PRODUCT NAME
INVOKANA™ (canagliflozin) film-coated tablets

DOSAGE FORMS AND STRENGTHS
100 mg – The tablet is yellow, capsule-shaped, immediate-release, and film-coated, with "CFZ" on one side and "100" on the other side. Each 100 mg tablet contains 102 mg canagliflozin hemihydrate, equivalent to 100 mg canagliflozin.

300 mg - The tablet is white, capsule-shaped, immediate-release, and film-coated, with "CFZ" on one side and "300" on the other side. Each 300 mg tablet contains 306 mg canagliflozin hemihydrate, equivalent to 300 mg of canagliflozin.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
Monotherapy and Combination Therapy

INVOKANA™ is indicated as an adjunct to diet and exercise and standard care therapy:

- to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) who have inadequate glycemic control.
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria >300mg/day.

Dosage and Administration
Dosage – Adults 18 years of age and older
The recommended dose of INVOKANA™ is 100 mg or 300 mg once daily. See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR). The 300 mg dose may be considered for patients with an eGFR $\geq$ 60 mL/min/1.73 m^2 [CrCl $\geq$ 60 mL/min], who need tighter glycemic control and who have a low risk of adverse reactions associated with reduced intravascular volume with INVOKANA™ treatment (see *below* and *Warnings and Precautions*).

A starting dose of 100 mg once daily should be used in patients on loop diuretics and patients $\geq$ 75 years of age. In patients with evidence of reduced intravascular volume, correcting this condition prior to initiation of INVOKANA™ is recommended. For those patients who are tolerating INVOKANA™ 100 mg and who need tighter glycemic control, the dose can be increased to INVOKANA™ 300 mg (see *Warnings and Precautions*).

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*).

Table 1: Dosage recommendation by eGFR

eGFR (mL/min/1.73 m^2) or CrCl (mL/min)	**Dosage Recommendation**
≥ 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.
30 to < 60*	100 mg once daily.
< 30	Initiation is not recommended; however patients with albuminuria greater than 300 mg/day may continue 100 mg once daily to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure.**

* If further glycemic control is needed, the addition of other anti hyperglycemic agents should be considered.

** In CREDENCE, treatment with INVOKANA™ 100 mg was continued in patients until the initiation of dialysis or in the event of renal transplantation.

Administration
INVOKANA™ should be taken orally once a day, preferably before the first meal of the day (see *Pharmacokinetic Properties*). Tablets are to be swallowed whole.

Missed dose
If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day.

Special populations
Pediatrics (< 18 years of age)
The safety and efficacy of INVOKANA™ have not been established in pediatric patients.

Elderly
In patients ≥ 75 years of age, the starting dose of INVOKANA™ is 100 mg once daily. Renal function and risk of volume depletion should be taken into account (see *Warnings and Precautions* and *Adverse Reactions*).

Contraindications
History of a serious hypersensitivity reaction to INVOKANA™.

Patients on dialysis.

Hypersensitivity to the active substance or to any of the excipients (see *Adverse Reactions*).

Warnings and Precautions

General

The safety and effectiveness of INVOKANA™ in patients with type 1 diabetes have not established. Use of INVOKANA™ should be avoided in these patients.

INVOKANA™ should not be used for the treatment of diabetic ketoacidosis (DKA).

The glycemic lowering efficacy of canagliflozin is reduced in patients with an eGFR < 45 mL/min/1.73 m^2 *[CrCl < 45 mL/min]* and likely absent in patients with an eGFR < 30 mL/min/1.73 m^2 *[CrCl < 30 mL/min]*; therefore, if further glycemic control is needed, the addition of other anti-hyperglycemic agents should be considered. For dose adjustment recommendations according to eGFR *[CrCl]* refer to Table 1.

Diabetic ketoacidosis

Patients with a history of diabetic ketoacidosis (DKA) were excluded from clinical studies. INVOKANA™ should be used with caution in patients with a history of DKA.

Rare cases of DKA, including life-threatening and fatal cases, have been reported in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus treated with SGLT2 inhibitors, including canagliflozin.

Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

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

In patients with type 2 diabetes mellitus, DKA has been reported with the use of INVOKANA™. In the clinical development program including two-long term cardiovascular studies, events of DKA were reported in 0.2% (17/11,078) of patients treated with INVOKANA™, most of whom were hospitalized. DKA has also been reported during postmarketing surveillance and has occurred in patients with blood glucose values less than 13.9 mmol/L *[250 mg/dL]* (see *Adverse Reactions*).

Therefore, in patients with type 2 diabetes presenting with metabolic acidosis, a diagnosis of DKA should be considered even if blood glucose levels are less than 13.9 mmol/L *[250 mg/dL]*. Patients on INVOKANA™ should be tested for ketones when they present with signs and symptoms of metabolic acidosis, such as difficulty breathing, nausea, vomiting, abdominal pain, feeling

confused, fruity-smelling breath, and unusual fatigue or sleepiness, in order to prevent delayed diagnosis and to ensure appropriate patient management.

In patients with type 2 diabetes with DKA, treatment with INVOKANA™ should be discontinued immediately. Temporarily discontinue treatment with INVOKANA™ in patients with type 2 diabetes who are hospitalized for major surgical procedures or acute serious medical illnesses. Monitoring for DKA is recommended in these patients. Based on canagliflozin half-life, glucosuria may persist longer than expected and DKA may be prolonged after discontinuation of INVOKANA™ in some patients (see *Pharmacokinetic Properties*). Treatment with INVOKANA™ may be restarted once the patient's condition has stabilized.

Lower limb amputation

In long-term clinical studies of INVOKANA™ in patients with type 2 diabetes with established cardiovascular disease (CVD) or at least two risk factors for CVD, INVOKANA™ was associated with an increased risk of lower limb amputation versus placebo (0.63 vs 0.34 events per 100 patient-years, respectively), and this increase occurred primarily in the toe and midfoot (see *Adverse Reactions*). In a long-term clinical study in patients with type 2 diabetes and diabetic kidney disease, the risk of lower limb amputations associated with the use of INVOKANA™ 100mg relative to placebo was 1.2 vs 1.1 events per 100 patient-years, respectively. As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown.

Before initiating INVOKANA™, consider factors in the patient history that may increase the risk for amputation. As precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with INVOKANA™ in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

Hypotension

INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™ (see *Adverse Reactions*) particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function

INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™ (see *Adverse Reactions*). More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia

INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia (see *Adverse Reactions*).

Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

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, or hypotension) include patients on loop diuretics, patients with moderate renal impairment, and patients ≥ 75 years of age (see *Dosage and Administration* and *Adverse Reactions*).

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*). Due to reduced intravascular volume, generally small mean dose-dependent increases in serum creatinine and concomitant decreases in eGFR were seen within the first six weeks of treatment initiation with INVOKANA™. In patients susceptible to greater reductions in intravascular volume as described above, larger decreases in eGFR (> 30%) were sometimes seen, which subsequently improved, and infrequently required interruption of treatment with INVOKANA™ (see *Adverse Reactions*).

Patients should be advised to report symptoms of reduced intravascular volume. These adverse reactions infrequently led to discontinuation of INVOKANA™ and were often managed by modification of the blood pressure-lowering drug regimen (including diuretics) while continuing therapy with INVOKANA™. In patients with volume depletion, correcting this condition prior to initiation of INVOKANA™ is recommended.

Renal function should be assessed prior to initiation of INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR < 60 mL/min/1.73 m^2 [CrCl < 60 mL/min].

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve *(see Contraindications and Adverse Reactions)*.

Low-Density Lipoprotein Cholesterol (LDL-C)
Dose-related increases in LDL-C occur with INVOKANA™ *(see Adverse Reactions)*. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

Macrovascular outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

Hypoglycemia in add-on therapy with other antihyperglycemic agents
When used alone or as add-on therapy with antihyperglycemic agents not associated with hypoglycemia, INVOKANA™ showed a low incidence of hypoglycemia. Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. 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 *Dosage and Administration* and *Adverse Reactions*).

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

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

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

Consistent with the mechanism of SGLT2 inhibition with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical studies (see *Adverse Reactions*). Male and female patients with a history of genital mycotic infections were more likely to develop an infection. Balanitis or balanoposthitis occurred primarily in uncircumcised male patients; events of phimosis were also reported. In a pooled analysis of 10 controlled studies, the incidence rate of circumcision was 0.38 events per 100 patient-years of exposure in uncircumcised male patients treated with canagliflozin. The majority of genital mycotic infections were treated with topical antifungal treatments, either prescribed by a healthcare professional or self-treated while continuing therapy with INVOKANA™.

Interactions

In vitro assessment of interactions

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

In *in vitro* studies, canagliflozin neither inhibited cytochrome P450 CYP1A2, CYP2A6, CYP2C19, CYP2D6, or CYP2E1, CYP2B6, CYP2C8, CYP2C9, nor induced CYP1A2, CYP2C19, CYP2B6, CYP3A4 at higher than therapeutic concentrations. Canagliflozin weakly inhibited CYP3A4 *in vitro*; however, based upon a clinical study, no clinically relevant interaction was observed. Therefore, canagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolized by these enzymes.

Canagliflozin is a P-glycoprotein (P-gp) substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency.

In vivo assessment of interactions

Specific drug interaction studies were conducted to investigate the effects of inhibitors or inducers of the drug-metabolizing enzymes UGT1A9 and UGT2B4 and transporters P-gp and Multidrug Resistance Protein 2 (MRP2) on canagliflozin pharmacokinetics, and also to assess the effects of canagliflozin on the pharmacokinetics of the P-gp substrate digoxin.

Effects of other drugs on canagliflozin

In clinical studies, the effects of other drugs on canagliflozin were assessed. Ciclosporin, hydrochlorothiazide, oral contraceptives (ethinyl estradiol and levonorgestrel), metformin, and probenecid had no clinically relevant effect on the pharmacokinetics of canagliflozin.

Rifampicin: Co-administration with rifampicin, a nonselective inducer of several UGT enzymes and drug transporters including UGT1A9, UGT2B4, P-gp, and MRP2, decreased canagliflozin exposure. These decreases in exposure to canagliflozin may decrease efficacy. If a combined inducer of these UGTs and drug transport systems (e.g., rifampicin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz, St John's wort [Hypericum perforatum]) must be co-administered with INVOKANA™, monitor HbA_{1c} in patients receiving INVOKANA™ 100 mg once daily with consideration to increasing the dose to 300 mg once daily if additional glycemic control is needed. In patients with an eGFR 45 to < 60 mL/min/1.73 m^2 [CrCl 45 to < 60 mL/min], taking INVOKANA™ 100 mg who are receiving concurrent therapy with a UGT enzyme inducer and who require additional glycemic control, other antihyperglycemic therapies should be considered.

Table 2. 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	
			AUC[2] (90% CI)	C_{max} (90% CI)
No dose adjustments of INVOKANA™ required for the following:				
Ciclosporin	400 mg	300 mg once daily for 8 days	1.23 (1.19; 1.27)	*1.01 (0.91; 1.11)*
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)*
Hydrochloro-thiazide	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)*
Metformin	2000 mg	300 mg once daily for 8 days	1.10 (1.05; 1.15)	*1.05 (0.96; 1.16)*
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)*
Rifampicin	600 mg once daily for 8 days	300 mg	0.49 (0.44; 0.54)	*0.72 (0.61; 0.84)*

[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.

Effects of canagliflozin on other drugs

In interaction studies conducted in healthy subjects, canagliflozin at steady-state had no clinically relevant effect on the pharmacokinetics of metformin, oral contraceptives (ethinyl estradiol and levonorgestrol), glyburide, simvastatin, paracetamol, hydrochlorothiazide, or warfarin.

Digoxin: The combination of canagliflozin 300 mg once daily for 7 days with a single dose of digoxin 0.5 mg followed by 0.25 mg daily for 6 days resulted in a 20% increase in AUC and a 36% increase in C_{max} of digoxin, possibly due to an interaction at the level of P-gp. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately.

Lithium: The concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during canagliflozin initiation and dosage changes.

Table 3. 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		
				AUC[2] (90% CI)	C_{max} (90% CI)
No dose adjustments of co-administered drug required for the following:					
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)
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)
			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)
			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	hydrochlorothia-zide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2000 mg	300 mg once daily for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Paracetamol	1000 mg	300 mg twice daily for 25 days	paracetamol	1.06[3] (0.98; 1.14)	1.00 (0.92; 1.09)
Simvastatin	40 mg	300 mg once daily for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			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)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (0.98; 1.03)	1.05 (0.99; 1.12)

[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] $AUC_{0\text{-}12h}$

Drug/Laboratory test interference

1,5-AG assay

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.

Urine glucose test

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

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see *Non-Clinical Information*). During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin in milk. It is not known if canagliflozin is excreted in human milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue INVOKANA™ therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (see *Non-Clinical Information*).

Fertility

The effect of canagliflozin on fertility in humans has not been studied. No effects on fertility were observed in animal studies (see *Non-Clinical Information*).

Effects on Ability to Drive and Use Machines

Canagliflozin has no known influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycemia when INVOKANA™ is used as add-on therapy with insulin or an insulin secretagogue, and to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness (see *Dosage and Administration*, *Warnings and Precautions*, and *Adverse Reactions*).

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of canagliflozin based on the comprehensive assessment of the available adverse event information.

