1. NAME OF THE MEDICINAL PRODUCT

Invokana® 100 mg film-coated tablets
Invokana® 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Invokana 100 mg film-coated tablets

Each tablet contains canagliflozin hemihydrate, equivalent to 100 mg canagliflozin.

Excipient(s) with known effect

Each tablet contains 39.2 mg lactose.

Invokana 300 mg film-coated tablets

Each tablet contains canagliflozin hemihydrate, equivalent to 300 mg canagliflozin.

Excipient(s) with known effect

Each tablet contains 117.78 mg lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Invokana 100 mg film-coated tablets

The tablet is yellow, capsule-shaped, approximately 11 mm in length, immediate-release and film-coated, with "CFZ" on one side and "100" on the other side.

Invokana 300 mg film-coated tablets

The tablet is white, capsule-shaped, approximately 17 mm in length, immediate-release and film-coated, with "CFZ" on one side and "300" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Add-On Combination in Patients with Established Cardiovascular Disease
INVOKANA is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adult with type 2 diabetes mellitus and established cardiovascular disease (CVD).

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

4.2 Posology and method of administration

Posology
The recommended starting dose of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg once daily (see *below* and section 4.4). For dose adjustment recommendations according to eGFR refer to Table 1.

Care should be taken when increasing the dose in patients ≥ 75 years of age, patients with known cardiovascular disease, or other patients for whom the initial canagliflozin-induced diuresis poses a risk (see section 4.4). In patients with evidence of volume depletion, correcting this condition prior to initiation of canagliflozin is recommended (see section 4.4).

When canagliflozin 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 4.5 and 4.8).

Special populations
Elderly
Renal function and risk of volume depletion should be taken into account (see section 4.4).

Renal impairment
For treatment of diabetic kidney disease as add on to standard of care (eg. ACE-inhibitors or ARBs), a dose of 100 mg canagliflozin once daily should be used (see table 1). Because the glycaemic lowering efficacy of canagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered. For dose adjustments, recommendations according to eGFR refer to Table 1.

Table 1: Dose adjustment recommendations[a]

eGFR (mL/min/1.73 m^2) or CrCl (mL/min)	Total daily dose of canagliflozin
≥ 60	Initiate with 100 mg. In patients tolerating 100 mg and requiring additional glycaemic control, the dose can be increased to 300 mg.

30 to < 60[b]	Use 100 mg.
< 30[b, c]	Continue 100 mg for patients already taking Invokana.[d] Invokana should not be initiated.

[a] See sections 4.4, 4.8, 5.1 and 5.2.
[b] If further glycaemic control is needed, the addition of other anti hyperglycaemic agents should be considered
[c] With urinary albumin/creatinine ratio > 300 mg/g
[d] Continue dosing until dialysis or renal transplantation

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

Canagliflozin 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 canagliflozin in children under 18 years of age have not yet been established. No data are available.

Method of administration
For oral use
INVOKANA should be taken orally once a day, preferably before the first meal of the day. Tablets should 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 on the same day.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Renal impairment
The efficacy of canagliflozin for glycaemic control is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2).

In patients with an eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported, particularly with the 300 mg dose. In addition, in such patients more events of elevated potassium and greater increases in serum creatinine and blood urea nitrogen (BUN) were reported (see section 4.8).

Therefore, the canagliflozin dose should be limited to 100 mg once daily in patients with eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min (see section 4.2).

Regardless of pretreatment eGFR patients on canagliflozin experienced an initial fall in eGFR that thereafter attenuated over time (see sections 4.8 and 5.1).

Monitoring of renal function is recommended as follows:
- Prior to initiation of canagliflozin and at least annually, thereafter (see sections 4.2, 4.8, 5.1, and 5.2)
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter

There is experience with canagliflozin for the treatment of diabetic kidney disease (eGFR ≥30 mL/min/1.73 m^2) both with and without albuminuria. While both groups of patients benefitted, patients with albuminuria may benefit more from treatment with canagliflozin.

Use in patients at risk for adverse reactions related to volume depletion
Due to its mechanism of action, canagliflozin, by increasing urinary glucose excretion (UGE) induces an osmotic diuresis, which may reduce intravascular volume and decrease blood pressure (see section 5.1). In controlled clinical studies of canagliflozin, increases in adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, or hypotension) were seen more commonly with the 300 mg dose and occurred most frequently in the first three months (see section 4.8).

Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an eGFR < 60 mL/min/1.73 m^2, patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥ 65 years of age) (see sections 4.2 and 4.8).

Due to volume depletion, generally small mean decreases in eGFR were seen within the first 6 weeks of treatment initiation with canagliflozin. 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 canagliflozin (see section 4.8).

Patients should be advised to report symptoms of volume depletion. Canagliflozin is not recommended for use in patients receiving loop diuretics (see section 4.5) or who are volume depleted, e.g., due to acute illness (such as gastrointestinal illness).

For patients receiving canagliflozin, 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. Temporary interruption of treatment with canagliflozin may be considered for patients who develop volume depletion while on canagliflozin therapy until the condition is corrected. If interrupted, consideration should be given to more frequent glucose monitoring.

Diabetic ketoacidosis
Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including canagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of canagliflozin. Risk of DKA appears to be higher in patients with moderately to severely decreased renal function who require insulin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with Invokana should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for acute serious medical illnesses. Withhold Invokana, if possible, for an appropriate period of time (days) prior to major surgery, including abdominal and bariatric, or any other invasive procedures associated with prolonged fasting. Monitoring for serum ketones is recommended. Consider alternative anti-hyperglycaemic therapy, including insulin.

Measurement of blood ketone levels is preferred to urine. Treatment with Invokana may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating Invokana, factors in the patient history that may predispose to ketoacidosis should be considered.

Diabetic ketoacidosis may be prolonged after discontinuation of Invokana in some patients, i.e. it may last longer than expected from the plasma half-life of canagliflozin (see section 5.2). Prolonged glucosuria has been observed along with persistent DKA. Canagliflozin-independent factors might be involved in prolonged periods of DKA. Insulin deficiency may contribute to prolonged diabetic ketoacidosis and has to be corrected when verified.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g., type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

The safety and efficacy of canagliflozin in patients with type 1 diabetes have not been established and canagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical studies suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

<u>Lower limb amputations</u>

In long-term clinical studies of canagliflozin in patients with type 2 diabetes with established cardiovascular disease (CVD) or at least 2 risk factors for CVD, Invokana was associated with an increased risk of lower limb amputation versus placebo (0.63 vs 0.34 events per 100 patient-years, respectively), and this increase occurred primarily in the toe and midfoot (see section 4.8). In a long-term clinical study in patients with type 2 diabetes and diabetic kidney disease, no difference in lower limb amputation risk was observed in patients treated with canagliflozin 100 mg relative to placebo. In this study precautionary measures as outlined below were applied. 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.

<u>Necrotising fasciitis of the perineum (Fournier's gangrene)</u>

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Invokana should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Elevated haematocrit
Haematocrit increase was observed with canagliflozin treatment (see section 4.8); therefore, careful monitoring in patients with already elevated haematocrit is warranted.

Elderly
Elderly patients may be at a greater risk for volume depletion, are more likely to be treated with diuretics, and to have impaired renal function. In patients ≥ 75 years of age, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported. In addition, in such patients greater decreases in eGFR were reported (see sections 4.2 and 4.8).

Genital mycotic infections
Consistent with the mechanism of sodium glucose co-transporter 2 (SGLT2) inhibition with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical studies with canagliflozin (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 which in some instances resulted in phimosis and/or 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.

Urinary tract infections
Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with canagliflozin, frequently leading to treatment interruption. Temporary interruption of canagliflozin should be considered in patients with complicated urinary tract infections.

Cardiac failure
Experience in New York Heart Association (NYHA) class III is limited, and there is no experience in clinical studies with canagliflozin in NYHA class IV.

Urine laboratory assessments
Due to its mechanism of action, patients taking canagliflozin will test positive for glucose in their urine.

