INVOKANA®

canagliflozin hemihydrate

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

INVOKANA® 100 mg film coated tablets

INVOKANA® 300 mg film coated tablets

2. QUALTITATIVE AND QUANTITATIVE COMPOSITION

INVOKANA is available as film-coated tablets containing 100 and 300 mg of canagliflozin present as 102 mg and 306 mg of canagliflozin hemihydrate in each tablet strength, respectively.

Excipient(s) with known effect

Each 100 mg tablet contains 39.2 mg lactose.

Each 300 mg tablet contains 117.78 mg lactose.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablet.

INVOKANA 100 mg film-coated tablets:

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

INVOKANA 300 mg film-coated tablets:

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INVOKANA is indicated in adults with type 2 diabetes mellitus, as an adjunct to diet and exercise, to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on combination therapy

Combination therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see **sections 5**, **Clinical Trials** and **4.4** for available data on different add-on therapies).

4.2 Dose and method of administration

INVOKANA should be taken orally once a day, preferably taken before the first meal of the day. Tablets are to be swallowed whole. If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken to make up for the missed one.

The management of therapy should be individualised.

The recommended dose of INVOKANA is 100 mg or 300 mg once daily. The 300 mg dose may be considered for patients with CKD stages 1 or 2 (eGFR ≥ 60 mL/min/1.73 m^2 or a creatinine clearance (CrCl) ≥ 60 mL/min), who need tighter glycemic control and who have a low risk of adverse reactions associated with reduced intravascular volume with INVOKANA treatment (see below and **section 4.4**).

A starting dose of 100 mg once daily should be used in patients on loop diuretics and patients ≥ 75 years of age. In patients with evidence of reduced intravascular volume, correcting this condition prior to initiation of INVOKANA is recommended. For those patients who are tolerating INVOKANA 100 mg and who need tighter glycemic control, the dose can be increased to INVOKANA 300 mg (see **section 4.4**).

When INVOKANA is used as add-on therapy with anti-hyperglycaemic agents other than insulin or an insulin secretagogue, the dose(s) of the anti-hyperglycaemic agents can be maintained and INVOKANA administered concomitantly.

When INVOKANA is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see **sections 4.4**; **4.8**).

Special populations

Elderly

In patients ≥ 75 years of age, the starting dose is 100 mg once daily. Renal function and risk of volume depletion should be taken into account (see **sections 4.4**; **4.8** and **5**).

Renal impairment

Assessment of renal function is recommended prior to initiation of INVOKANA therapy and periodically thereafter (see **section 4.4**).

For patients with mild renal impairment (CKD stage 2; eGFR 60 to < 90 mL/min/1.73m^2 or CrCl 60 to < 90 mL/min), no dose adjustment is required.

In patients with CKD stage 3A (eGFR 45 to < 60 mL/min/1.73m^2 or CrCl 45 to < 60 mL/min), the dose of INVOKANA is limited to 100 mg once daily.

INVOKANA should not be initiated in patients with an eGFR < 45 mL/min/1.73 m^2 or a CrCl < 45 mL/min. INVOKANA should be discontinued when eGFR is persistently < 45 mL/min/1.73 m^2 or CrCl is persistently < 45 mL/min (see **sections 4.4** and **4.8**).

INVOKANA should not be used in patients with an eGFR < 45 mL/min/1.73 m^2 as it would not be effective in these patient populations (see **section 4.3**).

Hepatic impairment

For patients with mild or moderate hepatic impairment, no dose adjustment is required.

INVOKANA has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see **section 5.2**).

Paediatric population

The safety and efficacy of INVOKANA in children under 18 years of age have not been established. No data are available.

4.3 Contraindications

- Hypersensitivity to INVOKANA or to any of the excipients.
- Patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30 mL/min/1.73 m^2 or CrCl < 30 mL/min) or eGFR persistently < 45 mL/min/1.73m^2 or CrCl persistently < 45 mL/min (CKD stage 3B). The efficacy of INVOKANA is dependent on renal function (see **section 4.4**).

4.4 Special warnings and precautions for use

General

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

INVOKANA should not be used for the treatment of diabetic ketoacidosis (DKA) or in patients with an eGFR < 45 mL/min/1.73 m^2 as it would not be effective in these settings.

Diabetic ketoacidosis

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

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

Type 1 diabetes mellitus

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

Type 2 diabetes mellitus

In patients with type 2 diabetes mellitus, DKA has been reported with the use of INVOKANA. In the clinical development program, serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were reported in 0.09% (10/10687) of patients treated with INVOKANA, all of whom were hospitalised. DKA has also been reported during postmarketing surveillance and has occurred in patients with blood glucose values less than 13.9 mmol/L (see **section 4.8**).

Therefore, in patients with type 2 diabetes presenting with metabolic acidosis, a diagnosis of DKA should be considered even if blood glucose levels are less than 13.9 mmol/L. Patients on INVOKANA should be tested for ketones when they present with signs and symptoms of metabolic acidosis, such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness, in order to prevent delayed diagnosis and to ensure appropriate patient management.

In patients with type 2 diabetes with DKA, treatment with INVOKANA should be discontinued immediately. Consider interrupting treatment with INVOKANA in patients with type 2 diabetes who are hospitalised for major surgical procedures or acute serious medical illnesses. Treatment with INVOKANA may be restarted once the patient's condition has stabilised.

Lower limb amputation

In long-term clinical studies of INVOKANA in type 2 diabetes patients with established cardiovascular disease (CVD) or at least two risk factors for CVD, an approximately 2-fold increased risk of lower limb amputation (primarily of the toe and midfoot) has been observed in patients treated with INVOKANA (see **section 4.8**). As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown.

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

Hyperkalaemia

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 hyperkalaemia (see **section 4.8**).

Serum potassium levels should be monitored periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalaemia due to medications or other medical conditions.

Reduced intravascular volume

Due to its mechanism of action, INVOKANA increases urinary glucose excretion (UGE) and induces an osmotic diuresis, which may reduce intravascular volume. Patients most susceptible to adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, or hypotension) include patients on loop diuretics, patients with moderate renal impairment, and patients ≥ 75 years of age (see **sections 4.2**; **4.8**).

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 **section 4.8**).

Due to reduced intravascular volume, generally small mean dose-dependent increases in serum creatinine and concomitant decreases in eGFR were seen within the first 6 weeks of treatment initiation with INVOKANA. In patients susceptible to greater reductions in intravascular volume as described above, larger decreases in eGFR (> 30%) were sometimes seen, which subsequently improved, and infrequently required interruption of treatment with INVOKANA (see **section 4.8**).

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

Renal function should be assessed prior to initiation of INVOKANA. More frequent renal function monitoring is recommended in patients with an eGFR < 60 mL/min/1.73 m^2. INVOKANA should not be used in patients with an eGFR < 45 mL/min/1.73 m^2 (see **section 4.3**).

Hypoglycemia in add-on therapy with other antihyperglycemic agents

When used alone or as add-on therapy with antihyperglycemic agents not associated with hypoglycemia, INVOKANA showed a low incidence of hypoglycemia. Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. When INVOKANA was used as add-on therapy with insulin or an insulin secretagogue (e.g., sulfonylurea), the incidence of hypoglycemia was increased over that of placebo.

Therefore, to lower the risk of hypoglycemia, a dose reduction of insulin or an insulin secretagogue may be considered (see **section 4.2** and **4.8**).

Genital mycotic infections

Consistent with the mechanism of SGLT2 inhibition with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical trials (see **section 4.8**). Male and female patients with a history of genital mycotic infections were more likely to develop an infection. Balanitis or balanoposthitis occurred primarily in uncircumcised male patients; events of phimosis were also reported. In a pooled analysis of 8 controlled trials, 0.2% of male patients underwent circumcision. The majority of genital mycotic infections were treated with topical

antifungal treatments, either prescribed by a healthcare professional or self treated while continuing therapy with INVOKANA.

Hypersensitivity Reactions

Hypersensitivity reactions (eg, generalized urticaria), some serious were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reaction occurs, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve (see **section 4.3**).

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in patients with renal impairment

The efficacy of INVOKANA is dependent on renal function. Patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30 mL/min/1.73 m^2 or CrCl < 30 mL/min) or eGFR persistently < 45 mL/min/1.73m^2 or CrCl persistently < 45 mL/min (CKD stage 3B) should not receive INVOKANA (see **section 4.3**).

- Monitoring of renal function is recommended as follows:
- prior to initiation of INVOKANA and at least yearly thereafter;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;
- for renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function consistently falls below Stage 3A CKD (eGFR < 45 mL/min/1.73 m^2 or CrCl < 45 mL/min) treatment with INVOKANA should be discontinued.

