European Union Risk Management Plan (EU-RMP)

INVOKANA & VOKANAMET (Canagliflozin & Canagliflozin/Metformin Hydrochloride (HCl) Fixed-dose Combination (FDC))

Final for Procedures EMEA/H/C/002649/WS2619/0066/G and EMEA/H/C/002649/WS2719/0068 (INVOKANA) and Procedures EMEA/H/C/002656/WS2619/0073/G and EMEA/H/C/002656/WS2719/0075 (VOKANAMET): 05 September 2024 (CHMP opinion)

CHMP Opinion Date = 05 Sept 2024

Active substance(s) (INN or common name):	Canagliflozin (alternate names: JNJ-28431754, JNJ-28431754-ZAE, TA-7284) (single-agent) Canagliflozin/Metformin HCl FDC
Pharmaco-therapeutic group (ATC Code):	INVOKANA®: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK02) VOKANAMET®: Drugs used in diabetes, combinations of oral blood glucose-lowering drugs (A10BD16)
Name of Marketing Authorization Holder:	Janssen-Cilag International, NV
Number of medicinal products to which this RMP refers:	2
Product(s) concerned (brand names):	INVOKANA® (canagliflozin) VOKANAMET® (canagliflozin/metformin HCl FDC)

Data-lock point for current RMP	31 March 2023	Version number	12.1
Date of final sign off	13 September 2024		

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	12.1
Rationale for submitting an updated RMP	The RMP has been updated to reflect the completion of the Category 3 retrospective drug utilization study included as a post-authorization safety study relevant for the risk of diabetic ketoacidosis with atypical presentation.
Summary of significant changes in this RMP:	Safety concerns: None. Pharmacovigilance plan: The pharmacovigilance plan has been updated to reflect the completion of the Category 3 retrospective drug utilization study included as a post-authorization safety study relevant for the risk of diabetic ketoacidosis with atypical presentation. Risk minimization measures: None. Annexes: Annexes have been revised as needed for consistency with changes made elsewhere in the RMP.

Other RMP Versions Under Evaluation

RMP Version Number	Submitted on	Procedure Number
13.1	11 July 2024	EMEA/H/C/002649/II/0069

QPPV Sign-off Date: 13 September 2024
RMP Version Number: 12.1
Supersedes Version: 11.3
EDMS Number: CCI [redacted]

PPD [redacted]

Details of the Currently Approved RMP

Version number of last agreed RMP:	11.3
Approved within procedures	EMEA/H/C/002649/WS2619/0066/G (INVOKANA) EMEA/H/C/002656/WS2619/0073/G (VOKANAMET)
Date of approval (opinion date)	05 September 2024 (CHMP opinion)

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PART I: PRODUCT(S) OVERVIEW

Part I. Product Overview

Active substance(s)	Canagliflozin
(INN or common name)	Canagliflozin/metformin HCl FDC
Pharmacotherapeutic group(s) (ATC Code)	INVOKANA®: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, SGLT2 inhibitors (A10BK02) VOKANAMET®: Drugs used in diabetes, combinations of oral blood glucose-lowering drugs (A10BD16)
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	2
Invented name(s) in the European Economic Area (EEA)	INVOKANA; VOKANAMET
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** Canagliflozin is a SGLT2 inhibitor. Canagliflozin/metformin HCl FDC combines 2 oral glucose-lowering active substances — canagliflozin, a SGLT2 inhibitor, and metformin, a biguanide with antihyperglycemic effects.
	Summary of mode of action Canagliflozin is an orally-active inhibitor of SGLT2. The high capacity/low-affinity SGLT2 in the proximal renal tubule reabsorbs the majority of glucose filtered by the renal glomerulus. Pharmacological inhibition of SGLT2 decreases renal glucose reabsorption, and thereby increases urinary glucose excretion and lowers the plasma glucose in patients with type 2 diabetes mellitus (T2DM). 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. Canagliflozin/metformin HCl FDC combines 2 oral glucose-lowering active substances with complementary mechanisms of action to improve glycemic control in patients with T2DM. Canagliflozin acts as described above. Metformin lowers both basal and postprandial plasma glucose. Metformin may act via 3 mechanisms: (a) by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; (b) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization; and (c) by delaying intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on

	glycogen synthase.
	Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT 1 and GLUT 4).
	Important information about its composition: Not applicable
Hyperlink to the product information	Module 1.3.1
Indication(s) in the EEA	**Current:** INVOKANA is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications; • in addition to other medicinal products for the treatment of diabetes. VOKANAMET is indicated in adults with T2DM as an adjunct to diet and exercise: • in patients insufficiently controlled on their maximally tolerated doses of metformin alone; • in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products; • in patients already being treated with the combination of canagliflozin and metformin as separate tablets.
	Proposed: Not applicable.
Dosage in the EEA	**Current:** The recommended starting dose of INVOKANA 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 creatinine clearance (CrCl) ≥60 mL/min and need tighter glycemic control, the dose can be increased to 300 mg once daily. See the SmPC for detailed dosage adjustment recommendations according to eGFR. For treatment of diabetic kidney disease (DKD) as add on to standard of care (angiotensin converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARBs]), a dose of 100 mg canagliflozin once daily should be used. Because the glycemic lowering efficacy of canagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycemic control is needed, the addition of other anti-hyperglycemic agents should be considered. See the SmPC for detailed dosage adjustment recommendations according to eGFR. The dose of VOKANAMET should be individualized based on the patient's current regimen, effectiveness, and tolerability, using the recommended daily dose of 100 mg or 300 mg canagliflozin and not

	exceeding the maximum recommended daily dose of metformin orally. For patients not adequately controlled on metformin, the recommended starting dose of VOKANAMET should provide canagliflozin dosed at 50 mg twice daily plus the dose of metformin already being taken or the nearest therapeutically appropriate dose. For patients who are tolerating a VOKANAMET dose containing canagliflozin 50 mg who need tighter glycemic control, the dose can be increased to VOKANAMET containing 150 mg canagliflozin twice daily. For patients switching from separate tablets of canagliflozin and metformin, VOKANAMET should be initiated at the same total daily dose of canagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin. Dose titration with canagliflozin (added to the optimal dose of metformin) should be considered before the patient is switched to VOKANAMET. In patients tolerating VOKANAMET containing canagliflozin 50 mg who need tighter glycemic control, increasing the dose to VOKANAMET containing canagliflozin 150 mg may be considered.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	**Current:** INVOKANA is available as an oral tablet: • canagliflozin 100 mg; • canagliflozin 300 mg. VOKANAMET is available as an oral tablet: • canagliflozin/metformin HCl 50 mg/850 mg; • canagliflozin/metformin HCl 50 mg/1000 mg; • canagliflozin/metformin HCl 150 mg/850 mg; • canagliflozin/metformin HCl 150 mg/1000 mg.
	Proposed: Not applicable

Is/will the product subject of additional monitoring in the EU? ☐ **Yes** ☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

SI.1. Epidemiology of the Indication(s) and Target Population(s)

Indication(s)

Relevant epidemiology (incidence, prevalence, demographics, risk factors, main treatment options, and natural history including mortality and morbidity) is summarized below for T2DM patients. The differences in the reported incidence and prevalence across various countries and populations could be attributable to differences in demographics, risk factor profiles, healthcare systems, and also study design, sampling, data collection and assessment methods.

Incidence:

A systemic review of population-based cohort studies, diabetes registries, and administrative and health insurance database studies on secular trends of the incidence of diabetes among adults found that between 2006 and 2014, increasing trends in the incidence of diabetes were reported in 33% (11/33) of populations, 30% (10/33) of populations had a stable incidence, while 36% (12/33) of populations reported a declining trend (Magliano, 2019).

Europe

In Switzerland, one study using Swiss healthcare claim data of a total of 920,402 patients estimated that the incidence of diabetes was 6.3 per 1,000 persons in 2007 and 5.8 per 1,000 persons in 2011 (Huber et al, 2014). In Italy, one study examined administrative health database of more than 9 million people and reported the incidence of diabetes remained stable from 2000-2007 with a rate of 4 per 1,000 persons per year (Monesi et al, 2012). In Denmark, based on data from national register of diabetic patients (approximately 360,000 in the Danish population), the incidence rate of diabetes was estimated to be 1.8 per 1,000 at age of 40 years and 10.0 per 1,000 at age of 70 years in 2004; the incidence rate increased 5% per year before 2004 and then stabilized (Carstensen et al, 2008). In the United Kingdom (UK), analysis using the Clinical Practice Research Datalink (CPRD), an electronic database based on primary care health records, showed that the standardized incidence rates of T2DM among individuals aged ≥16 years was 44.8 per 10,000 person-years in 2004 and remained stable overall until 2013, and decreased slightly to 36.9 per 10,000 person-years in 2014 (Zghebi et al, 2017).