Lactose intolerance
The tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics

Canagliflozin may add to the effect of diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, can cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with canagliflozin (see sections 4.2 and 4.8).

Pharmacokinetic interactions

Effects of other medicinal products on canagliflozin

The metabolism of canagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 1A9 (UGT1A9) and 2B4 (UGT2B4). Canagliflozin is transported by P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Enzyme inducers (such as St. John's wort [*Hypericum perforatum*], rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) may decrease the exposure to canagliflozin. Following co-administration of canagliflozin with rifampicin (an inducer of various active transporters and medicinal product-metabolising enzymes), 51% and 28% decreases in canagliflozin systemic exposure (AUC) and peak concentration (C_{max}) were observed. These decreases in exposure to canagliflozin may decrease efficacy.

If a combined inducer of these UGT enzymes and transport proteins must be co-administered with canagliflozin, monitoring of glycaemic control to assess response to canagliflozin is appropriate. If an inducer of these UGT enzymes must be co-administered with canagliflozin, increasing the dose to 300 mg once daily may be considered if patients are currently tolerating canagliflozin 100 mg once daily, have an eGFR ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min, and require additional glycaemic control. In patients with an 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 glucose-lowering therapies should be considered (see sections 4.2 and 4.4).

Cholestyramine may potentially reduce canagliflozin exposure. Dosing of canagliflozin should occur at least 1 hour before or 4-6 hours after administration of a bile acid sequestrant to minimise possible interference with their absorption.

Interaction studies suggest that the pharmacokinetics of canagliflozin are not altered by metformin, hydrochlorothiazide, oral contraceptives (ethinyl estradiol and levonorgestrol), ciclosporin, and/or probenecid.

Effects of canagliflozin on other medicinal products

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 Cmax of digoxin, probably due to inhibition of P-gp. Canagliflozin has been observed to inhibit P-gp in vitro. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately.

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

Dabigatran
The effect of concomitant administration of canagliflozin (a weak P-gp inhibitor) on dabigatran etexilate (a P-gp substrate) has not been studied. As dabigatran concentrations may be increased in the presence of canagliflozin, monitoring (looking for signs of bleeding or anaemia) should be exercised when dabigatran is combined with canagliflozin.

Simvastatin
The combination of canagliflozin 300 mg once daily for 6 days with a single dose of simvastatin (CYP3A4 substrate) 40 mg resulted in a 12% increase in AUC and a 9% increase in C_{max} of simvastatin and an 18% increase in AUC and a 26% increase in C_{max} of simvastatin acid. The increases in simvastatin and simvastatin acid exposures are not considered clinically relevant.

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

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

Medicinal product/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 glycaemic control. Therefore, 1,5-AG assays should not be used for assessment of glycaemic control in patients on canagliflozin. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of canagliflozin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued.

Breast-feeding
It is unknown whether canagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin/metabolites in milk, as well as pharmacologically mediated effects in breast-feeding offspring and juvenile rats exposed to canagliflozin (see section 5.3). A risk to newborns/infants cannot be excluded.
Canagliflozin should not be used during breast-feeding.

Fertility

The effect of canagliflozin on fertility in humans has not been studied. No effects on fertility were observed in animal studies (see section 5.3)

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of canagliflozin was evaluated in 22,645 patients with type 2 diabetes, including 13,278 patients treated with canagliflozin and 9,367 patients treated with comparator in 15 double-blind, controlled phase 3 and phase 4 clinical studies. A total of 10,134 patients were treated in two dedicated cardiovascular studies for a mean exposure duration of 149 weeks (223 weeks in CANVAS and 94 weeks in CANVAS-R), and 8,114 patients were treated in 12 double blind, controlled phase 3 and phase 4 clinical studies, for a mean exposure duration of 49 weeks. In a dedicated renal outcomes study, a total of 4,397 patients with type 2 diabetes and diabetic kidney disease had a mean exposure duration of 115 weeks.

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 polyuria or pollakiuria (i.e., urinary frequency). 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 (table 2) (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Adverse reactions in table 2 are based on the pooled analysis of the placebo- and active-controlled studies described above. Adverse reactions reported from world-wide postmarketing use of canagliflozin are also included in this tabulation. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions (MedDRA) from placebo-[e] and active-controlled studies[e] and from postmarketing experience

System organ class Frequency	**Adverse reaction**
Infections and infestations	
very common	Vulvovaginal candidiasis[b,j]
common	Balanitis or balanoposthitis[b,k], Urinary tract infection[c] (pyelonephritis and urosepsis have been reported postmarketing)
not known	Necrotising fasciitis of the perineum (Fournier's gangrene)[d]

Immune system disorders	
rare	Anaphylactic reaction
Metabolism and nutrition disorders	
very common uncommon rare	Hypoglycaemia in combination with insulin or sulphonylurea[c] Dehydration[a] Diabetic ketoacidosis[b]
Nervous system disorders	
uncommon	Dizziness postural[a], Syncope[a]
Vascular disorders	
uncommon	Hypotension[a], Orthostatic hypotension[a]
Gastrointestinal disorders	
common	Constipation, Thirst[f], Nausea
Skin and subcutaneous tissue disorders	
uncommon rare	Photosensitivity, Rash[g], Urticaria Angioedema
Musculoskeletal and connective tissue disorders	
uncommon	Bone fracture[h]
Renal and urinary disorders	
common uncommon	Polyuria or Pollakiuria[i] Renal failure (mainly in the context of volume depletion)
Investigations	
common uncommon	Dyslipidaemia[l], Haematocrit increased[b,m] Blood creatinine increased[b,n], Blood urea increased[b,o], Blood potassium increased[b,p], Blood phosphate increased[q]
Surgical and medical procedures	
uncommon	Lower limb amputations (mainly of the toe and midfoot) especially in patients at high risk for heart disease[b]

[a] Related to volume depletion; see section 4.4 and description of adverse reaction (AR) below.
[b] See section 4.4 and description of AR below.
[c] See description of AR below.
[d] See section 4.4.
[e] Safety data profiles from individual pivotal studies (including studies in moderately renally impaired patients; older patients [≥ 55 years of age to ≤ 80 years of age]; patients with increased CV- and renal risk) were generally consistent with the adverse reactions identified in this table.
[f] Thirst includes the terms thirst, dry mouth, and polydipsia.
[g] Rash includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular.

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[h] Related to bone fracture; see description of AR below.
[i] Polyuria or pollakiuria includes the terms polyuria, pollakiuria, micturition urgency, nocturia, and urine output increased.
[j] Vulvovaginal candidiasis includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.
[k] Balanitis or balanoposthitis includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection fungal.
[l] Mean percent increases from baseline for canagliflozin 100 mg and 300 mg *versus* placebo, respectively, were total cholesterol 3.4% and 5.2% *versus* 0.9%; HDL-cholesterol 9.4% and 10.3% *versus* 4.0%; LDL-cholesterol 5.7% and 9.3% *versus* 1.3%; non-HDL-cholesterol 2.2% and 4.4% *versus* 0.7%; triglycerides 2.4% and 0.0% *versus* 7.6%.
[m] Mean changes from baseline in haematocrit were 2.4% and 2.5% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.0% for placebo.
[n] Mean percent changes from baseline in creatinine were 2.8% and 4.0% for canagliflozin 100 mg and 300 mg, respectively, compared to 1.5% for placebo.
[o] Mean percent changes from baseline in blood urea nitrogen were 17.1% and 18.0% for canagliflozin 100 mg and 300 mg, respectively, compared to 2.7% for placebo.
[p] Mean percent changes from baseline in blood potassium were 0.5% and 1.0% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.6% for placebo.
[q] Mean percent changes from baseline in serum phosphate were 3.6% and 5.1% for canagliflozin 100 mg and 300 mg, compared to 1.5% for placebo.