The safety of INVOKANA™ (canagliflozin) was evaluated in 22,645 patients with type 2 diabetes, including 13,278 patients treated with INVOKANA™ and 9,367 patients treated with comparator

in 15 double-blind, controlled Phase 3 and Phase 4 clinical studies. A total of 10,134 patients were treated in two dedicated cardiovascular studies for a mean exposed duration of 149 weeks (223 weeks in CANVAS and 94 weeks in CANVAS-R), and 8,114 patients treated in 12 double-blind, controlled Phase 3 and Phase 4 clinical studies, for a mean follow-up duration of 49 weeks. In a dedicated renal outcomes study, a total of 4,397 patients with diabetic kidney disease had a mean duration of drug exposure of 115 weeks and a mean follow-up duration of 136 weeks.

Safety analyses were conducted in patients who received INVOKANA™ as monotherapy or as add-on therapy with other antihyperglycemic agents. 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 [HbA_{1c} > 10 and ≤ 12%]. Five placebo- or active-controlled studies investigated INVOKANA™ as add-on therapy with other antihyperglycemic agents: two with metformin (26 and 52 weeks); two with metformin and sulfonylurea (26 and 52 weeks), and one with metformin and pioglitazone (26 weeks). Two placebo-controlled studies investigated the use of INVOKANA™ added on to the current diabetes treatment regimen, one in older patients and one in patients with moderate renal impairment. Cardiovascular studies were completed in patients with type 2 diabetes; safety analyses were conducted that investigated INVOKANA™ as add-on therapy with a sulfonylurea and with insulin.

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, 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). Additional safety analyses (including long-term data) across the entire canagliflozin program (placebo- and active-controlled studies) were conducted to assess reported adverse events in order to identify adverse reactions.

Table 4 lists adverse reactions reported in ≥ 2% of INVOKANA™-treated patients in the four pooled, 26-week, placebo-controlled clinical studies (N=2313).

Table 4. Adverse Reactions From Four Pooled 26-Week Placebo-Controlled Studies[1] Reported in ≥ 2% of INVOKANA™-Treated Patients

System Organ Class Adverse Reaction	**INVOKANA™ 100 mg N=833 %**	**INVOKANA™ 300 mg N=834 %**	**Placebo N=646 %**
Gastrointestinal disorders			
Constipation	15 (1.8)	19 (2.3)	6 (0.9)
Nausea	18 (2.2)	19 (2.3)	10 (1.5)
Thirst[2]	23 (2.8)	19 (2.3)	1 (0.2)
Renal and urinary disorders			
Polyuria or Pollakiuria[3]	44 (5.3)	38 (4.6)	5 (0.8)
Urinary tract infection[4]	49 (5.9)	36 (4.3)	26 (4.0)
Reproductive system and breast disorders			

Table 4. Adverse Reactions From Four Pooled 26-Week Placebo-Controlled Studies[1] Reported in ≥ 2% of INVOKANA™-Treated Patients

System Organ Class Adverse Reaction	INVOKANA™ 100 mg N=833 %	INVOKANA™ 300 mg N=834 %	Placebo N=646 %
Balanitis or Balanoposthitis[5]	17 (4.2)	15 (3.7)	2 (0.6)
Vulvovaginal candidiasis[6]	44 (10.4)	49 (11.4)	10 (3.2)

[1] Includes monotherapy and add-on therapy with metformin, metformin and sulfonylurea, and metformin and pioglitazone.

[2] Thirst includes the terms Thirst (1.3%, 1.9%, 0.2%) with incidences for INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively, and also includes the terms Dry mouth and Polydipsia with incidences < 1% in any treatment group.

[3] Polyuria or Pollakiuria includes the terms Polyuria (0.7%, 1.4%, 0.0%) and Pollakiuria (4.2%, 3.1%, 0.6%) with incidences for INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively, and also includes the terms Urine output increased, Micturition urgency, and Nocturia with incidences < 1% in any treatment group.

[4] Urinary tract infection includes the term Urinary tract infection (5.5%, 4.1%, 4.0%) with incidences for INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively, and also includes the terms Cystitis, Kidney infection, and Urosepsis with incidences < 1% in any treatment group. There was no imbalance among INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo for kidney infection or urosepsis.

[5] Balanitis or Balanoposthitis includes the terms Balanitis (2.2%, 1.7%, 0.0%) and Balanoposthitis (1.0%, 0.7%, 0.3%) with incidences for INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively, and also includes the terms Balanitis candida and Genital infection fungal with incidences < 1% in any treatment group.

[6] Vulvovaginal candidiasis includes the terms Vulvovaginal candidiasis (1.6%, 2.8%, 1.0%), Vulvovaginal mycotic infection (5.9%, 5.3%, 1.3%), Vulvovaginitis (1.9%, 1.6%, 0.0%), and Vaginal infection (1.2%, 1.6%, 0.6%) with incidences for INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively, and also includes the terms Vulvitis and Genital infection fungal with incidences < 1% in any treatment group.

Other adverse reactions in clinical studies of INVOKANA™ that occurred at a rate < 2% in placebo-controlled studies were adverse reactions related to reduced intravascular volume (postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) (see below), skin rash, and urticaria.

The type and frequency of common adverse reactions observed in both the dedicated cardiovascular safety program and dedicated renal outcomes study with long-term follow up were consistent with those listed in Table 4.

Description of selected adverse reactions

Diabetic ketoacidosis

DKA was identified as an adverse reaction during postmarketing surveillance. In a review of the data from the type 2 diabetes mellitus clinical development program, incidence rates of adjudicated events of DKA were 0.06 (0.2%, 17/11,078) and 0.02 (0.1%, 4/7,170) per 100 patient-years of follow-up with INVOKANA™ combined dose groups, and comparator, respectively. Of the 17 patients on INVOKANA™, 4 (3 on INVOKANA™ 100 mg, 1 on INVOKANA™ 300 mg) were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or tested positive for GAD65 antibodies while no patients on comparator were diagnosed with autoimmune diabetes and 16 of the 17 patients were receiving insulin therapy (insulin use was unknown in one patient). The blood glucose values in 13 patients on INVOKANA™ around the time of admission ranged from 19.3 mmol/L *[347 mg/dL]* to 31.7 mmol/L *[571 mg/dL]*. Four patients had blood glucose values ranging from 8.2 mmol/L *[148 mg/dL]* to 17.8 mmol/L *[320 mg/dL]* (see *Warnings and Precautions*).

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, incidence rates of adjudicated events of DKA were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with INVOKANA™ 100 mg and placebo, respectively; of the 14 patients with DKA, 8 (7 on canagliflozin 100 mg and 1 on placebo) had an eGFR before treatment of 30 to < 45 mL/min/1.73 m^2 [CrCl 30 to < 45 mL/min].

Lower limb amputation

In patients with type 2 diabetes who had established cardiovascular disease or at least two risk factors for cardiovascular disease, INVOKANA™ was associated with an increased risk of lower limb amputation as observed in the Integrated CANVAS Program comprised of CANVAS and CANVAS-R, two large, long-term, randomized, placebo-controlled studies evaluating 10,134 patients. 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. Regardless of treatment with INVOKANA™ or placebo, the risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy. The risk of lower limb amputation was not dose-dependent. The amputation results for the Integrated CANVAS Program are shown in Table 5.

The risk of lower limb amputations associated with the use of INVOKANA™ 100mg relative to placebo was 1.2 vs 1.1 events per 100 patient-years, respectively [HR: 1.11; 95% CI 0.79, 1.56]) in CREDENCE, a long-term renal outcomes study of 4,397 patients with type 2 diabetes and diabetic kidney disease, with a mean follow-up duration of 136 weeks (see *Warnings and Precautions* and *Clinical Efficacy*). In other type 2 diabetes studies with INVOKANA™, which enrolled a general diabetic population of 8,114 patients, no difference in lower limb amputation risk was observed relative to control.

Table 5. Integrated Analysis of Amputations in CANVAS AND CANVAS-R

	Placebo N=4344	**INVOKANA™ N=5790**
Total number of subjects with events, n (%)	47 (1.1)	140 (2.4)
Incidence rate (per 100 subject-years)	0.34	0.63
HR (95% CI) vs. placebo		1.97 (1.41, 2.75)
Minor Amputation, n (%) *	34/47 (72.3)	99/140 (70.7)
Major Amputation, n (%) †	13/47 (27.7)	41/140 (29.3)

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. The percentage of minor and major amputations is based on the highest-level amputation for each patient.

* Toe and midfoot

† Ankle, below knee and above knee

Of the subjects who had an amputation event, the toe and midfoot were the most frequent sites (71%) in both treatment groups (see Table 5). Multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups.

Lower limb infections, diabetic foot ulcers, peripheral arterial disease, and gangrene, were the most common medical events associated with the need for an amputation in both treatment groups (see *Warnings and Precautions*).

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 with INVOKANA™ treatment in the two active-controlled studies was similar to comparators.

In one of the dedicated long-term cardiovascular studies (CANVAS), where patients were generally older with a higher prevalence of comorbidities, the incidence rates 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.

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) [(CrCl 30 to < 60 mL/min)], and patients ≥ 75 years of age had higher incidences of these adverse 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 < 60 mL/min/1.73 m^2 [CrCl < 60 mL/min], 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 *Dosage and Administration*, *Warnings and Precautions*, and *Pharmacokinetic Properties - Special populations*).

In the dedicated cardiovascular study and the larger pooled analysis, as well as in a dedicated renal outcomes study, discontinuations due to adverse reactions related to reduced intravascular volume and serious adverse reactions related to reduced intravascular volume were not increased with INVOKANA™. In the long-term renal outcomes trial, the incidence of hypotension was 2.8% in the INVOKANA™ 100mg group and 1.5% in the placebo group.

Hypoglycemia in add-on therapy with insulin or insulin secretagogues

The frequency of hypoglycemia was low (< 6%) among treatment groups when used as monotherapy or as an add-on to antihyperglycemic agents not associated with hypoglycemia. When INVOKANA™ was used as add-on therapy with insulin or sulfonylurea, hypoglycemia was reported more frequently, which is consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin or an insulin secretagogue (e.g., sulfonylurea). In the 18-week substudy when INVOKANA™ was added to insulin therapy, hypoglycemia was observed in 49.3%, 48.2%, and 36.8% of patients treated with INVOKANA™

100 mg, INVOKANA™ 300 mg, and placebo, respectively and severe hypoglycemia occurred in 1.8%, 2.7%, and 2.5% of patients treated with INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively. When INVOKANA™ was added to sulfonylurea therapy, hypoglycemia was observed in 4.1%, 12.5%, and 5.8% of patients treated with INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively (see *Dosage and Administration* and *Warnings and Precautions*).

Necrotizing fasciitis of the perineum (Fournier's gangrene)

Fournier's gangrene was identified as a SGLT2i class adverse reaction based on spontaneous adverse event reporting. These events had not been previously identified as ADRs because there were very few subjects in the canagliflozin Phase 3 and Phase 4 clinical development program (including the CANVAS and CREDENCE programs) with adverse events of Fournier's gangrene (incidences were <0.1% in the canagliflozin and comparator groups). All 4 adverse events of Fournier's gangrene (2 subjects treated with canagliflozin and 2 subjects treated with comparator) in the canagliflozin Phase 3 and Phase 4 clinical development program were serious.

Based on frequencies observed in clinical trials, this adverse reaction is categorized as 'rare' (≥1/10000 to <1/1000 [≥0.01% and <0.1%]) and 'very rare' based on spontaneous reporting rates (See Table 6).

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.

The incidence rate of phimosis was 0.56 events per 100 patient-years of exposure in uncircumcised males in a pooled analysis of 10 controlled studies. 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 (see *Warnings and Precautions*).

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, the incidence rates of female mycotic genital infection adverse events were 1.26 and 0.61 per 100 subject-years in the INVOKANA™ and placebo groups, respectively. The incidence rates of male mycotic genital infection were 0.84 and 0.09 per 100 subject-years in the INVOKANA™

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. Subjects responded to standard treatments while continuing canagliflozin treatment. The incidence of recurrent infections was not increased with canagliflozin.

Bone fracture

In a cardiovascular study (CANVAS) of 4,327 treated 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 two other long-term studies and in studies conducted in the general diabetes population, no difference in fracture risk was observed with INVOKANA™ relative to control. In a second cardiovascular study (CANVAS-R) of 5,807 treated 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 of 4,397 patients with type 2 diabetes and diabetic kidney disease, the incidence rates of all adjudicated bone fracture were 1.18 and 1.21 events per 100 patient-years of follow-up to INVOKANA™ 100 mg and placebo, respectively. In other type 2 diabetes studies with INVOKANA™, which enrolled a general diabetes population of 7,729 patients and where bone fractures were adjudicated, 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. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Laboratory tests

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 general, elevations were mild (< 6.5 mEq/L), transient, and did not require specific treatment.

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no absolute

(> 6.5 mEq/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 changes 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. These decreases in eGFR were often transient with fewer patients having this level of decrease at study endpoint, occurring in 0.7% of patients with INVOKANA™ 100 mg, 1.4% patients with INVOKANA™ 300 mg, and 0.5% of placebo-treated patients (see *Warnings and Precautions*).

After discontinuation of INVOKANA™ therapy, these changes in laboratory values improved or returned to baseline.

