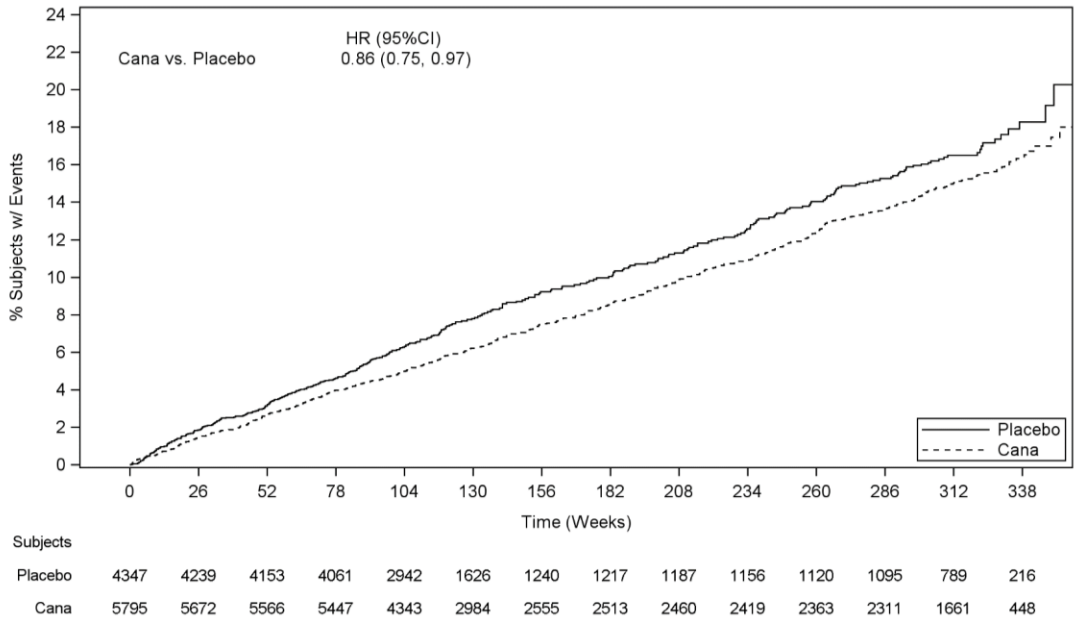
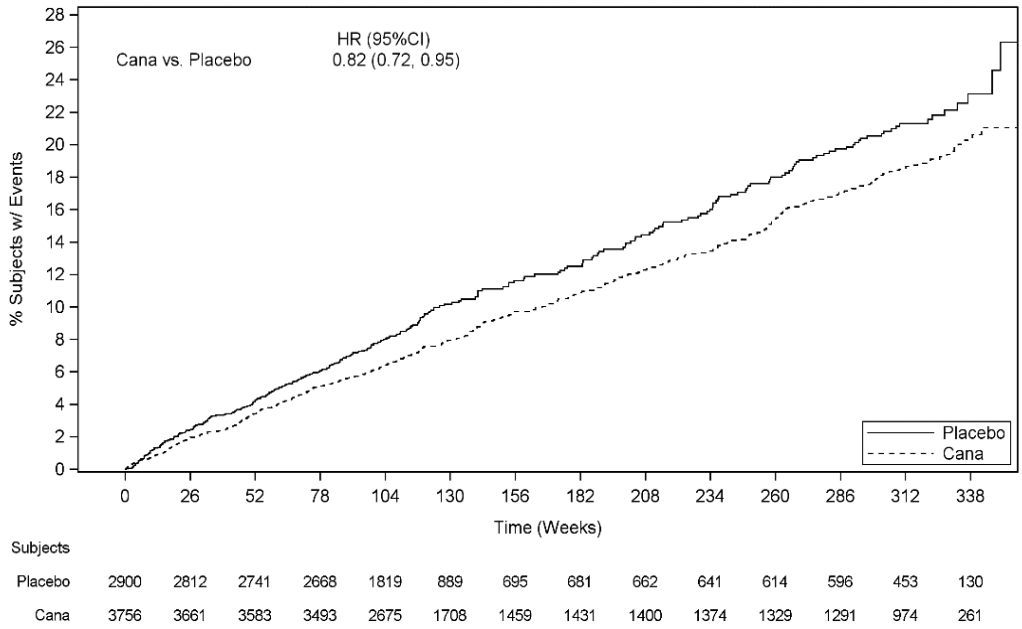


Figure 8: Time to First Occurrence of MACE (Subjects with Established CV Disease)



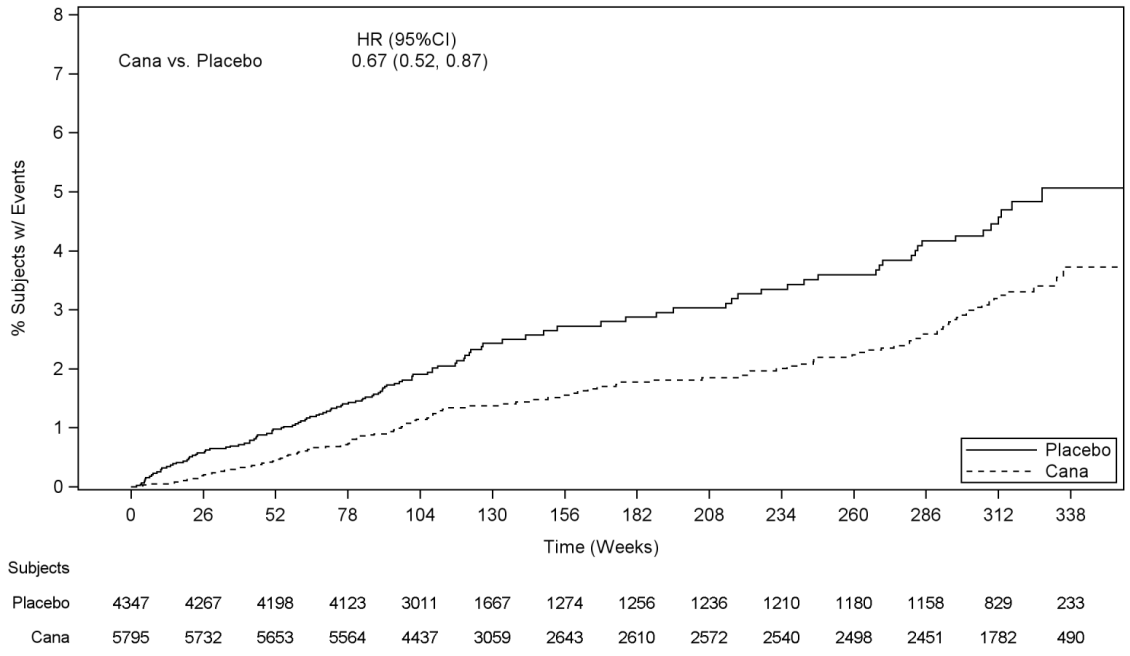
In the CANVAS program, subjects treated with INVOKANA® had a lower risk of hospitalization for heart failure compared to those treated with placebo.