Description of selected adverse reactions

Diabetic ketoacidosis

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with canagliflozin 100 mg and placebo, respectively; of the 14 patients with DKA, 8 (7 on canagliflozin 100 mg and 1 on placebo) had a pretreatment eGFR of 30 to < 45 mL/min/1.73 m^2 (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, canagliflozin was associated with an increased risk of lower limb amputation as observed in the Integrated CANVAS Program comprised of CANVAS and CANVAS R, two large, long-term, randomised, placebo-controlled trials evaluating 10,134 patients. The imbalance occurred as early as the first 26 weeks of therapy. Patients in CANVAS and CANVAS R were followed for an average of 5.7 and 2.1 years, respectively. Regardless of treatment with canagliflozin 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 3.

There was no difference in risk of lower limb amputations associated with the use of canagliflozin 100 mg relative to placebo (1.2 vs 1.1 events per 100 patient-years, respectively [HR: 1.11;95% CI 0.79, 1.56]) in CREDENCE, a long-term renal outcomes study of 4,397 patients with type 2 diabetes and diabetic kidney disease (see section 4.4). In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetic population of 8,114 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	**canagliflozin N = 5790**
Total number of subjects with events, n (%)	47 (1.1)	140 (2.4)
Incidence rate (per 100 patient-years)	0.34	0.63
HR (95% CI) vs. placebo		1.97 (1.41, 2.75)
Minor Amputation, n (%)*	34/47 (72.3)	99/140 (70.7)
Major Amputation, n (%)†	13/47 (27.7)	41/140 (29.3)

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

* Toe and midfoot

† Ankle, below knee and above knee

Of the subjects, within the CANVAS Program, who had an amputation, the toe and midfoot were the most frequent sites (71%) in both treatment groups (table 3). 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).

Adverse reactions related to volume depletion

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

In one of the dedicated long term cardiovascular studies (CANVAS), where patients were generally older with a higher rate of diabetes complications, the incidence rates of adverse reactions related to volume depletion were 2.3 with canagliflozin 100 mg, 2.9 with canagliflozin 300 mg, and 1.9 with placebo, events per 100 patient years.

To assess risk factors for these adverse reactions, a larger pooled analysis (N = 12,441) of patients from 13 controlled phase 3 and phase 4 studies including both doses of canagliflozin was conducted. In this pooled analysis, patients on loop diuretics, patients with a baseline eGFR 30 mL/min/1.73 m2 to < 60 mL/min/1.73 m2, and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidence rates were 5.0 on canagliflozin 100 mg and 5.7 on canagliflozin 300 mg compared to 4.1 events per 100 patient years of exposure in the control group. For patients with a baseline eGFR 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, the incidence rates were 5.2 on canagliflozin 100 mg and 5.4 on canagliflozin 300 mg compared to 3.1 events per 100 patient years of exposure in the control group. In patients ≥ 75 years of age, the incidence rates were 5.3 on canagliflozin 100 mg and 6.1 on canagliflozin 300 mg compared to 2.4 events per 100 patient years of exposure in the control group (see sections 4.2 and 4.4).

In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, incidence rate of events related to volume depletion was 2.84 and 2.35 events per 100 patient-years for canagliflozin 100 mg and placebo, respectively. The incidence rate was observed to increase with decreasing eGFR. In subjects with eGFR 30 to <45mL/min/1.73 m^2, the incidence rate of volume depletion was higher in the canagliflozin group (4.91 events per 100 patient-years) compared to the placebo group (2.60 events per 100 patient-years); however, in the subgroups eGFR >45 to <60 and eGFR 60 to <90mL/min/1.73 m^2, the between-group incidence rate was similar.

In the dedicated cardiovascular study and the larger pooled analysis, as well as in a dedicated renal outcomes study, discontinuations due to adverse reactions related to volume depletion and serious adverse reactions related to volume depletion were not increased with canagliflozin.

Hypoglycaemia in add-on therapy with insulin or insulin secretagogues
The frequency of hypoglycaemia was low (approximately 4%) among treatment groups, including placebo, when used as monotherapy or as an add-on to metformin. When canagliflozin was added to insulin therapy, hypoglycaemia was observed in 49.3%, 48.2%, and 36.8% of patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, and severe hypoglycaemia occurred in 1.8%, 2.7%, and 2.5% of patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. When canagliflozin was added to a sulphonylurea therapy, hypoglycaemia was observed in 4.1%, 12.5%, and 5.8% of patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively (see sections 4.2 and 4.5).

Genital mycotic infections
Vulvovaginal candidiasis (including vulvovaginitis and vulvovaginal mycotic infection) was reported in 10.4% and 11.4% of female patients treated with canagliflozin 100 mg and canagliflozin 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 canagliflozin, 2.3% experienced more than one infection. Overall, 0.7% of all female patients discontinued canagliflozin due to vulvovaginal candidiasis (see section 4.4). In the CANVAS Program, median duration of the infection was longer in the canagliflozin group compared to the placebo group.

Candidal balanitis or balanoposthitis occurred in male patients at a rate of 2.98 and 0.79 events per 100 patient-years on canagliflozin and placebo, respectively. Among male patients taking canagliflozin, 2.4% had more than one infection. Discontinuation of canagliflozin by male patients due to candidal balanitis or balanoposthitis occurred at a rate of 0.37 events per 100 patient years. Phimosis was reported at a rate of 0.39 and 0.07 events per 100 patient-years on canagliflozin and placebo, respectively. Circumcision was performed at rates of 0.31 and 0.09 events per 100 patient-years on canagliflozin and placebo, respectively (see section 4.4).

Urinary tract infections
In clinical studies, urinary tract infections were more frequently reported for canagliflozin 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 reactions. In these studies, subjects responded to standard treatments while continuing canagliflozin treatment.

However, post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with canagliflozin, frequently leading to treatment interruption.

Bone fracture

In a cardiovascular study (CANVAS) of 4,327 treated subjects with established or at least two risk factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.6, 1.8, and 1.1 per 100 patient-years of follow-up to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy.

In two other long-term studies and in studies conducted in the general diabetes population, no difference in fracture risk was observed with canagliflozin relative to control. In a second cardiovascular study (CANVAS-R) of 5,807 treated subjects with established or at least two risk factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.1 and 1.3 events per 100 patient-years of follow-up to canagliflozin and placebo, respectively.

In a long-term renal outcomes study of 4,397 treated subjects with type 2 diabetes and diabetic kidney disease, the incidence rates of all adjudicated bone fracture were 1.2 events per 100 patient-years of follow-up for both canagliflozin 100 mg and placebo. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of 7,729 patients, and where bone fractures were adjudicated, the incidence rates of all adjudicated bone fracture were 1.2 and 1.1 per 100 patient-years of follow-up to canagliflozin and control, respectively. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

<u>Special populations</u>

Elderly

In a pooled analysis of 13 placebo-controlled and active-controlled studies, the safety profile of canagliflozin in elderly patients was generally consistent with younger patients. Patients ≥ 75 years of age had a higher incidence of adverse reactions related to volume depletion (such as postural dizziness, orthostatic hypotension, hypotension) with incidence rates of 5.3, 6.1, and 2.4 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and in the control group, respectively. Decreases in eGFR (-3.4 and -4.7 mL/min/1.73 m^2) were reported with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to the control group (-4.2 mL/min/1.73 m^2). Mean baseline eGFR was 62.5, 64.7, and 63.5 mL/min/1.73 m^2 for canagliflozin 100 mg, canagliflozin 300 mg, and the control group, respectively (see sections 4.2 and 4.4).

Renal impairment in patients with insufficiently controlled type 2 diabetes mellitus

Patients with a baseline eGFR <60 mL/min/1.73 m^2 had a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) with incidence rates of 5.3, 5.1, and 3.1 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively (see sections 4.2 and 4.4).

The overall incidence rate of elevated serum potassium was higher in patients with moderate renal impairment with incidence rates of 4.9, 6.1, and 5.4 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. In general, elevations were transient and did not require specific treatment.

In patients with moderate renal impairment, increases in serum creatinine of 9.2 µmol/L and BUN of approximately 1.0 mmol/L were observed with both doses of canagliflozin.