In long-term cardiovascular outcome studies, patients treated with INVOKANA™ experienced an initial fall in mean eGFR that thereafter eGFR gradually increased over the duration of the studies (up to 6.5 years). Patients treated with placebo experienced a progressive decline in eGFR. The effect on eGFR reversed after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA™. Additionally, treatment with INVOKANA™ resulted in a delay in the progression to albuminuria, a marker of kidney injury.

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, patients treated with placebo experienced a progressive decline in eGFR, whereas patients treated with INVOKANA™ 100 mg experienced an acute decrease in mean eGFR at week 3, followed by an attenuated decline over time from week 3 to end of treatment. At the end of treatment, mean eGFR was 1.61 mL/min/1.73m^2 lower in the placebo group compared to the INVOKANA™ 100 mg group (see *Clinical Efficacy*).

Lipid changes

The mean percent changes from baseline relative to placebo for low density lipoprotein cholesterol (LDL-C) were 0.11 mmol/L *[4.4 mg/dL]* (4.5%) and 0.21 mmol/L [8.2 mg/dL] (8.0%) with INVOKANA™ 100 mg and INVOKANA™ 300 mg, respectively. Smaller increases in total cholesterol of 2.5% and 4.3% relative to placebo for INVOKANA™ 100 mg and INVOKANA™ 300 mg, respectively, were seen. Increases in high-density lipoprotein cholesterol (HDL-C) were 5.4%, and 6.3% 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. The LDL-C/HDL-C ratios did not change with either INVOKANA™ dose compared to placebo. Concentrations of ApoB and LDL-C particle number (measured in two studies) and non-HDL-C increased to a smaller extent compared to LDL-C changes.

Increases in hemoglobin

Mean changes (percent changes) from baseline in hemoglobin concentrations were 4.7 g/L (3.5%) with INVOKANA™ 100 mg, 5.1 g/L (3.8%) with INVOKANA™ 300 mg, and -1.8 g/L (-1.1%) with placebo. Commensurate small increases in the mean percent change from baseline in blood erythrocytes and hematocrit were observed. At the end of treatment, 4.0%, 2.7%, and 0.8% of patients treated with INVOKANA™ 100 mg, INVOKANA™ 300 mg, and placebo, respectively, had hemoglobin levels 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 studies, 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. In a pooled analysis (N=9439) of patients from eight controlled Phase 3 studies including both doses of INVOKANA™, events of nephrolithiasis were not increased.

Adverse reactions in specific populations

Elderly patients

The safety profile in elderly patients was generally consistent with that for younger patients. Patients ≥ 75 years of age had a higher incidence of adverse reactions related to reduced intravascular volume (such as postural dizziness, orthostatic hypotension, hypotension) 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 *Dosage and Administration* and *Warnings and Precautions*).

Patients with Moderate Renal Impairment

Patients with Type 2 Diabetes Mellitus with an eGFR 30 to < 60 mL/min/1.73 m^2 [CrCl 30 to < 60 mL/min] Treated for Glycemic Control or for the Reduction of MACE

An analysis of a pooled patient population (N=1087) with moderate renal impairment (baseline eGFR 30 to < 60 mL/min/1.73 m^2 *[CrCl 30 to < 60 mL/min]*) was conducted. In this population the incidence rates of adverse reactions related to reduced intravascular volume were 5.27 with INVOKANA™ 100 mg and 5.13 with INVOKANA™ 300 mg relative to 3.14 per 100 patient-years of exposure for placebo (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 8.39 and 9.91 µmol/L for INVOKANA™ 100 mg and 300 mg, respectively, relative to 7.51 µmol/L with placebo. BUN levels increased by 0.99 and 0.94 mmol/L for INVOKANA™ 100 mg and 300 mg, respectively, relative to 0.48 mmol/L with placebo. The incidence rates of decreases in eGFR (> 30%) at any time during treatment were 7.33, 8.12, and 6.47 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 3.26 for subjects treated with INVOKANA™ 100 mg, 2.68 for INVOKANA™ 300 mg, and 3.71 events per 100 patient-years of exposure for placebo (see *Warnings and Precautions*).

The incidence rates of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 4.89 with INVOKANA™ 100 mg, 6.09 with INVOKANA™ 300 mg and 5.43 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. In general, elevations were transient and did not require specific treatment.

The incidence rates of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 2.04 with INVOKANA™ 100 mg, 2.86 with INVOKANA™ 300 mg and 0.76 events per 100 patient-years of exposure for placebo. In general, elevations were transient and did not require specific treatment.

Patients with Type 2 Diabetes Mellitus with an eGFR 45 to < 60 mL/min/1.73 m^2 [CrCl 45 to < 60 mL/min] Treated for Glycemic Control or for the Reduction of MACE

An analysis of a pooled patient population (N=722) with baseline eGFR 45 to < 60 mL/min/1.73 m^2 *[CrCl 45 to < 60 mL/min]* was conducted. In this population the incidence rates of adverse reactions related to reduced intravascular volume were 4.61 for INVOKANA™ 100 mg and 4.37 for INVOKANA™ 300 mg relative to 3.00 events per 100 patient-years of exposure for placebo (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 5.92 and 6.98 µmol/L for INVOKANA™ 100 mg and 300 mg, respectively, relative to 7.03 µmol/L with placebo. BUN levels increased by 0.92 and 0.77 mmol/L for INVOKANA™ 100 mg and 300 mg, respectively, relative to 0.57 mmol/L with placebo. The incidence rates of decreases in eGFR (> 30%) 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 INVOKANA™ 300 mg, and 3.20 events per 100 patient-years of exposure for placebo (see *Warnings and Precautions*).

The incidence rates of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 4.11 for INVOKANA™ 100 mg, 4.33 for INVOKANA™ 300 mg, and 3.80 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. In general, elevations were transient and did not require specific treatment.

The incidence rates of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) 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. In general, elevations were transient and did not require specific treatment.

Patients with Type 2 Diabetes Mellitus with an eGFR 30 to < 45 mL/min/1.73 m^2 [CrCl 30 to < 45 mL/min] Treated for Glycemic Control or for the Reduction of MACE

An analysis of a pooled patient population (N=365) with baseline eGFR 30 to < 45 mL/min/1.73 m^2 *[CrCl 30 to < 45 mL/min]* was conducted. In this population the incidence rates of adverse reactions related to reduced intravascular volume were 7.07 with INVOKANA™ 100 mg and 7.02 with INVOKANA™ 300 mg relative to 3.64 per 100 patient-years of exposure for the placebo group (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 13.07 and 15.68 µmol/L for INVOKANA™ 100 mg and 300 mg, respectively, relative to 8.02 µmol/L with placebo. BUN levels increased by 1.07 and 1.24 mmol/L for INVOKANA™ 100 mg and 300 mg, respectively, relative to 0.35 mmol/L with placebo. The incidence rates of decreases in eGFR (> 30%) at any time during treatment were 14.46, 12.07, and 9.14 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 5.70 for subjects treated with INVOKANA™ 100 mg, 4.69 for INVOKANA™ 300 mg, and 5.78 events per 100 patient-years of exposure for placebo (see *Warnings and Precautions*).

The incidence rates of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 7.45 with INVOKANA™ 100 mg, 10.74 with INVOKANA™ 300 mg and 12.04 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. In general, elevations were transient and did not require specific treatment.

The incidence rates of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 5.70 with INVOKANA™ 100 mg, 7.38 with INVOKANA™ 300 mg and 0.96 events per 100 patient-years of exposure for placebo. In general, elevations were transient and did not require specific treatment.

Patients with Type 2 Diabetes Mellitus and Diabetic Kidney Disease with an eGFR 30 to < 60 mL/min/1.73 m^2 [CrCl 30 to < 60 mL/min]

In the long-term renal outcomes study, for the subgroup of patients with an eGFR before treatment of 30 to < 60 mL/min/1.73 m^2 *[CrCl 30 to < 60 mL/min]* the incidence rates of adverse reactions related to reduced intravascular volume were 3.58 with INVOKANA™ 100 mg relative to 2.58 per 100 patient-years of exposure for placebo (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 38.54 µmol/L with INVOKANA™ 100 mg, relative to 50.88 µmol/L with placebo. BUN levels increased by 1.94 with INVOKANA™ 100 mg, relative to 2.35 mmol/L with placebo. The incidence rates of decreases in eGFR (> 30%) at any time during treatment were 18.01 and 20.81 events per 100 patient-years of exposure for INVOKANA™ 100 mg and placebo, respectively. At the last post-baseline value, incidence rates for such decreases were 12.14 for subjects treated with INVOKANA™ 100 mg and 16.99 events per 100 patient-years of exposure for placebo (see *Warnings and Precautions*).

The incidence rates of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 8.23 with INVOKANA™ 100 mg and 8.79 events per 100 patient-years of exposure for placebo. No between group imbalance was observed in this study where 99.9% of subjects were on angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) at baseline.

The incidence rates of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 3.13 with INVOKANA™ 100 mg and 3.67 events per 100 patient-years of exposure for placebo.

Patients with Type 2 Diabetes Mellitus and Diabetic Kidney Disease with an eGFR 45 to < 60 mL/min/1.73 m^2 [CrCl 45 to < 60 mL/min]

In the long-term renal outcomes study, for the subgroup of patients with an eGFR before treatment of 45 to < 60 mL/min/1.73 m^2 *[CrCl 45 to < 60 mL/min]* the incidence rates of adverse reactions related to reduced intravascular volume were 2.32 with INVOKANA™ 100 mg relative to 2.57 per 100 patient-years of exposure for placebo (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 28.81 µmol/L with INVOKANA™ 100 mg, relative to 39.57 µmol/L with placebo. BUN levels increased by 1.68 with INVOKANA™ 100 mg, relative to 1.87 mmol/L with placebo. The incidence rates of decreases in eGFR (> 30%) at any time during treatment were 16.94 and 18.54 events per 100 patient-years of exposure for INVOKANA™ 100 mg and placebo, respectively. At the last post-baseline value, incidence rates for such decreases were 10.80 for subjects treated with INVOKANA™ 100 mg and 14.13 events per 100 patient-years of exposure for placebo (see *Warnings and Precautions*).

The incidence rates of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 7.45 with INVOKANA™ 100 mg and 7.58 events per 100 patient-years of exposure for placebo. No between group imbalance was observed in this study where 99.9% of subjects were on

angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) at baseline.

The incidence rates of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 2.19 with INVOKANA™ 100 mg and 3.24 events per 100 patient-years of exposure for placebo.

Patients with Type 2 Diabetes Mellitus and Diabetic Kidney Disease with an eGFR 30 to < 45 mL/min/1.73 m^2 [CrCl 30 to < 45 mL/min]

In the long-term renal outcomes study, for the subgroup of patients with an eGFR before treatment of 30 to < 45 mL/min/1.73 m^2 *[CrCl 30 to* < 45 *mL/min]* the incidence rates of adverse reactions related to reduced intravascular volume were 4.91 with INVOKANA™ 100 mg relative to 2.60 per 100 patient-years of exposure for placebo (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 48.12 µmol/L with INVOKANA™ 100 mg, relative to 61.96 µmol/L with placebo. BUN levels increased by 2.20 with INVOKANA™ 100 mg, relative to 2.81 mmol/L with placebo. The incidence rates of decreases in eGFR (> 30%) at any time during treatment were 19.15 and 23.11 events per 100 patient-years of exposure for INVOKANA™ 100 mg and placebo, respectively. At the last post-baseline value, incidence rates for such decreases were 13.57 for subjects treated with INVOKANA™ 100 mg and 19.90 events per 100 patient-years of exposure for placebo (see *Warnings and Precautions*).

The incidence rates of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 9.07 with INVOKANA™ 100 mg and 10.02 events per 100 patient-years of exposure for placebo. No between group imbalance was observed in this study where 99.9% of subjects were on angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) at baseline.

The incidence rates of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 4.14 with INVOKANA™ 100 mg and 4.11 events per 100 patient-years of exposure for placebo.

Postmarketing data

In addition to the adverse reactions identified from clinical studies, the following adverse reactions have been identified during postmarketing experience. 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. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10000 and < 1/1000 (≥ 0.01% and < 0.1%)
Very rare	< 1/10000, including isolated reports (< 0.01%)
Not known	Cannot be estimated from the available data.

Table 6. Adverse Reactions Identified During Postmarketing Experience with INVOKANA™

System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates***	**Frequency Category Estimated from Clinical Studies**
Metabolism and nutrition disorders		
Diabetic ketoacidosis	Very rare	Rare†
Immune system disorders		
Anaphylactic reaction	Very rare	Rare§
Skin and subcutaneous tissue disorders		
Angioedema	Very rare	Rare§
Renal and urinary disorders		
Pyelonephritis	Very rare	Uncommon‡
Renal failure (mainly related to volume depletion)	Very rare	Uncommon†
Urosepsis	Very rare	Rare§
Infections and infestations		
Fournier's gangrene (necrotizing fasciitis of the perineum)	Very rare	Rare§

* Postmarketing spontaneous reporting rates were based on estimated exposure of person-years of treatment
† Phase 3 and Phase 4 clinical studies, including Non-CANVAS/Non-CREDENCE studies and CANVAS Program
‡ Non-CANVAS/Non-CREDENCE, CANVAS-INT6, and CREDENCE clinical studies
§ Phase 3 and Phase 4 clinical studies, including CANVAS and CREDENCE Program

Overdose

Symptoms and signs

Single doses up to 1600 mg of INVOKANA™ in healthy subjects and INVOKANA™ 300 mg twice daily for 12 weeks in patients with type 2 diabetes were generally well-tolerated.

