PRODUCT MONOGRAPH

PrINVOKANA™

canagliflozin tablets

100 mg and 300 mg as anhydrous canagliflozin

Oral Antihyperglycemic Agent

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[Pr]INVOKANA™

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

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

Combination with Metformin or a Sulfonylurea
INVOKANA™ is indicated in combination with metformin or a sulfonylurea in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise plus monotherapy with one of these agents does not provide adequate glycemic control.

Combination with Metformin and either a Sulfonylurea or Pioglitazone
INVOKANA™ is indicated in combination with metformin and either a sulfonylurea or pioglitazone in adult patients with type 2 diabetes mellitus to improve glycemic control when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control.

Combination with Insulin
INVOKANA™ is indicated as add-on combination therapy with insulin (with or without metformin) in adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when diet and exercise, and therapy with insulin (with or without metformin) do not provide adequate glycemic control (see **CLINICAL TRIALS**).

Geriatrics

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

Pediatrics

The safety and efficacy of INVOKANA™ in pediatric patients under 18 years of age have not been established. Therefore, INVOKANA™ should not be used in this population.

CONTRAINDICATIONS

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

- Renally impaired patients with eGFR less than 45 mL/min/1.73 m^2, end stage renal disease or patients on dialysis.

WARNINGS AND PRECAUTIONS

General

INVOKANA™ has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients. INVOKANA™ should not be used for the treatment of diabetic ketoacidosis.

Cardiovascular

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 with moderate renal impairment, elderly patients, patients on loop diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g. angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), and patients with low systolic blood pressure (see **ADVERSE REACTIONS, DRUG**

INTERACTIONS and **DOSAGE AND ADMINISTRATION)**. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and any volume depletion corrected. Caution should also be exercised in other patients for whom a drop in blood pressure could pose a risk, such as patients with known cardiovascular disease. Monitor for signs and symptoms after initiating therapy. Patients should be advised to report symptoms of reduced intravascular volume.

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

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

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

Endocrine and Metabolism

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

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

Hyperkalemia
INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). Serum potassium levels should be monitored periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions (see **Monitoring and Laboratory Tests)**.

Hematologic

Elevated Hemoglobin and Hematocrit

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

Genitourinary

Genital Mycotic Infections

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

Renal

Impairment of renal function

INVOKANA™ increases serum creatinine and decreases eGFR in a dose dependent fashion. Renal function abnormalities can occur after initiating INVOKANA™. Patients with hypovolemia may be more susceptible to these changes (see **ADVERSE REACTIONS**).

Renal function should be assessed prior to initiation of INVOKANA™ and regularly thereafter. More frequent renal function monitoring is recommended in patients whose eGFR decreases to < 60 mL/min/1.73 m^2 after inititiating treatment.

Use in renal impairment

INVOKANA™ should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2, and should be discontinued when eGFR is below 45 mL/min/1.73 m^2, as it would not be effective in these patients and adverse reactions are more frequent (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY- Special Populations and Conditions**).

Special Populations

Pregnant Women: INVOKANA™ should not be used during pregnancy. There are no adequate and well-controlled studies in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose (see **TOXICOLOGY**).

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

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

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

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**). Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).

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

Monitoring and Laboratory Tests

Renal function

Renal function should be assessed prior to initiation of INVOKANA™ and regularly thereafter, with more frequent renal function monitoring in patients whose eGFR decreases to < 60 mL/min/1.73 m^2. INVOKANA™ should not be used in patients with an eGFR < 45 mL/min/1.73 m^2 (see **DOSAGE AND ADMINISTRATION)**.

Hyperkalemia

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

Reduced intravascular volume

Before intiating INVOKANA™, assess volume status, particularly in patients with moderate renal impairment, the elderly, in patients with low systolic blood pressure, or if on a loop diuretic, angiotensin-converting enzyme inhibitor (ACEi), or angiotensin receptor blocker (ARB).

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

For patients receiving INVOKANA™, in case of intercurrent conditions that may lead to volume depletion (such as a gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including renal function tests), and serum electrolytes is recommended.

LDL-cholesterol
LDL-C levels should be monitored during treatment with INVOKANA™ due to dose-dependent increases in LDL-C seen with therapy.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of INVOKANA™ (canagliflozin) was evaluated in 9 nine double-blind, controlled Phase 3 clinical studies involving 10,285 patients with type 2 diabetes, including 3,139 patients treated with INVOKANA™ 100 mg and 3,506 patients, treated with INVOKANA™ 300 mg.

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

A total of 8 serious adverse drug reactions were reported in the primary placebo-controlled safety population, including, 5 reports from patients taking INVOKANA™ 100 mg daily (2 urticaria, 2 UTI, and 1 nausea), 2 reports from patients taking INVOKANA™ 300 mg daily (1 UTI, 1 constipation) and 1 report from a patient in the placebo group (reduced intravascular volume). Of these serious adverse reactions, 2 led to discontinuation in the INVOKANA™ group (UTI and urticaria).

Clinical Trial Adverse Drug Reactions

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

Table 1 to

Table 7 include treatment-emergent adverse events (TEAEs) reported in ≥ 2% of INVOKANA™-treated patients.

Monotherapy (Study DIA3005)

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

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

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

Combination with Metformin (Studies DIA3006 and DIA3009)

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

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

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

	Study DIA3006 (26 weeks)				Study DIA3009 (52 weeks)		
System Organ Class / Preferred Term	**Placebo + Metformin n=183 n (%)**	**INVOKANA™ 100 mg + Metformin n=368 n (%)**	**INVOKANA™ 300 mg + Metformin N=367 n (%)**	**Sitagliptin 100 mg + Metformin n=366 n (%)**	**INVOKANA™ 100 mg + Metformin n=483 n (%)**	**INVOKANA™ 300 mg + Metformin n=485 n (%)**	**Glimepiride + Metformin n=482 n (%)**
Vulvovaginal Pruritus	0	4 (1.1)	5 (1.4)	1 (0.3)	6 (1.2)	20 (4.1)	1 (0.2)

*In either study

Combination with a Sulfonylurea (Study DIA3008 SU Substudy)

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

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

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

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

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

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

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

*In either study

Combination with Metformin and Pioglitazone (Study DIA3012)

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

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

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

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

The incidence of adverse events, reported regardless of causality in ≥ 2% of patients treated with INVOKANA™ 100 mg or 300 mg and more frequently than in the placebo group, in a study of

INVOKANA™ as add-on combination therapy with insulin is provided in Table 6, and as add-on combination therapy with insulin and metformin from the same study is provided in

Table 7. The core assessment period was 18 weeks for this placebo-controlled study.

