

INVOKANA™

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 to improve glycemic control in adults with type 2 diabetes mellitus.

Dosage and Administration

Dosage – Adults 18 years of age and older

The recommended dose of INVOKANA is 100 mg or 300 mg once daily. The 300 mg dose may be considered for patients with an eGFR ≥ 60 mL/min/1.73 m² [*CrCl* ≥ 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 ≥ 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*).

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*).

Renal impairment

In patients with an estimated glomerular filtration rate (eGFR) 45 to < 60 mL/min/1.73 m² [*CrCl* 45 to < 60 mL/min], the dose of INVOKANA is limited to 100 mg once daily. INVOKANA should not be initiated in patients with an eGFR < 45 mL/min/1.73 m² [*CrCl* < 45 mL/min]. INVOKANA should be discontinued when eGFR is persistently < 45 mL/min/1.73 m² [*CrCl* < 45 mL/min] (see *Warnings and Precautions* and *Adverse Reactions*).

INVOKANA should not be used in patients with an eGFR < 45 mL/min/1.73 m² [*CrCl* < 45 mL/min] as it would not be effective in these patient populations (see *Warnings and Precautions* and *Pharmacokinetic Properties - Special populations*).

Contraindications

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 been established. Use of INVOKANA should be avoided in these patients.

INVOKANA should not be used for the treatment of diabetic ketoacidosis (DKA) or in patients with an eGFR < 45 mL/min/1.73 m² [*CrCl* < 45 mL/min] as it would not be effective in these settings.

Diabetic ketoacidosis

Patients with a history of diabetic ketoacidosis (DKA) were excluded from clinical trials. 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.

Type 1 diabetes mellitus

There is an increased risk of DKA in patients with type 1 diabetes mellitus who take INVOKANA. In an 18-week clinical study (N=351), DKA was reported in 5.1% (6/117), 9.4% (11/117), and 0.0% (0/117) of patients on INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. The DKA events required hospitalization in 12 patients. Five of these patients presented with blood glucose values less than 13.9 mmol/L [250 mg/dL]. Concomitant conditions (e.g., infection, cessation of insulin therapy) known to increase the risk of developing DKA were identified in most patients.

Type 2 diabetes mellitus

In patients with type 2 diabetes mellitus, DKA has been reported with the use of INVOKANA. In the clinical development program, serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were reported in 0.09% (10/10687) of patients treated with INVOKANA, all 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. Consider interrupting treatment with INVOKANA in patients with type 2 diabetes who are hospitalized for major surgical procedures or acute serious medical illnesses. Treatment with INVOKANA may be restarted once the patient's condition has stabilized.

Lower limb amputation

In long-term clinical studies of INVOKANA in type 2 diabetes patients with established cardiovascular disease (CVD) or at least two risk factors for CVD, an approximately 2-fold increased risk of lower limb amputation (primarily of the toe and midfoot) has been observed in patients treated with INVOKANA (see *Adverse Reactions*). 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.

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 m² [*CrCl* < 60 mL/min]. INVOKANA should not be used in patients with an eGFR < 45 mL/min/1.73 m² [*CrCl* < 45 mL/min].

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*).

Genital mycotic infections

Consistent with the mechanism of SGLT2 inhibition with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical trials (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 8 controlled trials, 0.2% of male patients underwent circumcision. 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 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, phenobarbital, 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 m² [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 1: 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)
Hydrochlorothiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
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.

[Table 2: 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)
			Levo-norgestrel	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	Hydrochloro-thiazide	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_{0-12h}]

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. A causal relationship with canagliflozin cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of INVOKANA (canagliflozin) was evaluated in 10285 patients with type 2 diabetes, including 3139 patients treated with INVOKANA 100 mg and 3506 patients treated with INVOKANA 300 mg in nine double-blind, controlled Phase 3 clinical studies.

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} (A_{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 3 lists adverse reactions reported in ≥ 2% of INVOKANA-treated patients in the four pooled, 26-week, placebo-controlled clinical studies (N=2313).