Treatment

In the event of an overdose, it is 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Drugs used in diabetes. Blood glucose lowering drugs, excluding insulin, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK02

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 (UGE), lowering elevated plasma glucose concentrations by this insulin-independent mechanism in patients with

type 2 diabetes. The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in UGE results in a loss of calories and therefore a reduction in body weight, as has been 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.

Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure.

Pharmacodynamic effects

Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in UGE 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, suggesting a low risk for treatment-induced hypoglycemia. The reductions in RT_G 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%.

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 a renal and a non-renal mechanism.

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 QTc 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.

Clinical Efficacy

Glycemic Control Studies in Patients with Type 2 Diabetes Mellitus

INVOKANA™ has been studied as monotherapy, as add-on therapy with metformin, sulfonylurea, metformin and sulfonylurea, metformin and a thiazolidinedione (pioglitazone), and as add-on therapy with insulin (with or without other antihyperglycemic agents). The efficacy of INVOKANA™ was compared to a DPP-4 inhibitor (sitagliptin) and a sulfonylurea (glimepiride). INVOKANA™ was also evaluated in older patients, patients with moderate renal impairment, and patients with cardiovascular disease or at high risk for cardiovascular disease.

A total of 10,285 patients with type 2 diabetes participated 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 3,082 patients 65 years of age and older and 510 patients ≥ 75 years of age. One study was conducted in patients with moderate renal impairment with an eGFR 30 to < 50 mL/min/1.73m^2 [CrCl 30 to < 50 mL/min] (N=269) and three other studies included patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73m^2) [CrCl 30 to < 60 mL/min] (N=816).

In patients with type 2 diabetes, treatment with INVOKANA™ produced clinically and statistically significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG), compared to placebo. INVOKANA™ was effective in reducing HbA_{1c} in a broad range of patients regardless of disease duration and concomitant use of antihyperglycemic agents to treat type 2 diabetes. Statistically significant improvements in glycemic control relative to placebo were observed with INVOKANA™ when given as monotherapy, as initial add-on therapy with metformin or a sulfonylurea, add-on therapy with metformin and a sulfonylurea, metformin and pioglitazone, or add-on therapy with insulin (with or without other antihyperglycemic agents). In addition, significant improvements in HbA_{1c} were observed with INVOKANA™ in subjects with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73m^2 [CrCl 30 to < 60 mL/min]) and in older patients. Reductions in HbA_{1c} were observed across subgroups including age, gender, race, baseline body mass index (BMI), and baseline beta-cell function. Greater reductions in HbA_{1c} relative to placebo were observed in patients with higher baseline HbA_{1c} or eGFR values (see *Pharmacokinetic Properties).*

Monotherapy

A total of 584 patients with inadequate glycemic control (HbA_{1c} of ≥ 7% to ≤ 10%) with diet and exercise participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicenter 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

[CrCl 87 mL/min]. Patients taking other antihyperglycemic agents (N=281) discontinued the agent and underwent a diet, exercise, and 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 7, statistically significant ($p<0.001$) improvements in HbA_{1c}, FPG, PPG, body weight, and systolic blood pressure relative to placebo were observed. In addition, a greater percentage of patients achieved an $HbA_{1c} < 7.0\%$ compared to placebo.

Patients who were not eligible for inclusion in the main placebo-controlled study due to more severe hyperglycemia ($HbA_{1c} > 10$ and $\leq 12\%$) participated in a separate active-treatment substudy (N=91) and were treated with either INVOKANA™ 100 mg or INVOKANA™ 300 mg (see *Table 7*).

Table 7. 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)**
HbA_{1c} (%)			
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 $HbA_{1c} < 7\%$	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]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	126.7	128.5	127.7
Change from baseline (adjusted mean)	-3.3	-5.0	0.4
Difference from placebo (adjusted mean) (95% CI)	-3.7[2] (-5.9; -1.6)	-5.4[2] (-7.6; -3.3)	N/A[3]
	Separate Active-Treatment Substudy of Patients with High Baseline HbA_{1c} Levels (> 10 to ≤ 12%)		

Efficacy Parameter	INVOKANA™ 100 mg (N=47)	INVOKANA™ 300 mg (N=44)	
HbA_{1c} (%)			
Baseline (mean)	10.59	10.62	
Change from baseline (adjusted mean)	-2.13	-2.56	
Percent of Patients Achieving HbA_{1c} < 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	
Systolic Blood Pressure (mmHg)			
Baseline (mean)	125.0	126.6	
Change from baseline (adjusted mean)	-4.5	-5.0	

[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

A total of 1,284 patients with inadequate glycemic control (HbA_{1c} of ≥ 7% to ≤ 10.5%) on metformin monotherapy (2000 mg/day or at least 1500 mg/day if higher dose not tolerated) participated in a randomized, double-blind, placebo- and active-controlled, parallel-group, 4-arm, multicenter 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 [CrCl 89 mL/min]. 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 8, statistically significant (p<0.001) improvements in HbA_{1c}, FPG, PPG, body weight, and systolic blood pressure relative to placebo were observed. In addition, a greater percentage of patients achieved an HbA_{1c} < 7.0% compared to placebo. Fewer patients on INVOKANA™ required glycemic rescue therapy: 1.6% of patients receiving INVOKANA™ 100 mg, 0.3% of patients receiving INVOKANA™ 300 mg, and 14.8% of patients receiving placebo.

Table 8. 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)	
HbA_{1c} (%)			
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 HbA_{1c} < 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]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	128.0	128.7	128.0
Change from baseline (adjusted mean)	-3.8	-5.1	1.5
Difference from placebo (adjusted mean) (95% CI)	-5.4[2] (-7.3; -3.4)	-6.6[2] (-8.5; -4.6)	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

Initial combination therapy with metformin

A total of 1,186 patients with type 2 diabetes inadequately controlled with diet and exercise participated in a 26-week double-blind, active controlled, parallel group, 5-arm, multicenter study to evaluate the efficacy and safety of initial therapy with INVOKANA™ in combination with metformin XR. The median age was 56 years, 48% of patients were men, and the mean baseline eGFR was 87.6 mL/min/1.73 m^2 [CrCl 87.6 mL/min]. After completing a 2-week single blind placebo run in period, patients were randomly assigned for a double-blind treatment period of 26 weeks to 1 of 5 treatment groups (Table 9). The metformin XR dose was initiated at 500 mg/day for the first week of treatment and then increased to 1000 mg/day. Metformin XR or matching placebo was up titrated based on glycemic criteria to a maximum daily dose of 2000 mg/day, as tolerated. The median dose of metformin XR achieved was 2000 mg.

At the end of treatment, INVOKANA™ 100 mg and INVOKANA™ 300 mg in combination with metformin XR resulted in a statistically significant greater improvement in HbA1c compared to their respective INVOKANA™ doses (100 mg and 300 mg) alone or metformin XR alone. INVOKANA™ 100 mg and INVOKANA™ 300 mg in combination with metformin XR also led

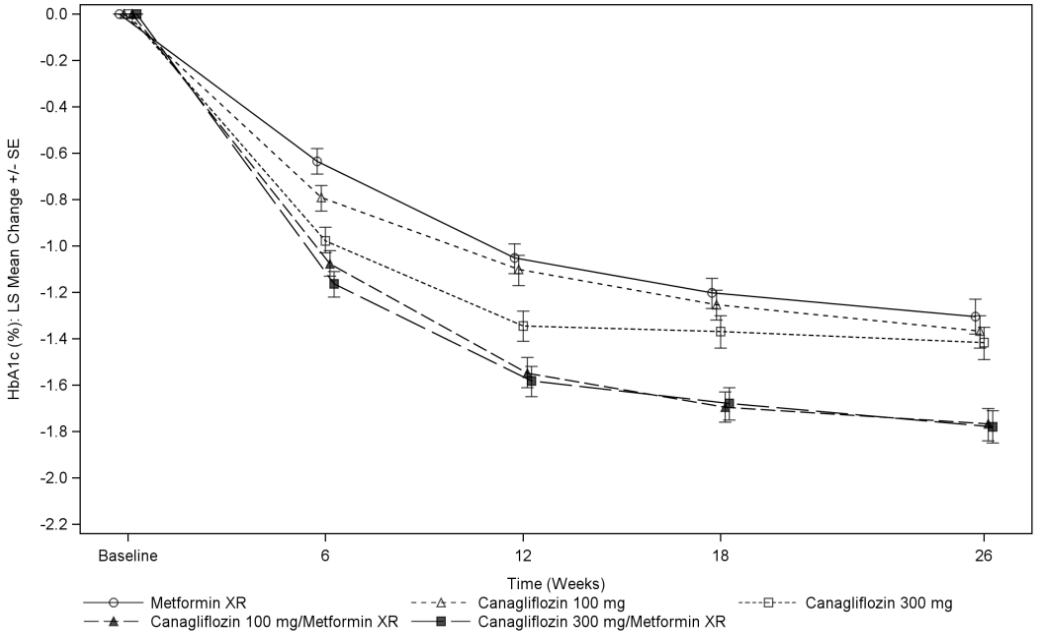
to a statistically significant greater proportion of patients with an HbA1c < 7% and a statistically significant reduction in body weight at Week 26 compared with metformin XR alone. INVOKANA™ 100 mg and INVOKANA™ 300 mg as monotherapy demonstrated non inferiority in HbA1c-lowering compared with metformin XR alone and provided a statistically significant greater reduction in body weight compared with metformin XR alone (see Table 9).

Table 9: Results from 26-Week Active-Controlled Clinical Study of INVOKANA™ as Initial Combination Therapy with Metformin[*]

Efficacy Parameter	Metformin XR (N=237)	INVOKANA™ 100 mg (N=237)	INVOKANA™ 300 mg (N=238)	INVOKANA™ 100 mg + Metformin XR (N=237)	INVOKANA™ 300 mg + Metformin XR (N=237)
HbA_{1c} (%)					
Baseline (mean)	8.81	8.78	8.77	8.83	8.90
Change from baseline (adjusted mean)	-1.30	-1.37	-1.42	-1.77	-1.78
Difference from INVOKANA™ 100 mg (adjusted mean) (95% CI) [†]				-0.40[‡] (-0.59, -0.21)	
Difference from INVOKANA™ 300 mg (adjusted mean) (95% CI) [†]					-0.36[‡] (-0.56, -0.17)
Difference from metformin XR (adjusted mean) (95% CI) [†]		-0.06[‡] (-0.26, 0.13)	-0.11[‡] (-0.31, 0.08)	-0.46[‡] (-0.66, -0.27)	-0.48[‡] (-0.67, -0.28)
Percent of patients achieving HbA_{1c} < 7%	43	39	43	50[§§]	57[§§]
Body Weight					
Baseline (mean) in kg	92.1	90.3	93.0	88.3	91.5
% change from baseline (adjusted mean)	-2.1	-3.0	-3.9	-3.5	-4.2
Difference from metformin XR (adjusted mean) (95% CI)[†]		-0.9[§§] (-1.6, -0.2)	-1.8[§] (-2.6, -1.1)	-1.4[‡] (-2.1, -0.6)	-2.1[‡] (-2.9, -1.4)

[*] Intent-to-treat population
[†] Least squares mean adjusted for covariates including baseline value and stratification factor
[‡] Adjusted p=0.001
[§] Adjusted p<0.01
[§§] Adjusted p<0.05

Figure 1: Mean Change from Baseline in HbA1c (%) Over Time (mITT Population)



Active-controlled study versus glimepiride as add-on therapy with metformin

A total of 1,450 patients with inadequate glycemic control (HbA_{1c} level of ≥ 7% to ≤ 9.5%) on metformin monotherapy (≥ 2000 mg/day or at least 1500 mg/day if higher dose not tolerated) participated in a randomized, double-blind, active-controlled, parallel-group, 3-arm, multicenter 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 [CrCl 90 mL/min]. 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 10 and Figure 2, after 52 weeks, treatment with INVOKANA™ 100 mg provided similar reductions in HbA_{1c} 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 HbA_{1c} compared to glimepiride (with the upper bound of the 95% confidence interval below 0). Statistically significant ($p<0.001$) improvements in body weight were observed with INVOKANA™ compared to glimepiride. The incidence of hypoglycemia with INVOKANA™ was significantly lower ($p<0.001$) compared to glimepiride. Fewer patients on INVOKANA™ required glycemic rescue therapy: 6.6% of patients receiving INVOKANA™ 100 mg, 4.9% of patients receiving INVOKANA™ 300 mg, and 10.6% of patients receiving glimepiride.

A subset of patients (N=208) who underwent DXA and abdominal CT scans for evaluation of body composition demonstrated that approximately two-thirds of the weight loss with canagliflozin was due to loss of fat mass with similar amounts of visceral and abdominal subcutaneous fat being lost.