Table 6: Adverse events (regardless of causality) reported in ≥2% of patients treated with INVOKANA™ and more frequently than in the placebo group in a double-blind clinical trial of INVOKANA™ in add-on combination use with insulin and compared to placebo (Study DIA3008 -Insulin Substudy)

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

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

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

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

Metabolism and nutrition disorders: dehydration[2]

[1] Adverse drug reactions (ADRs) were identified based on a comprehensive assessment of biological plausibility, mechanism of action, dose dependence in incidence rate, time of onset, seriousness and consistency of findings across four, 26-week placebo-controlled Phase 3 clinical studies. Additional supportive safety analyses were conducted on a large pooled dataset from eight active- and placebo-controlled Phase 3 clinical studies.

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

Description of Selected Adverse Reactions

Reduced intravascular volume

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

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 m^2), and patients ≥ 75 years of age had higher incidences of these 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 m^2, 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 **WARNINGS AND PRECAUTIONS**, **DOSING AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY-Special Populations and Conditions**).

Hypoglycemia

In individual clinical trials (see **CLINICAL TRIALS**), episodes of hypoglycemia occurred at a higher rate when INVOKANA™ was co-administered with insulin or sulfonylurea (Table 8; see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

[2] Related to reduced intravascular volume (see **Adverse reactions related to reduced intravascular volume**)
[3] Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular

Table 8: Incidence of Hypoglycemia[1] in Controlled Clinical Studies

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

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

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

Genital mycotic infections

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

Candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with INVOKANA™ 100 mg and INVOKANA™ 300 mg, respectively, compared to 0.6% in placebo-treated male patients. Among male patients taking INVOKANA™, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued INVOKANA™ due to candidial balanitis or balanoposthitis. 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.

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

Bone fractures
In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA™ (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA™ 100 mg, and INVOKANA™ 300 mg, respectively, with the fracture imbalance mainly manifest by an increase in low trauma, upper extremity fractures seen mostly in women, and within the first 26 weeks of therapy and not progressing thereafter. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density significantly.

Skin ulcers and peripheral ischemia
In the pool of 8 clinical studies with 78 weeks of mean duration of exposure, skin ulcers occurred in 0.7%, 1.1%, and 1.5% of patients and peripheral ischemia occurred in 0.1%, 0.4%, and 0.2% of patients receiving comparator, INVOKANA™ 100 mg, and INVOKANA™ 300 mg, respectively. An imbalance in these events generally were seen within the first 24 weeks of treatment and occurred in patients with known or at high risk for atherosclerotic disease, longer duration of diabetes, presence of diabetic complications, and diuretic use.

Adverse reactions in specific populations

Elderly patients
Compared to younger patients, patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. In particular, patients ≥ 75 years of age adverse reactions related to reduced intravascular volume occurred 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 m^2

In an analysis of patients with a baseline eGFR 45 to < 60 mL/min/1.73 m^2, 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.

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.

Cardiovascular safety

A prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from placebo-controlled Phase 2 and 3 clinical studies in 8492 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 placebo was 0.89 (95% CI 0.681,1.154). The hazard ratios for the 100 mg and 300 mg doses were similar. Therefore, there was no evidence of an increase in the primary endpoint with either INVOKANA™ 100 mg or INVOKANA™ 300 mg relative to placebo.

Clinical Chemistry and Hematology Findings

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

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

In a trial in patients with moderate renal impairment (eGFR 30 to < 50 mL/min/1.73 m^2), increases in serum potassium to > 5.4 mEq/L and 15% above baseline were seen in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA™ 100 mg, and INVOKANA™ 300 mg, respectively. Elevations to ≥ 6.5 mEq/L occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA™ 100 mg, and INVOKANA™ 300 mg, respectively.

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

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

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

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

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

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

DRUG INTERACTIONS

Overview

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

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

Canagliflozin is also a substrate of drug transporters P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP) and Multi-Drug Resistance-Associated Protein 2 (MRP2).

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

Drug-Drug Interactions

Effects of other drugs on canagliflozin
In clinical studies, the effects of other drugs on canagliflozin were assessed. Cyclosporin (P-gp

inhibitor), hydrochlorothiazide, oral contraceptives (ethinyl estradiol and levonorgestrel), metformin, and probenecid (UGT, MRP2, OATP, OAT1 and OAT3 inhibitor) had no clinically relevant effect on the pharmacokinetics of canagliflozin.

Table 9: Effect of Co-administered Drugs on Systemic Exposure of Canagliflozin

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

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

Effects of canagliflozin on other drugs

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

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

Table 10: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	Dose of Co-Administered Drug[1]	Dose of Canagliflozin[1]	Geometric Mean Ratio (Ratio With/Without Co-Administered Drugs) No Effect = 1.0			Clinical Comment
				AUC[2] (90% CI)	C_{max} (90% CI)	
Digoxin	0.5 mg once daily first day followed by 0.25 mg once daily for 6 days	300 mg once daily for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)	Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)	No dosage adjustment required for ethinyl estradiol and levonorgestrel
			levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)	
Glyburide	1.25 mg	200 mg once daily for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)	No dosage adjustment required for glyburide
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)	
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)	
Hydrochloro-thiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)	No dosage adjustment required for hydrochlorothiazide
Metformin	2000 mg	300 mg once daily for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)	No dosage adjustment required for metformin
Acetaminophen	1000 mg	300 mg twice daily for 25 days	acetaminophen	1.06[3] (0.98; 1.14)	1.00 (0.92; 1.09)	No dosage adjustment required for acetaminophen
Simvastatin	40 mg	300 mg once daily for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)	No dosage adjustment required for simvastatin
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)	
Warfarin	30 mg	300 mg once daily for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)	No dosage adjustment required for warfarin
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)	

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

Pharmacodynamic Interactions

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

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

Drug-Laboratory Interactions

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

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers
If an inducer of UGTs and drug transport systems (e.g. rifampin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz, St John's wort [*Hypericum perforatum*]) is co-administered with INVOKANA™, monitor A1C in patients receiving INVOKANA™ 100 mg once daily and consider increasing the dose to 300 mg once daily in patients currently tolerating INVOKANA™ 100 mg once daily with an eGFR $\geq$ 60 mL/min/1.73 m^2 or CrCl $\geq$ 60 mL/min and require additional glycemic control. Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.