The incidence rates for larger decreases in eGFR (> 30%) at any time during treatment were 7.3, 8.1, and 6.5 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. At the last post-baseline value, incidence rates of such decreases were 3.3 for patients treated with canagliflozin 100 mg, 2.7 for canagliflozin 300 mg, and 3.7 events per 100 patient-years of exposure for placebo (see section 4.4).

Patients treated with canagliflozin regardless of baseline eGFR experienced an initial fall in mean eGFR. Thereafter, eGFR was maintained or gradually increased during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting that haemodynamic changes may play a role in these renal function changes.

Renal impairment in patients with diabetic kidney disease in type 2 diabetes mellitus
In a long-term renal outcomes study in patients with type 2 diabetes and diabetic kidney disease, the incidence of renal-related events occurred frequently in both groups but less frequent in the canagliflozin group (5.71 events per 100 patient-years) compared with the placebo group (7.91 events per 100 patient-years). Serious and severe renal-related events were also lower in the canagliflozin group versus placebo. The incidence rates of renal-related events were lower with canagliflozin relative to placebo across all three eGFR strata; the highest incidence rate of renal-related events was seen in the eGFR 30 to <45 mL/min/1.73 m^2 stratum (9.47 vs 12.80 events per 100 patient-years for canagliflozin versus placebo, respectively).

In the long-term renal outcomes study, no difference in serum potassium, no increase in adverse events of hyperkalaemia, and no absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with canagliflozin 100 mg relative to placebo.

In general, there were no imbalances between treatment groups observed for abnormalities of phosphate, overall or in either eGFR category (45 to < 60 or 30 to < 45 mL/min/1.73 m^2 [CrCl 45 to < 60 or 30 to < 45 mL/min]).

4.9 Overdose
Single doses up to 1,600 mg of canagliflozin in healthy subjects and canagliflozin 300 mg twice daily for 12 weeks in patients with type 2 diabetes were generally well-tolerated.

<u>Therapy</u>
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. Canagliflozin is not expected to be dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excluding insulins. ATC code: A10BK02.

<u>Mechanism of action</u>
The SGLT2 transporter, 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 UGE, lowering elevated plasma glucose concentrations by this insulin-independent mechanism in patients with type 2 diabetes. The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in UGE

results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with type 2 diabetes.

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

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 the SGLT1 transporter). Studies have shown no glucose malabsorption with canagliflozin.

Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption thereby increasing tubuloglomerular feedback, which is associated with a reduction in intraglomerular pressure and a decrease in hyperfiltration in preclinical models of diabetes and clinical studies.

<u>Pharmacodynamic effects</u>
Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in UGE were observed. From a starting value of RT_G of approximately 13 mmol/L, maximal suppression of 24-hour mean RT_G was seen with the 300 mg daily dose to approximately 4 mmol/L to 5 mmol/L in patients with type 2 diabetes in phase 1 studies, 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 g/day to 119 g/day across the phase 1 studies; the UGE observed translates to a loss of 308 kcal/day 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 mL to 500 mL) in daily urine volume were seen that attenuated over several days of dosing. Urinary uric acid excretion was transiently increased by canagliflozin (increased by 19% compared to baseline on day 1 and then attenuating to 6% on day 2 and 1% on day 13). This was accompanied by a sustained reduction in serum uric acid concentration of approximately 20%.

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

<u>Clinical efficacy and safety</u>
Improvement in glycaemic control and reduction of cardiovascular and renal morbidity and mortality are integral parts of the treatment of type 2 diabetes.

<u>*Glycaemic efficacy and safety*</u>
A total of 10,501 patients with type 2 diabetes participated in ten double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of Invokana on glycaemic control. The racial distribution was 72% White, 16% Asian, 5% Black, and 8% other groups. 17% of patients were Hispanic. 58% of patients were male. Patients had an overall mean age of 59.5 years (range 21 years to 96 years), with 3,135 patients ≥ 65 years of age and 513 patients ≥ 75 years of age. 58% of patients had a body mass index (BMI) ≥ 30 kg/m^2. In the clinical development programme, 1,085 patients with a baseline eGFR 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 were evaluated.

Placebo-controlled studies

Canagliflozin was studied as monotherapy, dual therapy with metformin, dual therapy with a sulphonylurea, triple therapy with metformin and a sulphonylurea, triple therapy with metformin and pioglitazone, and as an add-on therapy with insulin (table 4). In general, canagliflozin produced clinically and statistically significant ($p < 0.001$) results relative to placebo in glycaemic control, including HbA_{1c}, the percentage of patients achieving $HbA_{1c} < 7\%$, change from baseline fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG). In addition, reductions in body weight and systolic blood pressure relative to placebo were observed.

Furthermore, canagliflozin was studied as triple therapy with metformin and sitagliptin and dosed with a titration regimen, using a starting dose of 100 mg and titrated to 300 mg as early as week 6 in patients requiring additional glycaemic control who had appropriate eGFR and were tolerating canagliflozin 100 mg (table 4). Canagliflozin dosed with a titration regimen produced clinically and statistically significant ($p < 0.001$) results relative to placebo in glycaemic control, including HbA_{1c} and change from baseline fasting plasma glucose (FPG), and a statistically significant ($p < 0.01$) improvement in the percentage of patients achieving $HbA_{1c} < 7\%$. In addition, reductions in body weight and systolic blood pressure relative to placebo were observed.

Table 4: Efficacy results from placebo-controlled clinical studies[a]

Monotherapy (26 weeks)			
	Canagliflozin		**Placebo (N = 192)**
	100 mg (N = 195)	**300 mg (N = 197)**	
HbA_{1c} (%)			
Baseline (mean)	8.06	8.01	7.97
Change from baseline (adjusted mean)	-0.77	-1.03	0.14
Difference from placebo (adjusted mean) (95% CI)	-0.91[b] (-1.09; -0.73)	-1.16[b] (-1.34; -0.98)	N/A[c]
Patients (%) achieving HbA_{1c} < 7%	44.5[b]	62.4[b]	20.6
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[b] (-2.9; -1.6)	-3.3[b] (-4.0; -2.6)	N/A[c]
Dual therapy with metformin (26 weeks)			
	Canagliflozin + 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[b] (-0.76; -0.48)	-0.77[b] (-0.91; -0.64)	N/A[c]
Patients (%) achieving HbA_{1c} < 7%	45.5[b]	57.8[b]	29.8
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[b] (-3.1; -1.9)	-2.9[b] (-3.5; -2.3)	N/A[c]

Triple therapy with metformin and sulphonylurea (26 weeks)			
	Canagliflozin + 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	-1.06	-0.13
Difference from placebo (adjusted mean) (95% CI)	-0.71[b] (-0.90; -0.52)	-0.92[b] (-1.11; -0.73)	N/A[c]
Patients (%) achieving HbA_{1c} < 7%	43.2[b]	56.6[b]	18.0
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[b] (-2.1; -0.7)	-2.0[b] (-2.7; -1.3)	N/A[c]
Add-on therapy with insulin[d] (18 weeks)			
	Canagliflozin + insulin		**Placebo + insulin (N = 565)**
	100 mg (N = 566)	**300 mg (N = 587)**	
HbA_{1c} (%)			
Baseline (mean)	8.33	8.27	8.20
Change from baseline (adjusted mean)	-0.63	-0.72	0.01
Difference from placebo (adjusted mean) (95% CI)	-0.65[b] (-0.73; -0.56)	-0.73[b] (-0.82; -0.65)	N/A[c]
Patients (%) achieving HbA_{1c} < 7%	19.8[b]	24.7[b]	7.7
Body weight			
Baseline (mean) in kg	96.9	96.7	97.7
% change from baseline (adjusted mean)	-1.8	-2.3	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-1.9[b] (-2.2; -1.5)	-2.4[b] (-2.8; -2.0)	N/A[c]