Table 3: Adverse Reactions From Four Pooled 26-Week Placebo-Controlled Studies¹ Reported in ≥ 2% of INVOKANA-Treated Patients

System Organ Class Adverse Reaction	INVOKANA	INVOKANA	Placebo
	100 mg N=833	300 mg N=834	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			
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,

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.

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 serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5337), 0.0763 (0.11%, 6/5350), and 0.0238 (0.03%, 2/6909) per 100 patient-years with INVOKANA 100 mg, INVOKANA 300 mg, and comparator, respectively. Of the 10 patients on INVOKANA, 6 (3 on INVOKANA 100 mg, 3 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 8 of the 10 patients were receiving insulin therapy. The blood glucose values in 9 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]. One patient 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*).

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 approximately 2-fold 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 trials evaluating 10142 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 4. In other type 2 diabetes studies with INVOKANA, which enrolled a general diabetic population of 8114 patients, no difference in lower limb amputation risk was observed relative to control.

Table 4: 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.

* 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 4). 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 the dedicated cardiovascular study, where patients were generally older with a higher prevalence of comorbidities, the incidences of adverse reactions related to reduced intravascular volume were 2.8% with INVOKANA 100 mg, 4.6% with INVOKANA 300 mg, and 1.9% with placebo.

To assess risk factors for these adverse reactions, a larger pooled analysis (N=9439) of patients from eight controlled Phase 3 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 m²) [(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 incidences were 3.2% on INVOKANA 100 mg and 8.8% on INVOKANA 300 mg compared to 4.7% in the control group. For patients with a baseline eGFR < 60 mL/min/1.73 m² [CrCl < 60 mL/min], the incidences were 4.8% on INVOKANA 100 mg and 8.1% on INVOKANA 300 mg compared to 2.6% in the control group. In patients ≥ 75 years of age, the incidences were 4.9% on INVOKANA 100 mg and 8.7% on INVOKANA 300 mg compared to 2.6% 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, discontinuations due to adverse reactions related to reduced intravascular volume and serious adverse reactions related to reduced intravascular volume were not increased with INVOKANA.

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*).

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 candidal balanitis or balanoposthitis. Phimosis was reported in 0.3% of uncircumcised males in a pooled analysis of 8 controlled trials. In this pooled analysis, circumcision was also reported in 0.2% of male patients treated with canagliflozin (see *Warnings and Precautions*).

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 of 4327 patients with known or at high risk for cardiovascular disease, the incidence rates of bone fracture were 16.3, 16.4, and 10.8 per 1000 patient years of exposure to INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with INVOKANA, which enrolled a general diabetes population of approximately 5800 patients, no difference in fracture risk was observed relative to control. 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.

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.

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 trials, the mean percent change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. Episodes of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were seen in 0.6% and 1.6% of patients treated with INVOKANA 100 mg and 300 mg, respectively, compared to 1.3% of patients treated with placebo.

Decreases in serum urate

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

Cardiovascular safety

A prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from Phase 2 and 3 clinical studies in 9632 patients with type 2 diabetes, including 4327 patients who are participating in an ongoing cardiovascular study (patients with cardiovascular disease or at high risk for cardiovascular disease) was conducted. The hazard ratio for the primary endpoint (time to event in composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and unstable angina requiring hospitalization) for INVOKANA (both doses pooled) versus combined active and placebo comparators was 0.91 (95% CI: 0.68, 1.22). The hazard ratios for the 100 mg and 300 mg doses were similar. Therefore, there was no evidence of an increase in cardiovascular risk with either INVOKANA 100 mg or INVOKANA 300 mg relative to comparators.

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

incidences of 4.9%, 8.7%, and 2.6% on INVOKANA 100 mg, INVOKANA 300 mg, and the control group, respectively. Decreases in eGFR (-3.6% and -5.2%) were reported with INVOKANA 100 mg and 300 mg, respectively, compared to the control group (-3.0%) (see *Dosage and Administration* and *Warnings and Precautions*).