United States

Using source data from 2013-2015 National Health Interview Survey (NHIS) and 2011-2014 National Health and Nutrition Examination Survey (NHANES), Centers for Disease Control and Prevention (CDC) reported that an estimated 1.5 million new cases of diabetes were diagnosed among adults in the United States (US) aged 18 years or older in 2015, corresponding to an incidence rate of 6.7 per 1,000 persons (CDC National Diabetes Statistics Report, 2017). An analysis of NHIS 1980-2012 data found that age-adjusted incidence of diagnosed diabetes increased sharply each year during 1990-2008 but leveled off with no significant change during

2008-2012 (Geiss et al, 2014), with the age-adjusted incidence per 1,000 persons of 3.2 in 1990, 8.8 in 2008, and 7.1 in 2012. This finding is corroborated by another study using electronic record data from 11 integrated healthcare delivery systems in the US (SUPREME-DM project), which reported a stable age- and sex-adjusted incidence of diabetes between 2006 and 2011 (ranging from 10.3 to 11.3 per 1,000 adults) (Nichols et al, 2015).

Prevalence:

According to a projection using data from 91 countries (Shaw et al, 2010), the global prevalence of diabetes in 2010 was 6.4% in adults aged 20-79 years, affecting 285 million people; of which, T2DM accounted for 87% to 91% of the global burden. More recently, the International Diabetes Federation (IDF) estimated that globally in 2019, 463 million (9.3%) adults aged 20-79 years had diabetes, with the regional prevalence (age-standardized to world population) ranging from 4.7% in Africa to 12.2% in the Middle East and North Africa. If the trends continue, 700.2 million adults aged 20-79 years are expected to be living with diabetes by 2045 (IDF, 2019). The increase in the prevalence of diabetes may have reflected not only increased incidence due to an epidemic of obesity and the widespread adoption of sedentary lifestyle, but also changes in diagnostic criteria, enhanced detection, and decreased overall mortality.

Europe

Data from The Health Improvement Network (THIN), a primary care medical records database in the UK, showed that the prevalence of T2DM increased from 2.47% in 1996 to 3.9% in 2005 (González et al, 2009). In the CPRD, the prevalence of T2DM among individuals aged ≥16 years in the UK increased from 3.2% to 5.3% between 2004 and 2014 (Zghebi et al, 2017). Similarly, the prevalence of T2DM in Uppsala county, Sweden increased from 2.2% to 3.5% between 1996 and 2003 (Ringborg et al, 2008). Based on data from countries with population-based diabetes registers, the age-specific diabetes prevalence in Denmark and Finland shows the same pattern with a peak between age 75 and 85 years, with prevalence ranging from 13% in Finland (2002) to 16% in Denmark (2008) (Carstensen & Borch-Johnsen, 2011).

United States

Analysis of data from the NHANES showed that the crude prevalence of diagnosed diabetes in adults aged ≥20 years increased from 6.5% during the period from 1999-2002 to 7.8% from 2003-2006 (Cowie et al, 2010). The analysis of NHIS 1980-2012 data reported age-adjusted prevalence of diabetes was 3.5% in 1990, 7.9% in 2008, and 8.3% in 2012 (Geiss et al, 2014). In the 2017 CDC National Diabetes Statistics Report, 7.2% of the US adult population in 2015 reported that they had diagnosed diabetes (CDC National Diabetes Statistics Report, 2017). According to a report from the Agency for Healthcare Research and Quality, among US Medicare beneficiaries aged 65 years and over, the prevalence of diabetes was 26.5% in 2006, 27.4% in 2007, and 28.0% in 2008 (Margolis et al, 2011). Most of the increase in diabetes prevalence since 1999 was attributable to T2DM.

Demographics of the Population in the Authorized Indication - Age, Sex, Racial, and/or Ethnic Origin, and Risk Factors for the Disease

Age

Type 2 diabetes mellitus is predominantly a disease of adulthood. In developed countries, the risk of diabetes increases progressively throughout life, with individuals aged 65 years and above accounting for the majority of cases (van Dieren et al, 2010). Analysis of data from NHANES 2003-2006 showed prevalence (95% confidence interval [CI]) by age groups 20-39, 40-59, 60-74, and ≥75 years of 2.5% (1.9-3.1%), 10.1% (8.7-11.5%), 21.1% (18.7-23.4), and 18.7% (16.6-20.9%), respectively. In the Ely cohort study in the UK, cumulative incidence of T2DM increased across increasing age groups with rates (95% CI) of 5.5 (3.5-8.8), 7.6 (5.0-11.7) and 9.5 (6.3-14.4) per 1,000 patient-years (PY) for ages 40-49, 50-59, and 60+ years, respectively (Forouhi et al, 2007).

Sex

Worldwide, there are more women living with T2DM than men. Although the prevalence of diabetes is slightly greater in men under the age of 60 years, it is higher in women above this age (van Dieren et al, 2010). In contrast, men appeared to have a higher incidence of T2DM than women. A study using the THIN data found a higher incidence of T2DM among males (4.86 per 1,000 PY; 95% CI: 4.80-4.92) compared with females (3.66 per 1,000 PY; 95% CI: 3.61-3.71) from 1996 to 2005 (González et al, 2009). Similarly, the Ely cohort study found the incidence of T2DM per 1,000 PY (95% CI) was higher in men than women, 10.2 (7.3-14.1) vs. 5.2 (3.5-7.7), respectively (Forouhi et al, 2007). Among participants in the prospective Copenhagen City Heart Study, Denmark, 2.5% of women (95% CI: 2.2-2.8) and 5.4% of men (95% CI: 5.1-5.7) developed incident diabetes during an average follow-up period of 12 years (Almdal et al, 2008).

Race and/or ethnic origin

Data from the US NHANES 2003-2006 showed that age- and sex-standardized prevalence (%) of total diabetes was about 2 times higher in non-Hispanic blacks (14.9 [95% CI: 13.4-16.5]) and Mexican Americans (15.6 [95% CI: 14.2-16.9]) versus non-Hispanic whites (7.6 [95% CI: 6.7-8.5]) (Cowie et al, 2010). In the Atherosclerosis Risk in Communities study, diabetes incidence per 1,000 PY was about 2.4-fold greater in African American women (25.1 [95% CI: 22.4-28.1] vs. 10.4 [95% CI: 9.4-11.4]) and about 1.5-fold greater in African-American men (23.4 [95% CI: 19.9-27.2] vs. 15.9 [95% CI: 14.6-17.2]) than in their white counterparts (Brancati et al, 2000). In the Multi-Ethnic Study of Atherosclerosis, diabetes incidence was lowest among white participants (11.1 per 1,000 PY) compared to Chinese (16.2), African Americans (21.6), and Hispanics (21.9) (Bertoni et al, 2010).

Risk factors for T2DM

Risk factors for T2DM include metabolic syndrome, obesity, physical inactivity, first-degree relative with diabetes, women who delivered a baby weighing more than 9 pounds or were diagnosed with gestational diabetes, hypertension (blood pressure ≥140/90 mmHg or on therapy

for hypertension), low high-density lipoprotein cholesterol level and/or a high triglyceride level, women with polycystic ovary syndrome, clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans), age above 45 years, and history of cardiovascular diseases (Rydén et al, 2007; American Diabetes Association [ADA], 2010).

Individuals having impaired fasting glucose (fasting plasma glucose levels of 5.6-6.9 mmol/L) or impaired glucose tolerance (2-h oral glucose tolerance test values of 7.8-11.0 mmol/L) or having a glycosylated hemoglobin (hemoglobin A1c [HbA1c]) between 5.7% and 6.4% have been referred to as having pre-diabetes, indicating the relatively high risk for the future development of diabetes (Rydén et al, 2007; ADA, 2010).