Table 30: Treatment Effect for Hospitalized Heart Failure and the Composite of Death or Hospitalization due to Heart Failure

	Placebo N=4347 Event rate per 100 patient-years	**INVOKANA® N=5795 Event rate per 100 patient-years**	**Hazard ratio vs. Placebo (95% CI)**
Hospitalized heart failure (time to first occurrence; intent-to-treat analysis set)	0.87	0.55	0.67 (0.52, 0.87)[1]
Death or Hospitalization due to heart failure (time to first occurrence; intent-to-treat analysis set)	0.97	0.64	0.70 (0.55, 0.89)

[1] p=0.0021; nominal value

Figure 9: Time to First Occurrence of Hospitalization of Heart Failure



Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Diabetic Nephropathy (CREDENCE DNE3001)

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) studied the effect of INVOKANA® 100 mg relative to placebo on progression to end-stage kidney disease (ESKD), doubling of serum creatinine, and renal or cardiovascular (CV) death in adults with type 2 diabetes and diabetic nephropathy with (eGFR) ≥ 30 to < 90 mL/min/1.73m^2 and albuminuria (> 33.9 to ≤ 565.6 mg/mmol of creatinine), who

were receiving standard of care including maximally tolerated labelled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). This study was a multicenter, randomized, double-blind, event-driven, placebo-controlled, parallel-group, 2-arm study.

In CREDENCE, subjects were randomly assigned 1:1 to INVOKANA® 100mg or placebo, stratified by screening estimated glomerular filtration rate (eGFR) ≥30 to <45, ≥45 to <60, ≥60 to <90mL/min/1.73 m^2. Treatment with INVOKANA® 100 mg was continued in patients until the initiation of dialysis or renal transplantation.

A total of 4,401subjects were randomized (2,199 randomly assigned to placebo and 2,202 to INVOKANA® 100mg), followed for a mean duration of 136 weeks, and included in the intent-to-treat analysis set. Four of the randomized subjects were not dosed, leading to 4,397 subjects (exposed for a mean duration of 115 weeks) in the on-treatment analysis set. Vital status was obtained for 99.9% of subjects across the study. The majority (67%) of the study population identified as White, 20% as Asian, and 5% as Black; 32% of all subjects were of Hispanic or Latino ethnicity. The mean age was 63 years and approximately 66% were male.

The mean baseline HbA1c was 8.3%, with 53.2% of subjects having baseline HbA1c ≥8%, and the baseline median urine albumin/creatinine was 104.75 mg/mmol. The most frequent antihyperglycemic agents (AHA) medications used at baseline were insulin (65.5%), biguanides (57.8%), and sulfonylureas (28.8%). Nearly all subjects (99.9%) were on ACEi or ARB at randomization. About 92% of the subjects were on cardiovascular therapies (not including ACEi/ARBs) at baseline, with approximately 60% taking an anti-thrombotic agent (including aspirin) and 69% on statins.

The mean baseline eGFR was 56.2 mL/min/1.73 m^2 and approximately 60% of the population had a baseline eGFR of <60 mL/min/1.73 m^2. Subjects had a mean duration of diabetes of approximately 16 years. The proportion of subjects with prior CV disease was 50.4%; 14.8% had a history of heart failure. While the entire study population had nephropathy at baseline, about 64% of the population had at least 2 microvascular complications (i.e. diabetic nephropathy and another microvascular complication). At baseline, 5.4% of subjects in the INVOKANA® 100mg arm had a history of amputation and 5.2% of subjects in the placebo arm.

The primary composite endpoint in the CREDENCE study was the time to first occurrence of ESKD (defined as an eGFR <15mL/min/1.73 m^2, initiation of chronic dialysis or renal transplant), doubling of serum creatinine, and renal or CV death. INVOKANA® 100 mg significantly reduced the risk of first occurrence of the primary composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death [p<0.0001; HR:0.70; 95% CI:0.59, 0.82] (see Figure 10 and Figure 11). The treatment effect reflected a reduction in progression to ESKD, doubling of serum creatinine and cardiovascular death. There were few renal deaths during the trial. The efficacy of INVOKANA® 100 mg on the primary endpoint composite was generally consistent across major demographic and disease subgroups, including a subgroup defined by the 3 screening eGFR strata.