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

Recommended Dose and Dosage Adjustment

Recommended Adult Dose (18 years of age and older)
The recommended starting dose of INVOKANA™ is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily and who need tighter glycemic control, the 300 mg dose may be considered for patients with an eGFR $\geq$ 60 mL/min/1.73 m^2 and who have a low risk of adverse reactions associated with reduced intravascular volume due to INVOKANA™ treatment (see **WARNINGS AND PRECAUTIONS)**.

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

In patients with evidence of reduced intravascular volume, this condition should be corrected prior to initiation of INVOKANA™.

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

Elderly
Renal function and risk of volume depletion should be taken into account. 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**, **ADVERSE REACTIONS**). See section below for dosing recommendations in renally impaired patients.

Renal Impairment
No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2 or greater).

INVOKANA™ should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2. In patients tolerating INVOKANA™ whose eGFR persistently falls below 60 mL/min/1.73 m^2, the dose of INVOKANA™ should be adjusted to or maintained at 100 mg once daily. INVOKANA™ should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 as it is not expected to be sufficiently effective in these patients and adverse reactions are more frequent (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**-**Special Populations and Conditions)**.

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

Missed Dose

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

OVERDOSAGE

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Patients with diabetes have been shown to have elevated renal glucose reabsorption which may contribute to persistent elevated glucose concentrations. Canagliflozin is an orally-active inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion, which decreases elevated plasma glucose concentrations by an insulin-independent mechanism in patients with type 2 diabetes. The increased urinary glucose excretion with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in urinary glucose excretion results in a loss of calories and therefore a reduction in body weight, as demonstrated in studies of patients with type 2 diabetes.

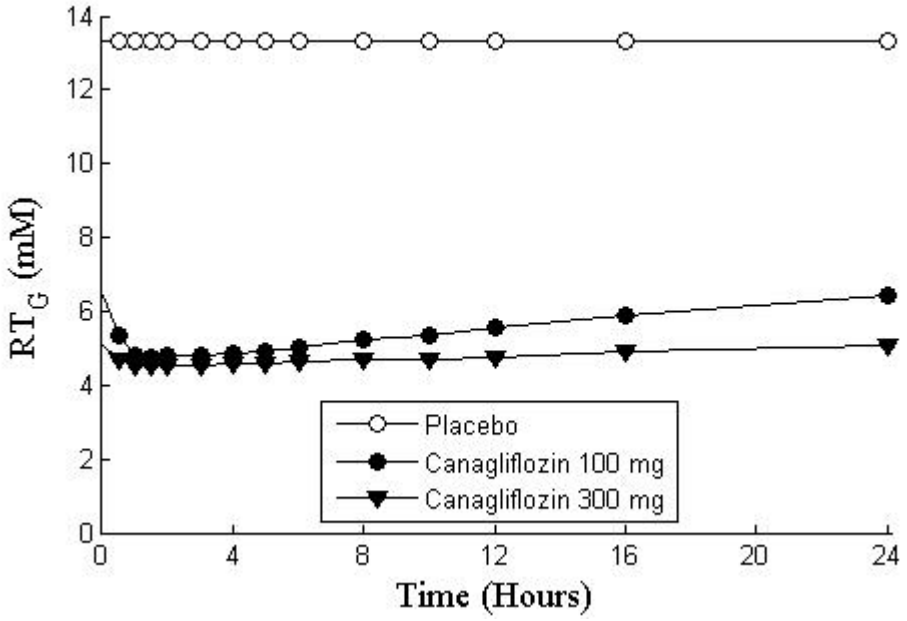
Canagliflozin's action to increase UGE directly lowering plasma glucose is independent of insulin. Improvement in homeostasis model assessment for beta-cell function (HOMA beta-cell) and improved beta-cell insulin secretion response to a mixed-meal challenge has been observed in clinical studies with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

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

Pharmacodynamics

Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in urinary glucose excretion were observed. From a starting value of RT_G of approximately 13 mmol/L, maximal suppression of 24-hour mean RT_G was seen with the 300 mg daily dose to approximately 4 to 5 mmol/L in patients with type 2 diabetes in Phase 1 studies (see model in Figure 1), 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%.

Figure 1: Predicted (PK/PD Modelled) 24 Hour Profile for RT_G in Subjects with Type 2 Diabetes Treated with Canagliflozin 100 mg and 300 mg



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

Cardiac electrophysiology

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

Pharmacokinetics

Pharmacokinetics of INVOKANA™ were comparable between healthy volunteers and type 2 diabetic patients based on clinical trials and population pharmacokinetic data. After single-dose oral administration of 100 mg and 300 mg in healthy subjects, canagliflozin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 2 hours post-dose. Plasma C_{max} and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life ($t_{1/2}$) (expressed as mean ± standard deviation) was 10.6 ± 2.13 hours to 13.1 ± 3.28 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg. Canagliflozin does not exhibit time-dependent pharmacokinetics, and accumulated in plasma up to 36% following multiple doses of 100 mg and 300 mg.

Table 11: Summary of Canagliflozin's Pharmacokinetic Parameters in Healthy Subjects and T2DM Patients at Steady State

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

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

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

Distribution
The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 119 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism
O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites. CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

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

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

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

Special Populations and Conditions

Pediatrics (< 18 years of age): Studies characterizing the pharmacokinetics of canagliflozin in pediatric patients have not been performed.

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

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

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

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

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

These differences are not considered to be clinically meaningful. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment and, therefore, INVOKANA™ is not recommended for use in this patient population.

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

The C_{max} of canagliflozin was moderately increased by 13%, 29%, and 29% in subjects with mild, moderate, and severe renal failure, respectively, but not in subjects on hemodialysis.