The Main Existing Treatment Options:

Various classes of antihyperglycemic agents (AHAs) are now available with different pharmacologic targets. Biguanides (metformin, registered for the treatment of T2DM in 1957 in Europe and in 1995 in the US) may act by reducing hepatic glucose production, increasing insulin sensitivity in muscle and improving peripheral glucose uptake and utilization, and delaying intestinal glucose absorption. Sulphonylureas and other insulin secretagogues (eg, meglitinides) increase beta-cell insulin secretion in a glucose-independent fashion. Insulin sensitizers (eg, thiazolidinediones) target adipocytes and muscle to decrease insulin resistance and increase cellular utilization of glucose. Alpha-glucosidase inhibitors (eg, acarbose) delay intestinal carbohydrate absorption. In addition to insulin and the traditionally available AHAs above, more recent treatment options include glucagon-like peptide-1 agonists (GLP-1) and dipeptidyl peptidase-4 (DPP-4) inhibitors, both target on the incretin hormone axis, leading to glucose dependent increased insulin secretion and lower glucagon levels. Sodium glucose co-transporter 2 inhibitors are the latest class of oral AHAs to become available with the approval of dapagliflozin (FORXIGA), canagliflozin (INVOKANA), empagliflozin (JARDIANCE), and ertugliflozin (STEGLATRO) in Europe.

Natural History of Type 2 Diabetes Mellitus in the Untreated Population, Including Mortality and Morbidity:

Natural history and morbidity

Type 2 diabetes mellitus is progressive, and the natural history of the disease process starts several years before diagnosis with increasing insulin resistance and beta-cell dysfunction (Piya et al, 2010). When the dysfunctional/failing beta cells are not able to cope with the increasing insulin resistance, plasma glucose starts to rise and the diagnosis of diabetes is made. In clinical practice, however, there is commonly a delay in diagnosis for several years.

Because of the progressive nature of T2DM, pharmacologic therapy with oral medicinal agents is often required as an adjunct to diet and exercise therapy. Increasingly complex pharmacologic intervention (including insulin therapy) is usually needed over time to maintain glycemic control (Tahrani et al, 2011). Type 2 diabetes mellitus patients have a significantly higher incidence of comorbidities that are already commonly present at the time of diagnosis, including microvascular

and macrovascular complications (ADA, 2010; Ramlo-Halsted & Edelman, 1999), see Important Comorbidities section of this EU-RMP. Type 2 diabetes mellitus remains a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations, and hospitalizations. It is also associated with increased risk of cancer, serious psychiatric illness, cognitive decline, chronic liver disease, accelerated arthritis, and other disabling or deadly conditions (Inzucchi et al, 2012).

Mortality

In the US, diabetes mellitus is ranked the seventh leading cause of death as listed on death certificates, with a crude death rate of about 25 per 100,000 in year 2007 (Xu et al, 2010). Age-adjusted death rates related to diabetes were higher in males, Hispanics, and blacks than in females, non-Hispanic, and whites, respectively.

Reductions in all-cause mortality among women and men with diabetes mellitus have occurred over time (Preis et al, 2009). However, mortality rates among individuals with diabetes mellitus remain about twice as high as those among individuals without diabetes mellitus (Preis et al, 2009).

Analysis of the Framingham Heart Study in the US estimated that life expectancy at age 50 and older for men and women with diabetes was on average 7.5 (95% CI: 5.5-9.5) and 8.2 years (95% CI: 6.1-10.4) shorter, respectively, when compared with men and women of the same age without diabetes (Franco et al, 2007).

The total number of excess deaths attributable to diabetes worldwide is estimated to be 3.96 million in the age group 20-79 years (6.8% of global all ages mortality) in year 2010, calculated using a computerized World Health Organization disease model. Diabetes accounted for 15.7% of deaths among adults in North America and 11.0% in Europe (Roglic & Unwin, 2010).

A cohort study using data from the General Practice Research Database (GPRD) reported an all-cause mortality rate in patients with T2DM of 60.3 per 1,000 person-years (95% CI: 59.2-61.4), which was nearly double the rate found in those without diabetes (Mulnier et al, 2006). The mortality rate in the GPRD study was slightly higher than that found by the Diabetes Audit and Research in Tayside, Scotland Study, which reported an annual rate of 50 per 1,000 (95% CI: 45.1-55.3) patients with T2DM (McAlpine et al, 2005). In Uppsala Sweden, age- and sex adjusted mortality rates in patients with T2DM were found to decrease by 4% per year between 1996 and 2003 with a reported rate of 4.1 per 1,000 in 2003 (Ringborg et al, 2008).

Important Co-morbidities:

Hypertension, hyperlipidemia, and cardiovascular disease are the most common comorbidities among patients with T2DM. Patients with T2DM have an increased risk of having major cardiovascular events with fatal outcomes or requiring surgical intervention, such as ischemic heart disease (myocardial infarction and angina), heart failure, and stroke. Patients with T2DM also have an increased risk of lower extremity amputation, DKD, neuropathy, and retinopathy.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Toxicity findings include: **Repeat-dose toxicity** *Hyperostosis* An increase in trabecular bone volume (hyperostosis) was seen in rats treated with canagliflozin for 2 weeks or more. This was reversible with cessation of canagliflozin treatment. Bone strength (normalized for bone size) was not altered in rats treated with canagliflozin. No evidence of demineralization (osteomalacia), abnormal bone architecture or involvement of cortical bone was observed. Despite achieving similar exposures, hyperostosis was not observed in mice or dogs treated with canagliflozin. Substantial dose-related increases (up to 18-fold at the high dose) in urinary calcium were seen in canagliflozin-treated rats, relative to vehicle control. Increase in intestinal absorption of radio-labelled calcium was demonstrated in canagliflozin-treated rats. Decreases in serum concentrations of 1,25-dihydroxyvitamin D, parathyroid hormone (PTH), calcitonin, and in markers of bone resorption and bone formation were also seen in rats treated with canagliflozin. Under treatment conditions causing hyperostosis in rats, canagliflozin is associated with carbohydrate (glucose/galactose) malabsorption. Sodium-glucose co-transporter-1 (SGLT1) is a transporter expressed on the luminal surface of enterocytes and is responsible for glucose/galactose absorption. In rats, canagliflozin exposures to the intestinal lumen following oral administration appear to be sufficient to inhibit SGLT1 and lead to glucose malabsorption. Due to fermentation in the distal intestine, canagliflozin-induced glucose malabsorption leads to a reduction in intestinal pH that is known to increase calcium solubility and enhance calcium absorption. Canagliflozin-induced hyperostosis in rats was prevented by a glucose/galactose-free fructose diet (which prevents carbohydrate malabsorption). Thus, canagliflozin-induced hyperostosis is a reversible lesion that was seen only in rats and that was shown to be due to glucose/galactose malabsorption and consequent markedly increased calcium absorption.	In clinical trials, to assess whether canagliflozin leads to glucose malabsorption, 2 sensitive techniques were applied: radio-labelled glucose absorption and a hydrogen breath test. At the highest proposed labelled dose (300 mg) using radio-labelled glucose absorption, and at 2-times the highest proposed labelled dose (300 mg twice-daily for 4 weeks) using the hydrogen breath test, canagliflozin did not cause glucose malabsorption. Clinical symptoms indicative of carbohydrate malabsorption (eg, diarrhea) were not meaningfully increased, relative to control, in subjects treated with canagliflozin in the Phase 3 program. Overall, no meaningful changes in serum and urinary calcium and serum PTH and 1,25-dihydroxyvitamin D were seen in subjects treated with canagliflozin. Unlike the rat, no decreases in markers of bone turnover were seen in subjects treated with canagliflozin. Based on the lack of carbohydrate malabsorption or alterations in calcium metabolism in humans treated with canagliflozin, hyperostosis seen in rats treated with canagliflozin is considered to be of no relevance to human safety.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Reproductive toxicity	
Canagliflozin had no effect on fertility in male and female rats. In a pre- and post-natal toxicity study in rats, canagliflozin had no adverse effects on offspring functional development or reproductive performance. In a toxicity study in juvenile rats the effects were consistent with those observed in adult rats including dilatation of the renal tubules and pelvis. Canagliflozin is excreted in the milk in rats at levels approximately 1.4-fold higher than the corresponding maternal plasma levels.	Based on results of reproductive and developmental toxicity studies in rats and rabbits, there is no evidence for potential direct adverse effects of canagliflozin on fertility or reproductive processes. Studies show ossification delays in developing rats that may be due to effects of canagliflozin on calcium metabolism in rats at ~ 19 times the human exposure at the maximum recommended human canagliflozin dose. A study in juvenile rats showed dilatation of the renal tubules and pelvis that are likely due to osmotic diuresis related to the mode of action (see SmPC Section 5.3). Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued. Use in pregnancy is considered Missing Information. 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. Canagliflozin should not be used during breast-feeding. Use in nursing mothers is considered Missing Information.
Developmental toxicity	
Canagliflozin was not teratogenic in developmental toxicity studies in rats and rabbits, and no embryotoxic effects were observed in rabbits. In rat embryo-fetal development studies with canagliflozin or in combination with metformin ossification delays were observed. Renal tubular and pelvic dilatation was observed in a study in juvenile rats.	Ossification delays were observed in rats at systemic exposures 19 times higher than the clinical exposures at the 300-mg dose and were associated with reduced maternal body weight gain. It is unknown whether ossification delays can be attributed to the effects of canagliflozin on calcium homeostasis observed in adult rats. These effects are considered to be a minor transient variation and are not considered to be a teratogenic effect. As ossification delays were observed at high exposures in rats, they are therefore not