Patients with an eGFR 45 to < 60 mL/min/1.73 m² [CrCl 45 to < 60 mL/min]

In an analysis of patients with a baseline eGFR 45 to < 60 mL/min/1.73 m² [CrCl 45 to < 60 mL/min], the incidences of adverse reactions related to reduced intravascular volume were 4.6% with INVOKANA 100 mg and 7.1% with INVOKANA 300 mg relative to 3.4% with placebo (see *Dosage and Administration* and *Warnings and Precautions*). Serum creatinine levels increased by 4.9% and 7.3% for INVOKANA 100 mg and 300 mg, respectively, relative to 0.2% with placebo. BUN levels increased by 13.2% and 13.6% for INVOKANA 100 mg and 300 mg, respectively, relative to 0.7% with placebo. The proportion of patients with larger decreases in eGFR (> 30%) at any time during treatment was 6.1%, 10.4%, and 4.3% with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. At study endpoint, 2.3% of patients treated with INVOKANA 100 mg, 4.3% with INVOKANA 300 mg, and 3.5% with placebo had such decreases (see *Warnings and Precautions*).

The incidences of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 5.2% with INVOKANA 100 mg, 9.1% with INVOKANA 300 mg, and 5.5% with 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.

Serum phosphate levels increased by 3.3% and 4.2% for INVOKANA 100 mg and 300 mg, respectively, compared to 1.1% for placebo. The incidences of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 1.4% with INVOKANA 100 mg, 1.3% with INVOKANA 300 mg and 0.4% with placebo. In general, elevations were transient and did not require specific treatment.

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 5: 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	Rare
Renal failure (related to volume depletion)	Very rare	Uncommon
Urosepsis	Very rare	Rare

* Postmarketing spontaneous reporting rates were based on estimated exposure of person-years of treatment

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. Other blood glucose lowering drugs, excluding insulin, ATC code: A10BX11

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.

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

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 10285 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 3082 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/1.73 m² (N=269) and three other studies included patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²) (N=816).

In patients with type 2 diabetes, treatment with INVOKANA produced clinically and statistically significant improvements in A_{1C}, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG), compared to placebo. INVOKANA was effective in reducing A_{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 A_{1C} were observed with INVOKANA in subjects with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²) and in older patients. Reductions in A_{1C} were observed across subgroups including age, gender, race, baseline body mass index (BMI), and baseline beta-cell function. Greater reductions in A_{1C} relative to placebo were observed in patients with higher baseline A_{1C} or eGFR values (see Pharmacokinetic Properties).

Monotherapy

A total of 584 patients with inadequate glycemic control (A_{1C} of $\geq 7\%$ to $\leq 10\%$) 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 m². 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 6, statistically significant ($p < 0.001$) improvements in A_{1C}, FPG, PPG, body weight, and systolic blood pressure

relative to placebo were observed. In addition, a greater percentage of patients achieved an A_{1C} < 7.0% compared to placebo.

Patients who were not eligible for inclusion in the main placebo-controlled study due to more severe hyperglycemia (A_{1C} > 10 and ≤12%) participated in a separate active-treatment substudy (N=91) and were treated with either INVOKANA 100 mg or INVOKANA 300 mg (see Table 6).

Table 6: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA as Monotherapy¹

<i>Efficacy Parameter</i>	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)	Placebo (N=192)
A_{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 A_{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 A_{1C} Levels (> 10 to ≤12%)			
	INVOKANA 100 mg (N=47)	INVOKANA 300 mg (N=44)	
Efficacy Parameter			
A_{1C} (%)			
Baseline (mean)	10.59	10.62	
Change from baseline (adjusted mean)	-2.13	-2.56	
Percent of Patients Achieving A_{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 1284 patients with inadequate glycemic control (A_{1C} of $\geq 7\%$ to $\leq 10.5\%$) 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 m². 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 7, statistically significant ($p < 0.001$) improvements in A_{1C} , FPG, PPG, body weight, and systolic blood pressure relative to placebo were observed. In addition, a greater percentage of patients achieved an $A_{1C} < 7.0\%$ 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 7: Results from Placebo-Controlled Clinical Study of INVOKANA as Add-on Therapy with Metformin¹

Efficacy Parameter	INVOKANA + Metformin 26 weeks		Placebo + Metformin (N=183)
	100 mg (N=368)	300 mg (N=367)	
A_{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 $A_{1C} < 7\%$	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 1186 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 m². 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 8). 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 HbA_{1C} 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 HbA_{1C} < 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 HbA_{1C}-lowering compared with metformin XR alone and provided a statistically significant greater reduction in body weight compared with metformin XR alone (see Table 8).