4.5 Interactions with other medicines

In vitro assessment of interactions

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

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

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

In vivo assessment of interactions

Effects of other medicinal products on canagliflozin

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

Rifampicin: Co-administration with rifampicin, a nonselective inducer of several UGT enzymes and medicinal product transporters including UGT1A9, UGT2B4, P-gp, and MRP2, decreased canagliflozin exposure. These decreases in exposure to canagliflozin may decrease efficacy. If a combined inducer of these UGTs and transport proteins (e.g., rifampicin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz, St John's wort [Hypericum perforatum]) must be co-administered with INVOKANA, monitor HbA_{1c} in patients receiving INVOKANA 100 mg once daily with consideration to increasing the dose to 300 mg once daily if additional glycaemic control is

needed. In patients with CKD stage 3A (eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 or CrCl 45 mL/min to < 60 mL/min) taking canagliflozin 100 mg who are receiving concurrent therapy with a UGT enzyme inducer and who require additional glycaemic control, other antihyperglycemic therapies should be considered (see **sections 4.2** and **4.4**).

Table 1: Effect of co-administered medicinal products on systemic exposure of canagliflozin

Co-administered medicinal product	Dose of co-administered medicinal product[1]	Dose of canagliflozin[1]	Geometric mean ratio (ratio with/without co-administered medicinal product) No effect=1.0	
			AUC[2] (90% CI)	C_{max} (90% CI)
No dose adjustments of INVOKANA required for the following:				
Cyclosporin	400 mg	300 mg once daily for 8 days	1.23 (1.19; 1.27)	1.01 (0.91; 1.11)
Ethinyl oestradiol and levonorgestrel	0.03 mg ethinyl oestradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
Hydrochlorothiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin	2,000 mg	300 mg once daily for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid	500 mg twice daily for 3 days	300 mg once daily for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)
Rifampicin	600 mg once daily for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)

[1] Single dose unless otherwise noted.

[2] AUCinf for medicinal products given as a single dose and AUC24h for medicinal products given as multiple doses.

Effects of canagliflozin on other medicinal products

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

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

Table 2: Effect of canagliflozin on systemic exposure of co-administered medicinal products

Co-administered medicinal product	Dose of Co-administered medicinal product[1]	Dose of canagliflozin[1]	Geometric mean ratio (ratio with/without co-administered medicinal product) No effect=1.0		
				AUC[2] (90% CI)	C_{max} (90% CI)
No dose adjustments of co-administered medicinal product required for the following:					
Digoxin	0.5 mg once daily first day followed by 0.25 mg once daily for 6 days	300 mg once daily for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
Ethinyl oestradiol and levonorgestrel	0.03 mg ethinyl oestradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	ethinyl oestradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)
			levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)

Co-administered medicinal product	Dose of Co-administered medicinal product[1]	Dose of canagliflozin[1]	Geometric mean ratio (ratio with/without co-administered medicinal product) No effect=1.0		
				AUC[2] (90% CI)	C_{max} (90% CI)
Glyburide	1.25 mg	200 mg once daily for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochloro-thiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg once daily for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Paracetamol	1,000 mg	300 mg twice daily for 25 days	paracetamol	1.06[3] (0.98; 1.14)	1.00 (0.92; 1.09)
Simvastatin	40 mg	300 mg once daily for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)
Warfarin	30 mg	300 mg once daily for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (0.98; 1.03)	1.05 (0.99; 1.12)

[1] Single dose unless otherwise noted.

[2] AUC_{inf} for medicinal products given as a single dose and AUC_{24h} for medicinal products given as multiple doses.

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

INR = International Normalised Ratio.

Medicinal Products/Laboratory Test Interference

1,5-AG assay

Increases in urinary glucose excretion with INVOKANA can falsely lower 1,5-anhydroglucitol (1,5-AG) levels and make measurements of 1,5 AG unreliable in assessing glycemic control. Therefore, 1,5-AG assays should not be used for assessment of glycemic control in patients on canagliflozin. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

Urine glucose test

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

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Category C

There are no adequate and well-controlled studies in pregnant women. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. (see **section 5.3**)

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin in milk. It is not known if canagliflozin is excreted in human milk. Data in juvenile rats directly exposed to canagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during

maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. A risk to the breast fed child cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from INVOKANA therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of canagliflozin on fertility in humans has not been studied. In fertility studies in male and female rats, canagliflozin had no adverse effects on early embryonic development, mating, and fertility up to the highest dose of 100 mg/kg/day (up to 12 and 15 times the clinical dose of 300 mg in the respective sexes based on AUC exposure).

4.7 Effect on ability to drive and use machines

Canagliflozin has no known influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia, especially when INVOKANA is used as add-on therapy with insulin or an insulin secretagogue, and to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness (see **sections 4.2**; **4.4**; **4.8**).

4.8 Undesirable effects

Clinical Trial Data

The safety of INVOKANA was evaluated in 10,285 patients with type 2 diabetes, including 3,092 patients treated with INVOKANA 100 mg and 3,462 patients treated with INVOKANA 300 mg, who received medicinal product in nine double-blind, controlled Phase 3 clinical studies.

The primary assessment of safety and tolerability was conducted in a pooled analysis (n=2,313) of four 26-week placebo-controlled clinical studies (monotherapy and add-on therapy with metformin, metformin and a sulphonylurea, and metformin and pioglitazone). The most commonly reported adverse reactions during treatment were hypoglycaemia in combination with insulin or a sulphonylurea, vulvovaginal candidiasis, urinary tract infection, and increased frequency and volume of urination. Adverse reactions leading to discontinuation of ≥ 0.5% of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of female patients) and balanitis or balanoposthitis (0.5% of male patients). Additional safety analyses (including long-term data) from data across the entire canagliflozin programme (placebo- and active-controlled studies) were conducted to assess reported adverse reactions in order to identify adverse reactions (see **Table 3**) (see **sections 4.4** and **4.2**).

Tabulated list of adverse reactions

Table 3 lists adverse reactions reported in ≥ 2% of INVOKANA-treated patients in the four pooled, 26-week, placebo-controlled clinical studies (N=2313). The safety profiles of the individual placebo-controlled studies in the pooled analysis were similar in adverse reactions and frequencies.

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

	INVOKANA 100 mg N=833 %	**INVOKANA 300 mg N=834 %**	**Placebo N=646 %**
System Organ Class Adverse Reaction			
Gastrointestinal Disorders			
Constipation	15 (1.8)	19 (2.3)	6 (0.9)
Nausea	18 (2.2)	19 (2.3)	10 (1.5)
Thirst	23 (2.8)	19 (2.3)	1 (0.2)
Renal and Urinary Disorders			

	INVOKANA 100 mg N=833 %	INVOKANA 300 mg N=834 %	Placebo N=646 %
Polyuria or Pollakiuria	44 (5.3)	38 (4.6)	5 (0.8)
Urinary tract infection	49 (5.9)	36 (4.3)	26 (4.0)
Reproductive System and Breast Disorders			
Balanitis or Balanoposthitis	17 (4.2)	15 (3.7)	2 (0.6)
Vulvovaginal candidiasis	44 (10.4)	49 (11.4)	10 (3.2)

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

Description of selected adverse reactions

Diabetic ketoacidosis

DKA was identified as an adverse reaction during postmarketing surveillance. In a review of the data from the type 2 diabetes mellitus clinical development program, incidence rates of serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5337), 0.0763 (0.11%, 6/5350), and 0.0238 (0.03%, 2/6909) per 100 patient years with INVOKANA 100 mg, INVOKANA 300 mg, and comparator, respectively. Of the 10 patients on INVOKANA, 6 (3 on INVOKANA 100 mg, 3 on INVOKANA 300 mg) were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or tested positive for GAD65 antibodies while no patients on comparator were diagnosed with autoimmune diabetes and 8 of the 10 patients were receiving insulin therapy. The blood glucose values in 9 patients on INVOKANA around the time of admission ranged from 19.3 mmol/L to 31.7 mmol/L. One patient had blood glucose values ranging from 8.2 mmol/L to 17.8 mmol/L (see **section 4.4**).

Lower limb amputation

In patients with type 2 diabetes who had established cardiovascular disease or at least two risk factors for cardiovascular disease, INVOKANA was associated with an approximately 2-fold increased risk of lower limb amputation as observed in the Integrated CANVAS Program comprised of CANVAS and CANVAS-R, two large, long-term, randomized, placebo-controlled trials evaluating 10142 patients. The imbalance occurred as early as the first 26 weeks of therapy. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. Regardless of treatment with INVOKANA or placebo, the risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy. The risk of lower limb amputation was not dose-dependent. The amputation results for the Integrated CANVAS Program are shown in Table 4. In other type 2 diabetes studies with INVOKANA, which enrolled a general diabetic population of 8114 patients, no difference in lower limb amputation risk was observed relative to control.