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
	considered to be clinically relevant. Potentially harmful effects on the kidney were observed in juvenile rats at an age corresponding to the second and third trimesters in humans. The effects showed full reversibility in the tubules and partial reversibility in the pelvis during a 1-month recovery period. Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued.
Carcinogenicity In a 2-year oral carcinogenicity study in mice administered 10, 30, or 100 mg/kg canagliflozin, there was no treatment-related increase in tumors. However, in a 2-year oral carcinogenicity study in Sprague-Dawley rats administered canagliflozin an increase in Leydig cell tumors (LCTs), pheochromocytomas and renal tubule tumors were seen. Using a standard battery of tests as outlined in the tripartite International Council for Harmonisation (ICH) guideline S2(R1), canagliflozin was not genotoxic. *Leydig Cell Tumors* In a 2-year oral carcinogenicity study in Sprague-Dawley rats administered 10, 30, or 100 mg/kg canagliflozin, an increase in LCTs was observed at all dose levels. In rats, a sustained increase in luteinizing hormone (LH), a Leydig cell mitogen, is an established mechanism for LCT formation. Rats have a high spontaneous incidence of LCT which, are very uncommon tumors in humans. Non-genotoxic agents causing LCTs in rats have not been associated with an increased risk for LCT in humans. It is also noted that carbohydrate malabsorption in rats (eg, due to non-absorbable sugars) is associated with LCTs. In male rats treated with canagliflozin, a decrease in secondary sex organ weights, consistent with hypogonadism, was seen. Relative to vehicle treated males, canagliflozin increased LH levels. Overall, these findings are consistent with a canagliflozin-induced increase in LH, possibly due to primary hypogonadism, as the etiology for LCT formation in rats treated with canagliflozin	Using archived specimens from males at baseline and the end of trial visit from a 12-week Phase 2 trial in subjects with T2DM, LH and testosterone were measured. Canagliflozin at doses of 100 mg and 300 mg was not associated with increases in LH or decreases in testosterone in these men. Based on nonclinical and clinical data, canagliflozin-induced LCTs in rats are deemed to be of no clinical relevance based on the following findings: canagliflozin is not genotoxic, canagliflozin causes LCTs in a single species (rats); LCTs caused by agents leading to carbohydrate malabsorption (eg, lactose) in rats have not been shown to be of relevance to human safety, and moreover, canagliflozin does not cause glucose malabsorption in humans; canagliflozin causes increases in LH, a Leydig cell mitogen known to cause LCTs in rats; and canagliflozin, indirectly by increasing LH, causes LCTs

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
	in rats, but does not increase LH in male subjects with T2DM treated with canagliflozin.
Pheochromocytomas and Renal Tubule Tumors In a 2-year oral carcinogenicity study in Sprague-Dawley rats administered 10, 30, or 100 mg/kg canagliflozin, an increased incidence of pheochromocytomas and renal tubule tumors were observed at the high dose level in males and females. Spontaneous pheochromocytomas occur relatively commonly in rats (particularly in male rats) in a strain-dependent fashion but are uncommon in humans. In rats, pheochromocytomas occur in association with a range of non-genotoxic structurally unrelated agents and medications (none of which has been associated with an increased incidence of pheochromocytomas in humans). In rats, pheochromocytomas are caused by agents associated with carbohydrate malabsorption, such as alpha glucosidase inhibitors (acarbose) and diets with indigestible sugars (eg, lactose). Induction of adrenal medullary tumors in rats by non-genotoxic agents is thought to reflect an exacerbation of the innate proclivity of the rat to spontaneously develop these tumors. Acarbose, an alpha glucosidase inhibitor associated with carbohydrate malabsorption, caused strain-specific (Sprague-Dawley) renal tubule tumors in rats but not in another species. Separating dosing from feeding to reduce carbohydrate malabsorption prevented acarbose-induced renal tubule tumor formation. Under treatment conditions causing pheochromocytomas and renal tubule tumors in rats, canagliflozin is associated with carbohydrate (glucose/galactose) malabsorption. Sodium-glucose co-transporter-1 is a sodium/glucose co-transporter expressed on the luminal surface of enterocytes and is responsible for glucose/galactose absorption. In rats, canagliflozin exposures to the intestinal lumen following oral administration and prior to its absorption appear to be sufficient to inhibit SGLT1 and lead to glucose malabsorption. Consistent with induction of glucose/galactose malabsorption, decreases in pH and increases in glucose content are found in the distal gastrointestinal tract in canagliflozin-treated rats. Due to fermentation in the distal intestine and the reduction in pH, canagliflozin-induced glucose malabsorption increases calcium solubility and enhances calcium absorption. Substantial dose-related increases (up to 18-fold at the high dose) in urinary calcium were seen in canagliflozin-treated	In clinical trials, to assess whether canagliflozin leads to glucose malabsorption, 2 sensitive techniques were applied: radio-labelled glucose absorption and a hydrogen breath test. At the highest proposed labelled dose (300 mg) using radio-labelled glucose absorption, and at 2-times the highest proposed labelled dose (300 mg twice daily) using hydrogen breath test, canagliflozin did not cause glucose malabsorption. Clinical symptoms indicative of carbohydrate malabsorption (eg, diarrhea) were not increased, relative to control, in subjects treated with canagliflozin in the Phase 3 program. Based on nonclinical and clinical data, canagliflozin-induced pheochromocytomas and renal tubule tumors in rats are deemed not to be of clinical relevance based on the following findings: canagliflozin is not genotoxic, canagliflozin causes these tumors in a single species, pheochromocytomas and renal tubule tumors caused by agents leading to carbohydrate-malabsorption (eg, lactose, acarbose) in rats have not been shown to be of relevance to human safety, and canagliflozin, indirectly by inducing carbohydrate malabsorption in rats, causes cell proliferation in adrenal medullary and renal tubule cells, a necessary step in tumor formation, but does not cause carbohydrate-malabsorption in humans (at a dose twice the top proposed daily dose).