INVOKANA® 100 mg significantly reduced the risk of the following secondary endpoints, as shown in Figure 10 below: Composite endpoint of CV Death and Hospitalized Heart Failure

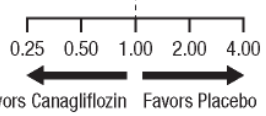
[HR:0.69; 95% CI: 0.57 to 0.83; p=0.0001], MACE (Major Adverse Cardiovascular Events) (comprised of non-fatal MI, non-fatal stroke and CV death) [HR:0.80; 95% CI:0.67 to 0.95; p=0.0121], Hospitalized Heart Failure [HR:0.61; 95% CI:0.47to 0.80; p=0.0003], and Renal composite endpoint (comprised of ESKD, doubling of serum creatinine, and renal death) [HR:0.66; 95% CI:0.53 to 0.81; p<0.0001].

For both primary and secondary endpoints, the HR in subjects treated with INVOKANA® 100 mg compared with placebo and its 95% CI were estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and stratified by screening eGFR (≥30 to <45, ≥45 to <60, ≥60 to <90mL/min/1.73 m^2).

Figure 10: Treatment Effect for the Primary and Secondary Composite Endpoints and their Components

Forest Plot of Hazard Ratios and 95% CI of the Primary Composite Endpoint, Secondary Endpoints, and Their Components (Intention-to-Treat Analysis Set)

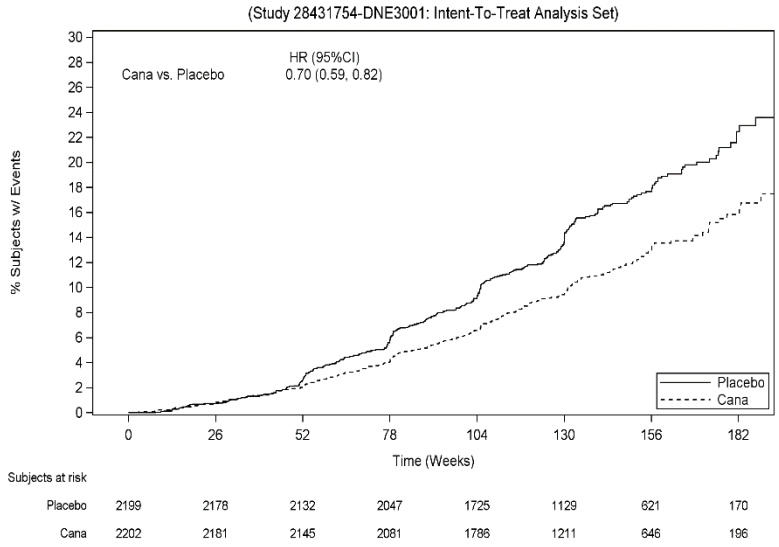
	Placebo		Canagliflozin			
Endpoint	n/N (%)	Event rate per 100 patient-years	n/N (%)	Event rate per 100 patient-years	Hazard ratio (95% CI)	*P* value*
Primary composite endpoint*	340/2199 (15.5)	6.12	245/2202 (11.1)	4.32	0.70 (0.59, 0.82)	<0.0001
ESKD	165/2199 (7.5)	2.94	116/2202 (5.3)	2.04	0.68 (0.54, 0.86)	0.0015
Doubling of serum creatinine	188/2199 (8.5)	3.38	118/2202 (5.4)	2.07	0.60 (0.48, 0.76)	<0.0001
Renal death	5/2199 (0.2)	0.09	2/2202 (0.1)	0.03	–	–
CV death†	140/2199 (6.4)	2.44	110/2202 (5.0)	1.90	0.78 (0.61, 1.00)	NS
Composite of CV death/HHF*	253/2199 (11.5)	4.54	179/2202 (8.1)	3.15	0.69 (0.57, 0.83)	0.0001
CV death, nonfatal MI, and nonfatal stroke (MACE)*	269/2199 (12.2)	4.87	217/2202 (9.9)	3.87	0.80 (0.67, 0.95)	0.0121
CV death†	140/2199 (6.4)	2.44	110/2202 (5.0)	1.90	0.78 (0.61, 1.00)	NS
Nonfatal MI	87/2199 (4.0)	1.55	71/2202 (3.2)	1.25	0.81 (0.59, 1.10)	–
Nonfatal stroke	66/2199 (3.0)	1.17	53/2202 (2.4)	0.93	0.80 (0.56, 1.15)	–
Fatal/nonfatal MI‡	95/2199 (4.3)	1.69	83/2202 (3.8)	1.46	0.86 (0.64, 1.16)	–
Fatal/nonfatal stroke‡	80/2199 (3.6)	1.42	62/2202 (2.8)	1.09	0.77 (0.55, 1.08)	–
HHF*	141/2199 (6.4)	2.53	89/2202 (4.0)	1.57	0.61 (0.47, 0.80)	0.0003
Composite of doubling of serum creatinine, ESKD, and renal death*	224/2199 (10.2)	4.04	153/2202 (6.9)	2.70	0.66 (0.53, 0.81)	<0.0001
CV death*,†	140/2199 (6.4)	2.44	110/2202 (5.0)	1.90	0.78 (0.61, 1.00)	NS
All-cause mortality*	201/2199 (9.1)	3.50	168/2202 (7.6)	2.90	0.83 (0.68, 1.02)	NS
Composite of CV death, nonfatal MI, nonfatal stroke, HHF, and hospitalization for unstable angina*	361/2199 (16.4)	6.69	273/2202 (12.4)	4.94	0.74 (0.63, 0.86)	NS



CI, confidence interval; ESKD, end-stage kidney disease; CV, cardiovascular; NS, not significant; HHF, hospitalization for heart failure; MI, myocardial infarction.
MACE is the 3-point Major Adverse Cardiac Event (CV death, nonfatal MI, and nonfatal stroke).
The individual components do not represent a breakdown of the composite outcomes, but rather the total number of subjects experiencing an event during the course of the study.
*Testing of the primary and the secondary efficacy endpoints was performed using a 2-sided alpha level of 0.022 and 0.038, respectively.
†CV death is being presented as a component of the primary composite endpoint, as a component of MACE, and as a secondary endpoint which underwent formal hypothesis testing.
‡Fatal/nonfatal MI and fatal/nonfatal stroke were not prespecified in the hierarchical testing sequence and are considered exploratory endpoints.