Triple therapy with metformin and sitagliptin[e] (26 weeks)		
	Canagliflozin + metformin and sitagliptin[g] (N = 107)	**Placebo + metformin and sitagliptin (N = 106)**
HbA_{1c} (%)		
Baseline (mean)	8.53	8.38
Change from baseline (adjusted mean)	-0.91	-0.01
Difference from placebo (adjusted mean) (95% CI)	-0.89[b] (-1.19; -0.59)	
Patients (%) achieving HbA_{1c} < 7%	32[f]	12
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	186	180
Change from baseline (adjusted mean)	-30	-3
Difference from placebo (adjusted mean) (95% CI)	-27[b] (-40; -14)	
Body Weight		
Baseline (mean) in kg	93.8	89.9

% change from baseline (adjusted mean)	-3.4	-1.6
Difference from placebo (adjusted mean) (95% CI)	-1.8[b] (-2.7; -0.9)	

[a] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.
[b] $p < 0.001$ compared to placebo.
[c] Not applicable.
[d] Canagliflozin as add-on therapy to insulin (with or without other glucose-lowering medicinal products).
[e] Canagliflozin 100 mg uptitrated to 300 mg
[f] $p < 0.01$ compared to placebo
[g] 90.7% of subjects in the canagliflozin group uptitrated to 300 mg

In addition to the studies presented above, glycaemic efficacy results observed in an 18-week dual therapy sub-study with a sulphonylurea and a 26-week triple therapy study with metformin and pioglitazone were generally comparable with those observed in other studies.

Active-controlled studies
Canagliflozin was compared to glimepiride as dual therapy with metformin and compared to sitagliptin as triple therapy with metformin and a sulphonylurea (table 5). Canagliflozin 100 mg as dual therapy with metformin produced similar reductions in HbA_{1c} from baseline and 300 mg produced superior ($p < 0.05$) reductions in HbA_{1c} compared to glimepiride, thus demonstrating non-inferiority. A lower proportion of patients treated with canagliflozin 100 mg (5.6%) and canagliflozin 300 mg (4.9%) experienced at least one episode/event of hypoglycaemia over 52 weeks of treatment compared to the group treated with glimepiride (34.2%). In a study comparing canagliflozin 300 mg to sitagliptin 100 mg in triple therapy with metformin and a sulphonylurea, canagliflozin demonstrated non-inferior ($p < 0.05$) and superior ($p < 0.05$) reduction in HbA_{1c} relative to sitagliptin. The incidence of hypoglycaemia episodes/events with canagliflozin 300 mg and sitagliptin 100 mg was 40.7% and 43.2%, respectively. Significant improvements in body weight and reductions in systolic blood pressure compared to both glimepiride and sitagliptin were also observed.

Table 5: Efficacy results from active-controlled clinical studies[a]

Compared to glimepiride as dual therapy with metformin (52 weeks)			
	Canagliflozin + metformin		**Glimepiride (titrated) + metformin**
	100 mg (N = 483)	**300 mg (N = 485)**	**(N = 482)**
HbA_{1c} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)	-0.01[b] (−0.11; 0.09)	-0.12[b] (−0.22; −0.02)	N/A[c]
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[b] (−5.7; −4.7)	-5.7[b] (−6.2; −5.1)	N/A[c]
Compared to sitagliptin as triple therapy with metformin and sulphonylurea (52 weeks)			
	Canagliflozin 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	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)	-0.37[b] (-0.50; -0.25)	N/A[c]
Patients (%) achieving HbA_{1c} < 7%	47.6	35.3
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[d] (-3.3; -2.2)	N/A[c]

[a] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.
[b] $p < 0.05$.
[c] Not applicable.
[d] $p < 0.001$.

Canagliflozin as initial combination therapy with metformin

Canagliflozin was evaluated in combination with metformin as initial combination therapy in patients with type 2 diabetes failing diet and exercise. Canagliflozin 100 mg and canagliflozin 300 mg in combination with metformin XR resulted in a statistically significant greater improvement in HbA_{1C} compared to their respective canagliflozin doses (100 mg and 300 mg) alone or metformin XR alone (table 6).

Table 6: Results from 26-week active-controlled clinical study of canagliflozin as initial combination therapy with metformin[*]

Efficacy Parameter	**Metformin XR (N = 237)**	**Canagliflozin 100 mg (N = 237)**	**Canagliflozin 300 mg (N = 238)**	**Canagliflozin 100 mg + Metformin XR (N = 237)**	**Canagliflozin 300 mg + Metformin XR (N = 237)**
HbA_{1c} (%)					
Baseline (mean)	8.81	8.78	8.77	8.83	8.90
Change from baseline (adjusted mean)	-1.30	-1.37	-1.42	-1.77	-1.78
Difference from canagliflozin 100 mg (adjusted mean) (95% CI) [†]				-0.40[‡] (-0.59, -0.21)	
Difference from canagliflozin 300 mg (adjusted mean) (95% CI) [†]					-0.36[‡] (-0.56, -0.17)

Difference from metformin XR (adjusted mean) (95% CI) †		-0.06‡ (-0.26, 0.13)	-0.11‡ (-0.31, 0.08)	-0.46‡ (-0.66, -0.27)	-0.48‡ (-0.67, -0.28)
Percent of patients achieving $HbA_{1c} < 7\%$	43	39	43	50§§	57§§
Body Weight					
Baseline (mean) in kg	92.1	90.3	93.0	88.3	91.5
% change from baseline (adjusted mean)	-2.1	-3.0	-3.9	-3.5	-4.2
Difference from metformin XR (adjusted mean) (95% CI)†		-0.9§§ (-1.6, -0.2)	-1.8§ (-2.6, -1.1)	-1.4‡ (-2.1, -0.6)	-2.1‡ (-2.9, -1.4)

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

Special populations

In three studies conducted in special populations (older patients, patients with an eGFR of 30 mL/min/1.73 m^2 to < 50 mL/min/1.73 m^2 and patients with or at high risk for cardiovascular disease), canagliflozin was added to patients' current stable diabetes treatments (diet, monotherapy, or combination therapy).

Elderly

A total of 714 patients ≥ 55 years of age to ≤ 80 years of age (227 patients 65 years of age to < 75 years of age and 46 patients 75 years of age to ≤ 80 years of age) with inadequate glycaemic control on current diabetes treatment (glucose-lowering medicinal products 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 -0.57% and -0.70% were observed for 100 mg and 300 mg, respectively (see sections 4.2 and 4.8).

Patients with eGFR < 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.

In a pooled analysis of patients (N = 348) with a baseline eGFR < 45 mL/min/1.73 m^2, canagliflozin provided a modest reduction in HbA_{1c} compared to placebo, with -0.23% for canagliflozin 100 mg and -0.39% for canagliflozin 300 mg.

The majority of patients with a baseline eGFR < 60 mL/min/1.73 m^2 were on insulin and/or a sulphonylurea. 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 canagliflozin as monotherapy or add-on therapy with one or two oral glucose-lowering medicinal products resulted in mean changes from baseline relative to placebo in FPG of -1.2 mmol/L to -1.9 mmol/L for canagliflozin 100 mg and -1.9 mmol/L to -2.4 mmol/L for canagliflozin 300 mg, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.

Postprandial glucose
Using a mixed-meal challenge, canagliflozin as monotherapy or add-on therapy with one or two oral glucose-lowering medicinal products reduced postprandial glucose (PPG) from baseline relative to placebo by -1.5 mmol/L to -2.7 mmol/L for canagliflozin 100 mg and -2.1 mmol/L to -3.5 mmol/L for 300 mg, respectively, due to reductions in the pre-meal glucose concentration and reduced postprandial glucose excursions.

Body weight
Canagliflozin 100 mg and 300 mg as monotherapy and as dual or triple add-on therapy resulted in statistically significant reductions in the percentage of body weight at 26 weeks relative to placebo. In two 52-week active-controlled studies comparing canagliflozin to glimepiride and sitagliptin, sustained and statistically significant mean reductions in the percentage of body weight for canagliflozin as add-on therapy to metformin were -4.2% and -4.7% for canagliflozin 100 mg and 300 mg, respectively, compared to the combination of glimepiride and metformin (1.0%) and -2.5% for canagliflozin 300 mg in combination with metformin and a sulphonylurea compared to sitagliptin in combination with metformin and a sulphonylurea (0.3%).