Table 3: Integrated Analysis of Amputations in CANVAS AND CANVAS-R

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

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

* Toe and midfoot

† Ankle, below knee and above knee

Of the subjects who had an amputation event, the toe and midfoot were the most frequent sites (71%) in both treatment groups (see Table 4). Multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups.

Lower limb infections, diabetic foot ulcers, peripheral arterial disease, and gangrene, were the most common medical events associated with the need for an amputation in both treatment groups (see **section 4.4**).

Cardiovascular events

A prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from Phase 2 and 3 clinical studies in 9,632 patients with type 2 diabetes, including 4,327 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 hospitalisation) for (both doses pooled) versus combined active and placebo comparators was 0.91 (95% CI: 0.68; 1.22). The hazard ratios for the 100 mg and 300 mg doses were 0.92 (95% CI: 0.65,1.28) and 0.91 (95%CI: 0.65, 1.28) respectivley. Therefore, there was no evidence of an increase in cardiovascular risk with either 100 mg or 300 mg relative to comparators.

Adverse reactions related to 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 (postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) was 1.2% for INVOKANA 100 mg, 1.3% INVOKANA 300 mg and 1.1% for placebo. The incidence with INVOKANA treatment in the two active controlled studies was similar to comparators.

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

To assess risk factors for these adverse reactions, a larger pooled analysis (N=9,439) 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 generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidences were 3.2% on INVOKANA 100 mg and 8.8% on INVOKANA 300 mg compared to 4.7% in the control group. For patients with a baseline eGFR < 60 mL/min/1.73 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 **sections 4.2**; **4.4**).

In the dedicated cardiovascular study and the larger pooled analysis, discontinuations due to adverse reactions related to reduced intravascular volume and serious adverse reactions related to reduced intravascular volume were not increased with INVOKANA..

Hypoglycaemia in add-on therapy with insulin or insulin secretagogues

The frequency of hypoglycemia was low (< 6%) among treatment groups when used as monotherapy or as an add-on to antihyperglycemic agents not associated with hypoglycemia. When INVOKANA was used as add-on therapy with insulin or sulphonylurea (with or without metformin), hypoglycaemia was reported more frequently, which is consistent with the expected increase of hypoglycaemia when an agent not associated with hypoglycaemia is added to insulin or an insulin secretagogue (e.g., sulphonylurea). In the 18-week substudy with when INVOKANA was added to insulin therapy, hypoglycaemia was observed in 49.3%, 48.2%, and 36.8% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. Severe hypoglycaemia occurred in 1.8%, 2.7%, and 2.5% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. When INVOKANA was added to sulphonylurea therapy, hypoglycaemia

was observed in 4.1%, 12.5%, and 5.8% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively (see **sections 4.2**; **4.4**).

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 **section 4.4**).

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 **section 4.4**).

Urinary tract infections

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

Bone fracture

In a cardiovascular study of 4327 patients with known or at high risk for cardiovascular disease, the incidence rates of bone fracture were 16.3, 16.4, and 10.8 per 1000 patient years of exposure to INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with INVOKANA, which enrolled a general diabetes population of approximately 5800 patients, no difference in fracture risk was observed relative to control. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Laboratory tests

The below incidence rates of abnormal laboratory values are derived from the pooled analysis of 26-week, placebo-controlled clinical studies unless otherwise noted.

Increases in serum potassium

Mean percent changes from baseline in blood potassium were 0.5% and 1.0% for INVOKANA 100 mg and 300 mg, respectively, compared to 0.6% for placebo. Episodes of elevated serum potassium (> 5.4 mEq/l and 15% above baseline) were seen in 4.4% of patients treated with INVOKANA 100 mg, 7.0% of patients treated with INVOKANA 300 mg, and 4.8% of patients treated with placebo. In general, elevations were mild (< 6.5 mEq/L), transient, and did not require specific treatment.

Increases in serum creatinine and urea

Mean percent changes from baseline in creatinine, with commensurate decreases in eGFR, were 2.8% and 4.0% for INVOKANA 100 mg and 300 mg, respectively, compared to 1.5% for placebo. Mean percent changes from baseline in urea 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 urea levels remained stable.

The proportion of patients with larger decreases in eGFR (> 30%) from baseline, occurring at any time during treatment, was 2.0% with INVOKANA 100 mg and 4.1% with INVOKANA 300 mg relative

to 2.1% with placebo. These decreases in eGFR were often transient with fewer patients having this level of decrease at study endpoint, occurring in 0.7% of patients with INVOKANA 100 mg, 1.4% of patients with INVOKANA 300 mg, and 0.5% of placebo-treated patients). (see **section 4.4**).

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

Lipid changes

The mean percent changes from baseline relative to placebo for low density lipoprotein cholesterol (LDL-C) were 0.11 mmol/L (4.5%) and 0.21 mmol/L (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. Smaller increases in total cholesterol of 2.5% and 4.3% relative to placebo for INVOKANA 100 mg and INVOKANA 300 mg, respectively, were seen. Increases in high density lipoprotein cholesterol (HDL-C) were 5.4%, and 6.3% relative to placebo for INVOKANA 100 mg and INVOKANA 300 mg, respectively. Increases in non-HDL-C relative to placebo were 0.05 mmol/L (1.5%) and 0.13 mmol/L (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The LDL-C/HDL-C ratios did not change with either INVOKANA dose compared to placebo. Concentrations of ApoB and LDL-C particle number (measured in two studies) and non-HDL-C increased to a smaller extent compared to LDL-C changes.

Increases in haemoglobin

Mean changes (percent changes) from baseline in hemoglobin concentrations were 4.7 g/L (3.5%) with INVOKANA 100 mg, 5.1 g/L (3.8%) with INVOKANA 300 mg, and -1.8 g/L (-1.1%) with placebo. Small increases in the mean percent change from baseline in hemoglobin concentration were observed in the INVOKANA 100 mg and 300 mg groups (3.5% and 3.8%, respectively) compared to a slight decrease in placebo (1.1%). Commensurate small increases in the mean percent change from baseline in blood erythrocytes and hematocrit were observed. At the end of treatment, 4.0%, 2.7%, and 0.8% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively, had hemoglobin levels above the upper limit of normal.

Increases in serum phosphate

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

Decreases in serum urate

Moderate decreases in the mean percent change from baseline in serum urate were observed in the INVOKANA 100 mg and 300 mg groups (-10.1% and -10.6%, respectively) compared with placebo, where a slight increase from baseline (1.9%) was observed. Decreases in serum urate in the INVOKANA groups were maximal or near maximal by week 6 and maintained with dosing. A transient increase in urinary uric acid excretion was seen, which was not persistent. In a pooled analysis (N=9,439) of patients from eight controlled Phase 3 studies including both doses of INVOKANA, events of nephrolithiasis were not increased.

Adverse reactions in specific populations

Elderly patients

The safety profile in elderly patients was generally consistent with that for younger patients. Patients ≥ 75 years of age had a higher incidence of adverse reactions related to reduced intravascular volume (such as postural dizziness, orthostatic hypotension, hypotension) with 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 **sections 4.2** and **4.4**).

Renal impairment

In an analysis of patients with a baseline eGFR 45 to < 60 mL/min/1.73 m^2 or CrCl 45 to < 60 mL/min (CKD stage 3A), 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 **sections 4.2** and **4.4**). Serum creatinine levels increased by 4.9% and 7.3% for INVOKANA 100 mg and 300 mg, respectively, relative to 0.2% with placebo. Blood urea nitrogen 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 **section 4.4**).

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 5.2% with placebo (see **section 4.4**). Rare, more severe elevations were seen in patients with moderate renal impairment who had prior elevated potassium concentrations and/or who were on multiple medications that reduce potassium excretion, such as potassium-sparing diuretics and angiotensin-converting-enzyme (ACE) inhibitors. In general, elevations were transient and did not require specific treatment.

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

Due to the reduced benefit and increased risks from use of INVOKANA in patients with an eGFR persistently < 45 mL/min/1.73 m^2 or CrCl persistently < 45 mL/min (CKD stage 3B), 4, and 5, INVOKANA is contraindicated in these patients (see **section 4.3**).