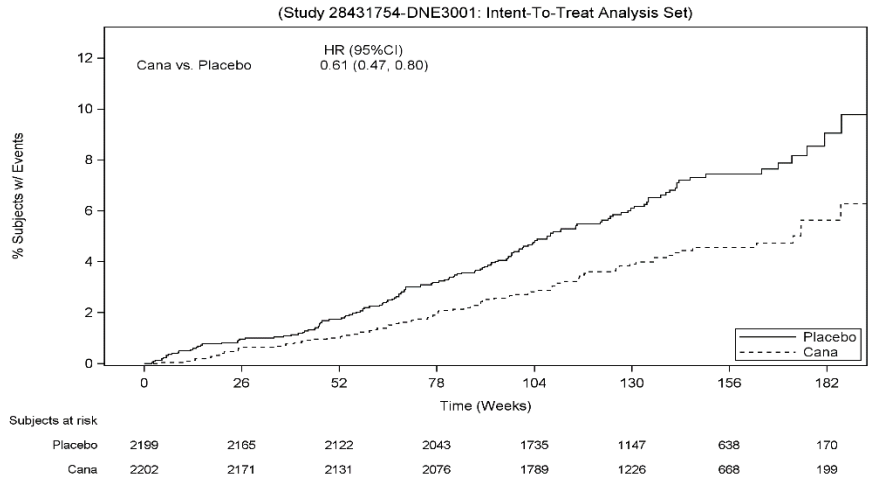
Based on the Kaplan-Meier plot for the time to first occurrence of the primary composite endpoint of ESKD, doubling of serum creatinine, renal death, and CV death shown below, the curves began to separate by Week 52 and continued to diverge thereafter (see Figure 11).

Figure 11: Time to First Occurrence of the Primary Composite Endpoint (ESKD, Doubling of Serum Creatinine, Renal Death, CV Death)



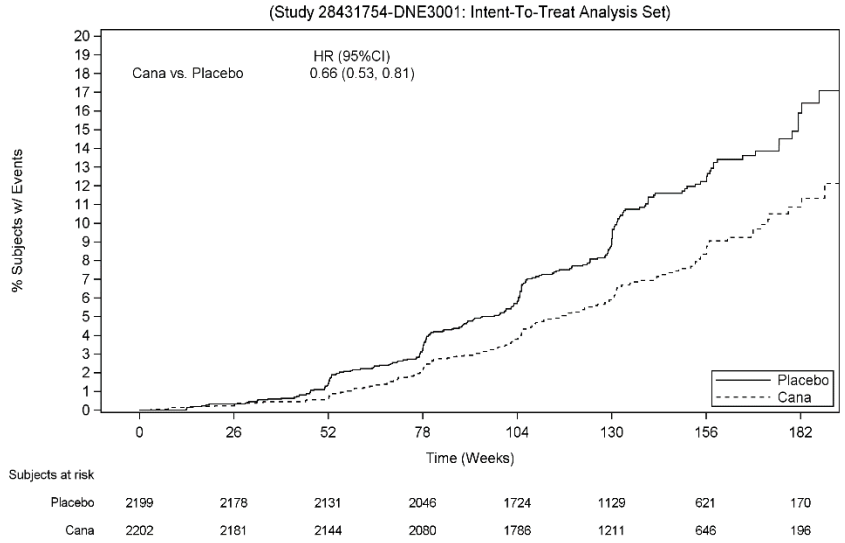
The Kaplan-Meier plot for the first occurrence of hospitalized heart failure over time is shown in Figure 12. Canagliflozin significantly reduced the risk of hospitalized heart failure as compared with placebo (HR: 0.61; 95% CI: 0.47, 0.80; p=0.0003). The Kaplan-Meier curves separated within the first 26 weeks of treatment and continued to diverge thereafter.

Figure 12: Time to First Occurrence of Hospitalized Heart Failure



The Kaplan-Meier plot for the first occurrence of the secondary renal composite endpoint of doubling of serum creatinine, ESKD, and renal death over time is shown in Figure 13. Canagliflozin significantly reduced the risk of the secondary renal composite endpoint as compared with placebo (HR: 0.66; 95% CI: 0.53, 0.81; p<0.0001). The Kaplan-Meier curves separated within the first 52 weeks of treatment and continued to diverge thereafter.

Figure 13: Time to First Occurrence of Renal Composite Endpoint (Doubling of Serum Creatinine/ESKD/Renal Death)



Studies in Special Populations

Study in older patients (DIA3010)

A total of 714 older patients (≥55 to ≤80 years of age) with inadequate glycemic control (baseline A1C level of ≥7.0 to ≤10.0%) on current diabetes therapy (either diet and exercise alone or in combination with oral or parenteral agents) participated in a randomized, double-blind, placebo-controlled study to evaluate the efficacy of INVOKANA® as add-on therapy with current diabetes treatment over 26 weeks. 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 with inadequate glycemic control on their current diabetes therapy were randomized to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo, administered once daily. As shown in Table 31, statistically significant (p<0.001) changes from baseline in A1C, FPG, and body weight were observed for INVOKANA® at Week 26. In addition, a greater percent of patients achieved an A1C of <7.0% compared to placebo (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). Statistically significant (p<0.001) reductions in systolic blood pressure were observed with INVOKANA® 100 mg and 300 mg relative to placebo of -4.6 mmHg and -7.9 mmHg, respectively.

A subset of patients (N=211) participated in the body composition substudy using DXA body composition analysis. This demonstrated that approximately two-thirds of the weight loss with INVOKANA® was due to loss of fat mass relative to placebo.