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
rats, relative to vehicle control. Increase in intestinal absorption of radio-labelled calcium was demonstrated in canagliflozin-treated rats. To assess if carbohydrate malabsorption was associated with canagliflozin-induced pheochromocytoma and renal tubule tumor formation in rats, the effects of preventing carbohydrate malabsorption in rats treated with canagliflozin under conditions causing pheochromocytomas and renal tubule tumors on proliferation of adrenal medullary and renal tubule cells, a proximate step in tumor formation were examined. Dietary conditions (ie, glucose/galactose-free fructose diet) that prevented carbohydrate malabsorption and increases in urinary calcium excretion also inhibited canagliflozin-mediated increases in adrenal medullary and renal tubule cell proliferation, indicating that pheochromocytomas and renal tubule tumors are due to indirect effects of canagliflozin-induced on carbohydrate malabsorption and not due to a direct effect of canagliflozin on the adrenal gland or kidney. Thus, canagliflozin-induced pheochromocytomas and renal tubule tumors were only seen in rats and are due to glucose/galactose malabsorption.	
<u>General safety pharmacology findings</u>:	
Phototoxicity Canagliflozin was phototoxic in vitro in mouse fibroblasts and phototoxic to the skin (≥50 mg/kg) but not the eye (500 mg/kg) of pigmented rats after a single oral dose. Canagliflozin was negative for photomutagenicity in a photo-Ames test.	Based upon nonclinical findings, Phase 1 clinical photosensitivity trials were conducted. Using wavebands representing the terrestrial solar spectrum and at irradiances 30-fold greater than natural sunlight, canagliflozin 300 mg once daily for 6 days was not associated with evidence of delayed photosensitivity reactions (the usual basis for clinically important photosensitivity manifest as an exaggerated erythematous response to sunlight [sunburn]); however, an immediate phototoxicity response (local swelling, redness) was observed within 30 minutes of light exposure. This immediate response was markedly attenuated or avoided when the phototest irradiance was reduced to from 30- to 3-fold above the irradiance of the most intense natural light or lighting used in tanning beds. This irradiance-dependent response suggested that the immediate phototoxicity response was unlikely to be of clinical relevance since people would not be exposed to the high irradiances

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
	used in the phototest trials.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy Use in nursing mothers

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

Canagliflozin is being developed globally by Janssen Research & Development, LLC (JRD), except in the following countries: Japan, Taiwan, and Indonesia, where the applicant's partner, Mitsubishi Tanabe Pharma Corporation (MTPC), is conducting an independent clinical development program under different development timelines. Trials conducted by MTPC, are CCI by a CCI. The full protocol number for all trials conducted by JRD in this EU-RMP begins with the prefix of "28431754" (the applicant's CCI CCI). For brevity, these trials are referred to throughout the EU-RMP without the numeric prefix (eg, trial 28431754DIA2001 is referred to as DIA2001).

Canagliflozin is being developed as a single-entity product and as a fixed-dose combination (FDC) product with metformin HCl immediate release (referred to as the canagliflozin/metformin HCl FDC or VOKANAMET). The trials completed to date include an evaluation of canagliflozin in special populations, including older adults with T2DM, subjects with T2DM who had moderate renal impairment, subjects with diabetic nephropathy, subjects with T2DM who had or were at high risk for cardiovascular disease, and subjects with hypertension.

The efficacy of canagliflozin for glycemic control in adults with insufficiently controlled T2DM as well as its demonstration as a safe and efficacious agent in adults with T2DM who had or were at high risk for cardiovascular disease is based on data from 14 Phase 3/4 trials. The demonstration that canagliflozin is a safe and efficacious agent in adults with T2DM and DKD is based on data from the Phase 3 trial, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial. Together, these 15 Phase 3/4 trials support the evidence for safety of canagliflozin in the target indication.

The evidence for the efficacy and safety of the canagliflozin/metformin HCl FDC in the target indication, ie, use in adults with T2DM who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients who are already treated with both canagliflozin and metformin, is primarily derived from 9 of the 15 Phase 3/4 trials conducted for the single-entity product, which evaluated once daily administration of canagliflozin 100 mg or 300 mg in subjects with T2DM on the background of metformin (alone or in combination with another AHA). These 9 Phase 3/4 trials include 8 trials in subjects on a defined AHA background of either metformin alone (in 3 trials: DIA3006, DIA3009, and DIA3011), metformin in combination with another AHA (in 4 trials: DIA3002, DIA3012, DIA3014, and DIA3015), or metformin in combination with sitagliptin (in 1 trial: DIA4004). The ninth Phase 3 trial offering primary support for the canagliflozin/metformin HCl FDC is the Insulin Substudy of DIA3008/Population 3 (CANVAS, Canagliflozin cardiovascular Study). The DIA3008 Insulin Substudy examined the use of canagliflozin as add-on therapy in subjects on insulin alone or in combination with other oral AHA and had a prespecified analysis of the efficacy and safety of the addition of canagliflozin to subjects on insulin and metformin (referred to as Population 3 of this substudy).

SIII.2. Clinical Trial Exposure

SIII.2.1 Clinical Trial Exposure: Canagliflozin (Single-agent)

For this RMP, the safety of canagliflozin (referred to as "CANA" in the tables) was evaluated in 22,645 patients with T2DM in the Phase 3/4 program, including 13,278 patients treated with canagliflozin and 9,367 patients treated with comparator in 15 double-blind, controlled Phase 3/4 clinical trials. A total of 10,134 patients were treated in two dedicated long-term cardiovascular safety studies, followed for a mean of 188 weeks (mean of 296 weeks in CANVAS and 108 weeks in CANVAS-R), and 8,114 patients treated in 12 double-blind, controlled Phase 3 and Phase 4 clinical studies, followed for a mean of 48 weeks. A total of 4,397 patients with diabetic nephropathy were treated in the CREDENCE trial to evaluate renal and cardiovascular outcomes and were followed for a mean of 136 weeks.

Safety analyses were conducted in subjects who received canagliflozin as monotherapy or with add-on to other AHAs as described below.

Trial Description	Number of Subjects Treated
Monotherapy **DIA3005:** Randomized, double-blind, parallel-group trial (with a 26-week, placebo-controlled, core double-blind period plus a 26-week, active-controlled, extension double-blind period) of canagliflozin 100 mg and 300 mg as monotherapy. This trial included a separate non-placebo-controlled substudy to investigate the efficacy and safety of canagliflozin in subjects with a poorer glycemic control (baseline HbA1c value of >10.0% and ≤ 12%, referred to as the High Glycemic Substudy) who were not eligible for the main trial (the High Glycemic Substudy was not included in the pooled datasets, as there was no concurrent control group).	Main study: ALL CANA: 392 Non-CANA: 192 High Glycemic Substudy: ALL CANA: 91
Add-on to Metformin **DIA3006:** Randomized, double-blind, parallel-group trial (with a 26-week placebo- and active [sitagliptin]-controlled, core double-blind period and a 26-week active [sitagliptin]-controlled, extension double-blind period) of canagliflozin 100 mg and 300 mg as add-on therapy to metformin.	ALL CANA: 735 Non-CANA: 549
DIA3009: Randomized, double-blind, active (glimepiride)-controlled, parallel-group trial (with a 52-week core double-blind period and a 52-week extension double-blind period) of canagliflozin 100 mg and 300 mg as add-on therapy to metformin.	ALL CANA: 968 Non-CANA: 482
DIA3011: Randomized, double-blind, 5-arm, parallel-group, 26-week trial of canagliflozin (100 mg or 300 mg) in combination with metformin as initial combination therapy.	ALL CANA: 949 Non-CANA: 237
Add-on to Metformin and Sulphonylurea **DIA3002:** Randomized, double-blind, placebo-controlled, parallel-group trial (with a 26-week, core double-blind period plus a 26-week, extension double-blind period) of canagliflozin 100 mg and 300 mg as add-on therapy to metformin and sulphonylurea therapy.	ALL CANA: 313 Non-CANA: 156
DIA3014: Randomized, double-blind, placebo-controlled, 3-arm, parallel-group, 18-week trial of canagliflozin compared with placebo as add-on therapy to metformin alone or in combination with sulphonylurea.	ALL CANA: 454 Non-CANA: 226