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

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

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

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

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

Composition
Each tablet contains the following non-medicinal ingredients:

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

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: canagliflozin

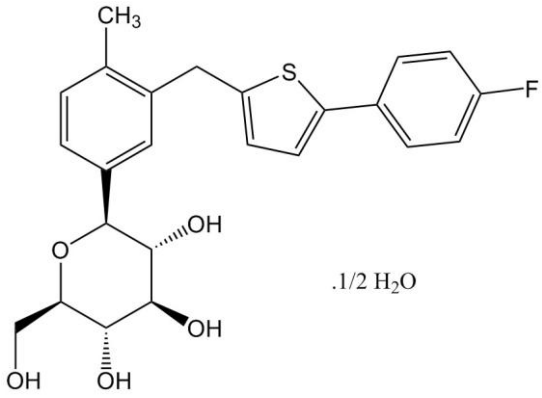
Chemical name: (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

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

Molecular mass:

- Hemihydrate: 453.53
- Anhydrous: 444.52

Structural formula:



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

CLINICAL TRIALS

INVOKANA™ was studied as monotherapy in one placebo-controlled study of 26 weeks duration, which included an active-treatment substudy in patients with more severe hyperglycaemia (HbA_{1c} [A1C] > 10 and ≤ 12%). Five placebo- or active-controlled studies investigated INVOKANA™ as add-on therapy with other antihyperglycemic agents: two studies with metformin (26 and 52 weeks); two studies with metformin and sulfonylurea (26 and 52 weeks), and one study with metformin and pioglitazone (26 weeks). Two placebo-controlled studies investigated the use of INVOKANA™, added onto the current diabetes treatment regimen, one in older patients, and one in patients with moderate renal impairment. An ongoing dedicated cardiovascular study has been conducted in patients with type 2 diabetes; safety analyses were conducted that investigated INVOKANA™ as add-on therapy with a sulfonylurea and with insulin.

Study Demographics and Trial Design

Table 12: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
Monotherapy					
DIA3005	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Placebo 26-week	Total: 584 INVOKANA™ 100 mg: 195 INVOKANA™ 300 mg: 197 Placebo: 192	55.4 (24-79)	55.8/44.2
Add-on Therapy with Metformin (≥ 1500 mg/day)					
DIA3006	Randomized, double-blind, active-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Sitagliptin 100 mg/day or Placebo 26-week	Total: 1284 INVOKANA™ 100 mg: 368 INVOKANA™ 300 mg: 367 Sitagliptin 100 mg: 366 Placebo: 183	55.4 (21-79)	52.9/47.1
DIA3009	Randomized, double-blind, active-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Glimepiride 1- 8 mg (titration protocol) 52-week	Total: 1450 INVOKANA™ 100 mg: 483 INVOKANA™ 300 mg: 485 Glimepiride: 482	56.2 (22-80)	47.9/52.1
Add-on Therapy with a Sulfonylurea (stable dose)					
DIA3008 SU Substudy	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Placebo 18-week	Total: 127 INVOKANA™ 100 mg: 42 INVOKANA™ 300 mg: 40 Placebo: 45	64.8 (44-82)	43.3/56.7

Add-on Therapy with Metformin (≥ 1500 mg/day) and a Sulfonylurea (stable dose)					
DIA3002	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Placebo 26-week	Total: 469 INVOKANA™ 100 mg: 157 INVOKANA™ 300 mg: 156 Placebo: 156	56.8 (27-79)	49.0/51.0
DIA3015	Randomized, double-blind, active-controlled, parallel-group, multicentre	INVOKANA™ 300 mg/day or Sitagliptin 100 mg/day or Placebo 52-week	Total: 755 INVOKANA™ 300 mg: 377 Sitagliptin 100 mg: 378	56.7 (21-91)	44.1/55.9
Add-on Therapy with Metformin (≥ 1500 mg/day) and Pioglitazone (30 or 45 mg/day)					
DIA3012	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Placebo 26-week	Total: 342 CANA 100 mg: 113 CANA 300 mg: 114 Placebo: 115	57.4 (27-78)	36.8/63.2
Add-on with Insulin (≥20 units/day) as monotherapy or in combination with other AHA(s)[1]					
DIA3008 Insulin Substudy	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day or Placebo 18-week	Total: 1718 INVOKANA™ 100 mg: 566 INVOKANA™ 300 mg: 587 Placebo: 565	62.8 (32-85)	33.5/66.5
Special Populations					
DIA3010 (Older Adults)	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day + any AHA[1] or Placebo + any AHA[1] 26-week	Total: 714 INVOKANA™ 100 mg: 241 INVOKANA™ 300 mg: 236 Placebo: 237	63.6 (55-80)	44.5/55.5
DIA3004 (Renal Impairment)	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	INVOKANA™ 100 or 300 mg/day + any AHA[1] or Placebo + any AHA[1] 26-week	Total: 269 INVOKANA™ 100 mg: 90 INVOKANA™ 300 mg: 89 Placebo: 90	68.5 (39-96)	39.4/60.6

[1] AHA = antihyperglycemic agent

A total of 10,285 patients with type 2 diabetes were randomized in nine double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of INVOKANA™ on glycemic control. The racial distribution was 72% White, 16% Asian, 4% Black, and 8% other groups. Approximately 16% of patients were Hispanic. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 to 96 years), with 3082 patients 65 years of age and older and 510 patients 75 years of age and older. One study was conducted

in patients with moderate renal impairment with an eGFR 30 to < 50 mL/min/1.73 m^2 (N=269) and three other studies included patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2) (N=816).

Study Results

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

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

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

Monotherapy (Study DIA3005)
A total of 584 patients with inadequate glycemic control (A1C of ≥ 7% to ≤ 10%) on diet and exercise participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA™ over 26 weeks. The mean age was 55 years, 44% of patients were men, and the mean baseline eGFR was 87 mL/min/1.73 m^2. Patients taking other antihyperglycemic agents (N=281) discontinued the agent and underwent a drug washout period of approximately 8 weeks immediately followed by a 2-week, single-blind, placebo run-in period. Patients not taking an oral antihyperglycemic agent (off therapy for at least 8 weeks) (N=303) with inadequate glycemic control entered a 2-week, single-blind, placebo run-in period. Patients were randomized to take INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo, administered once daily. As shown in Table 13, statistically significant ($p<0.001$) reductions in A1C, FPG, PPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an A1C < 7.0% compared to placebo. Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -3.7 mmHg and -5.4 mmHg, respectively.

Patients who were not eligible for inclusion in the main placebo-controlled study due to more severe hyperglycaemia (A1C > 10 and ≤ 12%) participated in a separate active-treatment substudy (N=91) and were treated with either INVOKANA™ 100 mg or INVOKANA™ 300 mg (see Table 13).