Table 31: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Antihyperglycemic Agents in Older Patients Inadequately Controlled on Antihyperglycemic Agents (AHAs)[1]

Efficacy Parameter	INVOKANA® + Current AHA 26 Weeks		Placebo + Current AHA N=237
	100 mg N=241	300 mg N=236	
A1C (%)			
Baseline (mean)	7.77	7.69	7.76
Change from baseline (adjusted mean)	-0.60	-0.73	-0.03
Difference from placebo (adjusted mean) (95% CI)	-0.57[2] (-0.71; -0.44)	-0.70[2] (-0.84; -0.57)	N/A[3]
Percent of patients achieving A1C < 7%	47.7[2]	58.5[2]	28.0
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	8.93	8.49	8.68
Change from baseline (adjusted mean)	-1.00	-1.13	0.41
Difference from placebo (adjusted mean) (95% CI)	-1.41[2] (-1.76; -1.07)	-1.54[2] (-1.88; -1.19)	N/A[3]
Body Weight			
Baseline (mean) in kg	88.4	88.8	91.3
% change from baseline (adjusted mean)	-2.4	-3.1	-0.1
Difference from placebo (adjusted mean) (95% CI)	-2.3[2] (-2.8; -1.7)	-3.0[2] (-3.5; -2.4)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] p<0.001 compared to placebo
[3] N/A = Not applicable

Patients with renal impairment (DIA3004)

A total of 269 patients with moderate renal impairment and eGFR 30 to <50 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy (baseline A1C level of ≥7.0 to ≤10.5%) participated in a randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy of INVOKANA® as add-on therapy with current diabetes treatment (diet or antihyperglycemic agent therapy with most patients on insulin and/or sulfonylurea) over 26 weeks. 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 with inadequate glycemic control on their current diabetes therapy were randomized to the addition of INVOKANA® 100 mg, INVOKANA® 300 mg, or placebo administered once daily.

As shown in Table 32, significant reductions in A1C relative to placebo were observed for INVOKANA® 100 mg and INVOKANA® 300 mg, respectively at Week 26. In addition, a greater percentage of patients achieved an A1C <7.0% compared to placebo. Patients treated with INVOKANA® exhibited mean decreases in percent change from baseline body weight compared to placebo. Reductions in systolic blood pressure were observed with INVOKANA®

100 mg and 300 mg relative to placebo of -5.7 mmHg and -6.1 mmHg, respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Table 32: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA® as Add-on Therapy with Antihyperglycemic Agents (AHAs) in Patients with Moderate Renal Impairment[1]

Efficacy Parameter	INVOKANA® + AHA (if any) 26 Weeks		Placebo + AHA (if any) N=90
	100 mg N=90	300 mg N=89	
A1C (%)			
Baseline (mean)	7.89	7.97	8.02
Change from baseline (adjusted mean)	-0.33	-0.44	-0.03
Difference from placebo (adjusted mean) (95% CI)	-0.30 (-0.53; -0.07)	-0.40[2] (-0.63; -0.17)	N/A[3]
Percent of patients achieving A1C <7%	27.3	32.6	17.2
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.41	8.80	8.93
Change from baseline (adjusted mean)	-0.83	-0.65	0.03
Difference from placebo (adjusted mean) (95% CI)	-0.85 (-1.58; -0.13)	-0.67 (-1.41; 0.06)	N/A[3]
Body Weight			
Baseline (mean) in kg	90.5	90.2	92.7
% change from baseline (adjusted mean)	-1.2	-1.5	0.3
Difference from placebo (adjusted mean) (95% CI)	-1.6[2] (-2.3; -0.8)	-1.8[2] (-2.6; -1.0)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] $p<0.001$ compared to placebo
[3] N/A = Not applicable

Integrated analysis of patients with moderate renal impairment:
An analysis of a pooled patient population (N=1085) with moderate renal impairment (baseline eGFR 30 to <60 mL/min/1.73 m^2) from four placebo-controlled studies was conducted to evaluate the change from baseline A1C and percent change from baseline in body weight in these patients. The mean eGFR in this analysis was 48 mL/min/1.73 m^2, which was similar across all treatment groups. Most patients were on insulin and/or sulfonylurea.

This analysis demonstrated that INVOKANA® provided statistically significant ($p<0.001$) reductions in A1C and body weight compared to placebo (see Table 33). An increased incidence of hypoglycemia was observed in this integrated analysis (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Table 33: Integrated Analysis of Four Phase 3 Clinical Studies in Patients with Moderate Renal Impairment[1]

Efficacy Parameter	INVOKANA® + AHA (if any) 100 mg N=338	INVOKANA® + AHA (if any) 300 mg N=365	Placebo + AHA (if any) N=382
A1C (%)			
Baseline (mean)	8.10	8.10	8.01
Change from baseline (adjusted mean)	-0.52	-0.62	-0.14
Difference from placebo (adjusted mean) (95%CI)	-0.38[2] (-0.50; -0.26)	-0.47[2] (-0.59; -0.35)	N/A[3]
Body Weight			
Baseline (mean) in kg	90.3	90.1	92.4
% change from baseline (adjusted mean)	-2.0	-2.4	-0.5
Difference from placebo (adjusted mean) (95%CI)	-1.6[2] (-2.0; -1.1)	-1.9[2] (-2.3; -1.5)	N/A[3]

[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy
[2] $p<0.001$
[3] N/A = Not applicable

DETAILED PHARMACOLOGY

In Vitro Pharmacology Studies

In Chinese hamster ovary K1 (CHOK1) cells overexpressing either human SGLT1 (hSGLT1) or hSGLT2, canagliflozin was found to be a potent and selective inhibitor of SGLT2 with IC_{50} values of 4.2 nM and 663 nM against hSGLT2 and hSGLT1, respectively. Similar IC_{50} values of 3.7 nM and 555 nM were obtained for rat SGLT2 and SGLT1 expressed in CHOK1 cells, respectively.