Trial Description	Number of Subjects Treated
DIA3015: Randomized, double-blind, 52-week active (sitagliptin)-controlled trial of canagliflozin 300 mg as add-on therapy to metformin and sulphonylurea therapy.	CANA: 377 Non-CANA: 378
Add-on to Metformin and Pioglitazone **DIA3012:** Randomized, double-blind, parallel-group trial (with a 26-week, placebo-controlled, core double-blind period plus a 26-week, active [sitagliptin]-controlled, extension double-blind period) of canagliflozin 100 mg and 300 mg as add-on therapy to metformin plus pioglitazone.	ALL CANA: 227 Non-CANA: 115
Add-on to Metformin and Sitagliptin **DIA4004:** Randomized, double-blind, placebo controlled, 2-arm, parallel-group, 26-week, trial of canagliflozin (100 mg up-titrated to 300 mg) as add-on therapy to metformin and sitagliptin.	ALL CANA: 108 Non-CANA: 108
Use in Special Populations **DIA3004:** Moderate Renal Impairment: Randomized, double-blind, placebo-controlled, parallel-group trial (with a 26-week, core double-blind period plus a 26-week, extension double-blind period) of canagliflozin 100 mg and 300 mg in subjects with T2DM who had moderate renal impairment with an eGFR 30- to <50 mL/min/1.73 m^2.	ALL CANA: 179 Non-CANA: 90
DIA3010: Older Subjects: Randomized, double-blind, placebo-controlled, parallel-group trial (with a 26-week, core double-blind period plus a 78-week, extension double-blind period) of canagliflozin 100 mg and 300 mg in subjects with T2DM who were ≥ 55-≤ 80 years of age	ALL CANA: 477 Non-CANA: 237
DIA3008: Cardiovascular Trial (CANVAS): Randomized, double-blind, placebo-controlled, parallel-group trial of canagliflozin 100 mg and 300 mg in subjects with T2DM, on a wide range of current diabetes treatments (diet/exercise or oral AHAs or insulin), who have either a history of or are high risk of cardiovascular disease. Substudies were included in the CANVAS trial to evaluate the efficacy and safety of canagliflozin 100 mg and 300 mg in subjects on specific background AHAs: 3008 Insulin Substudy*:* Placebo-controlled, 18-week substudy of canagliflozin 100 mg and 300 mg as add-on to insulin (given as monotherapy or in combination with another AHA). 3008 Sulphonylurea Substudy*:* Placebo-controlled, 18-week substudy of canagliflozin 100 mg and 300 mg as add-on to sulphonylurea therapy.	ALL CANA:2886 Non-CANA:1441
DIA4002: Hypertension: Randomized, double-blind, placebo-controlled, parallel-group, trial to evaluate efficacy, blood pressure reduction, safety, and tolerability of canagliflozin (100 mg or 300 mg) in subjects with T2DM and hypertension (6-week double-blind treatment period).	ALL CANA: 113 Non-CANA: 56
DIA4003: Cardiovascular Trial (CANVAS-R): Randomized, double-blind, parallel, placebo-controlled trial of the effects of canagliflozin on renal endpoints in subjects with T2DM and an elevated risk of cardiovascular events.	ALL CANA:2904 Non-CANA:2903
DNE3001: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE): Randomized, double-blind, event-driven, placebo-controlled, multicenter study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy.	ALL CANA:2200 Non-CANA:2197

Key: AHA = antihyperglycemic agent, CANA = canagliflozin, eGFR = estimated glomerular filtration rate, T2DM = type 2 diabetes mellitus.

The Phase 3/4 data were summarized in the integrated safety analyses by different datasets, which are briefly outlined below.

Pooled Phase 3 Placebo-controlled Trials Dataset
(Short Name: **Placebo-controlled Trials Dataset [DS1]**)

This dataset included four placebo-controlled 52-week Phase 3 trials (DIA3002, DIA3005, DIA3006, and DIA3012), with data up to and including the primary endpoint for these trials (Week 26). These trials had a common core double-blind period duration (26 weeks) and a double-blind extension period (26 weeks), with similar enrollment criteria (varying only by the specific concomitant treatment for T2DM). The High Glycemic Substudy (HbA1c >10% to ≤12%) in DIA3005 was not included in this dataset because this substudy had no concomitant control group (blinded only to dose of canagliflozin). The sitagliptin treatment group in DIA3006 was not included in this dataset because the comparison in this dataset was with placebo rather than active control.

Pooled Phase 3 and Phase 4 Trials (without CANVAS, CANVAS-R, and CREDENCE)
(Short Name: **Pooled Non-CANVAS/Non-CREDENCE Dataset [DS12]**)

The 12 Phase 3/4 previously completed trials (DIA3002, DIA3004, DIA3005, DIA3010, DIA3012, DIA3014, DIA4002 DIA4004, DIA3009, DIA3011, DIA3015, and DIA3006) excluding the CANVAS Program and CREDENCE trial have been included in this summary to permit comparison of adverse event data in a population with high cardiovascular risk from a population with relatively less cardiovascular risk (ie, Non-CANVAS/Non-CREDENCE trials), which were not limited to placebo-controlled studies.

As these Non-CANVAS/Non-CREDENCE trials were generally short-term glycemic efficacy studies, the efficacy evaluation was most commonly assessed by HbA1c at either Week 26 or 52. Unlike the CANVAS Program, the populations enrolled into these trials were not enriched for patients with prior cardiovascular disease or at least 2 cardiovascular risk factors. The lower limit of the HbA1c was typically 7%, and ranged from 7.0% to 7.5%, and the upper limit ranged from 9.5% to 12%, most commonly 10.5%. Exclusions for renal function ranged from eGFRs of <50 mL/min/1.73 m^2 to <60 mL/min/1.73m^2, most commonly <55 mL/min/1.73 m^2. For the moderate renal impairment trial, the required eGFR was ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2. The duration of most trials was at least 52 weeks; two trials (DIA3009 and DIA3010) were of 104-week duration; four shorter trials, in specific populations, ranged in duration from 6 to 26 weeks.

Pooled Phase 3 Moderate Renal Impairment Subject Population Dataset
(Short Name: **Moderate Renal Impairment Dataset [DS2]**)

This dataset included subjects with moderate renal impairment (eGFR at baseline of 30-<60 mL/min/1.73 m^2) from trials DIA3004, DIA3005, DIA3008 (up to INT-6), and DIA3010. Trial DIA4003 was excluded from this pooling because adverse event collection in this study was streamlined. Subjects with eGFR values <60 mL/min/1.73 m^2 were to be excluded from

enrollment in other Phase 3 trials because of the required use of metformin as background therapy in those trials. The High Glycemic Substudy (HbA1c >10% to ≤12%) in DIA3005 was not included in this dataset because this substudy had no concomitant control group (blinded only to dose of canagliflozin). The applicable eGFR ranges (ie, contributing to this dataset) at screening for each trial were ≥30 to <50 mL/min/1.73 m^2 for trial DIA3004, ≥50 to <60 mL/min/1.73 m^2 for trial DIA3005, ≥30 to <60 mL/min/1.73 m^2 for trial DIA3008, and ≥50 to <60 mL/min/1.73 m^2 for trial DIA3010.

CANVAS through Protocol Amendment INT-6 Dataset
(Short Name: **CANVAS Through Amendment INT-6 Dataset [CANVAS INT-6]**)

This dataset included subjects from the DIA3008 trial, which enrolled subjects at increased risk for cardiovascular events, incorporating both secondary prevention (with prior cardiovascular event) and primary prevention (with at least 2 risk factors for a cardiovascular event) populations. DIA3008 recruited approximately 60% and 40% from the secondary-prevention and primary-prevention populations, respectively. Subjects were men or women with T2DM with inadequate glycemic control (HbA1c ≥7.0 and ≤10.5%), an eGFR ≥30 mL/min/1.73 m^2, and could be receiving AHA monotherapy or combination therapy, or not receiving an AHA at screening. Subjects were to receive a background of standard of care for the treatment of hyperglycemia and cardiovascular risk factors (ie, blood pressure and lipids) with trial investigators counselled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate. From the beginning of the trial until Amendment INT-6 all adverse events (both serious and non-serious) were collected. After Amendment INT-6, adverse event collection was streamlined, with the exception of selected adverse events of interest. The CANVAS INT-6 dataset is the best reflection of any adverse events where collection was streamlined after the amendment.

Pooled CANVAS and CANVAS-R Dataset
(Short Name: **The CANVAS Integrated Dataset [CANVAS/CANVAS-R]**)

This dataset included subjects from trials DIA3008 and DIA4003, which were of similar design and enrolled subjects who were at increased risk for cardiovascular events, incorporating both secondary prevention (with prior cardiovascular event) and primary prevention (with at least 2 risk factors for a cardiovascular event) populations. DIA3008 recruited approximately 60% and 40% from the secondary prevention and primary-prevention populations, respectively. DIA4003 recruited approximately 70% and 30% from the secondary-prevention and primary prevention populations, respectively. Subjects were men or women with T2DM with inadequate glycemic control (HbA1c ≥7.0 and ≤10.5%), an eGFR ≥30 mL/min/1.73m^2, and could be receiving AHA monotherapy or combination therapy, or not receiving an AHA at screening. Subjects were to receive a background of standard of care for the treatment of hyperglycemia and cardiovascular risk factors (ie, blood pressure and lipids) with trial investigators counselled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

CREDENCE Dataset
(Short Name: **CREDENCE Dataset [CREDENCE]**)

This dataset included subjects from the DNE3001 trial, which enrolled subjects with diabetic nephropathy (TD2M with Stage 2 or 3 DKD and albuminuria) who were receiving standard of care. Subjects were men or women ≥30 years-old with T2DM with an HbA1c ≥6.5% to ≤12.0%, an eGFR ≥30 to <90 mL/min/1.73 m^2 (as determined using the Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] equation), and a urine albumin-to-creatinine ratio of >300 mg/g to ≤5,000 mg/g (>33.9 mg/mmol-≤565.6 mg/mmol). Subjects were to receive a background of standard of care including a stable maximum tolerated labeled daily dose of an ACEi or ARB for at least 4 weeks before randomization. Subjects were randomized by screening eGFR into one of three strata (ie, eGFR 30-<45, 45- <60, or 60- <90 mL/min/1.73 m^2).