Postmarketing data

In addition to the adverse reactions identified from clinical studies, the following adverse reactions have been identified during postmarketing experience. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

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

Table 5: Adverse Reactions Identified During Postmarketing Experience with INVOKANA

System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates***	**Frequency Category Estimated from Clinical Studies**
Metabolism and nutrition disorders		
Diabetic ketoacidosis	Very rare	Rare
Immune system disorders		
Anaphylactic reaction	Very rare	Rare
Skin and subcutaneous tissue disorders		
Angioedema	Very rare	Rare
Renal and urinary disorders		
Pyelonephritis	Very rare	Rare
Renal failure (related to volume depletion)	Very rare	Uncommon

Urosepsis	Very rare	Rare

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

4.9 Overdosage

During controlled clinical studies in healthy subjects, single doses up to 1600 mg (equivalent to 5.3 times the recommended dose) and 300 mg twice daily for 12 days were generally well tolerated. There is no experience with single doses above 1600 mg or 300 mg twice daily for 12 days in humans.

Management of Overdosage

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute clinical measures if required. Canagliflozin was negligibly removed during a 4-hour haemodialysis session. It is not known whether canagliflozin is dialyzable by peritoneal dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excluding insulins. ATC code: A10BX11.

Mechanism of Action

INVOKANA is an inhibitor of 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 blood glucose concentrations. Canagliflozin is an orally-active inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE), lowering elevated plasma glucose concentrations by an insulin-independent mechanism in patients with type 2 diabetes. The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in UGE results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with type 2 diabetes (see **Clinical Trials**).

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.

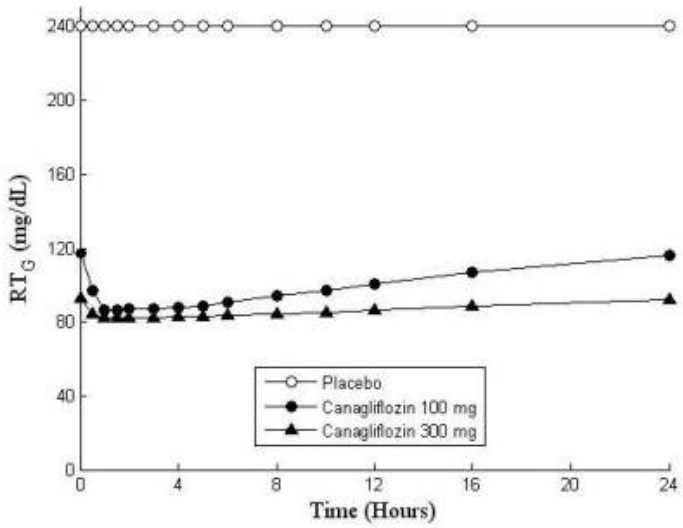
In Phase 3 studies, pre-meal administration of canagliflozin 300 mg provided a greater reduction in postprandial glucose excursion than observed with the 100 mg dose This effect at the 300 mg dose of canagliflozin may, in part, be due to local inhibition of intestinal SGLT1 (an important intestinal glucose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

Pharmacodynamic effects

Following single and multiple oral doses of canagliflozin in patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RT_G) and increases in UGE were observed. From a starting value of RT_G of approximately 13 mmol/L, maximal suppression of 24-hour mean RT_G was seen with the 300 mg daily dose to approximately 4 to 5 mmol/L in patients with type 2 diabetes in Phase 1 studies (see **Figure 1**), suggesting a low risk for treatment-induced

hypoglycaemia. 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 RTG 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 a nonrenal mechanism.

Cardiac Electrophysiology

In a randomised, double-blind, placebo-controlled, active-comparator, 4-way crossover study, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1,200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QTc interval were observed with either the recommended dose of 300 mg or the 1,200 mg dose. At the 1,200 mg dose, peak canagliflozin plasma concentrations were approximately 1.4 times the steady-state peak concentrations following a 300 mg once-daily dose.

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N=2,313), mean reductions in systolic blood pressure relative to placebo were observed with canagliflozin 100 mg (-3.9 mmHg), canagliflozin 300 mg (-5.3 mmHg), and placebo (-0.1 mmHg). In this same population, there was a smaller effect on diastolic blood pressure with mean changes of -2.1 mmHg with canagliflozin 100 mg, -2.5 mmHg with canagliflozin 300 mg, and -0.3 mmHg with placebo. There was no discernible change in heart rate.

Lipid effects

In an integrated analysis of four placebo-controlled studies of 26 weeks, patients with type 2 diabetes treated with both doses of canagliflozin had increased serum concentrations of total cholesterol, LDL-C, and HDL-C (high-density lipoprotein cholesterol) compared to small changes in placebo, while serum concentrations of triglycerides decreased compared to placebo. At week 26, the LDL-C/HDL-C ratio minimally changed compared to baseline in all three treatment groups. Similar

to changes observed in non-HDL-C, concentrations of ApoB and LD particle number (measured in two studies) increased to a smaller extent than LDL-C changes in the monotherapy and 26-week metformin add-on therapy study (see **section 4.8**).

Clinical trials

INVOKANA has been studied as monotherapy (DIA3005), in combination with metformin (DIA3006 and DIA3009), sulfonylurea (DIA3008), metformin and sulfonylurea (DIA3002 and DIA3015), metformin and a thiazolidinedione (i.e. pioglitazone; DIA3012), and in combination with insulin (with or without other antihyperglycemic agents; DIA3008).

INVOKANA has also been studied in patients 55 to 80 years of age (DIA3010) and in patients with moderate renal impairment (DIA3004). In these studies, INVOKANA was added to patients' existing diabetic therapy (eg, metformin, sulfonylurea, pioglitazone, alpha-glucosidase inhibitor, DPP4 inhibitors, or GLP1 agonists).

A total of 10,285 patients with type 2 diabetes participated in nine double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of INVOKANA on glycaemic control. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 to 96 years), with 3,082 patients 65 years of age and older and 510 patients ≥ 75 years of age. One study was conducted in patients with renal impairment with an eGFR 30 to < 50 mL/min/1.73 m^2 (N=269) and three other studies included patients with renal impairment with an eGFR 30 to < 60 mL/min/1.73 m^2 (N=816).

INVOKANA produced clinically and statistically significant improvements relative to placebo in glycaemic control, including HbA_{1c}, percentage of patients achieving HbA_{1c} < 7%, change from baseline fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG), and clinically relevant improvement in percent change in body weight. The reductions in HbA_{1c} were similar across different subgroups including age, gender, race, body mass index (BMI), and baseline beta-cell function. Greater reductions in HbA_{1c} relative to placebo were observed in patients with higher baseline HbA_{1c} or higher eGFR values.

For patients treated with canagliflozin there are no clinical data regarding substitution of canagliflozin with another SGLT2 inhibitor.

Efficacy of canagliflozin is dependent on renal function. Reductions in mean HbA1c relative to placebo ranged from 0.62 to 0.91 for the 100 mg canagliflozin dose and 0.76 to 1.16 for the 300 mg dose. The effect was reduced in older subjects (mean reduction of 0.57 and 0.70 for the 100 mg and 300 mg doses respectively), subjects taking insulin (mean reduction of 0.65 and 0.73 for the 100 mg and 300 mg doses respectively) and in subjects with moderate renal impairment (mean reductions of 0.3 and 0.4 for the 100 mg and 300 mg doses respectively).

Table 6: HbA1c (%) Change from Baseline to Primary Assessment Timepoint - LOCF: Study-by-Study Comparison (ISE Phase 3 Studies: Modified Intent-to-Treat Analysis Set)

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Monotherapy					
DIA3005					
Baseline, mean (SD)	7.97(0.955)	8.06(0.959)	8.01(0.988)		
Change from baseline, LS mean (SE)	0.14(0.065)	-0.77(0.065)	-1.03(0.064)		
Diff of LS mean (SE) (minus placebo)		-0.91(0.091)	-1.16(0.091)		
95% CI[a]		(-1.088;-0.729)	(-1.342;-0.985)		
Dual therapy					
DIA3006					
Add-on to metformin					
Baseline, mean (SD)	7.96(0.896)	7.94(0.879)	7.95(0.931)	7.92(0.875)	
Change from baseline, LS mean (SE)	-0.17(0.060)	-0.79(0.044)	-0.94(0.044)	-0.82(0.044)	
Diff of LS mean (SE) (minus placebo)		-0.62(0.071)	-0.77(0.071)		