Table 13: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA™ as Monotherapy[1]

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

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

Add-on Therapy

Add-on Therapy with Metformin (Study DIA3006)

A total of 1284 patients with inadequate glycemic control (A1C of ≥ 7% to ≤10.5%) on metformin monotherapy (2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated)

participated in a randomized, double-blind, placebo- and active-controlled, parallel-group, 4-arm, multicentre clinical study to evaluate the efficacy of INVOKANA™ as add-on therapy with metformin over 26 weeks. The mean age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on metformin (N=1009) at screening with inadequate glycemic control completed a 2-week, single-blind, placebo run-in period. Other patients on metformin and another oral agent or a lower than required dose of metformin (N=275) were switched to a regimen of metformin monotherapy. After at least 8 weeks on a stable dose of metformin monotherapy, patients entered a 2-week, single-blind, placebo run-in period. Patients were randomized to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, sitagliptin 100 mg, or placebo, administered once daily.

As shown in Table 14, statistically significant ($p<0.001$) reductions in A1C, FPG, PPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an A1C < 7.0% compared to placebo. Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -5.4 mmHg and -6.6 mmHg, respectively.

Table 14: Results from Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Metformin[1]

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

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

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

A total of 1450 patients with inadequate glycemic control (A1C level of ≥ 7% to ≤ 9.5%) on metformin monotherapy (≥ 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a randomized, double-blind, active-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA™ as add-on therapy with metformin over 52 weeks. The mean age was 56 years, 52% of patients were men, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients on metformin (N=927) at a stable protocol-specified dose entered a 2-week, single-blind, placebo run-in period. Other patients (N=525) 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 15 and **Error! Reference source not found.**, after 52 weeks, treatment with INVOKANA™ 100 mg provided similar reductions in A1C from baseline compared to glimepiride (with the upper bound of the 95% confidence interval around the between-group difference less than the pre-specified non-inferiority margin of 0.3%); INVOKANA™ 300 mg provided a superior ($p<0.05$) reduction from baseline in A1C compared to glimepiride (with the upper bound of the 95% confidence interval below 0). Statistically significant ($p<0.001$) reductions in body weight were observed with INVOKANA™ compared to glimepiride. Reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to glimepiride of -3.5 mmHg and -4.8 mmHg, respectively. The incidence of hypoglycemia with INVOKANA™ was significantly lower ($p<0.001$) compared to glimepiride.

Table 15: Results from 52-Week Clinical Study Comparing INVOKANA™ to Glimepiride as Add-on Therapy with Metformin[1]

Efficacy Parameter	INVOKANA™ + Metformin 52 Weeks		Glimepiride (titrated) + Metformin (N=482)
	100 mg (N=483)	300 mg (N=485)	
A1C (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)	-0.01[2] (-0.11; 0.09)	-0.12[2] (-0.22; -0.02)	N/A[3]
Percent of patients achieving A1C < 7%	53.6	60.1	55.8
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.18	9.09	9.20
Change from baseline (adjusted mean)	-1.35	-1.52	-1.02
Difference from glimepiride (adjusted mean) (95% CI)	-0.33 (-0.56; -0.11)	-0.51 (-0.73; -0.28)	N/A[3]
Body Weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.2[4] (-5.7; -4.7)	-5.7[4] (-6.2; -5.1)	N/A[3]

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

[2] Met pre-specified criteria for non-inferiority to glimepiride (with the upper bound of the 95% CI around

Table 15: Results from 52-Week Clinical Study Comparing INVOKANA™ to Glimepiride as Add-on Therapy with Metformin[1]

	INVOKANA™ + Metformin 52 Weeks		Glimepiride (titrated) + Metformin (N=482)
Efficacy Parameter	**100 mg (N=483)**	**300 mg (N=485)**	

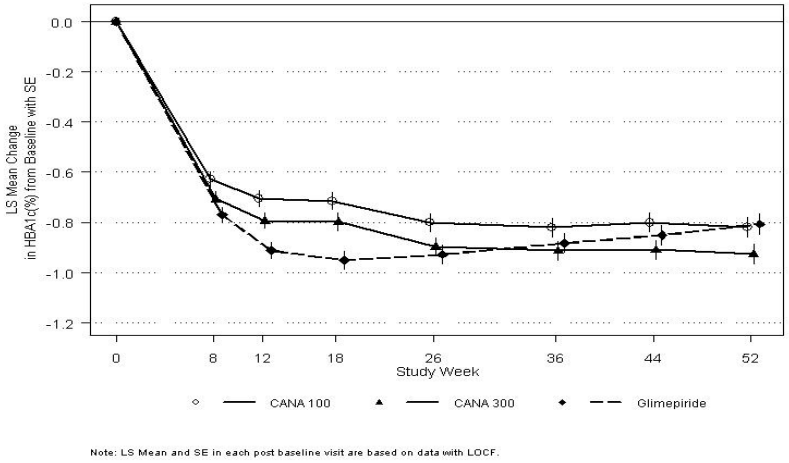
the between-group difference less than the pre-specified non-inferiority margin of < 0.3%). In a pre-specified assessment, the upper bound of the 95% CI for INVOKANA™ 300 mg, but not for INVOKANA™ 100 mg was < 0, indicating a superior ($p<0.05$) reduction in A1C relative to glimepiride with INVOKANA™ 300 mg.

[3] N/A = Not applicable

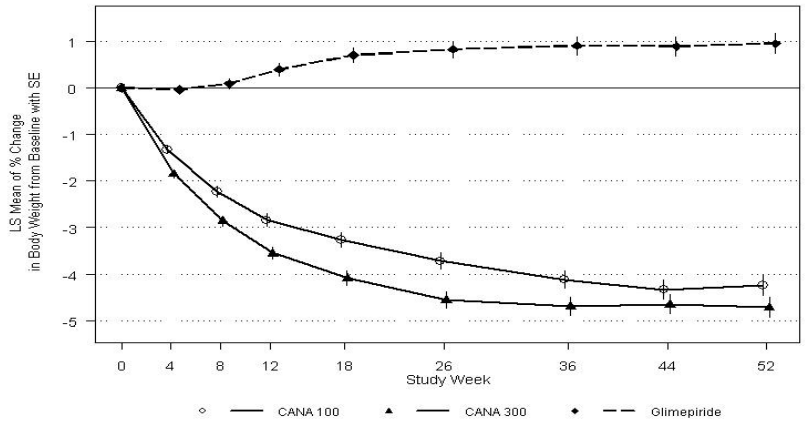
[4] $p<0.001$

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

Figure 2: Mean Changes from Baseline for A1C (%) and Body Weight Over 52 Weeks in a Study Comparing INVOKANA™ to Glimepiride as Add-on Therapy with Metformin



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



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

Add-on Therapy with Sulfonylurea (DIA3008 Substudy)

A total of 127 patients with inadequate glycemic control (A1C of ≥ 7% to ≤ 10.5%) on sulfonylurea monotherapy participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre substudy of a cardiovascular outcomes study to evaluate the efficacy of INVOKANA™ as add-on therapy with sulfonylurea over 18 weeks. The mean age was 65 years, 57% of patients were men, and the mean baseline eGFR was 69 mL/min/1.73 m^2. Patients on sulfonylurea monotherapy at a stable protocol-specified dose (≥ 50% maximal dose) for at least 10 weeks completed a 2-week, single-blind, placebo run-in period. After the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo, administered once daily.