CREDENCE Moderate Renal Impairment Subpopulation
(Short Name: **CREDENCE Moderate Renal Impairment Subpopulation [CREDENCE Moderate Renal Impairment]**)

This subpopulation included the subset of the subjects from the DNE3001 trial with moderate renal impairment based on screening eGFR strata assignments; ie, includes subjects from the 30 to <45 mL/min/1.73 m^2 stratum combined with those from the 45 to <60 mL/min/1.73 m^2 stratum.

Pooled Phase 3 and Phase 4 Trials (with CANVAS, CANVAS-R, and CREDENCE)
(Short Name: **Pooled Phase 3/4 Studies Dataset [DS8]**)

This dataset combined the Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12), CANVAS Integrated Dataset (CANVAS/CANVAS-R), and CREDENCE Dataset. It included a diverse population of diabetic patients, across a broad range of ages and renal function (including those with and without established diabetic nephropathy), with varied degrees of microvascular complications, and including those with and without established cardiovascular disease or multiple cardiovascular risk factors. It represented data from all 15 Phase 3/4 studies of canagliflozin and was the broadest possible pooling to allow for the assessment of less common but serious adverse events that were unlikely to have increased risk based on renal function (namely, pancreatitis).

Exposure in Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12)

Exposure to canagliflozin in the Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12) is summarized in Tables SIII.1 through SIII.4 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.1: Clinical Trial Exposure for Canagliflozin in Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	5288 (100)	4968.84
0 - <6 months	1107 (20.9)	278.23
6 - <12 months	1266 (23.9)	687.78
12 - <18 months	1802 (34.1)	1809.51
18 - <24 months	73 (1.4)	118.43
24 - <30 months	1040 (19.7)	2074.90

Note: Duration of exposure = last dose date - first dose date + 1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_D12 (EU-RMP 7.3).

Table SIII.2: Clinical Trial Exposure for Canagliflozin in Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12) by AGE GROUP AND SEX

	Men		Women	
Age category	**Persons, n (%)**	**Person-years**	**Persons, n (%)**	**Person-years**
INDICATION: T2DM				
Total	2693 (100)	2563.97	2595 (100)	2404.88
18 - <35 years	38 (1.4)	30.42	46 (1.8)	41.60
35 - <65 years	2087 (77.5)	1955.41	2018 (77.8)	1866.34
65 - <75 years	479 (17.8)	471.11	473 (18.2)	432.38
≥75 years	89 (3.3)	107.03	58 (2.2)	64.57
≥85 years	3 (0.1)	3.01	3 (0.1)	3.03

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_D12 (EU-RMP 7.3).

Table SIII.3: Clinical Trial Exposure for Canagliflozin in Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12) by ETHNIC ORIGIN

Ethnic origin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	5288 (100)	4968.84
White	3550 (67.1)	3462.31
Black or African American	277 (5.2)	243.70
Asian	1013 (19.2)	815.26
American Indian or Alaska Native	31 (0.6)	28.02
Native Hawaiian or other Pacific Islander	7 (0.1)	8.30
Multiple	39 (0.7)	51.48
Other	362 (6.8)	352.77
Unknown[a]	3 (0.1)	1.55
Not reported[b]	6 (0.1)	5.45

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
[b] The subject did not provide any information regarding ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_D12 (EU-RMP 7.3).

Table SIII.4: Clinical Trial Exposure for Canagliflozin in Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12) by BASELINE RENAL STATUS

Baseline eGFR group	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	5288 (100)	4968.84
<60 mL/min/1.73 m^2	381 (7.2)	351.70
≥60 - <90 mL/min/1.73 m^2	2657 (50.2)	2531.91
≥90 mL/min/1.73 m^2	2250 (42.5)	2085.23

Note: The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_D12 (EU-RMP 7.3).

Exposure in Moderate Renal Impairment Dataset (DS2)

Exposure to canagliflozin in the Moderate Renal Impairment Dataset (DS2) is summarized in Tables SIII.5 through SIII.8 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.5: Clinical Trial Exposure for Canagliflozin in Moderate Renal Impairment Dataset (DS2) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	704 (100)	1390.28
0 - <6 months	86 (12.2)	19.03
6 - <12 months	41 (5.8)	26.16
12 - <18 months	179 (25.4)	182.18
18 - <24 months	20 (2.8)	32.86
24 - <30 months	68 (9.7)	137.64
30 - <36 months	22 (3.1)	56.62
36 - <42 months	156 (22.2)	474.10
42 - <48 months	107 (15.2)	365.86
48 - <54 months	25 (3.6)	95.83

Note: Duration of exposure = last dose date - first dose date + 1 (in days). For subjects in DIA3008 whose last dose date was after cutoff date (07 January 2014), duration of exposure = cutoff date – first dose date +1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_D2 (EU-RMP 7.3).

Table SIII.6: Clinical Trial Exposure for Canagliflozin in Moderate Renal Impairment Dataset (DS2) by AGE GROUP AND SEX

	Men		Women	
Age category	Persons, n (%)	Person-years	Persons, n (%)	Person-years
INDICATION: T2DM				
Total	408 (100)	828.34	296 (100)	561.94
18 - <35 years	0	0	0	0
35 - <65 years	153 (37.5)	341.85	116 (39.2)	212.80
65 - <75 years	182 (44.6)	367.11	134 (45.3)	263.48
≥75 years	73 (17.9)	119.39	46 (15.5)	85.66
≥85 years	4 (1.0)	5.00	2 (0.7)	2.01

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_D2 (EU-RMP 7.3).

Table SIII.7: Clinical Trial Exposure for Canagliflozin in Moderate Renal Impairment Dataset (DS2) by ETHNIC ORIGIN

Ethnic origin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	704 (100)	1390.28
White	540 (76.7)	1071.10
Black or African American	23 (3.3)	34.73
Asian	91 (12.9)	205.55
American Indian or Alaska Native	3 (0.4)	5.00
Native Hawaiian or other Pacific Islander	4 (0.6)	8.66
Multiple	2 (0.3)	4.68
Other	40 (5.7)	57.68
Unknown[a]	1 (0.1)	2.89

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_D2 (EU-RMP 7.3).

Table SIII.8: Clinical Trial Exposure for Canagliflozin in Moderate Renal Impairment Dataset (DS2) by BASELINE RENAL STATUS

Baseline eGFR group	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	704 (100)	1390.28
<60 mL/min/1.73m^2	704 (100)	1390.28

Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_D2 (EU-RMP 7.3).

Exposure in CANVAS Through Amendment INT-6 Dataset (CANVAS INT-6)

Exposure to canagliflozin in the CANVAS through Amendment INT-6 Dataset (CANVAS INT-6) is summarized in Tables SIII.9 through SIII.12 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.9: Clinical Trial Exposure for Canagliflozin in CANVAS Through Amendment INT-6 Dataset (CANVAS INT-6) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	2886 (100)	7586.75
0 - <6 months	254 (8.8)	50.53
6 - <12 months	165 (5.7)	108.29
12 - <18 months	125 (4.3)	142.78
18 - <24 months	97 (3.4)	154.92
24 - <30 months	101 (3.5)	210.06
30 - <36 months	91 (3.2)	231.76
36 - <42 months	1095 (37.9)	3318.61
42 - <48 months	729 (25.3)	2493.59
48 - <54 months	229 (7.9)	876.20

Note: Duration of exposure = last dose date - first dose date + 1 (in days). For subjects in DIA3008 whose last dose date was after cutoff date (07 January 2014), duration of exposure = cutoff date – first dose date +1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_DC6 (EU-RMP 7.3).