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
95% CI[a]		(-0.758;-0.481)	(-0.914;-0.636)		
DIA3009					
Add-on to metformin					
Baseline, mean (SD)		7.78(0.787)	7.79(0.779)		7.83(0.795)
Change from baseline, LS mean (SE)		-0.82(0.039)	-0.93(0.039)		-0.81(0.039)
Diff of LS mean (SE) (minus glimepiride)		-0.01(0.050)	-0.12(0.050)		
95% CI[a]		(-0.109;0.085)	(-0.217;-0.023)		
DIA3008 substudy					
Add-on to SU					
Baseline, mean (SD)	8.49(1.130)	8.29(0.831)	8.28(1.005)		
Change from baseline, LS mean (SE)	0.04(0.146)	-0.70(0.145)	-0.79(0.147)		
Diff of LS mean (SE) (minus placebo)		-0.74(0.206)	-0.83(0.207)		
95% CI[a]		(-1.145;-0.329)	(-1.237;-0.415)		
Triple therapy					
DIA3002					
Add-on to metformin and SU					
Baseline, mean (SD)	8.12(0.896)	8.13(0.926)	8.13(0.942)		
Change from baseline, LS mean (SE)	-0.13(0.075)	-0.85(0.075)	-1.06(0.076)		
Diff of LS mean (SE) (minus placebo)		-0.71(0.097)	-0.92(0.097)		
95% CI[a]		(-0.904;-0.524)	(-1.114;-0.732)		
DIA3012					
Add-on to metformin and pioglitazone					
Baseline, mean (SD)	8.00(1.010)	7.99(0.940)	7.84(0.911)		
Change from baseline, LS mean (SE)	-0.26(0.069)	-0.89(0.069)	-1.03(0.070)		
Diff of LS mean (SE) (minus placebo)		-0.62(0.095)	-0.76(0.096)		
95% CI[a]		(-0.811;-0.437)	(-0.951;-0.575)		
DIA3015					
Add-on to metformin and SU					
Baseline, mean (SD)			8.12 (0.910)	8.13 (0.916)	
Change from baseline, LS mean (SE)			-1.03 (0.048)	-0.66 (0.049)	
Diff of LS mean (SE) (minus sitagliptin)			-0.37 (0.064)		
95% CI[a]			(-0.500;-0.250)		
Add-on to insulin					
With or without other antihyperglycaemic agent					
DIA3008 substudy					
Baseline, mean (SD)	8.20(0.837)	8.33(0.905)	8.27(0.894)		
Change from baseline, LS mean (SE)	0.01(0.032)	-0.63(0.031)	-0.72(0.030)		
Diff of LS mean (SE) (minus placebo)		-0.65(0.044)	-0.73(0.043)		
95% CI[a]		(-0.731;-0.559)	(-0.815;-0.645)		
Special populations					
DIA3004					
Moderate renal impairment					

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Baseline, mean (SD)	8.02(0.917)	7.89(0.898)	7.97(0.805)		
Change from baseline, LS mean (SE)	-0.03(0.090)	-0.33(0.090)	-0.44(0.089)		
Diff of LS mean (SE) (minus placebo)		-0.30(0.117)	-0.40(0.117)		
95% CI[a]		(-0.529;-0.066)	(-0.635;-0.174)		
DIA3010					
Older adults (≥ 55 years)					
Baseline, mean (SD)	7.76(0.785)	7.77(0.773)	7.69(0.779)		
Change from baseline, LS mean (SE)	-0.03(0.063)	-0.60(0.063)	-0.73(0.064)		
Diff of LS mean (SE) (minus placebo)		-0.57(0.069)	-0.70(0.070)		
95% CI[a]		(-0.708;-0.436)	(-0.841;-0.566)		

[a] Pairwise comparison: CIs are based on the ANCOVA model with treatment, study specific stratification factors and baseline HbA1c.

Key: CANA=canagliflozin, CI = confidence interval, ISE = Integrated Summary of Efficacy, LOCF = last observation carried forward, LS = least squares, N = number, SD= standard deviation, SE = standard error, SU=sulfonylurea.

Note: Predefined timepoint of primary endpoint: Week 18 LOCF (DIA3008 SU and Insulin substudies), Week 26 LOCF (DIA3002, DIA3004, DIA3005 [excluding High Glycemic substudy], DIA3006, DIA3010, DIA3012) and Week 52 LOCF (DIA3009, DIA3015).

Note: Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification), while data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥ 30 IU/day).

Monotherapy study (INVOKANA as monotherapy in patients ineligible for metformin)

Study DIA3005

INVOKANA as monotherapy produced statistically significant ($p<0.001$) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, statistically significant improvements relative to placebo were observed for the percent change in body weight. Patients with more severe hyperglycaemia ($HbA_{1c} > 10$ and $\leq 12\%$) participated in a separate active-treatment substudy; canagliflozin produced significant reductions in HbA_{1c} and body weight.

Table 7: Results from 26-week placebo-controlled clinical study with INVOKANA as monotherapy[1]

Efficacy parameter	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)	Placebo (N=192)
HbA_{1c} (%)			
Baseline (mean)	8.06	8.01	7.97
Change from baseline (adjusted mean)	-0.77[2]	-1.03[2]	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
Patients (%) achieving $HbA_{1c} < 7\%$	44.5[2]	62.4[2]	20.6
Body weight			
Baseline (mean) in kg	85.9	86.9	87.5
% change from baseline (adjusted mean)	-2.8[2]	-3.9[2]	-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
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	126.7	128.5	127.7
Change from baseline (adjusted mean)	-3.3	-5.0	0.4
Difference from placebo (adjusted mean) (95% CI)	-3.7[2] (-5.9; -1.6)	-5.4[2] (-7.6; -3.3)	N/A

	Active-treatment substudy of patients with high baseline HbA_{1c} concentrations (> 10 to ≤ 12%)		
Efficacy parameter	**INVOKANA 100 mg (N=47)**	**INVOKANA 300 mg (N=44)**	
HbA_{1c} (%)			
Baseline (mean)	10.59	10.62	
Change from baseline (adjusted mean)	-2.13	-2.56	
Patients (%) achieving HbA_{1c} < 7%	17.4	11.6	
Body weight			
Baseline (mean) in kg	83.2	81.6	
% change from baseline (adjusted mean)	-3.0	-3.8	
Systolic Blood Pressure (mmHg)			
Baseline (mean)	125.0	126.6	
Change from baseline (adjusted mean)	-4.5	-5.0	

1 Intent-to-treat population using last observation in study prior to metformin rescue.

2 p<0.001 compared to placebo.

N/A = Not applicable.

Dual therapy studies (INVOKANA with metformin or sulphonylurea)

Study DIA3006

INVOKANA as dual therapy with metformin produced statistically significant (p<0.001) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, significant and sustained improvements relative to placebo were observed for the percent change in body weight.

Table 8: Results from 26-week placebo-controlled clinical study of INVOKANA as dual therapy with metformin[1]

Efficacy parameter	**INVOKANA + metformin**		**Placebo + metformin (N=183)**
	100 mg (N=368)	**300 mg (N=367)**	
HbA_{1c} (%)			
Baseline (mean)	7.94	7.95	7.96
Change from baseline (adjusted mean)	-0.79	-0.94	-0.17
Difference from placebo (adjusted mean) (95% CI)	-0.62[2] (-0.76; -0.48)	-0.77[2] (-0.91; -0.64)	N/A
Patients (%) achieving HbA_{1c} < 7%	45.5[2]	57.8[2]	29.8
Body weight			
Baseline (mean) in kg	88.7	85.4	86.7
% change from baseline (adjusted mean)	-3.7[2]	-4.2[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
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	128.0	128.7	128.0
Change from baseline (adjusted mean)	-3.8	-5.1	1.5
Difference from placebo (adjusted mean) (95% CI)	-5.4[2] (-7.3; -3.4)	-6.6[2] (-8.5; -4.6)	N/A

Efficacy parameter	INVOKANA + metformin		Placebo + metformin (N=183)
	100 mg (N=368)	300 mg (N=367)	

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

[2] p<0.001 compared to placebo.

N/A = Not applicable

Study DIA3009

INVOKANA as dual therapy with metformin produced similar reductions in HbA_{1c} with INVOKANA 100 mg from baseline compared to glimepiride and superior (p<0.05) reductions in HbA_{1c} with INVOKANA 300 mg compared to glimepiride. These reductions were sustained over the course of the 52-week period. In the glimepiride arm of the study, glimepiride was titrated to optimise glycaemic control throughout the 52-week study. In addition, significant improvements relative to glimepiride were observed for the percent change in body weight.