As shown in Table 16, statistically significant ($p<0.001$) reductions in A1C and FPG relative to placebo were observed at Week 18. In addition, a greater percentage of patients achieved an A1C < 7.0% compared to placebo. Patients treated with INVOKANA™ 300 mg exhibited reductions in body weight compared to placebo. Reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -0.1 mmHg and -1.8 mmHg, respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS)**.

Table 16: Results from Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with a Sulfonylurea[1]

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

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

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

A total of 469 patients with inadequate glycemic control (A1C level of ≥ 7% to ≤ 10.5%) on the combination of metformin (2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximal or near-maximal effective dose) participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the

efficacy of INVOKANA™ as add-on therapy with metformin and sulfonylurea over 26 weeks. The mean age was 57 years, 51% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients on near-maximal or maximal effective doses of metformin and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) entered a metformin and sulfonylurea dose titration and dose stabilization/antihyperglycemic agent washout period of up to 12 weeks, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo administered once daily.

As shown in Table 17, statistically significant ($p<0.001$) reductions in A1C, FPG, and body weight relative to placebo were observed. In addition, a greater percentage of patients achieved an A1C < 7.0% compared to placebo. Reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -2.2 mmHg and -1.6 mmHg, respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Table 17: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Metformin and Sulfonylurea[1]

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

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

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

A total of 755 patients with inadequate glycemic control (A1C level of ≥ 7.0% to ≤ 10.5%) on the combination of metformin (2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (near-maximal or maximal effective dose) participated in a double-blind, active-controlled, parallel-group, 2-arm, multicentre clinical study to evaluate the efficacy

of INVOKANA™ 300 mg as add-on therapy with metformin and sulfonylurea versus sitagliptin 100 mg as add-on therapy with metformin and sulfonylurea over 52 weeks. The mean age was 57 years, 56% of patients were men, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients on near-maximal or maximal effective doses of metformin and sulfonylurea (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) entered a metformin and sulfonylurea dose titration and dose stabilization period of up to 12 weeks, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA™ 300 mg or sitagliptin 100 mg.

As shown in Table 18 and Figure 3, after 52 weeks, INVOKANA™ 300 mg provided a superior ($p<0.05$) reduction in A1C compared to sitagliptin 100 mg (with the upper bound of the 95% confidence interval around the between-group difference below 0). In addition, a greater percent of patients achieved an A1C of < 7.0% with INVOKANA™ 300 mg relative to sitagliptin: 47.6% of patients receiving INVOKANA™ 300 mg and 35.3% of patients receiving sitagliptin. Patients treated with INVOKANA™ 300 mg exhibited a significant mean decrease in percent change from baseline body weight compared to patients administered sitagliptin 100 mg. A statistically significant ($p<0.001$) reduction in systolic blood pressure was observed with INVOKANA™ 300 mg of -5.9 mmHg relative to sitagliptin. A similar increased incidence of hypoglycemia was observed with both INVOKANA™ 300 mg and sitagliptin in this study, consistent with the expected increase of hypoglycemia when agents not associated with hypoglycemia are added to sulfonylurea (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**). The proportion of patients who met glycemic withdrawal criteria (based on FPG until Week 26 and A1C thereafter) was lower with INVOKANA™ 300 mg (10.6%) compared with sitagliptin 100 mg (22.5%).

Table 18: Results from 52-Week Clinical Study Comparing INVOKANA™ to Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea[1]

Efficacy Parameter	**INVOKANA™ 300 mg + Metformin and Sulfonylurea (N=377)**	**Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)**
A1C (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)	-0.37[2] (-0.50; -0.25)	N/A[4]
Percent of patients achieving A1C < 7%	47.6	35.3
Fasting Plasma Glucose (mmol/L)		
Baseline (mean)	9.42	9.09
Change from baseline (adjusted mean)	-1.66	-0.32
Difference from sitagliptin (adjusted mean) (95% CI)	-1.34 (-1.66; -1.01)	N/A[4]
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI)	-2.8[3] (-3.3; -2.2)	N/A[4]

Table 18: Results from 52-Week Clinical Study Comparing INVOKANA™ to Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea[1]

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

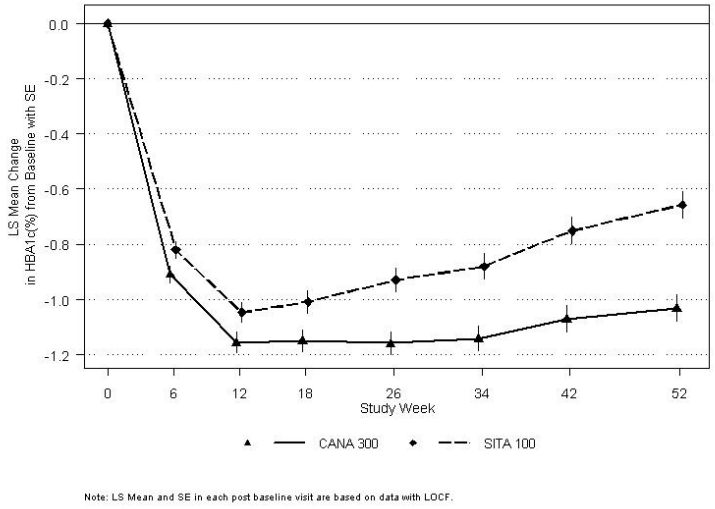
[1] Intent-to-treat population using last observation in study prior to glycemic rescue therapy

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

[3] $p<0.001$

[4] N/A = Not applicable

Figure 3: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study Comparing INVOKANA™ to Sitagliptin as Add-on Therapy with Metformin and Sulfonylurea