Table 8: 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

<i>Change from baseline (adjusted mean)</i>	-1.30	-1.37	-1.42	-1.77	-1.78
<i>Difference from INVOKANA 100 mg (adjusted mean) (95% CI) †</i>				-0.40 [‡] (-0.59, -0.21)	
<i>Difference from INVOKANA 300 mg (adjusted mean) (95% CI) †</i>					-0.36 [‡] (-0.56, -0.17)
<i>Difference from metformin XR (adjusted mean) (95% CI) †</i>		-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					
<i>Baseline (mean) in kg</i>	92.1	90.3	93.0	88.3	91.5
<i>% change from baseline (adjusted mean)</i>	-2.1	-3.0	-3.9	-3.5	-4.2
<i>Difference from metformin XR (adjusted mean) (95% CI) †</i>		-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

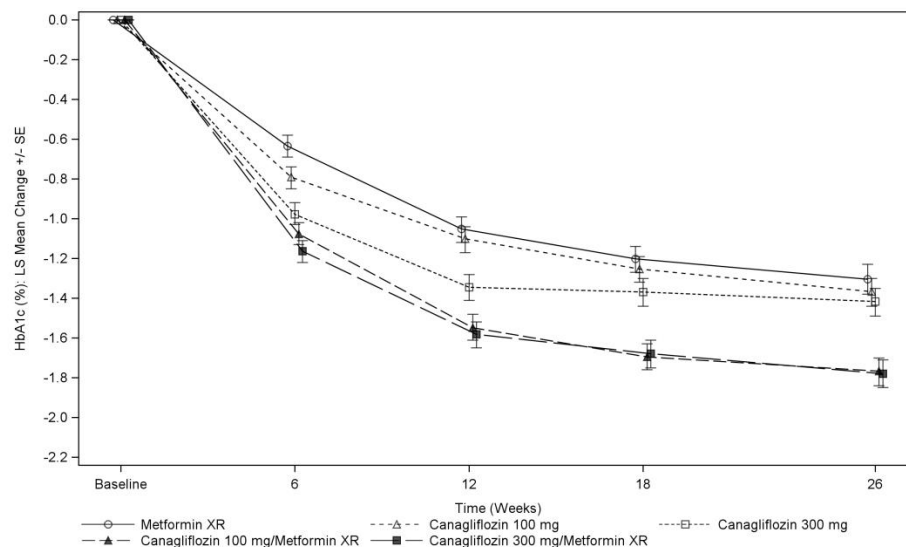
† Least squares mean adjusted for covariates including baseline value and stratification factor

‡ Adjusted p=0.001

§ Adjusted p<0.01

§§ Adjusted p<0.05

Figure 1: Mean Change from Baseline in HbA_{1c} (%) Over Time (mITT Population)



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

A total of 1450 patients with inadequate glycemic control (A_{1C} level of $\geq 7\%$ to $\leq 9.5\%$) 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 m². 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 9 and Figure 2, after 52 weeks, treatment with INVOKANA 100 mg provided similar reductions in A_{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 A_{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 9: Results from 52-Week Clinical Study Comparing INVOKANA to Glimepiride as Add-on Therapy with Metformin¹

Efficacy Parameter	INVOKANA + Metformin 52 Weeks		Glimepiride (titrated) + Metformin (N=482)
	100 mg (N=483)	300 mg (N=485)	
A_{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 $A_{1C} < 7\%$	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