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

Table 9: Results from 52-week clinical study comparing INVOKANA to glimepiride as dual therapy with metformin[1]

Efficacy parameter	INVOKANA + metformin		Glimepiride (titrated) + metformin (N=482)
	100 mg (N=483)	300 mg (N=485)	
HbA_{1c} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82[2]	-0.93[2]	-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
Patients (%) achieving HbA_{1c} < 7%	53.6	60.1	55.8
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
Systolic Blood Pressure (mmHg[5])			
Baseline (mean)	130.0	130.0	129.5
Change from baseline (adjusted mean)	-3.3	-4.6	0.2
Difference from glimepiride (adjusted mean) (95% CI)	-3.5 (−4.9; −2.1)	-4.8 (−6.2; −3.4)	N/A

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

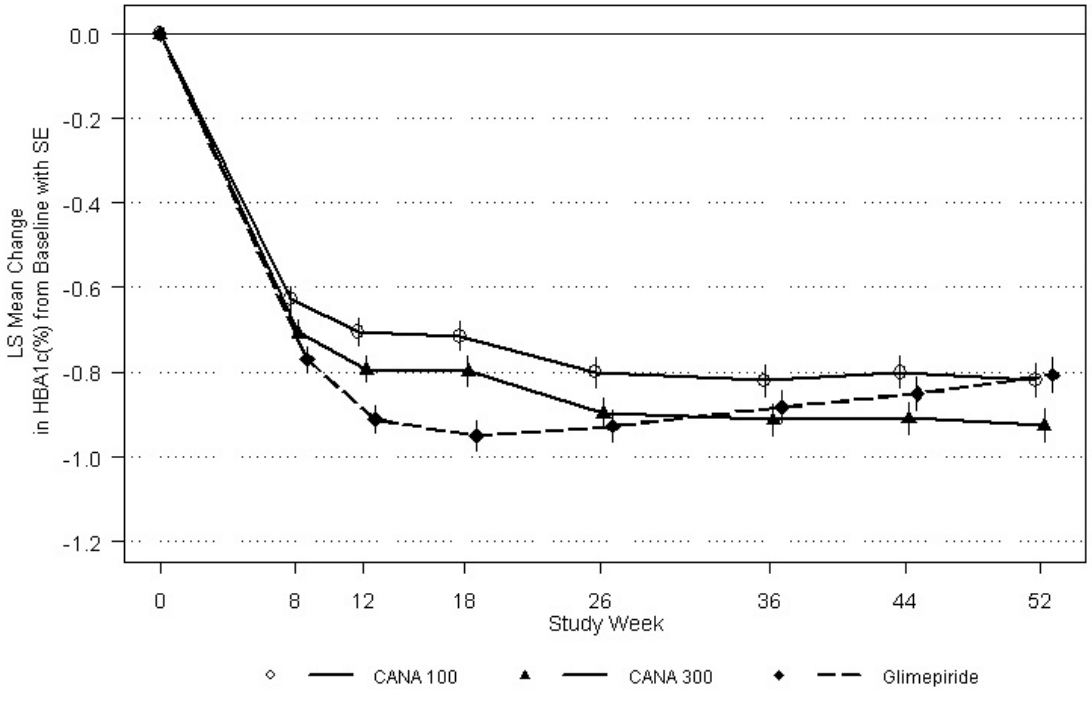
[2] 95% confidence intervals - 100 mg (−0.11;0.09), 300 mg (−0.22;−0.02). Met pre-specified criteria for non-inferiority to glimepiride (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of < 0.3%). In a pre-specified assessment, the upper bound of the 95% CI for INVOKANA 300 mg, but not for INVOKANA 100 mg was < 0, indicating greater reduction in A1C for INVOKANA 300 mg relative to glimepiride.

[3] p<0.001.

N/A = Not applicable

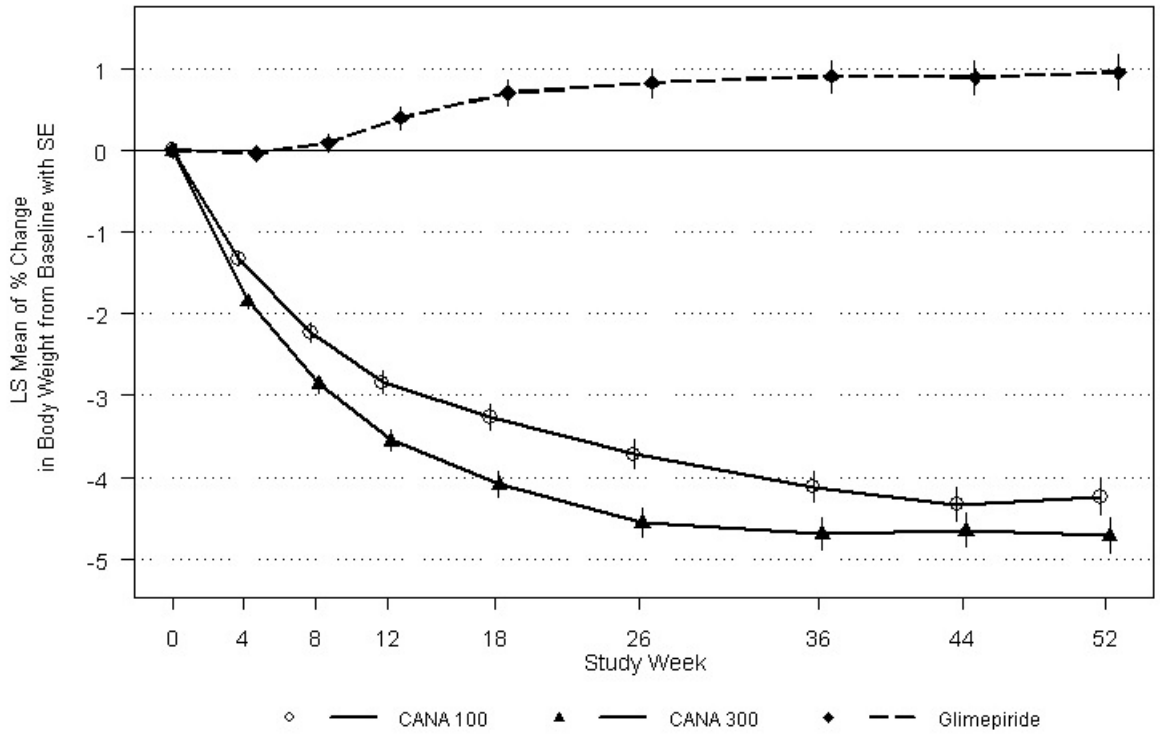
[4] Includes only patients who had both baseline and post-baseline values

Figure 1. Mean Changes from Baseline for HbA_{1C} (%) Over 52 Weeks in a Study Comparing INVOKANA to Glimepiride in Combination with Metformin



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

Figure 2. Mean Changes from Baseline for Body Weight Over 52 Weeks in a Study Comparing INVOKANA to Glimepiride in Combination with Metformin



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

Study DIA3008 – Sulphonylurea Substudy

INVOKANA as dual therapy with sulphonylurea produced statistically significant (p<0.001) improvements in HbA_{1c} over 18 weeks. In addition, INVOKANA as dual therapy with sulphonylurea resulted in a reduction in the percent change in body weight relative to placebo.

Table 10: Results from 18-week placebo-controlled clinical study of INVOKANA as dual therapy with sulphonylurea[1]

Efficacy parameter	INVOKANA + sulphonylurea		Placebo + sulphonylurea (N=45)
	100 mg (N=42)	300 mg (N=40)	
HbA_{1c} (%)			
Baseline (mean)	8.29	8.28	8.49
Change from baseline (adjusted mean)	-0.70[2]	-0.79[2]	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
Patients (%) achieving HbA_{1c} < 7%	25.0[3]	33.3[3]	5.0
Body weight			
Baseline (mean) in kg	85.1	80.4	85.5
% change from baseline (adjusted mean)	-0.6	-2.0	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.4 (-1.8; 1.0)	-1.8 (-3.2; -0.4)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	138	133.5	137.3
Change from baseline (adjusted mean)	-3.5	-5.1	-3.4
Difference from placebo (adjusted mean) (95% CI)	-0.1 (-6.5; 6.2)	-1.8 (-8.2; 4.7)	N/A

1 Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

2 p<0.001 compared to placebo.

3 p<0.01

N/A = Not applicable

Triple therapy studies (INVOKANA with metformin and sulphonylurea or metformin and pioglitazone)

Study DIA3002

INVOKANA as triple therapy with metformin and sulphonylurea produced statistically significant (p<0.001) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, statistically significant improvements in the percent change in body weight were observed.