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. Two hundred eleven (211) patients from the clinical study in older patients participated in a body composition substudy using DXA body composition analysis. This demonstrated that approximately two-thirds of the weight loss associated with canagliflozin was due to loss of fat mass relative to placebo. There were no meaningful changes in bone density in trabecular and cortical regions.

Blood pressure
In placebo-controlled studies, treatment with canagliflozin 100 mg and 300 mg resulted in mean reductions in systolic blood pressure of -3.9 mmHg and -5.3 mmHg, respectively, compared to placebo (-0.1 mmHg) and a smaller effect on diastolic blood pressure with mean changes for canagliflozin 100 mg and 300 mg of -2.1 mmHg and -2.5 mmHg, respectively, compared to placebo (-0.3 mmHg). There was no notable change in heart rate.

Patients with baseline HbA_{1c} > 10% to ≤ 12%
A substudy of patients with baseline HbA_{1c} > 10% to ≤ 12% with canagliflozin as monotherapy resulted in reductions from baseline in HbA_{1c} (not placebo-adjusted) of -2.13% and -2.56% for canagliflozin 100 mg and 300 mg, respectively.

Cardiovascular outcomes in the CANVAS Program

The effect of canagliflozin on cardiovascular events in adults with type 2 diabetes who had established cardiovascular (CV) disease or were at risk for CVD (two or more CV risk factors), was evaluated in the CANVAS Program (integrated analysis of the CANVAS and the CANVAS-R study). These studies were multi-centre, multi-national, randomised, double-blind, parallel group, with similar inclusion and exclusion criteria and patient populations. The CANVAS Program compared the risk of experiencing a Major Adverse Cardiovascular Event (MACE) defined as the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, between canagliflozin and placebo on a background of standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

In CANVAS, subjects were randomly assigned 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. In CANVAS-R, subjects were randomly assigned 1:1 to canagliflozin 100 mg or matching placebo, and titration to 300 mg was permitted (based on tolerability and glycaemic needs) after Week 13. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, according to the standard care for these diseases.

A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) for a mean exposure duration of 149 weeks (223 weeks in CANVAS and 94 weeks in CANVAS-R). Vital status was obtained for 99.6% of subjects across the studies. The mean age was 63 years and 64% were male. Sixty-six percent of subjects had a history of established cardiovascular disease, with 56% having a history of coronary disease, 19% with cerebrovascular disease, and 21% with peripheral vascular disease; 14% had a history of heart failure.

The mean HbA_{1c} at baseline was 8.2% and mean duration of diabetes was 13.5 years.

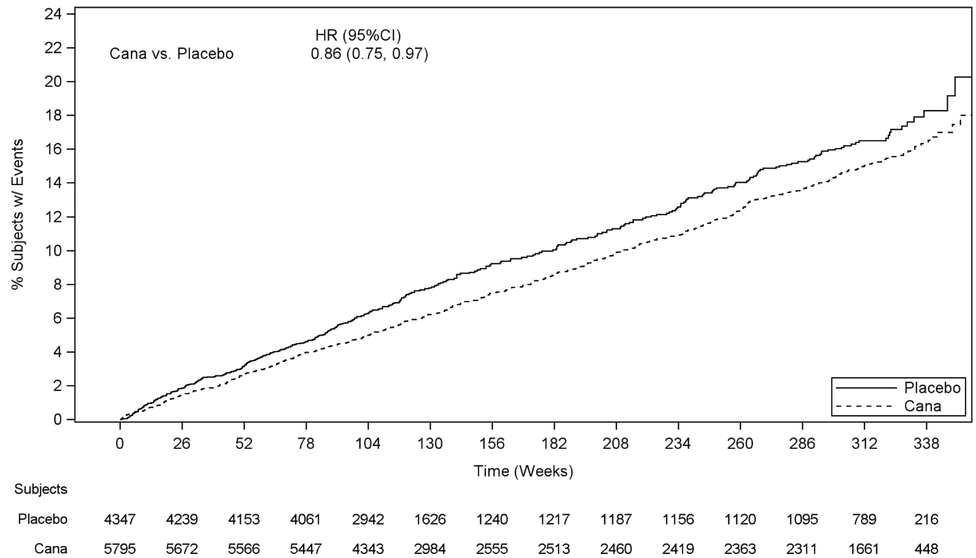
Patients were required to have an eGFR > 30 mL/min/1.73 m^2 at study entry. Baseline renal function was normal or mildly impaired in 80% of patients and moderately impaired in 20% of patients (mean eGFR 77 mL/min/1.73 m^2). At baseline, patients were treated with one or more antidiabetic medicinal product including metformin (77%), insulin (50%), and sulfonylurea (43%).

The primary endpoint in the CANVAS Program was the time to first occurrence of a MACE. Secondary endpoints within a sequential conditional hypothesis testing were all-cause mortality and cardiovascular mortality.

Patients in the pooled canagliflozin groups (pooled analysis of canagliflozin 100 mg, canagliflozin 300 mg, and canagliflozin up-titrated from 100 mg to 300 mg) had a lower rate of MACE as compared to placebo: 2.69 *versus* 3.15 patients per 100 patient-years (HR of the pooled analysis: 0.86; 95% CI (0.75, 0.97).

Based on the Kaplan-Meier plot for the first occurrence of MACE, shown below, the reduction in MACE in the canagliflozin group was observed as early as Week 26 and was maintained throughout the remainder of the study (see Figure 1).

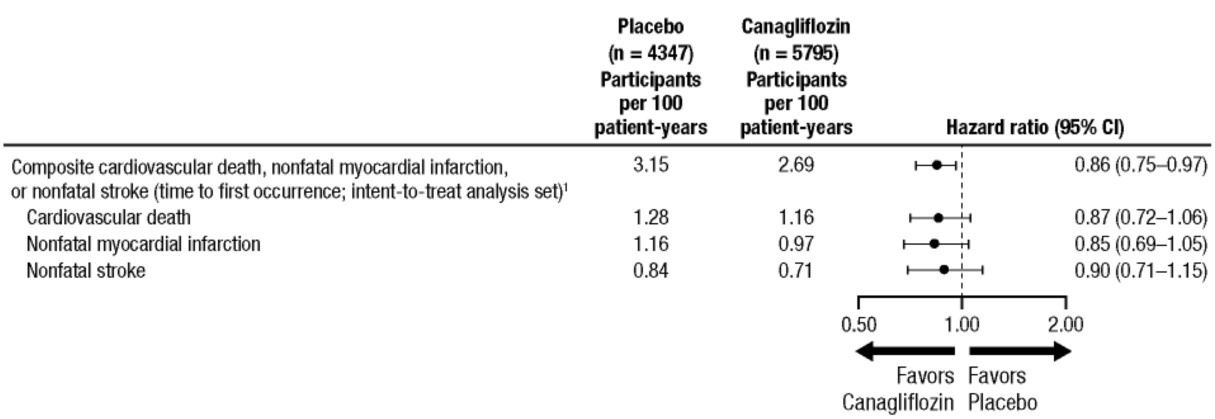
Figure 1: Time to first occurrence of MACE



There were 2,011 patients with eGFR 30 to < 60 mL/min/1.73 m^2. The MACE findings in the 30 to < 60 mL/min/1.73 m^2, 30 to < 45 mL/min/1.73 m^2 and 45 to < 60 mL/min/1.73 m^2 subgroups were consistent with the overall findings.

Each MACE component positively contributed to the overall composite, as shown in Figure 2. Results for the 100 mg and 300 mg canagliflozin doses were consistent with results for the combined dose groups.

Figure 2: Treatment effect for the primary composite endpoint and its components



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

All-cause mortality in the CANVAS Program

In the combined canagliflozin group, the HR for all-cause mortality versus placebo was 0.87; 95% CI (0.74, 1.01).