In Vivo Pharmacology Studies

In diabetic mice, rats, and obese dogs, canagliflozin increased urinary glucose excretion (UGE) in a dose-related manner and also decreased plasma glucose. In the oral glucose tolerance test (OGTT), canagliflozin improved glucose tolerance in normal mice, Zucker diabetic Fatty (ZDF) rats, and obese dogs. Canagliflozin treatment (1 mg/kg single oral dose) markedly lowered the mean renal threshold of glucose (RT_G) in ZDF rats from 415 to 140 mg/dL (~23 to 8 mmol/L). Repeated daily treatment for 4 weeks with canagliflozin dose-dependently lowered fed and fasted blood glucose levels, lowered A1C, and improved beta-cell function as reflected by a dose-dependent increase in plasma insulin levels in ZDF rats. In addition, repeated dosing of canagliflozin for up to 4 weeks in obese (*ob/ob)* and diet-induced obese mice reduced body weight and improved glucose handling during an OGTT.

TOXICOLOGY

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. In a study in juvenile rats, dilatation of the renal pelvis and tubules was noticed beginning at the lowest dose tested, 4 mg/kg, an exposure greater than or equal to 0.5 times the maximum clinical dose of 300 mg, and the pelvic

dilatation did not fully reverse within the approximately 1-month recovery period. Persistent renal findings in juvenile rats can most likely be attributed to reduced ability of the developing rat kidney to handle canagliflozin-increased urine volumes, as functional maturation of the rat kidney continues through 6 weeks of age.

Single and Repeat-Dose Toxicity
Canagliflozin has relatively low acute oral toxicity, with maximum non-lethal single doses of 2000 mg/kg in mice (both sexes) and male rats, and 1000 mg/kg in female rats.

Repeat-dose oral toxicity studies were conducted in mice, rats and dogs for up to 3, 6 and 12 months, respectively. Canagliflozin was generally well tolerated up to oral doses of 4 mg/kg/day in rats and 100 mg/kg/day in mice and dogs (up to approximately 0.5, 11, and 20 times the clinical dose of 300 mg based on AUC exposure for rats, mice and dogs, respectively). The major adverse effects, observed mainly in rats, were related to the pharmacologic mode of action of canagliflozin, and these included increased urinary glucose, increased urine volume, increased urinary excretion of electrolytes, decreased plasma glucose at high dose levels, and reduced body weight. The primary targets of toxicity were the kidney and bone. In the 3-month rat study, minimal mineralization of renal interstitium and/or pelvis were observed in some animals given doses of ≥4 mg/kg/day. In the 6-month rat study, renal tubular dilatation was seen at all doses (4, 20 and 100 mg/kg/day), and an increased incidence and severity of transitional epithelial hyperplasia in the renal pelvis was observed at 100 mg/kg/day. In dogs, treatment-related tubular regeneration/degeneration and tubular dilatation occurred only at the high dose of 200/100 mg/kg/day. Trabecular hyperostosis was observed in the repeat-dose studies in rats, but not in mice and dogs. In the 2-week rat study, canagliflozin at 150 mg/kg/day caused minimal to mild hyperostosis but in 3- and 6-month rat studies, hyperostosis was detected at 4 mg/kg/day, the lowest dose tested. A 1-month mechanistic rat study showed that hyperostosis occurred in young, actively growing animals (6 to 8 weeks old, as in the toxicity studies) but not in older (6-month old) animals where bone growth has substantially slowed.

Carcinogenicity
The carcinogenicity of canagliflozin was evaluated in 2-year studies in mice and rats at oral doses of 10, 30, or 100 mg/kg/day. Canagliflozin did not increase the incidence of tumors in male and female mice up to 100 mg/kg/day (up to 14 times the clinical dose of 300 mg based on AUC exposure).

The incidence of testicular Leydig cell tumors increased significantly in male rats at all doses tested (≥1.5 times the clinical dose of 300 mg based on AUC exposure). The Leydig cell tumors are associated with an increase in luteinizing hormone (LH), which is a known mechanism of Leydig cell tumor formation in rats. In a 12-week clinical study, unstimulated LH did not increase in males treated with canagliflozin.

The incidence of pheochromocytomas and renal tubular tumors increased significantly in male and female rats given high doses of 100 mg/kg/day (approximately 12 times the clinical dose of 300 mg based on AUC exposure). Canagliflozin-induced renal tubule tumors and pheochromocytomas in rats may be caused by carbohydrate malabsorption; mechanistic clinical

studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2 times the recommended clinical dose of 300 mg.

Mutagenicity
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.

Reproductive and Developmental Toxicity
In rat fertility studies, canagliflozin had no adverse effects on mating, fertility, or early embryonic development up to the highest dose of 100 mg/kg/day (up to 19 times the clinical dose of 300 mg based on AUC exposure), although there were slight sperm morphological changes at this dose level.

Canagliflozin was not teratogenic at any dose tested when administered orally to pregnant rats and rabbits during the period of organogenesis. In both rats and rabbits, a slight increase in the number of fetuses with reduced ossification, indicative of a slight developmental delay, was observed at the high doses (approximately 19 times the clinical dose of 300 mg based on AUC exposure) in the presence of maternal toxicity.

In a pre- and postnatal development study, canagliflozin administered orally to female rats from gestation Day 6 to lactation Day 20 resulted in decreased body weights in male and female offspring at maternally toxic doses of ≥30 mg/kg/day (≥5.9 times the clinical dose of 300 mg based on AUC exposure). Maternal toxicity was limited to decreased body weight gain.

In a juvenile toxicity study in which canagliflozin was dosed orally to young rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg, increased kidney weights and a dose-related increase in the incidence and severity of renal pelvic and renal tubular dilatation were reported at all dose levels. Exposure at the lowest dose tested was approximately 0.5 times the maximum recommended clinical dose of 300 mg. The renal pelvic dilatations observed in juvenile animals did not fully reverse within the 1-month recovery period. Additionally, shortened ulna growth and delays in sexual maturation were observed in juvenile rats at doses that were greater than or equal to 3 times and 9 times the clinical dose of 300 mg based on AUC exposure, respectively.