Table 10. 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)	
HbA_{1c} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)	-0.01[2] (−0.11; 0.09)	-0.12[2] (−0.22; −0.02)	N/A[3]
Percent of patients achieving HbA_{1c} < 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]
Systolic Blood Pressure (mmHg)[5]			
Baseline (mean)	130.0	130.0	129.5
Change from baseline (adjusted mean)	-3.3	-4.6	0.2
Difference from glimepiride (adjusted mean) (95% CI)	-3.5 (−4.9; −2.1)	-4.8 (−6.2; −3.4)	N/A[3]

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

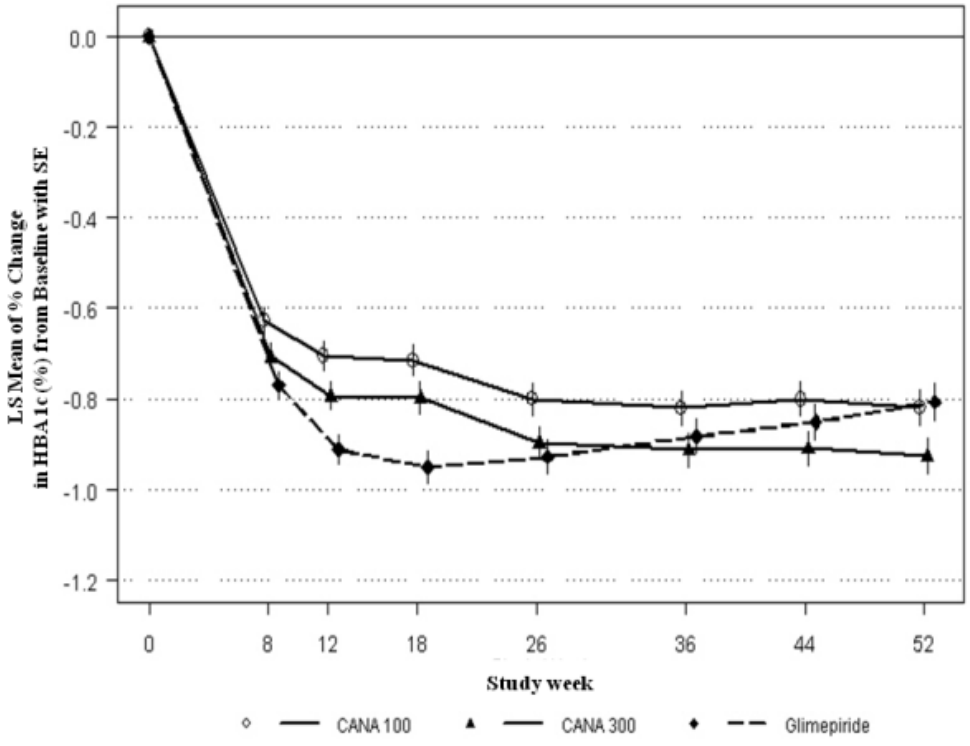
[2] Met pre-specified criteria for non-inferiority to glimepiride (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of < 0.3%). In a pre-specified assessment, the upper bound of the 95% CI for INVOKANA™ 300 mg, but not for INVOKANA™ 100 mg was < 0, indicating a superior ($p<0.05$) reduction in HbA_{1c} relative to glimepiride with INVOKANA™ 300 mg.

[3] N/A = Not applicable

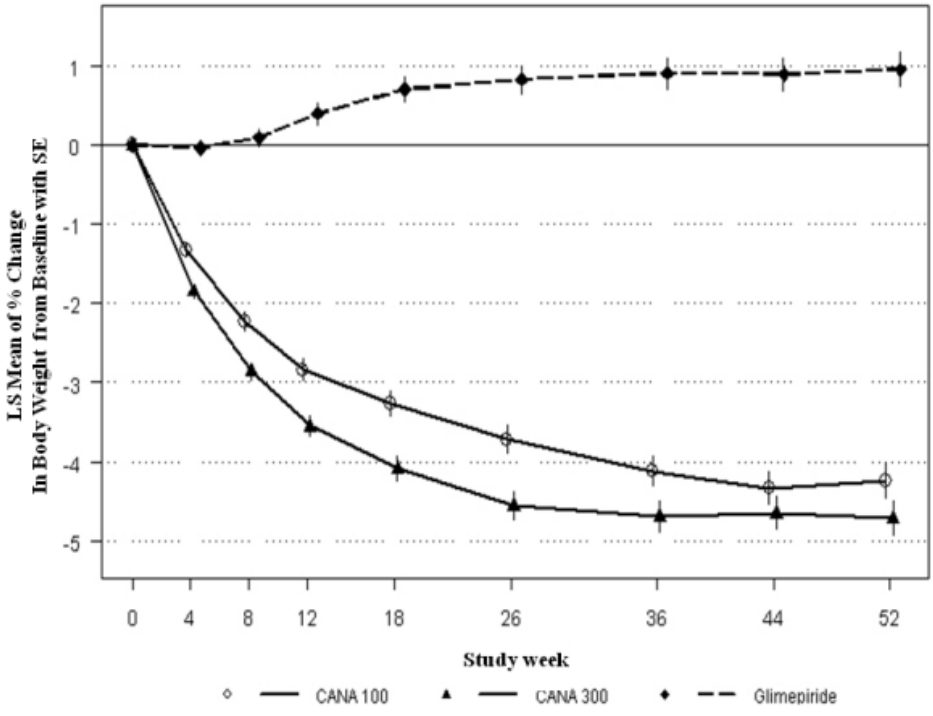
[4] $p<0.001$

[5] Includes only patients who had both baseline and post-baseline values

Figure 2. Mean Changes from Baseline for HbA_{1c} (%) 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

A total of 127 patients with inadequate glycemic control (HbA_{1c} of ≥ 7% to ≤ 10.5%) on sulfonylurea monotherapy participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicenter substudy of a cardiovascular 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 [CrCl 69 mL/min]. 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 11, statistically significant (p<0.001) improvements in HbA_{1c} and FPG relative to placebo were observed at Week 26. In addition, a greater percentage of patients achieved an HbA_{1c} < 7.0% compared to placebo. Fewer patients on INVOKANA™ required glycemic rescue therapy: 4.8% of patients receiving INVOKANA™ 100 mg, 0.0% of patients receiving INVOKANA™ 300 mg, and 17.8% of patients receiving placebo. Patients treated with INVOKANA™ 300 mg exhibited reductions in body weight compared to placebo. An increased incidence of hypoglycemia was observed in this study, consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to sulfonylurea (see *Warnings and Precautions* and *Adverse Reactions*).

Table 11. Results from Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Sulfonylurea[1]

	INVOKANA™ + Sulfonylurea 18 weeks		**Placebo + Sulfonylurea (N=45)**
Efficacy Parameter	**100 mg (N=42)**	**300 mg (N=40)**	
HbA_{1c} (%)			
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 HbA_{1c} < 7 %	25.0[3]	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] (-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 (-3.2; -0.4)	N/A[4]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	138	133.5	137.3
Change from baseline (adjusted mean)	-3.5	-5.1	-3.4
Difference from placebo (adjusted mean) (95% CI)	-0.1 (-6.5; 6.2)	-1.8 (-8.2; 4.7)	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

Table 11. Results from Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Sulfonylurea[1]

Efficacy Parameter	INVOKANA™ + Sulfonylurea 18 weeks		Placebo + Sulfonylurea (N=45)
	100 mg (N=42)	300 mg (N=40)	

[3] p<0.01
[4] N/A = Not applicable

Add-on therapy with metformin and sulfonylurea

A total of 469 patients with inadequate glycemic control (HbA_{1c} level of ≥ 7% to ≤ 10.5%) on the combination of metformin (2000 mg/day or at least 1500 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, multicenter 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 [CrCl 89 mL/min]. 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 12, statistically significant (p<0.001) improvements in HbA_{1c}, FPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an HbA_{1c} < 7.0% compared to placebo. Fewer patients on INVOKANA™ required glycemic rescue therapy: 1.3% of patients receiving INVOKANA™ 100 mg, 1.9% of patients receiving INVOKANA™ 300 mg, and 12.8% of patients receiving placebo. An increased incidence of hypoglycemia was observed in this study, consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to sulfonylurea (see *Warnings and Precautions* and *Adverse Reactions*).

Table 12. 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)	
HbA_{1c} (%)			
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 HbA_{1c} < 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			

Table 12. 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)	
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]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	130.4	130.8	130.1
Change from baseline (adjusted mean)	-4.9	-4.3	-2.6
Difference from placebo (adjusted mean) (95% CI)	-2.2 (-4.7; 0.2)	-1.6 (-4.1; 0.9)	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

A total of 755 patients with inadequate glycemic control (HbA_{1c} level of ≥ 7.0% to ≤ 10.5%) on the combination of metformin (2000 mg/day or at least 1500 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, multicenter 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 [CrCl 88 mL/min]. 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 13 and Figure 3, after 52 weeks, INVOKANA™ 300 mg provided a superior (p<0.05) reduction in HbA_{1c} 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 HbA_{1c} 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 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 HbA_{1c} thereafter) was lower with INVOKANA™ 300 mg (10.6%) compared with sitagliptin 100 mg (22.5%).

Table 13. 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)
HbA_{1c} (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)	-0.37[2] (-0.50; -0.25)	N/A[4]
Percent of patients achieving HbA_{1c} < 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]
Systolic Blood Pressure (mmHg)		
Baseline (mean)	131.2	130.1
Change from baseline (adjusted mean)	-5.1	0.9
Difference from sitagliptin (adjusted mean) (95% CI)	-5.9[3] (-7.6; -4.2)	N/A[4]

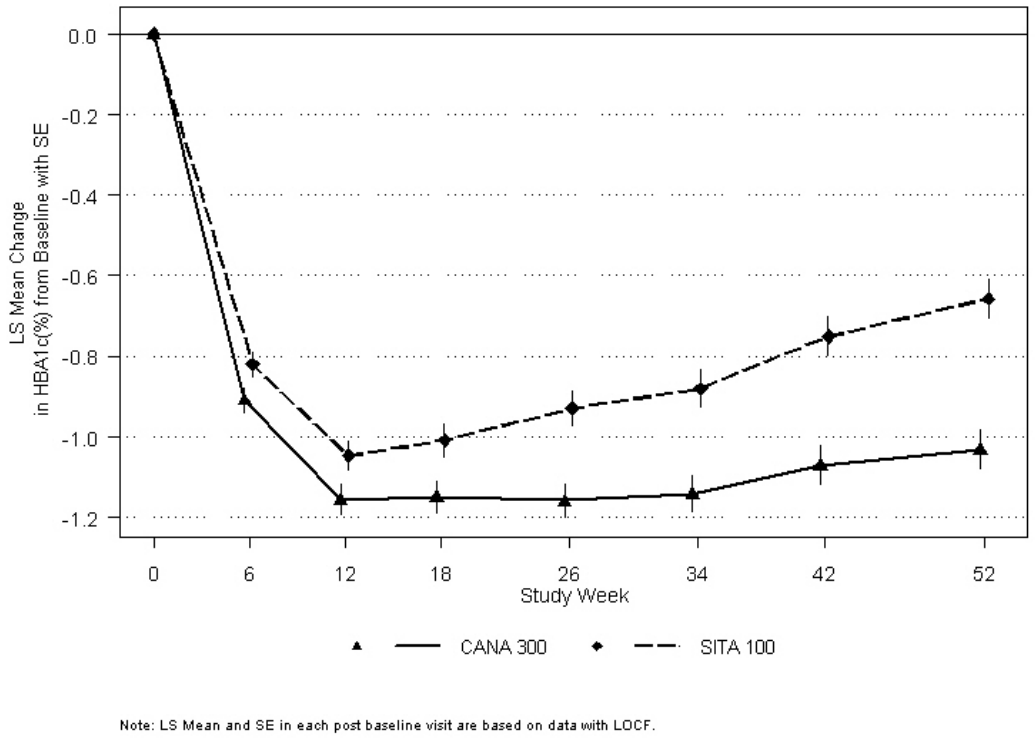
[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy

[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 HbA_{1c} relative to sitagliptin with INVOKANA™ 300 mg.

[3] $p<0.001$

[4] N/A = Not applicable

Figure 3. Mean Change from Baseline for HbA_{1c} (%) 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

A total of 342 patients with inadequate glycemic control (HbA_{1c} level of ≥ 7.0% to ≤ 10.5%) on the combination of metformin (2000 mg/day or at least 1500 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, multicenter 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 [CrCl 86 mL/min]. 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 14, statistically significant ($p<0.001$) improvements in HbA_{1c}, FPG, and body weight relative to placebo were observed for INVOKANA™ at Week 26. In addition, a greater percent of patients achieved an HbA_{1c} of < 7.0% compared to placebo. Fewer patients on INVOKANA™ required glycemic rescue therapy: 0.9% of patients receiving INVOKANA™ 100 mg, 0.0% of patients receiving INVOKANA™ 300 mg, and 12.2% of patients receiving placebo.

Table 14. 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)	
HbA_{1c} (%)			
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 HbA_{1c} < 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]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	126.4	126.7	128.2
Change from baseline (adjusted mean)	-5.3	-4.7	-1.2
Difference from placebo (adjusted mean) (95% CI)	-4.1 (-6.9; -1.3)	-3.5 (-6.3; -0.6)	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 or not measured in this study

Add-on combination therapy with metformin and dipeptidyl-peptidase-4-inhibitor

A total of 213 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 1500 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 m2 [CrCl 90.5 mL/min]. Patients already on the protocol-specified doses of metformin and sitagliptin (N=213) entered a 2-week, single-blind, placebo run-in period. Following the run-in period, patients were randomized to INVOKANA™ 100 mg or placebo, administered once daily as add-on to metformin and sitagliptin. Up-titration to INVOKANA™ 300 mg was made as early as Week 6 in patients requiring additional glycemic control who had appropriate eGFR and who were tolerating INVOKANA™ 100 mg.