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

A total of 342 patients with inadequate glycemic control (A1C level of ≥ 7.0% to ≤ 10.5%) on the combination of metformin (2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre clinical study to evaluate the efficacy of INVOKANA™ as add-on therapy with metformin and pioglitazone over 26 weeks. The mean age was 57 years, 63% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and pioglitazone (N=163) entered a 2-week, single-blind, placebo run-in period. Other patients (N=181) entered a metformin and pioglitazone dose titration and dose stabilization period for up to 12 weeks with at least 8 weeks on stable doses of metformin and pioglitazone, immediately followed by the 2-week run-in period. Following the run-in period, patients with inadequate glycemic control were randomized

(N=344) to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo, administered once daily. As shown in Table 19, statistically significant (p<0.001) reductions in A1C, baseline FPG, and body weight relative to placebo were observed for INVOKANA™ at Week 26. In addition, a greater percent of patients achieved an A1C of < 7.0% compared to placebo. Statistically significant reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -4.1 mmHg (p=0.005) and -3.5 mmHg (p=0.016), respectively.

Table 19: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Metformin and Pioglitazone[1]

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

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

Add-on Therapy with Insulin (with or without Metformin) (Derived from DIA3008 substudy)
A total of 1718 patients with inadequate glycemic control (A1C level of ≥ 7.0 to ≤ 10.5%) on insulin ≥ 30 units/day or insulin add-on therapy with other antihyperglycemic agents participated in a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre substudy of a cardiovascular outcomes study; this substudy evaluated the efficacy of INVOKANA™ as add-on therapy with insulin over 18 weeks. The mean age was 63 years, 66% of patients were men, and the mean baseline eGFR was 75 mL/min/1.73 m^2. Patients on basal, bolus, or basal/bolus insulin, with the majority on a background basal/bolus insulin regimen, for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. After the run-in period, patients with inadequate glycemic control were randomized to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo, administered once daily. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups.

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

Table 20a and Table 20b show statistically significant (p<0.001) reductions in A1C, FPG, and body weight relative to placebo were observed for INVOKANA™ at Week 18 in patients both on an insulin monotherapy and insulin+metformin background. In addition, a greater percentage of patients achieved an A1C < 7.0% compared to placebo. In the insulin monotherapy stratum, reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -2.9 mmHg (p=0.027) and -4.2 mmHg (p=0.001), respectively. In the insulin and metformin only stratum, reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -2.9 mmHg (p=0.011) and -4.8 mmHg (p<0.001), respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**).

Table 20a: Results from 18-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Insulin ≥ 30 Units/Day (With Insulin Only)[1]

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

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

Table 20b: Results from 18-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Insulin ≥ 30 Units/Day (With Insulin and Metformin)[1]

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

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

Studies in Special Populations

Study in older patients (*DIA3010)*

A total of 714 older patients (≥ 55 to ≤ 80 years of age) with inadequate glycemic control (baseline A1C level of ≥ 7.0 to ≤ 10.0%) on current diabetes therapy (either diet and exercise alone or in combination with oral or parenteral agents) participated in a randomized, double-blind, placebo-controlled study to evaluate the efficacy of INVOKANA™ as add-on therapy with current diabetes treatment over 26 weeks. The mean age was 64 years, 55% of patients were men, and the mean baseline eGFR was 77 mL/min/1.73 m^2. Patients with inadequate glycemic control on their current diabetes therapy were randomized to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo, administered once daily. As shown in Table 21, statistically significant ($p<0.001$) changes from baseline in A1C, FPG, and body weight were observed for INVOKANA™ at Week 26. In addition, a greater percent of patients achieved an A1C of < 7.0% compared to placebo (see **ACTION AND CLINICAL PHARMACOLOGY-Special Populations and Conditions**). Statistically significant ($p<0.001$) reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -4.6 mmHg and -7.9 mmHg, respectively.

A subset of patients (N=211) participated in the body composition substudy using DXA body composition analysis. This demonstrated that approximately two-thirds of the weight loss with INVOKANA™ was due to loss of fat mass relative to placebo. There were no meaningful changes in bone density in trabecular and cortical regions.

Table 21: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Antihyperglycemic Agents in Older Patients Inadequately Controlled on Antihyperglycemic Agents (AHAs)[1]

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

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

Patients with renal impairment (DIA3004)

A total of 269 patients with moderate renal impairment and eGFR 30 to < 50 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy (baseline A1C level of ≥ 7.0 to ≤ 10.5%) participated in a randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy of INVOKANA™ as add-on therapy with current diabetes treatment (diet or antihyperglycemic agent therapy with most patients on insulin and/or sulfonylurea) over 26 weeks. The mean age was 68 years, 61% of patients were men, and the mean baseline eGFR was 39 mL/min/1.73 m^2. Patients with inadequate glycemic control on their current diabetes therapy were randomized to the addition of INVOKANA™ 100 mg, INVOKANA™ 300 mg, or placebo administered once daily.

As shown in Table 22, significant reductions in A1C relative to placebo were observed for INVOKANA™ 100 mg and INVOKANA™ 300 mg, respectively at Week 26. In addition, a greater percentage of patients achieved an A1C < 7.0% compared to placebo. Patients treated with INVOKANA™ exhibited mean decreases in percent change from baseline body weight compared to placebo. Reductions in systolic blood pressure were observed with INVOKANA™ 100 mg and 300 mg relative to placebo of -5.7 mmHg and -6.1 mmHg, respectively. An increased incidence of hypoglycemia was observed in this study (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, and **ACTION AND CLINICAL PHARMACOLOGY**-**Special Populations and Conditions**).