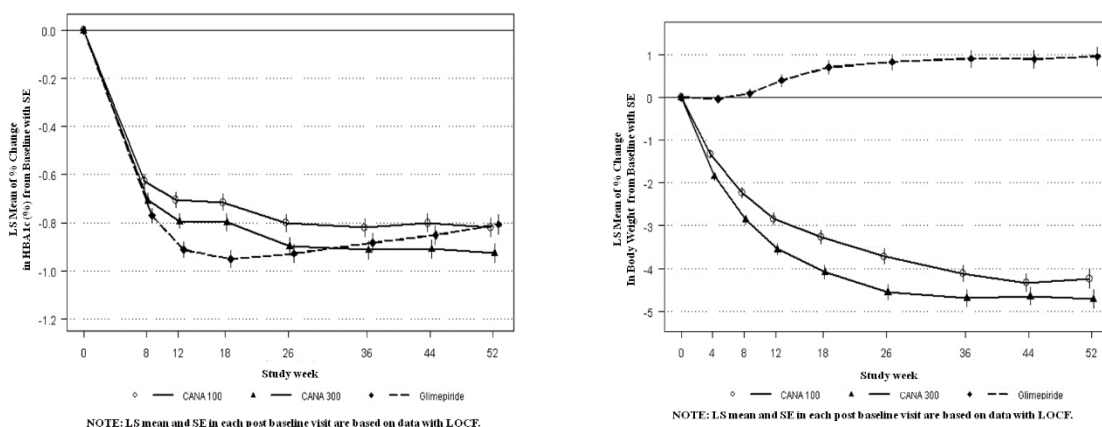
² Met pre-specified criteria for non-inferiority to glimepiride (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of < 0.3%). In a pre-specified assessment, the upper bound of the 95% CI for INVOKANA 300 mg, but not for INVOKANA 100 mg was < 0, indicating a superior ($p < 0.05$) reduction in A_{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 A_{1C} (%) and Body Weight Over 52 Weeks in a Study Comparing INVOKANA to Glimepiride as Add-on Therapy with Metformin



Add-on therapy with sulfonylurea

A total of 127 patients with inadequate glycemic control (A_{1C} of $\geq 7\%$ to $\leq 10.5\%$) 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 m². Patients on sulfonylurea monotherapy at a stable protocol-specified dose ($\geq 50\%$ 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 10, statistically significant ($p < 0.001$) improvements in A_{1C} and FPG relative to placebo were observed at Week 26. In addition, a greater percentage of patients achieved an $A_{1C} < 7.0\%$ 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 10: Results from Placebo-Controlled Clinical Study of INVOKANA as Add-on Therapy with Sulfonylurea¹

Efficacy Parameter	INVOKANA + Sulfonylurea 18 weeks		Placebo + Sulfonylurea (N=45)
	100 mg (N=42)	300 mg (N=40)	
A_{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 A _{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

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 (A_{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 m². 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 11, statistically significant ($p < 0.001$) improvements in A_{1C} , FPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an $A_{1C} < 7.0\%$ 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 11: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA as Add-on Therapy with Metformin and Sulfonylurea¹

Efficacy Parameter	INVOKANA + Metformin and Sulfonylurea 26 Weeks		Placebo + Metformin and Sulfonylurea (N=156)
	100 mg (N=157)	300 mg (N=156)	
A_{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 $A_{1C} < 7\%$	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			
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 (A_{1C} level of $\geq 7.0\%$ to $\leq 10.5\%$) 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 m². 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 12 and Figure 3, after 52 weeks, INVOKANA 300 mg provided a superior ($p < 0.05$) reduction in A_{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 A_{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 A_{1C} thereafter) was lower with INVOKANA 300 mg (10.6%) compared with sitagliptin 100 mg (22.5%).