At the end of treatment, INVOKANA™ once daily resulted in a statistically significant improvement in HbA1c (p<0.001) compared to placebo when added to metformin and sitagliptin. INVOKANA™ once daily also resulted in a statistically significant improvement in the proportion of patients achieving an HbA1c less than 7%, a statistically significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and sitagliptin (see Table 15). A statistically significant (p<0.001) mean change from

baseline in systolic blood pressure relative to placebo of -5.85 mmHg was observed with INVOKANA™ once daily. For patients taking INVOKANA™, the percentage experiencing an adverse event or discontinuing due to an adverse event occurred in 39.8% and 0.9%, respectively as compared with placebo which occurred in 44.4% and 2.8%, respectively.

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

Efficacy Parameter	Placebo + Metformin and Sitagliptin (N=106)	INVOKANA™ + Metformin and Sitagliptin (N=107)
HbA_{1c} (%)		
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 HbA_{1c} < 7%	12	32
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	180	186
Change from baseline (adjusted mean)	-3	-30
Difference from placebo (adjusted mean) (95% CI)†		-27‡ (-40; -14)
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)

* Intent-to-treat population
† Adjusted mean and CI are derived from a mixed model for repeated measures
‡ p<0.001

Add-on therapy with insulin (with or without other antihyperglycemic agents)

A total of 1,718 patients with inadequate glycemic control (HbA_{1c} 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, multicenter substudy of a cardiovascular study; this substudy evaluated the efficacy of INVOKANA™ as add-on therapy with insulin (with or without other antihyperglycemic agents) 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 [CrCl 75 mL/min]. 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.

As shown in Table 16, statistically significant (p<0.001) improvements in HbA_{1c}, FPG, and body weight relative to placebo were observed for INVOKANA™ at Week 18. In addition, a greater percentage of patients achieved an HbA_{1c} < 7.0% compared to placebo. Fewer patients on

INVOKANA™ required glycemic rescue therapy: 4.1% of patients receiving INVOKANA™ 100 mg, 3.1% of patients receiving INVOKANA™ 300 mg, and 8.7% of patients receiving placebo. An increased incidence of hypoglycemia was observed in this study, which is consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin (see *Warnings and Precautions* and *Adverse Reactions*).

Table 16. Results from 18-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Insulin ≥ 30 Units/Day (With or Without Other Oral Antihyperglycemic Agents)[1]

Efficacy Parameter	INVOKANA™ + Insulin 18 Weeks		Placebo + Insulin (N=565)
	100 mg (N=566)	300 mg (N=587)	
HbA_{1c} (%)			
Baseline (mean)	8.33	8.27	8.20
Change from baseline (adjusted mean)	-0.63	-0.72	0.01
Difference from placebo (adjusted mean) (95% CI)	-0.65[2] (-0.73; -0.56)	-0.73[2] (-0.82; -0.65)	N/A[3]
Percent of patients achieving HbA_{1c} < 7%	19.8[2]	24.7[2]	7.7
Fasting Plasma Glucose (mmol/L)			
Baseline	9.43	9.33	9.38
Change from baseline (adjusted mean)	-1.03	-1.39	0.22
Difference from placebo (adjusted mean) (97.5% CI)	-1.25[2] (-1.55; -0.96)	-1.61[2] (-1.90; - 1.31)	N/A[3]
Body Weight			
Baseline (mean) in kg	96.9	96.7	97.7
% change from baseline (adjusted mean)	-1.8	-2.3	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-1.9[2] (-2.2; -1.5)	-2.4[2] (-2.8; -2.0)	N/A[3]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	137.0	138.2	138.2
Change from baseline (adjusted mean)	-5.1	-6.9	-2.5
Difference from placebo (adjusted mean) (97.5% CI)	-2.6[2] (-4.1; -1.1)	-4.4[2] (-5.8; -2.9)	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

Studies in special populations

Study in older patients

A total of 714 older patients (≥ 55 to ≤ 80 years of age) with inadequate glycemic control (baseline HbA_{1c} 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 [CrCl 77 mL/min]. 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 17, statistically significant (p<0.001) changes from baseline in HbA_{1c}, FPG, and body weight were observed for INVOKANA™ at Week 26. In addition, a greater percent of patients achieved an

HbA_{1c} of < 7.0% compared to placebo. Fewer patients on INVOKANA™ required glycemic rescue therapy: 2.1% of patients receiving INVOKANA™ 100 mg, 0.4% of patients receiving INVOKANA™ 300 mg, and 11.0% of patients receiving placebo (see *Pharmacokinetic Properties - Special populations*).

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. There were no meaningful changes in bone density in trabecular and cortical regions.

Table 17. 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
	100 mg N=241	300 mg N=236	N=237
HbA_{1c} (%)			
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 HbA_{1c} < 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]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	130.6	131.1	131.4
Change from baseline (adjusted mean)[2]	−3.5	−6.8	1.1
Difference from placebo (adjusted mean)[2] (95% CI)	−4.6[2] (−6.9; −2.4)	−7.9[2] (−10.1; −5.6)	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

Patients with renal impairment

A total of 269 patients with moderate renal impairment and eGFR 30 to < 50 mL/min/1.73m^2 [CrCl 30 to < 50 mL/min] inadequately controlled on current diabetes therapy (baseline HbA_{1c} 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 [CrCl 39 mL/min]. 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 18, significant improvements in HbA_{1c} 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 $HbA_{1c} < 7.0\%$ compared to placebo. Fewer patients on INVOKANA™ required glycemic rescue therapy: 4.4% of patients receiving INVOKANA™ 100 mg, 3.4% of patients receiving INVOKANA™ 300 mg, and 14.4% of patients receiving placebo. Patients treated with INVOKANA™ exhibited mean decreases in percent change from baseline body weight compared to placebo. An increased incidence of hypoglycemia was observed in this study, consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin and/or sulfonylurea (see *Warnings and Precautions*, *Adverse Reactions*, and *Pharmacokinetic Properties - Special populations*).

Table 18. 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	
HbA_{1c} (%)			
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 $HbA_{1c} < 7\%$	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]
Systolic Blood Pressure (mmHg)			
Baseline (mean)	135.9	136.7	132.1
Change from baseline (adjusted mean)	-6.0	-6.4	-0.3
Difference from placebo (adjusted mean) (95% CI)	-5.7 (-9.5; -1.9)	-6.1 (-10.0; -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

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/1.73m^2 [CrCl 30 to < 60 mL/min]) from four placebo-controlled studies

was conducted to evaluate the change from baseline HbA_{1c} and percent change from baseline in body weight in these patients. The mean eGFR in this analysis was 48 mL/min/1.73m^2 [CrCl 48 mL/min], which was similar across all treatment groups. Most patients were on insulin and/or sulfonylurea.

This analysis demonstrated that INVOKANA™ provided statistically significant ($p<0.001$) improvements in HbA_{1c} and body weight compared to placebo (see Table 19). An increased incidence of hypoglycemia was observed in this integrated analysis, consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin and/or sulfonylurea (see *Warnings and Precautions* and *Adverse Reactions*).

Table 19. 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
HbA_{1c} (%)			
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

Cardiovascular outcomes

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 parallel group, 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.

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) after Week 13. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) and exposed for a mean of 149 weeks (exposed for a mean of 223 weeks in CANVAS and 94 weeks in CANVAS-R). Vital status was obtained for 99.6% of subjects across the studies. 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. The effects on the primary MACE composite outcome was consistent across all racial subgroups including Asians (with no evidence of statistical heterogeneity – see Figure 6).

All patients in the study had inadequately controlled type 2 diabetes mellitus at screening (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. Approximately 31%, 21% and 18% reported a past history of neuropathy, retinopathy and nephropathy, respectively. 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 [CrCl 77 mL/min]). At baseline, 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 89 mg/dL, the mean HDL was 46 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 115 mg/g. At baseline, approximately 80% of patients were treated with renin angiotensin system inhibitors, 54% with beta-blockers, 13% with loop diuretics, 36% with non-loop diuretics, 75% with statins, and 74% with antiplatelet agents (mostly aspirin).

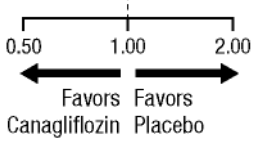
The primary endpoint in the CANVAS Program was the time to first occurrence of a MACE. The MACE HR in patients treated with canagliflozin compared with placebo and its 95% CI was estimated using a stratified Cox proportional hazards regression model with stratification by study and by established cardiovascular disease.

INVOKANA™ significantly reduced the risk of first occurrence of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (HR: 0.86; 95% CI 0.75, 0.97). Each MACE component contributed to the overall composite, as shown in Figure 4. Results for the 100 mg and 300 mg canagliflozin doses were consistent with results for the combined dose groups. The efficacy of INVOKANA™ on MACE was generally consistent across major demographic and disease subgroups, including presence or absence of established cardiovascular disease (see Figure 6).

There were 2,011 patients with eGFR 30 to < 60 mL/min/1.73 m^2 [CrCl 30 to < 60 mL/min]. The MACE findings in this subgroup were consistent with the overall findings (see Figure 6).

Figure 4. Treatment Effect for the Primary Composite Endpoint and its Components

	Placebo (n = 4347) Participants per 100 patient-years	Canagliflozin (n = 5795) Participants per 100 patient-years	Hazard ratio (95% CI)
Composite cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (time to first occurrence; intent-to-treat analysis set)[1]	3.15	2.69	0.86 (0.75–0.97)
Cardiovascular death	1.28	1.16	0.87 (0.72–1.06)
Nonfatal myocardial infarction	1.16	0.97	0.85 (0.69–1.05)
Nonfatal stroke	0.84	0.71	0.90 (0.71–1.15)



[1] P value for superiority (2-sided) = 0.0158.

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

Figure 5. Time to First Occurrence of MACE

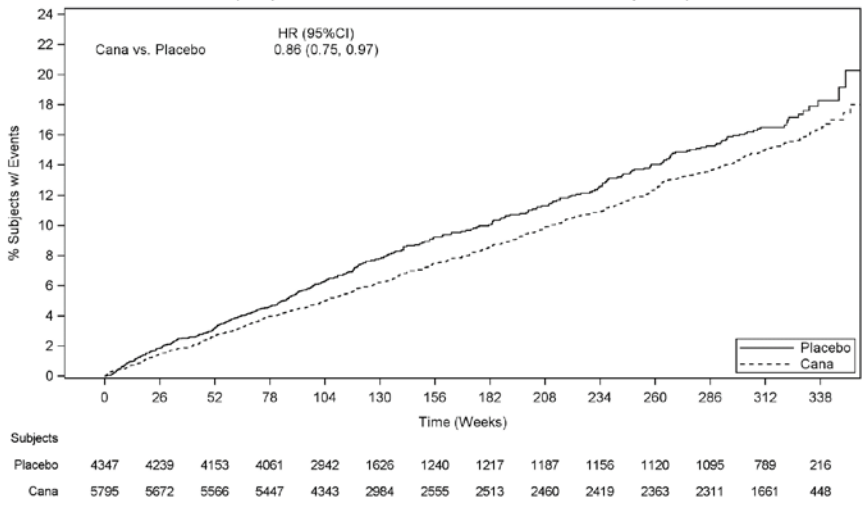
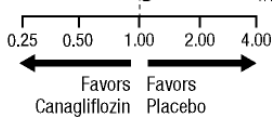


Figure 6. Effects of Canagliflozin on the Primary Cardiovascular Outcome (MACE) in Subgroups

Subgroup	Placebo Participants per 100 patient-years	Canagliflozin Participants per 100 patient-years	Hazard ratio (95% CI)	P Value
All patients	3.15	2.69	0.86 (0.75–0.97)	
Study				**0.60**
CANVAS	3.04	2.69	0.88 (0.75–1.03)	
CANVAS-R	3.30	2.71	0.82 (0.66–1.01)	
Age				**0.26**
<65 yr	2.36	2.20	0.91 (0.76–1.10)	
≥65 yr	4.23	3.38	0.80 (0.67–0.95)	
Sex				**0.80**
Male	3.51	2.98	0.86 (0.74–1.00)	
Female	2.50	2.17	0.84 (0.66–1.06)	
Race				**0.40**
White	3.42	2.91	0.84 (0.73–0.96)	
Black or African American	3.70	1.86	0.45 (0.19–1.03)	
Asian	1.84	1.88	1.08 (0.72–1.64)	
Other	2.45	2.53	1.01 (0.57–1.80)	
Region				**0.89**
North America	3.03	2.67	0.84 (0.65–1.09)	
Central/South America	3.38	2.67	0.84 (0.53–1.33)	
Europe	3.50	2.81	0.80 (0.65–0.99)	
Rest of the world	2.82	2.60	0.94 (0.75–1.18)	
BMI				**0.29**
<30 kg/m^2	2.78	2.56	0.97 (0.79–1.20)	
≥30 kg/m^2	3.40	2.78	0.79 (0.67–0.93)	
Blood pressure control				**0.64**
SBP ≥140 mmHg or DBP ≥90 mmHg	3.40	2.81	0.84 (0.70–1.01)	
SBP <140 mmHg and DBP <90 mmHg	2.95	2.61	0.88 (0.74–1.04)	
Duration of diabetes				**0.33**
≥10 yr	3.32	2.70	0.81 (0.70–0.95)	
<10 yr	2.77	2.66	0.96 (0.76–1.22)	
Glycated hemoglobin				**0.29**
<8%	2.69	2.47	0.94 (0.77–1.15)	
≥8%	3.53	2.88	0.80 (0.68–0.94)	
eGFR				**0.20**
30 to <60 ml/min/1.73 m^2	4.93	3.64	0.70 (0.55–0.90)	
60 to <90 ml/min/1.73 m^2	2.90	2.68	0.95 (0.80–1.13)	
≥90 ml/min/1.73 m^2	2.36	2.08	0.84 (0.62–1.12)	
History of CV disease				**0.18**
Yes	4.13	3.41	0.82 (0.72–0.95)	
No	1.55	1.58	0.98 (0.74–1.30)	
History of peripheral vascular disease				**0.47**
Yes	4.32	3.39	0.75 (0.58–0.97)	
No	2.88	2.54	0.89 (0.77–1.03)	
History of heart failure*				**0.51**
Yes	5.14	4.22	0.80 (0.61–1.05)	
No	2.83	2.48	0.87 (0.76–1.01)	
History of amputation				**0.36**
Yes	7.43	4.44	0.56 (0.28–1.13)	
No	3.08	2.65	0.86 (0.76–0.98)	
Insulin use				**0.96**
Yes	3.74	3.20	0.85 (0.72–1.00)	
No	2.56	2.19	0.87 (0.71–1.06)	
Statin use				**0.45**
Yes	3.16	2.63	0.84 (0.72–0.97)	
No	3.11	2.88	0.91 (0.71–1.16)	
Antithrombotic use				**0.85**
Yes	3.48	3.02	0.87 (0.75–1.00)	
No	2.25	1.85	0.82 (0.61–1.09)	
RAAS inhibitor use				**0.38**
Yes	3.14	2.76	0.88 (0.76–1.01)	
No	3.18	2.44	0.77 (0.58–1.03)	
Beta-blocker use				**0.01**
Yes	3.90	2.95	0.75 (0.64–0.88)	
No	2.32	2.42	1.04 (0.85–1.28)	
Diuretic use				**0.0001**
Yes	4.10	2.76	0.66 (0.56–0.79)	
No	2.40	2.64	1.11 (0.93–1.34)	