Heart failure requiring hospitalization in the CANVAS Program

Canagliflozin reduced the risk for heart failure requiring hospitalisation compared to placebo (HR: 0.67; 95% CI (0.52, 0.87)).

Renal endpoints in the CANVAS Program

For time to first adjudicated nephropathy event (doubling of serum creatinine, need for renal-replacement therapy, and renal death), the HR was 0.53 (95% CI: 0.33, 0.84) for canagliflozin (0.15 events per 100 patient-years) versus placebo (0.28 events per 100 patient-years). In addition, canagliflozin reduced progression of albuminuria by 25.8% versus placebo 29.2% (HR: 0.73; 95% CI: 0.67, 0.79) in patients with baseline normo- or micro-albuminuria.

Renal outcomes in the CREDENCE study

The effect of canagliflozin 100 mg on renal events in adults with type 2 diabetes and diabetic kidney disease (DKD) with estimated glomerular filtration rate (eGFR) 30 to < 90 mL/min/1.73 m^2 and albuminuria (>300 to 5000 mg/g of creatinine), was evaluated in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE). This was a multi-centre, multi-national, randomised, double-blind, event-driven, placebo-controlled, parallel-group study. The CREDENCE study compared the risk of experiencing DKD defined as the composite of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death, between canagliflozin 100 mg and placebo on a background of standard of care treatments for DKD, including angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Canagliflozin 300 mg was not investigated in this study.

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

A total of 4,397 subjects were treated and exposed for a mean of 115 weeks. The mean age was 63 years and 66% were male.

The mean baseline HbA1c was 8.3% and baseline median urine albumin/creatinine was 927 mg/g. The most frequent antihyperglycaemic agents (AHA) used at baseline were insulin (65/5%), biguanides (57.8%), and sulfonylureas (28.8%). Nearly all subjects (99.9%) were on ACEi or ARB at randomization. About 92% of the subjects were on cardiovascular therapies (not including ACEi/ARBs) at baseline, with approximately 60% taking an anti-thrombotic agent (including acetylsalicylic acid) and 69% on statins.

The mean baseline eGFR was 56.2 mL/min/1.73 m^2 and approximately 60% of the population had a baseline eGFR of < 60 mL/min/1.73 m^2. The proportion of subjects with prior CV disease was 50.4%, 14.8% had a history of heart failure.

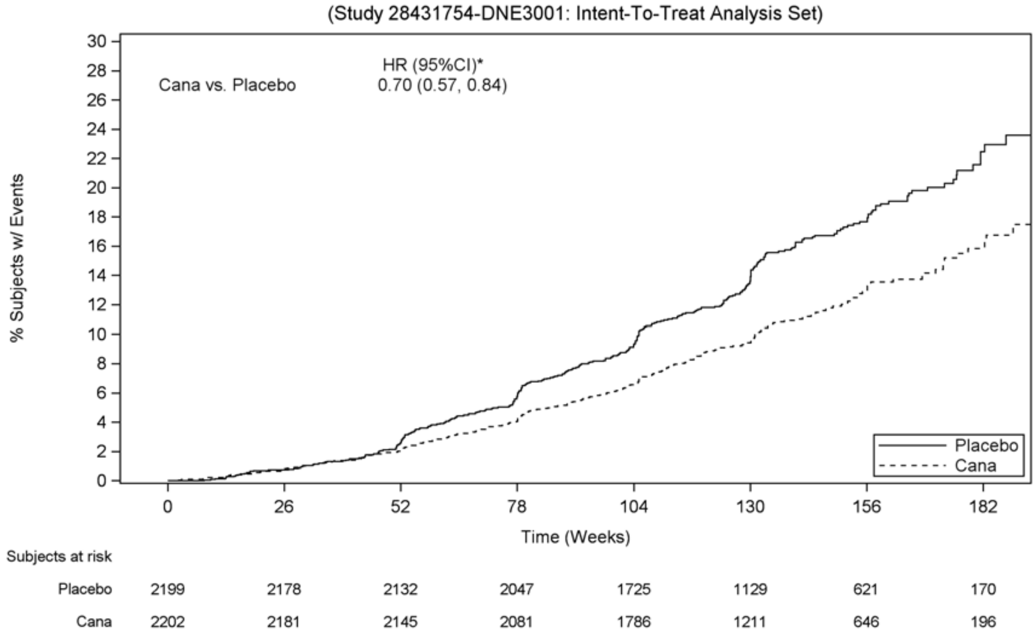
The primary composite endpoint in the CREDENCE study was the time to first occurrence of ESKD (defined as an eGFR < 15 mL/min/1.73 m^2, initiation of chronic dialysis or renal transplant), doubling of serum creatinine, and renal or CV death.

Canagliflozin 100 mg significantly reduced the risk of first occurrence of the primary composite endpoint of ESKD, doubling of serum creatinine, and renal or CV death [p<0.0001; HR: 0.70; 95% CI: 0.57, 0.84] (see Figure 4). Treatment effect was consistent across subgroups, including all three eGFR strata and subjects with or without a history of CV disease.

Based on the Kaplan-Meier plot for the time to first occurrence of the primary composite endpoint shown below, the treatment effect was evident beginning from Week 52 with canagliflozin 100 mg and was maintained through the end of study (see Figure 3).

Canagliflozin 100 mg significantly reduced the risk of cardiovascular secondary endpoints, as shown in Figure 4.

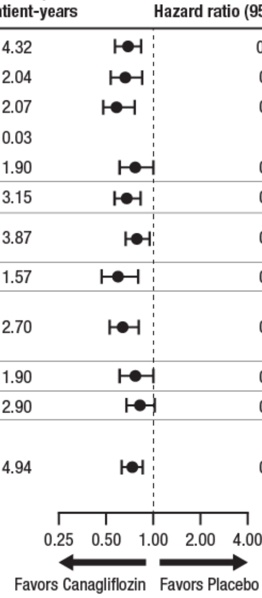
Figure 3: CREDENCE: Time to first occurrence of the primary composite endpoint



* 95% RCI (Repeated Confidence Interval) for the primary endpoint with family-wise type I error-rate controlled at a 2-sided significance level of 0.05.

Figure 4: Treatment effect for the primary composite endpoint and its components and secondary endpoints