Table 22: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA™ as Add-on Therapy with Antihyperglycemic Agents (AHAs) in Patients with Moderate Renal Impairment[1]

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

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

Integrated analysis of patients with moderate renal impairment

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

This analysis demonstrated that INVOKANA™ provided statistically significant (p<0.001) reductions in A1C and body weight compared to placebo (see Table 23). An increased incidence of hypoglycemia was observed in this integrated analysis (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Table 23: Integrated Analysis of Four Phase 3 Clinical Studies in Patients with Moderate Renal Impairment[1]

Efficacy Parameter	INVOKANA™ + AHA (if any)		Placebo + AHA (if any) N=382
	100 mg N=338	300 mg N=365	
A1C (%)			
Baseline (mean)	8.10	8.10	8.01
Change from baseline (adjusted mean)	-0.52	-0.62	-0.14
Difference from placebo (adjusted mean) (95%CI)	-0.38[2] (-0.50; -0.26)	-0.47[2] (-0.59; -0.35)	N/A[3]

Table 23: Integrated Analysis of Four Phase 3 Clinical Studies in Patients with Moderate Renal Impairment[1]

Efficacy Parameter	INVOKANA™ + AHA (if any) 100 mg N=338	INVOKANA™ + AHA (if any) 300 mg N=365	Placebo + AHA (if any) N=382
Body Weight			
Baseline (mean) in kg	90.3	90.1	92.4
% change from baseline (adjusted mean)	-2.0	-2.4	-0.5
Difference from placebo (adjusted mean) (95%CI)	-1.6[2] (-2.0; -1.1)	-1.9[2] (-2.3; -1.5)	N/A[3]

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

DETAILED PHARMACOLOGY

In Vitro Pharmacology Studies

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

In Vivo Pharmacology Studies

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

TOXICOLOGY

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. In a study in juvenile rats, dilatation of the renal pelvis and tubules was noticed beginning at the lowest dose tested, 4 mg/kg, an exposure greater than or equal to 0.5 times the maximum clinical dose of 300 mg, and the pelvic dilatation did not fully reverse within the approximately 1-month recovery period. Persistent renal findings in juvenile rats can most likely be attributed to reduced ability of the developing rat kidney to handle canagliflozin-increased urine volumes, as functional maturation of the rat kidney continues through 6 weeks of age.

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

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

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

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

The incidence of pheochromocytomas and renal tubular tumors increased significantly in male and female rats given high doses of 100 mg/kg/day (approximately 12 times the clinical dose of 300 mg based on AUC exposure). Canagliflozin-induced renal tubule tumors and pheochromocytomas in rats may be caused by carbohydrate malabsorption; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2 times the recommended clinical dose of 300 mg.

Mutagenicity
Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the *in vitro* mouse lymphoma assay with but not without

metabolic activation. Canagliflozin was not mutagenic or clastogenic in an *in vivo* oral micronucleus assay in rats and an *in vivo* oral Comet assay in rats.

Reproductive and Developmental Toxicity

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

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

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

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

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PART III: CONSUMER INFORMATION

PrINVOKANA™
canagliflozin tablets

This leaflet is Part III of a three-part "Product Monograph" published when INVOKANA™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INVOKANA™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

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

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

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

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

- are allergic (hypersensitive) to canagliflozin or any of the nonmedicinal ingredients listed below.
- have type 1 diabetes (a disease in which your body does not produce any insulin).
- have diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea, or vomiting).
- have severe kidney problems or you are on dialysis.

What the medicinal ingredient is:
Canagliflozin

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

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

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

WARNINGS AND PRECAUTIONS

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

- have type 1 diabetes (your body does not produce any insulin). INVOKANA™ is not recommended for use in patients with type 1 diabetes.
- are taking a diuretic medicine also known as water pills (used to remove excess water from the body), such as furosemide; or taking medicines to lower your blood pressure such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB); or have or have had low blood pressure (hypotension). Taking INVOKANA™ with any of these medicines may increase the risk of becoming dehydrated and/or low blood pressure (hypotension).
- are older than 65 years of age.
- have kidney problems.
- are taking medicines to lower your blood sugar such as glyburide, gliclazide or glimepiride (sulfonylureas) or insulin. Taking INVOKANA™ with any of these medicines can increase the risk of having low blood sugar (hypoglycemia). Take precautions to avoid the potential for low blood sugar while driving or using heavy machinery.
- have liver problems.
- have heart problems.
- have intolerance to some milk sugars. INVOKANA™ tablets contain lactose.
- are pregnant or are planning to have a baby. INVOKANA™ is not recommended for use in pregnant women.
- are breast-feeding. INVOKANA™ should not be used during breast-feeding.

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

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

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

Driving and using machines
INVOKANA™ may cause dizziness or lightheadedness. DO NOT drive or use machines until you know how the medicine affects you.

INTERACTIONS WITH THIS MEDICATION

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

Medicines that may interact with INVOKANA™ include:

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

PROPER USE OF THIS MEDICATION

Usual starting dose:
100 mg by mouth each day. Your doctor may increase your dose to 300 mg However, if you have a kidney problem your doctor will limit your dose to100 mg.

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

Overdose:

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

Missed dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, INVOKANA™ can cause side effects.

Very common side effects (may affect more than 1 in 10 people):

- Low blood sugar (hypoglycemia) when used with sulfonylurea (such as glimepiride, gliclazide, and glyburide) or insulin. The symptoms of low blood sugar include blurred vision, tingling lips, trembling, sweating, pale looking, a change in mood or feeling anxious or confused. You should ask your doctor or pharmacist what to do if you have any of the symptoms above.
- Vaginal yeast infection. The symptoms include vaginal odor, white or yellowish vaginal discharge, and/or itching.

Common side effects (may affect up to 1 in 10 people):

- Rash or redness of the penis or foreskin (yeast infection or balantis).
- Urinary tract infection (burning sensation when urinating, cloudy urine, strong odor).
- Changes in urination such as urinating more often or in larger amounts, an urgent need to urinate, and a need to urinate at night.
- Constipation
- Nausea
- Feeling thirsty

Uncommon side effects (may affect up to 1 in 100 people):

- Dehydration (not having enough water in your body). The symptoms include passing out (fainting) or feeling dizzy or lightheaded due to a drop in blood pressure when you stand up, have low blood pressure, very dry or sticky mouth, feeling very thirsty, weak or tired, passing little or no urine and/or fast heartbeat. Dehydration happens more often in older people (over 65 years of age) or people with kidney problems, and people taking water pills.
- Rash
- Hives (raised red patches on the skin)

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Vaginal yeast infection (vaginal odor, white or yellowish vaginal discharge, and/or itching)		✓	
Common	Rash or redness of the penis or foreskin		✓	
Common	Urinary tract infection (changes in urination)		✓	
Common	Constipation	✓		
Uncommon	Dehydration (feeling very thirsty)		✓	✓
Uncommon	Fainting or lightheadedness with standing		✓	✓
Uncommon	Rash or Hives		✓	✓
Rare	Severe hypoglycemia/ disorientation/ loss of consciousness/ seizure (when used with insulin or a sulfonylurea)		✓	

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

HOW TO STORE IT

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

http://www.janssen.ca
or by contacting the sponsor, Janssen Inc., at:
1-800-567-3331 and 1-800-387-8781

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