NOTE: The figure above presents effects of MACE in various subgroups most of which are baseline characteristics and which were pre-specified (except heart failure, as noted by the asterisk). The 95% confidence intervals (CIs) that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment of other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted. The p value of <0.05 represents significance for subgroup heterogeneity.

Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Diabetic Kidney Disease

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 kidney disease with (eGFR) ≥ 30 to < 90 mL/min/1.73 m^2 [CrCl ≥ 30 to < 90 mL/min] and albuminuria (> 300 to ≤ 5000 mg/g 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™ 100 mg or placebo, stratified by screening estimated glomerular filtration rate (eGFR) ≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min/1.73 m^2 [CrCl ≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min]. Treatment with INVOKANA™ 100 mg was continued in patients until the initiation of dialysis or in the event of renal transplantation.

A total of 4,401 subjects were randomized (2,199 randomly assigned to placebo and 2,202 to INVOKANA™ 100 mg). Four of the randomized subjects were not dosed, leading to 4,397 subjects (exposed for a mean of 115 weeks) in both On-Study and On-Treatment analysis sets. 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 HbA_{1c} was 8.3%, with 53.2% of subjects having baseline HbA_{1c} ≥ 8%, and baseline median urine albumin/creatinine was 927 mg/g. 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 [CrCl 56.2 mL/min] and approximately 60% of the population had a baseline eGFR of < 60 mL/min/1.73 m^2 [CrCl < 60 mL/min]. 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 kidney disease and another microvascular complication).

The primary composite endpoint in the CREDENCE study was the time to first occurrence of ESKD (defined as an eGFR < 15 mL/min/1.73 m^2 [CrCl < 15 mL/min], initiation of chronic dialysis or renal transplant), doubling of serum creatinine, and renal or CV death.

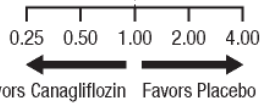
INVOKANA™ 100 mg significantly reduced the risk of first occurrence of the primary composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death [p<0.0001; HR: 0.70; 95% CI: 0.59, 0.82] (see Figure 8). Additionally, each individual component was consistent with the overall results of the primary composite endpoint as shown in Figure 7. The efficacy of INVOKANA™ 100 mg on primary endpoint composite was generally consistent across major demographic and disease subgroups, including all three eGFR strata and subjects with or without a history of CV disease.

INVOKANA™ 100 mg significantly reduced the risk of the following secondary endpoints, as shown in Figure 7 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: 0.47 to 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 was 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 <90 mL/min/1.73 m^2) [CrCl ≥30 to <45, ≥45 to <60, ≥60 to <90 mL/min].

Figure 7: Treatment Effect for the Primary and Secondary Composite Endpoints and their Components

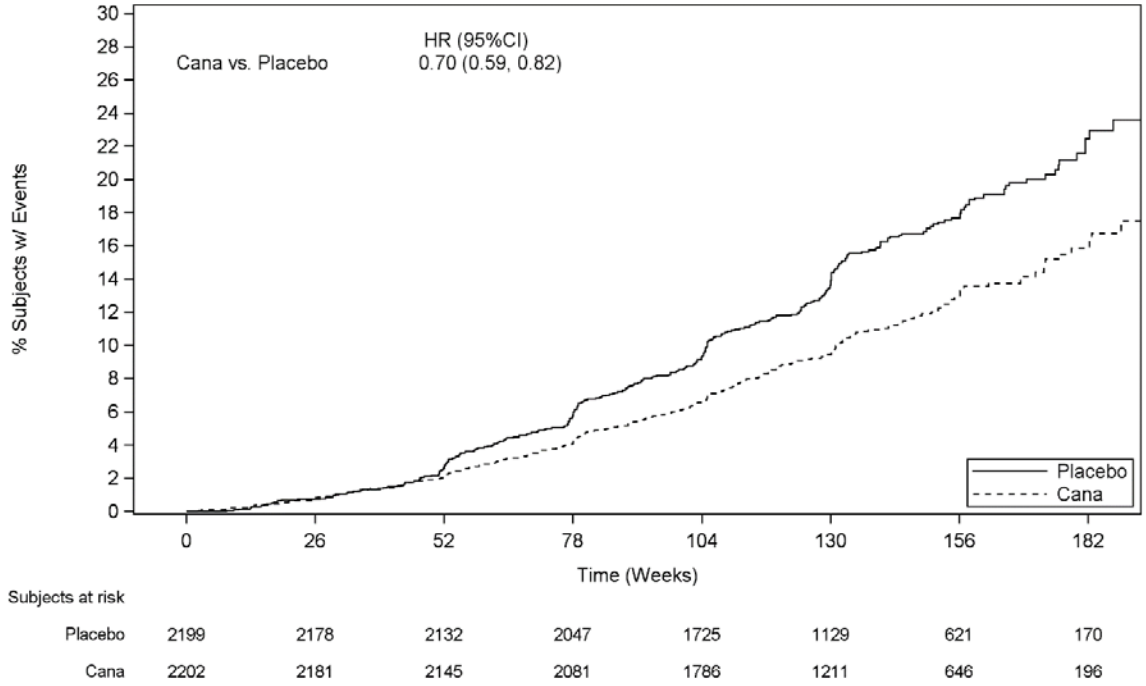
Endpoint	Placebo n/N (%)	Placebo Event rate per 100 patient-years	Canagliflozin n/N (%)	Canagliflozin Event rate per 100 patient-years	Hazard ratio (95% CI)	*P* value*
Primary composite endpoint*	340/2199 (15.5)	6.12	245/2202 (11.1)	4.32	0.70 (0.59, 0.82)	<0.0001
ESKD	165/2199 (7.5)	2.94	116/2202 (5.3)	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
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)	–
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.

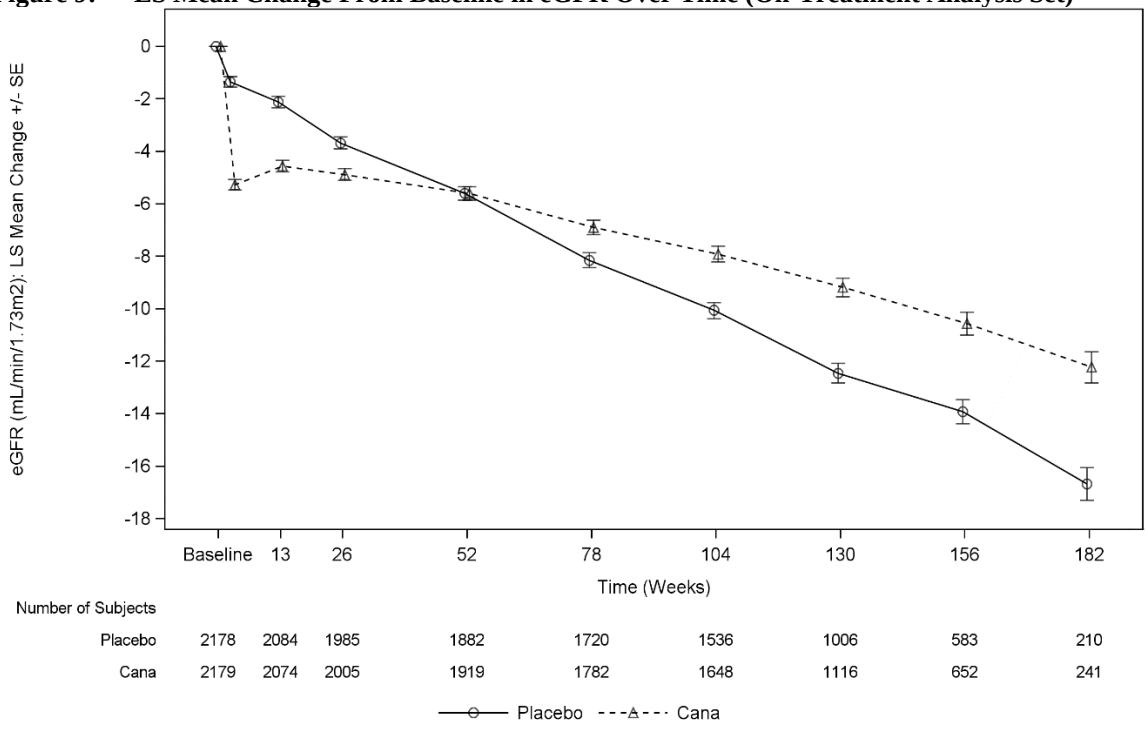
Based on the Kaplan-Meier plot for the time to first occurrence of the primary composite endpoint shown below, curves began to separate by Week 52 and continued to diverge thereafter.

Figure 8: CREDENCE: Time to First Occurrence of the Primary Composite Endpoint



As shown in Figure 9, the eGFR in placebo-treated patients demonstrated a progressive linear decline over time; in contrast, the canagliflozin group showed an acute decrease at Week 3, followed by an attenuated decline over time; after Week 52, the LS mean decrease in eGFR was smaller in the canagliflozin group than in the placebo group, and the treatment effect was maintained through the end of treatment.

Figure 9: LS Mean Change From Baseline in eGFR Over Time (On-Treatment Analysis Set)



Diabetic comorbidities

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N=2313), mean reductions in systolic blood pressure relative to placebo were observed with INVOKANA™ 100 mg (-3.9 mmHg), INVOKANA™ 300 mg (-5.3 mmHg), and placebo (-0.1 mmHg) regardless of antihypertensive medication use at baseline. In this same population, there was a smaller effect on diastolic blood pressure with mean changes of -2.1 mmHg with INVOKANA™ 100 mg, -2.5 mmHg with INVOKANA™ 300 mg, and -0.3 mmHg with placebo, regardless of antihypertensive medication use at baseline. There was no discernible change in heart rate.

Lipid effects

In an integrated analysis of four placebo-controlled studies of 26 weeks, patients with type 2 diabetes treated with both doses of INVOKANA™ had increased serum levels of total cholesterol, LDL-C, and HDL-C (high-density lipoprotein cholesterol) compared to small changes in placebo, while serum levels of triglycerides decreased compared to placebo (see Table 20). At Week 26, the LDL-C/HDL-C ratio minimally changed compared to baseline in all three treatment groups. Similar to changes in non-HDL-C, apolipoprotein B and LDL-C particle number (measured in the monotherapy and 26-week metformin add-on therapy study) increased to a smaller extent compared to LDL-C changes (see *Adverse Reactions*).