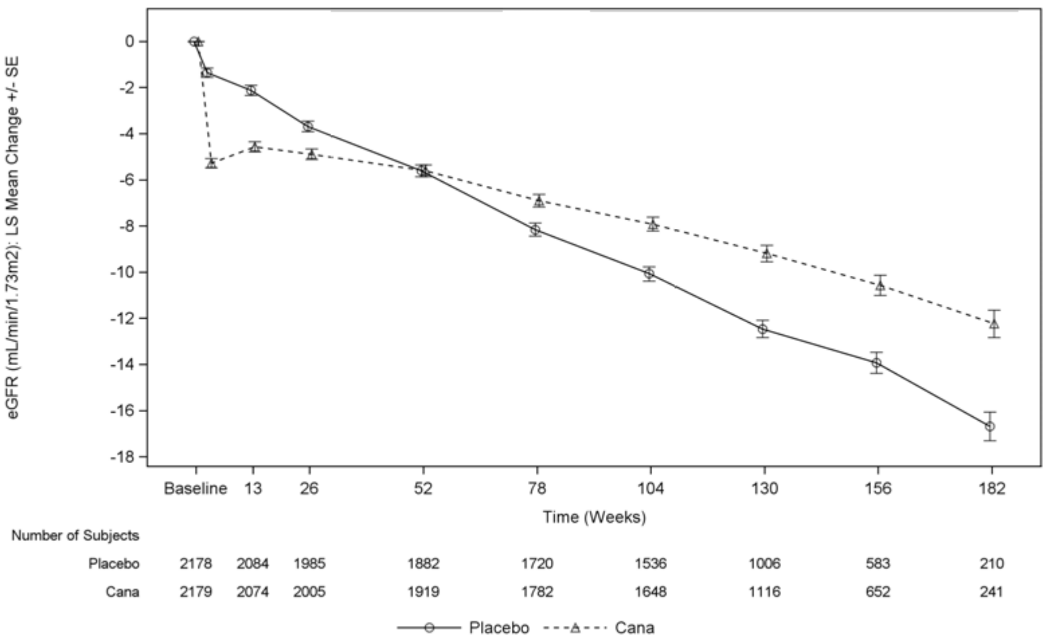
	Placebo		Canagliflozin			
Endpoint	n/N (%)	Event rate per 100 patient-years	n/N (%)	Event rate per 100 patient-years	Hazard ratio (95% CI)	*P* value
Primary composite endpoint	340/2199 (15.5)	6.12	245/2202 (11.1)	4.32	0.70 (0.57, 0.84)*	<0.0001
ESKD	165/2199 (7.5)	2.94	116/2202 (5.3)	2.04	0.68 (0.54, 0.86)	0.0015
Doubling of serum creatinine	188/2199 (8.5)	3.38	118/2202 (5.4)	2.07	0.60 (0.48, 0.76)	<0.0001
Renal death	5/2199 (0.2)	0.09	2/2202 (0.1)	0.03	–	–
CV death†	140/2199 (6.4)	2.44	110/2202 (5.0)	1.90	0.78 (0.61, 1.00)	NS
Composite of CV death/HHF	253/2199 (11.5)	4.54	179/2202 (8.1)	3.15	0.69 (0.57, 0.83)	0.0001
CV death, nonfatal MI, and nonfatal stroke	269/2199 (12.2)	4.87	217/2202 (9.9)	3.87	0.80 (0.67, 0.95)	0.0121
HHF	141/2199 (6.4)	2.53	89/2202 (4.0)	1.57	0.61 (0.47, 0.80)	0.0003
Composite of doubling of serum creatinine, ESKD, and renal death	224/2199 (10.2)	4.04	153/2202 (6.9)	2.70	0.66 (0.53, 0.81)	<0.0001
CV death†	140/2199 (6.4)	2.44	110/2202 (5.0)	1.90	0.78 (0.61, 1.00)	NS
All-cause mortality	201/2199 (9.1)	3.50	168/2202 (7.6)	2.90	0.83 (0.68, 1.02)	NS
Composite of CV death, nonfatal MI, nonfatal stroke, HHF, and hospitalization for unstable angina	361/2199 (16.4)	6.69	273/2202 (12.4)	4.94	0.74 (0.63, 0.86)	NS



CI, confidence interval; ESKD, end-stage kidney disease; CV, cardiovascular; NS, not significant; HHF, hospitalization for heart failure; MI, myocardial infarction.
*95% RCI (repeated confidence interval) for the primary endpoint with family-wise type I error-rate controlled at a 2-sided significance level of 0.05.
Testing of the primary and the secondary efficacy endpoints was performed using a 2-sided alpha level of 0.022 and 0.038, respectively.
†CV death is being presented as both a component of the primary composite endpoint and a secondary endpoint which underwent formal hypothesis testing.

As shown in Figure 5, the eGFR in placebo-treated patients demonstrated a progressive linear decline over time; in contrast, the canagliflozin group showed an acute decrease at Week 3, followed by an attenuated decline over time; after Week 52, the LS mean decrease in eGFR was smaller in the canagliflozin group than in the placebo group, and the treatment effect was maintained through the end of treatment.

Figure 5: LS mean change from baseline in eGFR over time (on-treatment analysis set)



In CREDENCE, the incidence rate for renal-related adverse events was lower in the canagliflozin 100 mg group compared with the placebo group (5.71 and 7.91 per 100 patient-years in canagliflozin 100 mg and placebo, respectively).

<u>Paediatric population</u>
The European Medicines Agency has deferred the obligation to submit the results of studies with canagliflozin in one or more subsets of the paediatric population in type 2 diabetes (see section 4.2 for information on paediatric use).

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 hour 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 days 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.

<u>Absorption</u>
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 be taken before the first meal of the day (see sections 4.2 and 5.1).

Distribution
The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 litres, 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.

Biotransformation
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.

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. No clinically relevant effect on CYP3A4 was observed *in vivo* (see section 4.5).

Elimination
Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in 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 of canagliflozin 100 mg and 300 mg doses ranged from 1.30 mL/min to 1.55 mL/min.

Canagliflozin is a low-clearance substance, 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 CrCl based on the Cockroft-Gault equation) compared to healthy subjects. The study included 8 subjects with normal renal function (CrCl ≥ 80 mL/min), 8 subjects with mild renal impairment (CrCl 50 mL/min to < 80 mL/min), 8 subjects with moderate renal impairment (CrCl 30 mL/min to < 50 mL/min), and 8 subjects with severe renal impairment (CrCl < 30 mL/min) as well as 8 subjects with ESKD on haemodialysis.

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 haemodialysis. 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 ESKD subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Hepatic impairment
Relative to subjects with normal hepatic function, the geometric mean ratios for C_{max} and AUC_{∞} of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic

impairment) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate) hepatic impairment following administration of a single 300 mg dose of canagliflozin.

These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment.

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

Paediatric population
A paediatric phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Other special populations
Pharmacogenetics
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. The effect of being homozygote (UGT1A9*3/*3, frequency < 0.1%) is probably more marked, but has not been investigated.

Gender, race/ethnicity, or body mass index had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

Canagliflozin showed no effects on fertility and early embryonic development in the rat at exposures up to 19 times the human exposure at the maximum recommended human dose (MRHD).

In an embryo-foetal development study in rats, ossification delays of metatarsal bones were observed at systemic exposures 73 times and 19 times higher than the clinical exposures at the 100 mg and 300 mg doses. It is unknown whether ossification delays can be attributed to effects of canagliflozin on calcium homeostasis observed in adult rats. Ossification delays were also observed for the combination of canagliflozin and metformin, which were more prominent than for metformin alone at canagliflozin exposures 43 times and 12 times higher than clinical exposures at 100 mg and 300 mg doses.

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

A study in juvenile rats administered canagliflozin from day 21 through day 90 postnatal did not show increased sensitivity compared to effects observed in adults rats. However, dilatation of the renal pelvis was noticed with a No Observed Effect Level (NOEL) at exposures 2.4 times and 0.5 times the clinical exposures at 100 mg and 300 mg doses, respectively, and 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.

Canagliflozin did not increase the incidence of tumours in male and female mice in a 2-year study at doses of 10, 30, and 100 mg/kg. The highest dose of 100 mg/kg provided up to 14 times the clinical dose of 300 mg based on AUC exposure. Canagliflozin increased the incidence of testicular Leydig cell tumours in male rats at all doses tested (10, 30, and 100 mg/kg); the lowest dose of 10 mg/kg is approximately 1.5 times the clinical dose of 300 mg based on AUC exposure. The higher doses of canagliflozin (100 mg/kg) in male and female rats increased the incidence of pheochromocytomas and renal tubular tumours. Based on AUC exposure, the NOEL of 30 mg/kg/day for pheochromocytomas and renal tubular tumours is approximately 4.5 times the exposure at the daily clinical dose of 300 mg. Based on preclinical and clinical mechanistic studies, Leydig cell tumours, renal tubule tumours, and pheochromocytomas are considered to be rat-specific. Canagliflozin-induced renal tubule tumours and pheochromocytomas in rats appear to be caused by carbohydrate malabsorption as a consequence of intestinal SGLT1 inhibitory activity of canagliflozin in the gut of rats; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the maximum recommended clinical dose. The Leydig cell 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, unstimulated LH did not increase in male patients treated with canagliflozin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Tablet core</u>
Lactose
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate

<u>Film-coating</u>
<u>*Invokana 100 mg film-coated tablets*</u>
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)

<u>*Invokana 300 mg film-coated tablets*</u>
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.
This medicinal product does not require any special storage conditions.
Keep out of the sight and reach of children.

6.5 Nature and contents of container

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

Pack sizes of 30 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal products or waste material should be disposed of in accordance with local requirements.

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