Table 12: Results from 52-Week Clinical Study Comparing INVOKANA to Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea¹

Efficacy Parameter	INVOKANA 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
A_{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 A_{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

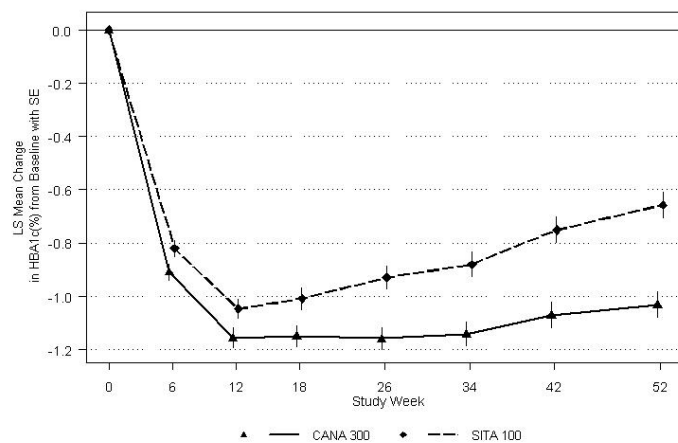
² Met pre-specified criteria for non-inferiority to sitagliptin (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of < 0.3%); in a pre-specified

assessment, the upper bound of the 95% CI for INVOKANA 300 mg was < 0 , indicating a superior ($p < 0.05$) reduction in A_{1C} relative to sitagliptin with INVOKANA 300 mg.

³ $p < 0.001$

⁴ N/A = Not applicable

Figure 3: Mean Change from Baseline for A_{1C} (%) Over 52 Weeks in a Study Comparing INVOKANA to Sitagliptin as Add-on Therapy with Metformin and Sulfonyleurea



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 (A_{1C} level of $\geq 7.0\%$ to $\leq 10.5\%$) 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 m². 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 13, statistically significant ($p < 0.001$) improvements in A_{1C} , FPG, and body weight relative to placebo were observed for INVOKANA at Week 26. In addition, a greater percent of patients achieved an A_{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 13: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA as Add-on Therapy with Metformin and Pioglitazone¹

Efficacy Parameter	INVOKANA + Metformin and Pioglitazone 26 Weeks		Placebo + Metformin and Pioglitazone (N=115)
	100 mg (N=113)	300 mg (N=114)	
A_{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 A_{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. 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 HbA_{1c} (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 HbA_{1c} 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 14). 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 14: 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 1718 patients with inadequate glycemic control (A_{1c} level of ≥ 7.0 to $\leq 10.5\%$) 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 m². 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 15, statistically significant ($p < 0.001$) improvements in A_{1c} , FPG, and body weight relative to placebo were observed for INVOKANA at Week 18. In addition, a greater

percentage of patients achieved an A_{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 15: 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)	
A_{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 A _{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 A_{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 m². 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 16, statistically significant

($p < 0.001$) changes from baseline in A_{1C}, FPG, and body weight were observed for INVOKANA at Week 26. In addition, a greater percent of patients achieved an A_{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 16: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA as Add-on Therapy with Antihyperglycemic Agents in Older Patients Inadequately Controlled on Antihyperglycemic Agents (AHAs)¹

Efficacy Parameter	INVOKANA + Current AHA 26 Weeks		Placebo + Current AHA N=237
	100 mg N=241	300 mg N=236	
A_{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 A _{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/1.73 m² inadequately controlled on current diabetes therapy (baseline A_{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 m². 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, significant improvements in A_{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 A_{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 17: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA as Add-on Therapy with Antihyperglycemic Agents (AHAs) in Patients with Moderate Renal Impairment¹

Efficacy Parameter	INVOKANA + AHA (if any) 26 Weeks		Placebo + AHA (if any) N=90
	100 mg N=90	300 mg N=89	
A_{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 A_{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/1.73 m²) from four placebo-controlled studies was conducted to evaluate the change from baseline A_{1C} and percent change from baseline in body weight in these patients. The mean eGFR in this analysis was 48 mL/min/1.73 m², which was similar across all treatment groups. Most patients were on insulin and/or sulfonyleurea.

This analysis demonstrated that INVOKANA provided statistically significant ($p < 0.001$) improvements in A_{1C} and body weight compared to placebo (see Table 18). 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 sulfonyleurea (see Warnings and Precautions and Adverse Reactions).

Table 18: Integrated Analysis of Four Phase 3 Clinical Studies in Patients with Moderate Renal Impairment¹

Efficacy Parameter	INVOKANA + AHA (if any)		Placebo + AHA (if any) N=382
	100 mg N=338	300 mg N=365	
A_{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

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 19). 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 19: Effect of INVOKANA on Lipid Measurements in Four 26-Week Placebo-Controlled Studies¹

	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.