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PART III: CONSUMER INFORMATION

PrINVOKANA®
canagliflozin tablets

This leaflet is Part III of a three-part "Product Monograph" published when INVOKANA® was approved for sale in Canada and is designed specifically for Consumers. Read this carefully before you start taking INVOKANA® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about INVOKANA®.

ABOUT THIS MEDICATION

What the medication is used for:
INVOKANA® is used along with diet and exercise to improve blood sugar levels in adults with type 2 diabetes. INVOKANA® can be used:

- alone, in patients who cannot take metformin, or
- along with metformin, or
- along with a sulfonylurea, or
- along with metformin and a sulfonylurea, or
- along with metformin and a pioglitazone, or
- along with metformin and sitagliptin or
- along with insulin (with or without metformin).

INVOKANA® can also be used, along with diet and exercise, if you have type 2 diabetes and:

- an increased cardiovascular risk. This means that you have or may have health problems due to your heart and blood vessels. INVOKANA® can be used to lower your risk of dying from events related to your heart or blood vessels. It may also lower your risk of having heart attacks and strokes.

- diabetic kidney disease. This is when your kidneys are damaged as a result of your diabetes. INVOKANA® can be used to lower the risk that your kidney function will worsen to the point where your kidneys fail and you need dialysis. As well, INVOKANA® may also lower your risk of dying from events related to your heart and blood vessels.

What it does:
INVOKANA® works by increasing the amount of sugar removed from the body in the urine, which reduces the amount of sugar in the blood.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and/or does not use the insulin that your body produces as well as it should. When this happens, sugar (glucose) builds up in the blood. This can lead to serious problems.

When it should not be used:
Do not take INVOKANA® if you:

- are allergic to canagliflozin or any of the other ingredients in this medication.
- have type 1 diabetes. This is a disease where your body does not produce any insulin.
- have or have had diabetic ketoacidosis (DKA). This is a complication of diabetes.
- you are on dialysis.

What the medicinal ingredient is:
Canagliflozin

What the nonmedicinal ingredients are:
Croscarmellose sodium, hydroxypropyl cellulose, iron oxide yellow (100 mg tablet only), lactose anhydrous, Macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide.

What dosage forms it comes in:
100 mg tablets: Yellow, capsule-shaped tablets with "CFZ" on one side and "100" on the other side.

300 mg tablets: White, capsule-shaped tablets with "CFZ" on one side and "300" on the other side.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Diabetic Ketoacidosis (DKA)

- DKA is a serious and life-threatening condition that requires urgent hospitalization. DKA has been reported in patients with type 2 diabetes mellitus (T2DM), with normal or high blood sugar levels, who are treated with INVOKANA® and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Some cases of DKA have led to death.

- Seek medical attention right away and stop taking INVOKANA® immediately if you have any of the following symptoms (even if your blood sugar levels are normal): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty, feeling unusually tired, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.

- If you have diabetic kidney disease, you may have a higher chance of DKA while you are taking INVOKANA®.

- INVOKANA® should not be used in patients with type 1 diabetes.

- INVOKANA® should not be used to treat DKA or if you have a history of DKA.

Lower Limb Amputation

- INVOKANA® may increase your risk of lower limb amputations. Amputations mainly involve removal

of the toe or part of the foot but could also involve the leg, below and above the knee. Some people had more than one amputation, some on both sides of the body.

- Seek medical attention 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® if you have any of these signs or symptoms. Talk to your doctor about proper foot care and keeping hydrated.

BEFORE you use INVOKANA® talk to your doctor or pharmacist if you:

- have an increased chance of developing DKA, including if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
  - are on a very low carbohydrate diet; drink a lot of alcohol;
  - have/have had problems with your pancreas, including pancreatitis or surgery on your pancreas;
  - are hospitalized for major surgery, serious infection or serious medical illnesses;
  - have diabetic kidney disease;
  - have a history of diabetic ketoacidosis (DKA).
- have an increased chance of needing an amputation, including 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 a lower limb infection
  - are dehydrated
- if you have or have had low pressure (hypotension) or are taking medicines to:
  - remove excess water from your body. These are called diuretics or water pills. An example is furosemide.
  - lower your blood pressure. Examples are angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB).

  Taking INVOKANA® with any of these medicines may increase your risk for dehydration and/or low blood pressure.
- are older than 65 years of age.
- are taking medicines to lower your blood sugar such as glyburide, gliclazide or glimepiride (sulfonylureas) or insulin. Taking INVOKANA® with any of these medicines can increase the risk of having low blood sugar (hypoglycemia). Take precautions to avoid the potential for low blood sugar while driving or using heavy machinery.
- are taking medicines used to treat pain and reduce inflammation and fever knowns as NSAIDs (nonsteroidal anti-inflammatory drugs). Taking INVOKANA® with these medicines can increase the risk for kidney problems.
- have liver problems.
- have heart problems.
- have intolerance to some milk sugars. INVOKANA® tablets contain lactose.
- are pregnant or are planning to have a baby. INVOKANA® should not be used during pregnancy.
- are breast-feeding. INVOKANA® should not be used during breast-feeding.
- often get urinary tract infections

INVOKANA® is not recommended for use in patients under 18 years of age.

INVOKANA® will cause your urine to test positive for sugar (glucose).

Taking INVOKANA® increases your risk of breaking a bone. Talk to your doctor about factors that may increase your risk of bone fracture.

While taking INVOKANA® your doctor may order a blood test to check your kidney function, blood fat levels (Low-Density Lipoprotein cholesterol or LDL-C) amount of red blood cells in your blood (haematocrit), and potassium blood levels.