Table 11: Results from 26-week placebo-controlled clinical study of INVOKANA as triple therapy with metformin and sulphonylurea[1]

Efficacy parameter	INVOKANA + metformin and sulphonylurea		Placebo + metformin and sulphonylurea (N=156)
	100 mg (N=157)	300 mg (N=156)	
HbA_{1c} (%)			
Baseline (mean)	8.13	8.13	8.12
Change from baseline (adjusted mean)	-0.85[2]	-1.06[2]	-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
Patients (%) achieving HbA_{1c} < 7%	43.2	56.6	18.0
Body weight			
Baseline (mean) in kg	93.5	93.5	90.8

Efficacy parameter	INVOKANA + metformin and sulphonylurea		Placebo + metformin and sulphonylurea (N=156)
	100 mg (N=157)	300 mg (N=156)	
%change from baseline (adjusted mean)	-2.1[2]	-2.6[2]	-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
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	130.4	130.8	130.1
Change from baseline (adjusted mean)	-4.9	-4.3	-2.6
Difference from placebo (adjusted mean) (95% CI)	-2.2 (-4.7; 0.2)	-1.6 (-4.1; 0.9)	N/A

1 Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

2 p<0.001 compared to placebo.

N/A = Not applicable or not measured in this study

Study DIA3015

INVOKANA as triple therapy with metformin and sulphonylurea provided superior (p<0.05) reductions in HbA_{1c} compared with sitagliptin over 52 weeks. Significant improvements in percent change in body weight compared with sitagliptin were also observed.

Table 12: Results from 52-week clinical study comparing INVOKANA to sitagliptin as triple therapy with metformin and sulphonylurea[1]

Efficacy parameter	INVOKANA 300 mg + metformin and sulphonylurea (N=377)	Sitagliptin 100 mg + metformin and sulphonylurea (N=378)
HbA_{1c} (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03[2]	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)	0.37[2] (0.50; 0.25)	N/A
Patients (%) achieving HbA_{1c} < 7%	47.6	35.3
Body weight		
Baseline (mean) in kg	87.4	89.1
% change from baseline (adjusted mean)	-2.5[3]	0.3
Difference from sitagliptin (adjusted mean) (95% CI)	2.8[3] (3.3; 2.2)	N/A
Systolic Blood Pressure (mmHg)[1]		
Baseline (mean)	131.2	130.1
Change from baseline (adjusted mean)	-5.1	-0.9
Difference from sitagliptin (adjusted mean) (95% CI)	-5.9 (-7.6; -4.2)	N/A

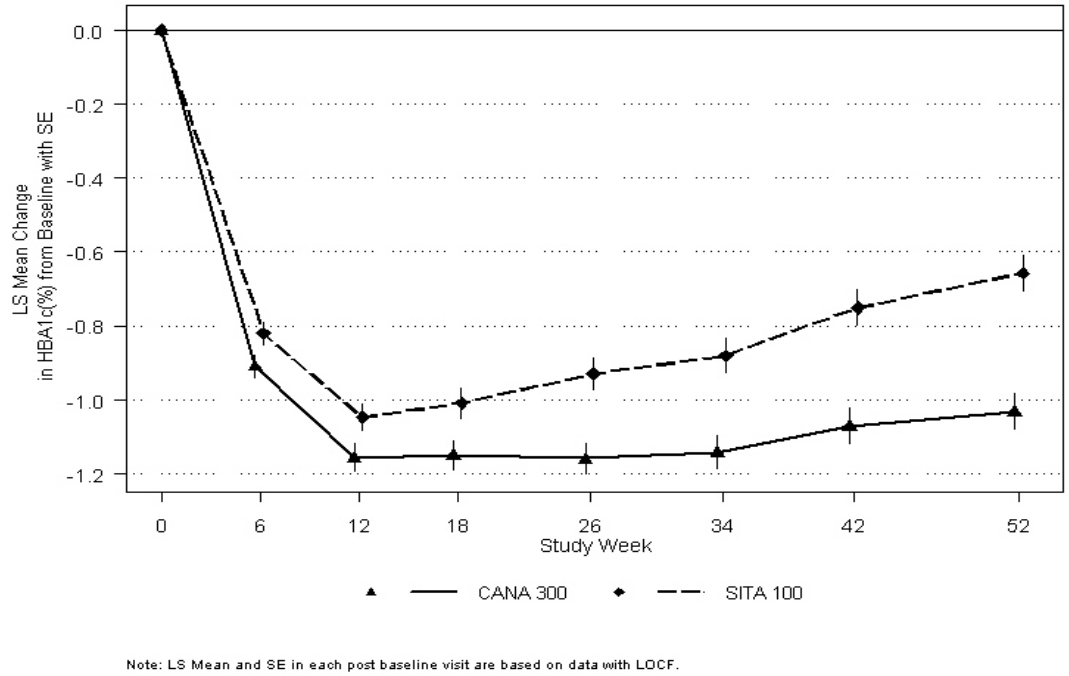
1 Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

2 95% confidence intervals for 300 mg - (-0.50; -0.25). 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 greater reduction in A1C with INVOKANA 300 mg relative to sitagliptin.

3 p<0.001.

N/A = Not applicable

Figure 3. Mean Change from Baseline for HbA_{1C} (%) Over 52 Weeks in a Study Comparing INVOKANA to Sitagliptin in Combination with Metformin and Sulfonylurea



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

Study DIA3012

INVOKANA as triple therapy with metformin and pioglitazone produced statistically significant ($p<0.001$) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, statistically significant improvements relative to placebo in the percent change in body weight were observed.

Table 13: Results from 26-week placebo-controlled clinical study of INVOKANA as triple therapy with metformin and pioglitazone[1]

Efficacy parameter	INVOKANA + metformin and pioglitazone 26 weeks		Placebo + metformin and pioglitazone (N=115)
	100 mg (N=113)	300 mg (N=114)	
HbA_{1c} (%)			
Baseline (mean)	7.99	7.84	8.00
Change from baseline (adjusted mean)	-0.89	-1.03	-0.26
Difference from placebo (adjusted mean) (95% CI)	-0.62[2] (-0.81; -0.44)	-0.76[2] (-0.95; -0.58)	N/A
Patients (%) achieving HbA_{1c} < 7%	46.9	64.3	32.5
Mean body weight (kg)			
Baseline	94.2	94.4	94.0
% change from baseline (adjusted mean)	-2.8[2]	-3.8[2]	-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
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	126.4	126.7	128.2
Change from baseline (adjusted mean)	-5.3	-4.7	-1.2
Difference from placebo (adjusted mean) (95% CI)	-4.1 (-6.9; -1.3)	-3.5 (-6.3; -0.6)	N/A

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

[2] p<0.001 compared to placebo.

N/A = Not applicable or not measured in this study

Studies as add-on therapy with insulin

Study DIA3008 – Insulin Substudy

INVOKANA as add-on therapy with insulin (with or without other anti-hyperglycaemic agents) produced statistically significant (p<0.001) improvements in HbA_{1c} and percent change in body weight relative to placebo over 18 weeks. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups. The majority of patients were on basal/bolus insulin regimen.

Table 14: Results from 18-week placebo-controlled clinical study of INVOKANA as add-on therapy with insulin ≥ 30 units/day (with or without other oral anti-hyperglycaemic agents)[1]

Efficacy parameter	INVOKANA + insulin 18 weeks		Placebo + insulin (N=565)
	100 mg (N=566)	300 mg (N=587)	
HbA_{1c} (%)			
Baseline (mean)	8.33	8.27	8.20
Change from baseline (adjusted mean)	-0.63[2]	-0.72[2]	0.01
Difference from placebo (adjusted mean) (95% CI)	-0.65[2] (-0.73; -0.56)	-0.73[2] (-0.82; -0.65)	N/A
Patients (%) achieving HbA_{1c} < 7%	19.8[2]	24.7[2]	7.7[2]
Body weight			
Baseline (mean) in kg	96.9	96.7	97.7
% change from baseline (adjusted mean)	-1.8[2]	-2.3[2]	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-1.9[2] (-2.2; -1.5)	-2.4[2] (-2.8; -2.0)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	137.0	138.2	138.2
Change from baseline (adjusted mean)	-5.1	-6.9	-2.5
Difference from placebo (adjusted mean) (95% CI)	-2.6[2] (-4.1; -1.1)	-4.4[2] (-5.8; -2.9)	N/A

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

[2] p<0.001 compared to placebo.

N/A = Not applicable or not measured in this study

Special populations

Older patients

Study DIA3010

A total of 714 patients ≥ 55 to ≤ 80 years of age with inadequate glycaemic control on current diabetes treatment (anti-hyperglycaemic agents and/or diet and exercise) participated in a double-blind, placebo-controlled study over 26 weeks. Statistically significant (p<0.001) changes from baseline HbA_{1c} relative to placebo of -0.60% and -0.73% were observed for 100 mg and 300 mg, respectively. Statistically significant improvements relative to placebo were seen with INVOKANA treatment in FPG lowering and the percentage of patients achieving HbA_{1c} < 7%. Patients treated with INVOKANA100 mg and INVOKANA 300 mg exhibited a statistically significant improvement in percent change in body weight relative to placebo of -2.4% and -3.1%, respectively (see **sections 4.2**; **4.8**).