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 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites. 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 [¹⁴C] 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/1.73 m²), 10 subjects with mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m²), 9 subjects with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²), and 10 subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m²) 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)

Studies characterizing the pharmacokinetics of canagliflozin in pediatric patients have not been performed.

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

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. A study in juvenile rats administered canagliflozin from postnatal Day 21 through Day 90 did not show increased sensitivity compared to effects observed in adult rats.

Carcinogenicity and Mutagenicity

Canagliflozin did not increase the incidence of tumors in male and female mice in a 2-year study at doses of 10, 30, and 100 mg/kg. The highest dose of 100 mg/kg provided up to 14 times the clinical dose of 300 mg based on AUC exposure. Canagliflozin increased the incidence of testicular Leydig cell tumors in male rats at all doses tested (10, 30, and 100 mg/kg); the lowest dose of 10 mg/kg is approximately 1.5 times the clinical dose of 300 mg based on AUC exposure.

The higher doses of canagliflozin (100 mg/kg) in male and female rats increased the incidence of pheochromocytomas and renal tubular tumors; based on AUC exposure, the No Observable Effect Level (NOEL) of 30 mg/kg/day for pheochromocytomas and renal tubular tumors is approximately 4.5 times the exposure at the daily clinical dose of 300 mg. Based on preclinical and clinical mechanistic studies, the Leydig cell tumors, renal tubule tumors, and pheochromocytomas are considered to be rat-specific. Canagliflozin-induced renal tubule tumors and pheochromocytomas in rats appear to be caused by carbohydrate malabsorption as a consequence of intestinal SGLT1 inhibitory activity of canagliflozin in the gut of rats; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the maximum recommended clinical dose. The Leydig cell tumors are associated with an increase in luteinizing hormone (LH), which is a known mechanism of Leydig cell tumor formation in rats. In a 12-week clinical study, unstimulated LH did not increase in males treated with canagliflozin.

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

Reproductive Toxicology

In a pre- and postnatal development study, canagliflozin administered to female rats from gestation Day 6 to lactation Day 20 resulted in decreased body weights in male and female offspring at maternally toxic doses > 30 mg/kg/day (exposures \geq 5.9 times the human exposure to canagliflozin at the maximum recommended human dose [MRHD]). Maternal toxicity was limited to decreased body weight gain.

In rat studies, canagliflozin had no adverse effects on early embryonic development, mating, and fertility up to the highest dose of 100 mg/kg (up to 19 times the clinical dose of 300 mg based on AUC exposure).

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

Tablets are individually packaged in PVC/Aluminum foil blisters with 10 tablets per blister strip. Cartons are packaged as follows: 10 tablets (1 blister strip), 30 tablets (3 blister strips), 90 tablets (9 blister strips), and 100 tablets (10 blister strips)

Instructions for Use and Handling

No special requirements.

Manufactured by

Janssen ortho, LLC, Gurabo, Puerto Rico

Marketing Authorization numbers

Invokana 100 mg – 1C 36/58 (N)

Invokana 300 mg – 1C 37/58 (N)

Date of Authorization

7 April 2015

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Mitsubishi Tanabe Pharma Corporation

IMPORTED BY

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Warnings according to the announcement of Ministry of Public Health

1. Do not use in people with known allergy to this medicine.

2. Do not use for treatment of diabetes mellitus type 1, patients with ketoacidosis, patients with severe infection, people having severe accident.
3. Pregnant women should avoid using this medicine and nursing women should be cautious of using this medicine.
4. Should not use this medicine with alcoholic beverages.
5. If patients have nausea, vomiting, anorexia, stomachache, abnormal thirsty, weakness, difficult breath, and confusion, even though the level of blood sugar is not quite high, consult doctor or pharmacist as diabetic ketoacidosis may occur.
6. Should be cautious of bacterial and mycotic infection of genital and urinary tract system in patients using this medicine.