INVOKANA® may cause necrotizing fasciitis of the perineum (area between and around the anus and genitals). This is a rare but serious and potentially life-threatening infection that can affect both men and women. It is also known as Fournier's gangrene and requires urgent treatment. If you experience tenderness, redness or swelling of the genitals or the area from the genitals back to the rectum, especially if you also have a fever or are feeling very weak, tired, or uncomfortable, seek medical attention immediately. These may be signs of Fournier's gangrene.

Driving and using machines: INVOKANA® may cause dizziness or light-headedness. DO NOT drive or use machines until you know how the medicine affects you.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because this medicine may affect the way INVOKANA® works.

Drugs that may interact with INVOKANA® include:

- digoxin, a medicine used to treat heart problems.
- furosemide or other diuretics (water pills).
- an ACE inhibitor or an ARB (to lower your blood pressure).
- insulin or a sulfonylurea (such as glimepiride, gliclazide, or glyburide).
- carbamazepine, phenytoin or phenobarbital.
- efavirenz or ritonavir.
- rifampin.
- St. John's wort.

PROPER USE OF THIS MEDICATION

Usual starting dose:
100 mg by mouth each day with or without food. Your doctor may increase your dose to 300 mg per day. However, if you have a kidney problem, your dose may stay at 100 mg per day.

It is best to take INVOKANA® before the first meal of the day and at the same time each day. Swallow the tablet whole with water.

Before starting INVOKANA®, your doctor will do tests to see how well your kidneys are working.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
- If you forget to take a dose of INVOKANA®, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose and follow your usual schedule.
- Do not take two doses on the same day to make up for a forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects you may feel when taking INVOKANA®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

- Changes in urination such as urinating more often or in larger amounts, an urgent need to urinate, and a need to urinate at night.
- Nausea.
- Feeling thirsty.

Diabetic Ketoacidosis (DKA) is a serious medical condition with normal or high blood glucose levels. Get medical help right away if you have any of the symptoms in the table below under DKA, even if your blood glucose levels are normal.

Tell your doctor if you are hospitalized for major surgery, serious infection or serious medical illness.

Increased need for lower leg or toe amputation (removal) especially if you are at high risk of heart disease. Talk to your doctor if you experience symptoms including leg pain, poor circulation, bluish, cold skin, and poor hair and toe nail growth. Good foot care and drinking an adequate amount of fluid are recommended.

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency / Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	**Vaginal yeast infection:** vaginal odor, white or yellowish vaginal discharge and/or itching		✓	
Very Common	**Hypoglycemia (low blood sugar), especially if you are also taking a sulfonylurea or insulin:** shaking, sweating, pale skin, rapid heartbeat, change in vision, hunger, headache and change in mood, feeling anxious or confused		✓	
Common	**Balantis (yeast infection of the penis):** red, swollen, itchy head of penis, thick, lumpy discharge under foreskin, unpleasant odour, difficulty retracting foreskin, pain passing urine or during sex		✓	

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	Urinary tract infection: burning sensation when passing urine, pain in the pelvis, or mid-back pain, or increased need to urinate		✓	
	Constipation	✓		
	Bone fracture (broken bones)		✓	
	Skin Ulcer (a break or sore on the skin with tissue breakdown) predominantly of the lower leg: It may start off red then get swollen and tender. Next, blisters can form with loss of skin layers. It can lead to an open round crater with a bad smell. Ulcers take a long time or may not heal.		✓	
Uncommon	**Peripheral Ischemia (blocked or narrow blood vessels)**: Leg pain with walking that gets better with rest. Poor circulation, bluish, cold skin, and poor nail and hair growth. It can lead to **Skin Ulcers** and **Lower Leg or Toe Amputation.**		✓	

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	Dehydration (not having enough water in your body): feeling very thirsty, weak or tired, passing little or no urine and/or fast heartbeat; it can be from nausea, vomiting and/or diarrhea or not drinking enough liquids		✓	
	Hypotension (low blood pressure): dizziness, fainting or lightheadedness; may occur when you go from lying to sitting to standing up.		✓	
	Rash or hives			✓
	Kidney problems: nausea, vomiting, diarrhea; muscle cramps; swelling of the legs, ankles, feet, face and/or hands; shortness of breath due to extra fluid on the lungs; more frequent urination or in greater amounts than usual, with pale urine; or, less frequent urination, or in smaller amounts than usual, with dark coloured urine.		✓	

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	**Severe hypoglycemia (low blood sugar), especially when used with insulin or a sulfonylurea:** disorientation, loss of consciousness, seizure			✓
	Diabetic Ketoacidosis (when your body produces high levels of blood acids called ketones): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty and feeling unusual tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat			✓
	Anaphylactic reaction (Severe allergic reaction): swelling of the face, lips, mouth, tongue or throat that may lead to difficulty breathing or swallowing			✓

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	**Acute kidney infection:** painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul-smelling urine, blood in your urine			✓
	Urosepsis (severe infection that spreads from the urinary tract and throughout the body): fever or low body temperature, rapid breathing, chills, rapid heartbeat, pain with urination, difficulty urinating, frequent urination			✓
	Pancreatitis (inflammation of the pancreas): severe stomach pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
	Fournier's gangrene (a serious infection affecting soft tissue around the groin): pain or tenderness, redness of the skin, or swelling in the genital or perineal area, with or without fever or feeling very weak, tired, or uncomfortable			✓

This is not a complete list of side effects. For any unexpected effects while taking INVOKANA®, contact your doctor or pharmacist.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

- This medicine does not require any special storage conditions.
- Store at room temperature (15-30°C).
- Keep out of the reach and sight of children.
- Do not use INVOKANA® after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
- Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing

For questions, concerns, or the Product Monograph go to
www.janssen.com/canada
or call:
1-800-567-3331 and 1-800-387-8781

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