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.

CKD Stage 3A moderate renal impairment (eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2)

In a pooled analysis of patients (N=721) with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, canagliflozin provided clinically meaningful reduction in HbA_{1c} compared to placebo, with -0.47% for canagliflozin 100 mg and -0.52% for canagliflozin 300 mg. Patients with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 treated with canagliflozin 100 mg and 300 mg exhibited mean improvements in percent change in body weight relative to placebo of -1.8% and -2.0%, respectively.

The majority of patients with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 were on insulin and/or a sulphonylurea (85% [N = 614]). Consistent with the expected increase of hypoglycaemia when a medicinal product not associated with hypoglycaemia is added to insulin and/or sulphonylurea, an increase in hypoglycaemia episodes/events was seen when canagliflozin was added to insulin and/or a sulphonylurea (see **section 4.8**).

Fasting plasma glucose

In four placebo-controlled studies, treatment with INVOKANA as monotherapy or add-on therapy with one or two oral anti-hyperglycaemic agents resulted in mean changes from baseline relative to placebo in FPG of -1.2 mmol/L to -1.9 mmol/L for INVOKANA 100 mg and -1.9 mmol/l to -2.4 mmol/l for INVOKANA 300 mg, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.

Postprandial glucose

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

Cardiovascular risk

Preliminary results from a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from Phase 2 and 3 clinical studies (including a long-term study in patients with established cardiovascular disease or who are at high risk of cardiovascular disease) has not shown evidence of an increase in cardiovascular risk with canagliflozin relative to comparators.

Body weight

In general, clinically relevant, statistically significant, and dose-related weight loss, compared to placebo, was observed with canagliflozin across the placebo-controlled studies; the only exception was the lack of meaningful weight loss in the DIA3008 SU substudy at the 100 mg canagliflozin dose. Across the placebo-controlled Phase 3 studies (excluding the results from the 100 mg dose in the DIA3008 SU substudy), the placebo-subtracted LS mean percent changes from baseline in body weight (at time of primary efficacy assessment) ranged from approximately -1.8% to -3.7% with the canagliflozin 300 mg dose and from approximately -1.4% to -2.7% with the canagliflozin 100 mg dose.

In the pooled population of 5 placebo-controlled studies, treatment with canagliflozin lowered body weight in a dose-related manner at the primary assessment time point. The LS mean percent change from baseline in body weight relative to placebo, was -2.0% (range, -1.4% to -2.7%) for the 100 mg dose and -2.7% (-2.0% to 3.7%) for the 300 mg dose. The lowest weight loss seen was in the metformin and sulphonylurea add-on study. A subset of patients (N=208) from the active controlled dual therapy study with metformin who underwent dual energy X ray densitometry (DXA) and abdominal computed tomography (CT) scans for evaluation of body composition demonstrated that approximately two thirds of the weight loss with canagliflozin was due to loss of fat mass with similar amounts of visceral and abdominal subcutaneous fat being lost. Similar findings on the relative

contribution of fat to lean mass loss with canagliflozin were seen in the Phase 3 study in older subjects.

5.2 Pharmacokinetic properties

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

Absorption:

The mean absolute oral bioavailability of canagliflozin is approximately 65%. Co-administration of a high-fat meal with canagliflozin had no effect on the pharmacokinetics of canagliflozin; therefore, canagliflozin 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 canagliflozin be taken before the first meal of the day (see **sections 4.2**; **5.1**).

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 (98%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism:

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites. Increases in AUC of canagliflozin (26% and 18%) were observed in subjects carrying the UGT1A9*3 allele and UGT2B4*2 allele, respectively. These increases in canagliflozin exposure are not expected to be clinically relevant. CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

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 medicinal product, with a mean systemic clearance of approximately 192 mL/min in healthy subjects following intravenous administration.

Special Populations:

Renal Impairment:

A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects. The study included 3 subjects with normal renal function (CKD stage 1;

eGFR ≥ 90 mL/min/1.73 m^2), 10 subjects with mild renal impairment (CKD stage 2; eGFR 60 to <90 mL/min/1.73 m^2), 9 subjects with moderate renal impairment (CKD stage 3; eGFR 30 to < 60 mL/min/1.73 m^2), and 10 subjects with severe renal impairment (CKD stage 4; eGFR 15 to < 30 mL/min/1.73 m^2) as well as 8 subjects with end-stage renal disease on haemodialysis (CKD stage 5).

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 end stage renal disease subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Hepatic Impairment:

Relative to subjects with normal hepatic function, the C_{max} and AUC_{∞} of canagliflozin increased by 7% and 10%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and decreased by 4% and increased by 11%, respectively, in subjects with Child-Pugh class B (moderate hepatic impairment) following administration of a single 300 mg dose of canagliflozin.

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

Elderly:

Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis (see **sections 4.2**; **4.4**; **4.8**).

Paediatric:

Studies characterising the pharmacokinetics of canagliflozin in paediatric patients have not been performed.

Characteristics of other special populations:

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

Two-year oral carcinogenicity studies were conducted in mice and rats. Canagliflozin did not increase the incidence of tumours in mice at doses up to 100 mg/kg/day. This dose was provided up to 7 (males) or 14 times (females) the exposure (plasma AUC) at the clinical dose of 300 mg. Canagliflozin increased the incidence of testicular Leydig cell tumours in male rats at all doses tested; the lowest dose of 10 mg/kg/day is approximately 1.5 times the clinical dose of 300 mg based on AUC exposure. Higher doses of canagliflozin (100 mg/kg/day) increased the incidence of pheochromocytomas and renal tubular adenomas and carcinomas in male and female rats;; based on AUC exposure, this dose is approximately 12 (males) or 21 times (females) at the clinical dose of 300 mg. Based on preclinical and clinical mechanistic studies, the Leydig and renal tubule tumours and pheochromocytomas are seen to be due to mechanisms not considered to be of human relevance. Canagliflozin-induced renal tubule tumours and pheochromocytomas in rats appear to be

caused by carbohydrate malabsorption; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the maximum recommended human dose. The Leydig cell tumours are associated with an increase in luteinizing hormone (LH), which is a known mechanism of Leydig cell tumour formation in rats. In a 12-week clinical study, LH did not increase in male patients treated with canagliflozin.

Pregnancy

Placental transfer of canagliflozin and/or its metabolites was demonstrated in the rat.

In conventional studies in animals, canagliflozin was not teratogenic and did not affect embryofetal viability or fetal weight when administered during the period of organogenesis at oral doses up to 100 mg/kg/day (rats) or 160 mg/kg/day (rabbits), yielding 19 times the human exposure to canagliflozin at the maximum recommended human dose (MRHD) of 300 mg once daily. In rats, slight increases in the number of fetuses with reduced ossification, indicative of a slight developmental delay and an increased incidence in rudimentary 14th ribs, were observed at 100 mg/kg (relative exposure, 19x). In rabbits, an increased incidence of additional 13th ribs (a minor skeletal abnormality) was seen at all doses tested (≥ 10 mg/kg/day; relative exposure, ≥ 0.4x).

Canagliflozin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring at maternally toxic doses only (≥ 30 mg/kg/day; exposures ≥ 5.9 times the human exposure to canagliflozin at the MRHD). Some developmental delays (attributed to decreased pup body weight) and impaired reproductive performance were observed in the offspring of rats treated at 100 mg/kg/day. No adverse effects on postnatal development were noted at 10 mg/kg/day (relative exposure, 1.6x).

In juvenile rats dosed for 10 weeks (Day 21 to 90 postnatal) with canagliflozin, renal and bone findings were consistent with those in repeat-dose toxicity studies in adult rats. These effects are considered to be pharmacological effects that show reversibility and may be suspected of causing harmful effects on the human fetus or neonate without causing malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Lactose anhydrous

Croscarmellose sodium

Hydroxypropyl cellulose

Magnesium stearate

Polyvinyl alcohol

Titanium dioxide

Macrogol 3350

Talc-purified.

In addition, the 100 mg strength contains iron oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Store below 25^{o}C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinyl chloride/Aluminum (PVC/Alu) perforated unit dose blister.

Pack size: Blister packs of 10, 30 or 100^ tablets.

^ Not all presentations may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND
Telephone: 0800 800 806
Fax: (09) 588 1398
Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

20 November 2014

10. DATE OF REVISION OF THE TEXT

13 September 2017

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Summary table of changes

Section changes	Summary of new information
All 4.4 & 4.8	1. Datasheet reformat 2. New safety information – lower limbs amputations