Table 20. Effect of INVOKANA™ on Lipid Measurements in Four 26-Week Placebo-Controlled Studies[1]

	INVOKANA™ 100 mg (N=833)	INVOKANA™ 300 mg (N=834)	Placebo (N=646)
Total cholesterol			
Baseline mean (median) in mmol/L	4.89 (4.81)	4.81 (4.73)	4.96 (4.87)
Least squares mean (median) change in mmol/L	0.10 (0.10)	0.18 (0.21)	-0.02 (-0.04)
Least squares mean (median) % change in total cholesterol	3.4 (2.0)	5.2 (4.7)	0.9 (-0.8)
LDL-C			
Baseline mean (median) in mmol/L	2.76 (2.74)	2.70 (2.64)	2.83 (2.74)
Least squares mean (median) change in mmol/L	0.06 (0.05)	0.15 (0.15)	-0.06 (-0.05)
Least squares mean (median) % change in LDL-C	5.7 (2.0)	9.3 (6.0)	1.3 (-2.3)
HDL-C			
Baseline mean (median) in mmol/L	1.19 (1.14)	1.20 (1.16)	1.17 (1.14)
Least squares mean (median) change in mmol/L	0.09 (0.08)	0.11 (0.11)	0.03 (0.05)
Least squares mean (median) % change in HDL-C	9.4 (7.8)	10.3 (9.6)	4.0 (3.5)
Non-HDL-C			
Baseline mean (median) in mmol/L	3.70 (3.60)	3.61 (3.52)	3.79 (3.70)
Least squares mean (median) change in mmol/L	-0.00 (-0.01)	0.07 (0.08)	-0.06 (-0.08)
Least squares mean (median) % change in non-HDL-C	2.2 (-0.3)	4.3 (2.0)	0.7 (-2.4)
LDL-C/HDL-C Ratio			
Baseline mean (median)	2.5 (2.4)	2.4 (2.3)	2.5 (2.4)
Least squares mean (median) change	-0.1 (-0.1)	-0.1 (-0.1)	-0.2 (-0.1)
Least squares mean (median) % change in ratio	-1.4 (-5.2)	0.8 (-2.1)	-0.8 (-6.5)
Triglycerides			
Baseline mean (median) in mmol/L	2.06 (1.73)	2.04 (1.70)	2.10 (1.85)
Least squares mean (median) change in mmol/L	-0.11 (-0.10)	-0.22 (-0.13)	-0.00 (-0.03)
Least squares mean (median) % change in triglycerides	2.4 (-6.0)	0.0 (-9.2)	7.6 (-2.2)

[1] As monotherapy or add-on therapy with metformin, metformin and sulfonylurea, and metformin and pioglitazone

Patients with baseline HbA_{1c} > 10% to ≤ 12%

A substudy of patients with baseline HbA_{1c} > 10 to ≤ 12% with canagliflozin as monotherapy resulted in reductions from baseline in HbA_{1c} of -2.13% and -2.56% for canagliflozin 100 mg and 300 mg, respectively.

Fasting plasma glucose

In four placebo-controlled studies, treatment with INVOKANA™ as monotherapy or add-on therapy with one or two oral antihyperglycemic drugs resulted in mean changes from baseline relative to placebo in FPG of -1.2 mmol/L to -1.9 mmol/L for INVOKANA™ 100 mg

and -1.9 mmol/L to -2.4 mmol/L for INVOKANA™ 300 mg, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.

Post-prandial glucose

Using a standardized mixed meal tolerance test, post-prandial glucose was measured in three placebo-controlled clinical studies as monotherapy or add-on therapy with one or two oral antihyperglycemic drugs. INVOKANA™ resulted in mean change reductions from baseline relative to placebo in postprandial glucose of -1.5 mmol/L to -2.7 mmol/L for INVOKANA™ 100 mg and -2.1 mmol/L to -3.5 mmol/L for INVOKANA™ 300 mg, respectively, due to reductions in the pre-meal glucose concentration and reduced post-prandial glucose excursions.

Beta-cell function

Clinical studies in a subset of patients with type 2 diabetes (N=297) with INVOKANA™ for 26 weeks indicate improved beta-cell function based on measures such as the homeostasis model assessment for beta-cell function (HOMA2-%B) and the improved insulin secretion rate with mixed-meal tolerance testing.

Hospitalized heart failure

Hospitalized heart failure was set as an exploratory endpoint. In a long-term cardiovascular outcome study, subjects treated with INVOKANA™ had a lower risk of hospitalized heart failure compared to those treated with placebo.

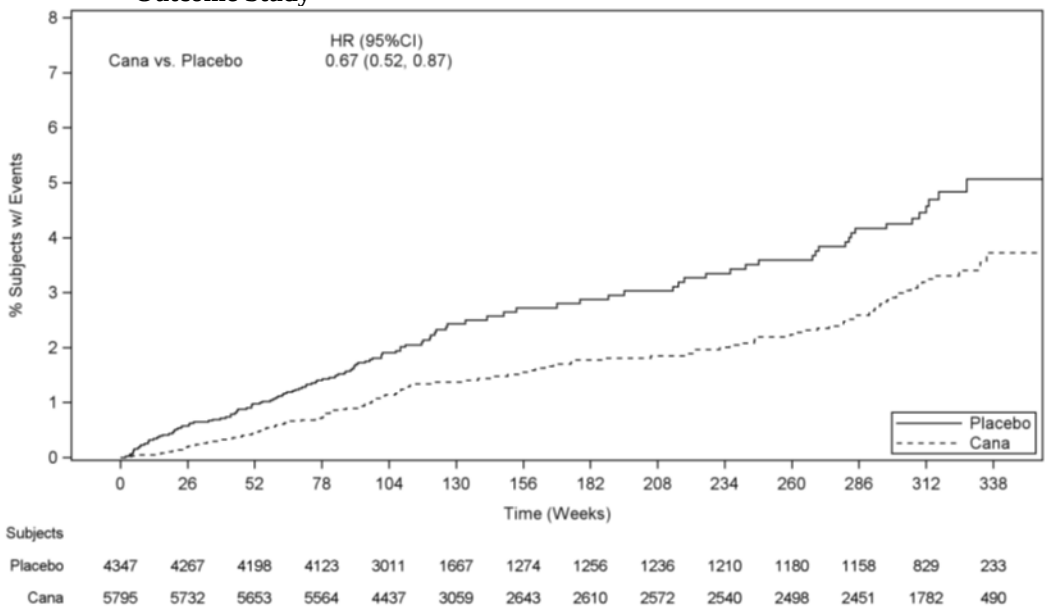
Table 21. In a Long-term Cardiovascular Outcome Study, Treatment Effect for Hospitalized Heart Failure and the Composite of Cardiovascular Death and Hospitalized Heart Failure

	Placebo N=4,347 Event rate per 100 patient-years	**INVOKANA™ N=5,795 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]
Composite of cardiovascular death and hospitalized heart failure (time to first occurrence; intent-to-treat analysis set)	2.08	1.63	0.78 (0.67, 0.91)[2]

[1] p=0.0021; nominal value

[2] p=0.0019; nominal value

Figure 10. Time to First Occurrence of Hospitalization of Heart Failure in a Long-term Cardiovascular Outcome Study



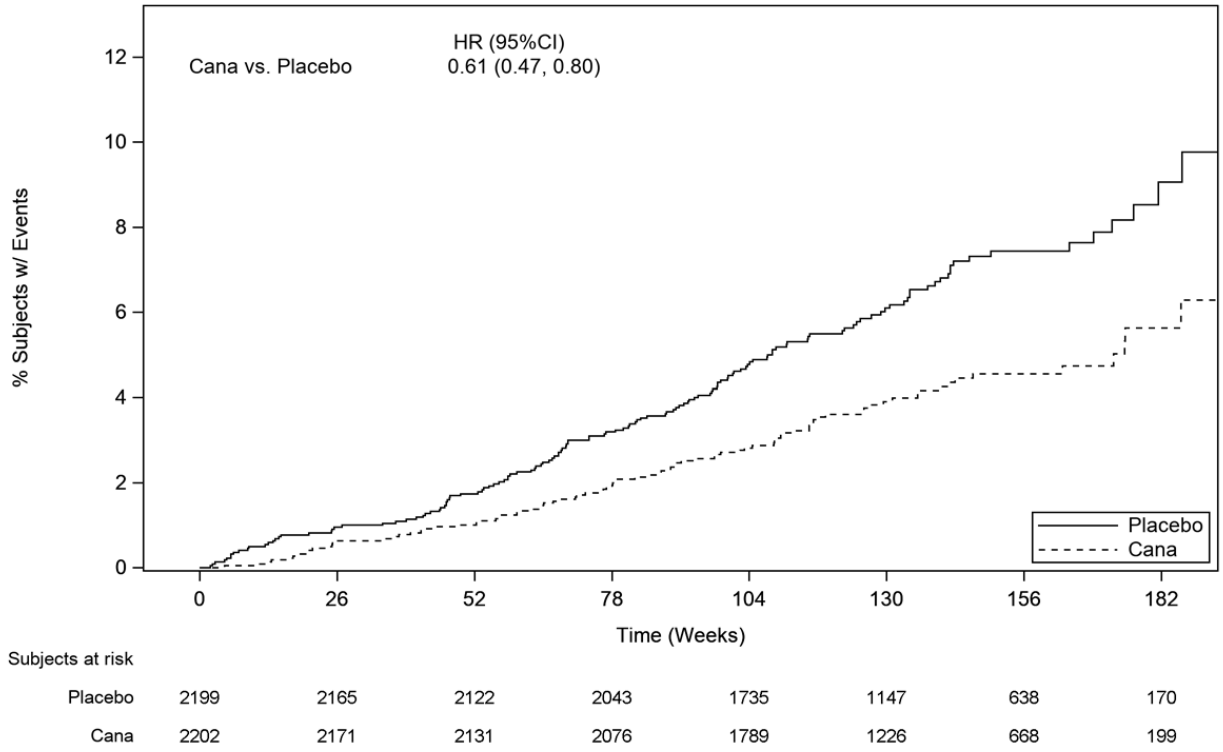
In a long-term renal outcome study, subjects treated with INVOKANA™ had a lower risk of hospitalized heart failure compared to those treated with placebo.

Table 22: In a Long-term Renal Outcome Study, Treatment Effect for Hospitalized Heart Failure and the Composite of Cardiovascular Death and Hospitalized Heart Failure

	Placebo N=2199 Event rate per 100 patient-years	**INVOKANA™ N=2202 Event rate per 100 patient-years**	**Hazard ratio vs. Placebo (95% CI)**
Hospitalized heart failure (time to first occurrence; intent-to-treat analysis set)	2.53	1.57	0.61 (0.47, 0.80)[1]
Composite of cardiovascular death and hospitalized heart failure (time to first occurrence; intent-to-treat analysis set)	4.54	3.15	0.69 (0.57, 0.83)[2]

[1] p=0.0003
[2] p=0.0001

Figure 11: Time to First Occurrence of Hospitalized Heart Failure in a Long-term Renal Outcome Study



Pharmacokinetic Properties

The pharmacokinetics of canagliflozin are essentially similar in healthy subjects and patients with type 2 diabetes. 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 and 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.

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 83.5L, 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. Increases in AUC of canagliflozin (26% and 18%) were observed in subjects carrying the UGT1A9*3 allele and UGT2B4*2 allele, respectively. These increases in canagliflozin exposure are not expected to be clinically relevant. CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

Elimination

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

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as O-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance 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

Renal impairment

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 $\geq$ 90 mL/min/1.73m^2 [CrCl $\geq$ 90 mL/min]), 10 subjects with mild renal impairment (eGFR 60 to < 90 mL/min/1.73m^2 [CrCl 60 to < 90 mL/min]), 9 subjects with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73m^2 [CrCl 30 to < 60 mL/min]), and 10 subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73m^2 [CrCl 15 to < 30 mL/min]) 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 (see *Dosage and Administration, Warnings and Precautions,* and *Adverse Reactions*).

Canagliflozin was negligibly removed by hemodialysis.

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

These differences are not considered to be clinically meaningful. 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.

Elderly (≥ 65 years of age)
Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis (see *Dosage and Administration*, *Warnings and Precautions*, and *Adverse Reactions*).

Pediatrics (< 18 years of age)
A pediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus who were on a stable dose of metformin. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. The safety and efficacy of INVOKANA™ in the pediatric population have not been established.

Other populations
No dose adjustment is necessary based on gender, race/ethnicity, or body mass index. These characteristics had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis.

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

Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone (LH), increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg). In a 12-week clinical study, LH did not increase in males treated with canagliflozin.

Renal tubular adenoma and carcinoma increased significantly in male and female rats dosed 100 mg/kg, or approximately 12-times exposure from a 300 mg clinical dose. Also, adrenal pheochromocytoma increased significantly in males and numerically in females dosed 100 mg/kg. Carbohydrate malabsorption associated with high doses of canagliflozin was considered a necessary proximal event in the emergence of renal and adrenal tumors in rats.

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

Mutagenesis

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay.

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

Impairment of Fertility

Canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (approximately 14 times and 18 times the 300 mg clinical dose in males and females, respectively), although there were minor alterations in a number of reproductive parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered.

Reproduction and Development

In a juvenile toxicity study in which canagliflozin was dosed directly 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 renal pelvic and renal tubular dilatation were reported at all dose levels. Exposure at the lowest dose tested was greater than or equal to 0.5 times the maximum clinical dose of 300 mg. The renal pelvic dilatations observed in juvenile animals did not fully reverse within the 1-month recovery period. Similar effects on the developing kidney were not seen when canagliflozin was administered to pregnant rats or rabbits during the period of organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21 and pups were indirectly exposed *in utero* and throughout lactation.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis in humans. No developmental toxicities were observed at any dose tested other than a slight increase in the number of fetuses with reduced ossification at a dose that was associated with maternal toxicity and that is approximately 19 times the human exposure to canagliflozin at the 300 mg clinical dose.

PHARMACEUTICAL INFORMATION

List of Excipients

The canagliflozin tablet core contains croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The film-coating contains iron

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

Incompatibilities
Not applicable.

Shelf Life
See expiry date on the outer pack.

Storage Conditions
Do not store above 30°C. Keep out of the sight and reach of children.

Nature and Contents of Container
Polyvinylchloride (PVC)/aluminum blisters containing 10 tablets per blister.

Pack Size
10’s x1, 10’s x3, 10’s x9, 10’s x10

Instructions for Use and Handling
No special requirements.

PRODUCT REGISTRANT
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#07-13, Ascent
Singapore Science Park 1
Singapore 118222

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