Table SIII.10: Clinical Trial Exposure for Canagliflozin in CANVAS Through Amendment INT-6 Dataset (CANVAS INT-6) by AGE GROUP AND SEX

	Men		Women	
Age category	**Persons, n (%)**	**Person-years**	**Persons, n (%)**	**Person-years**
INDICATION: T2DM				
Total	1905 (100)	5068.72	981 (100)	2518.03
18 - <35 years	2 (0.1)	3.79	0	0
35 - <65 years	1136 (59.6)	3134.42	583 (59.4)	1492.51
65 - <75 years	635 (33.3)	1633.68	337 (34.4)	875.92
≥75 years	132 (6.9)	296.82	61 (6.2)	149.60
≥85 years	2 (0.1)	3.75	0	0

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_DC6 (EU-RMP 7.3).

Table SIII.11: Clinical Trial Exposure for Canagliflozin in CANVAS Through Amendment INT-6 Dataset (CANVAS INT-6) by ETHNIC ORIGIN

Ethnic origin	**Persons, n (%)**	**Person-years**
INDICATION: T2DM		
Total	2886 (100)	7586.75
White	2114 (73.3)	5660.99
Black or African American	70 (2.4)	146.34
Asian	533 (18.5)	1382.18
American Indian or Alaska Native	2 (0.1)	3.42
Native Hawaiian or other Pacific Islander	5 (0.2)	10.55
Multiple	21 (0.7)	49.17
Other	139 (4.8)	328.18
Unknown[a]	2 (0.1)	5.91

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_DC6 (EU-RMP 7.3).

Table SIII.12: Clinical Trial Exposure for Canagliflozin in CANVAS Through Amendment INT-6 Dataset (CANVAS INT-6) by BASELINE RENAL STATUS

Baseline eGFR group	**Persons, n (%)**	**Person-years**
INDICATION: T2DM		
Total	2885 (100)	7585.30
<60 mL/min/1.73 m^2	458 (15.9)	1131.74
≥60 - <90 mL/min/1.73 m^2	1734 (60.1)	4605.76
≥90 mL/min/1.73 m^2	693 (24.0)	1847.80

Note: One subject had no baseline eGFR value. The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_DC6 (EU-RMP 7.3).

Exposure in the CANVAS Integrated Dataset (CANVAS/CANVAS-R)

Exposure to canagliflozin in the CANVAS Integrated Dataset (CANVAS/CANVAS-R) is summarized in Tables SIII.13 through SIII.16 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.13: Clinical Trial Exposure for Canagliflozin in the CANVAS Integrated Dataset (CANVAS/CANVAS-R) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	5790 (100)	17989.46
0 - <6 months	395 (6.8)	80.57
6 - <12 months	281 (4.9)	184.18
12 - <18 months	267 (4.6)	303.78
18 - <24 months	1011 (17.5)	1699.82
24 - <30 months	1187 (20.5)	2463.20
30 - <36 months	590 (10.2)	1460.79
36 - <42 months	73 (1.3)	216.91
42 - <48 months	70 (1.2)	240.92
48 - <54 months	72 (1.2)	280.42
54 - <60 months	55 (0.9)	241.78
60 - <66 months	64 (1.1)	310.23
66 - <72 months	72 (1.2)	382.71
≥72 months	1653 (28.5)	10124.13

Note: Duration of exposure = last dose date - first dose date + 1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_DCV (EU-RMP 7.3).

Table SIII.14: Clinical Trial Exposure for Canagliflozin in the CANVAS Integrated Dataset (CANVAS/CANVAS-R) by AGE GROUP AND SEX

	Men		Women	
Age category	**Persons, n (%)**	**Person-years**	**Persons, n (%)**	**Person-years**
INDICATION: T2DM				
Total	3756 (100)	11880.92	2034 (100)	6108.54
18 - <35 years	4 (0.1)	6.82		
35 - <65 years	2081 (55.4)	7064.05	1143 (56.2)	3555.98
65 - <75 years	1344 (35.8)	4036.13	718 (35.3)	2132.29
≥75 years	327 (8.7)	773.92	173 (8.5)	420.27
≥85 years	11 (0.3)	18.68	4 (0.2)	8.84

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_DCV (EU-RMP 7.3).

Table SIII.15: Clinical Trial Exposure for Canagliflozin in the CANVAS Integrated Dataset (CANVAS/CANVAS-R) by ETHNIC ORIGIN

Ethnic origin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	5790 (100)	17989.46
White	4505 (77.8)	13885.32
Black or African American	175 (3.0)	383.41
Asian	777 (13.4)	2778.79
American Indian or Alaska Native	16 (0.3)	31.04
Native Hawaiian or other Pacific Islander	13 (0.2)	32.28
Multiple	30 (0.5)	99.28
Other	271 (4.7)	765.66
Unknown[a]	3 (0.1)	13.68

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_DCV (EU-RMP 7.3).

Table SIII.16: Clinical Trial Exposure for Canagliflozin in the CANVAS Integrated Dataset (CANVAS/CANVAS-R) by BASELINE RENAL STATUS

Baseline eGFR group	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	5789 (100)	17988.01
<60 mL/min/1.73 m^2	1110 (19.2)	2946.21
≥60 - <90 mL/min/1.73 m^2	3262 (56.3)	10564.32
≥90 mL/min/1.73 m^2	1417 (24.5)	4477.48

Note: One subject had no baseline eGFR value. The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_DCV (EU-RMP 7.3).

Exposure in CREDENCE Dataset (CREDENCE)

Exposure to canagliflozin in the CREDENCE Dataset is summarized in Tables SIII.17 through SIII.20 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.17: Clinical Trial Exposure for Canagliflozin in CREDENCE Dataset (CREDENCE) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	2200 (100)	4915.79
0 - <6 months	125 (5.7)	26.19
6 - <12 months	110 (5.0)	71.81
12 - <18 months	123 (5.6)	136.38
18 - <24 months	195 (8.9)	326.97
24 - <30 months	533 (24.2)	1091.47
30 - <36 months	429 (19.5)	1088.27
36 - <42 months	412 (18.7)	1224.08
42 - <48 months	228 (10.4)	777.73
48 - <54 months	40 (1.8)	151.63
54 - <60 months	5 (0.2)	21.26
60 - <66 months	0	0
66 - <72 months	0	0
≥72 months	0	0

Note: Duration of exposure = last dose date - first dose date + 1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_DNE3001_RMP.

Table SIII.18: Clinical Trial Exposure for Canagliflozin in CREDENCE Dataset (CREDENCE) by AGE GROUP AND SEX

	Men		Women	
Age category	**Persons, n (%)**	**Person-years**	**Persons, n (%)**	**Person-years**
INDICATION: T2DM				
Total	1439 (100)	3225.13	761 (100)	1690.66
18 - <35 years	2 (0.1)	2.09	3 (0.4)	5.02
35 - <65 years	769 (53.4)	1713.69	426 (56.0)	940.75
65 - <75 years	536 (37.2)	1227.99	257 (33.8)	584.80
≥75 years	132 (9.2)	281.36	75 (9.9)	160.09
≥85 years	1 (0.1)	2.24	5 (0.7)	9.59

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_DNE3001_RMP.

Table SIII.19: Clinical Trial Exposure for Canagliflozin in CREDENCE Dataset (CREDENCE) by ETHNIC ORIGIN

Ethnic origin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	2200 (100)	4915.79
White	1486 (67.5)	3393.25
Black or African American	111 (5.0)	230.73
Asian	425 (19.3)	933.22
American Indian or Alaska Native	36 (1.6)	74.01
Native Hawaiian or other Pacific Islander	9 (0.4)	20.91
Multiple	32 (1.5)	59.52
Other	95 (4.3)	196.24
Unknown[a]	1 (0.0)	1.60
Not reported[b]	5 (0.2)	6.32

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
[b] The subject did not provide any information regarding ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_DNE3001_RMP.

Table SIII.20: Clinical Trial Exposure for Canagliflozin in CREDENCE Dataset (CREDENCE) by BASELINE RENAL STATUS

Baseline eGFR group	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	2199 (100)	4913.59
<60 mL/min/1.73 m^2	1306 (59.4)	2845.12
≥60 - <90 mL/min/1.73 m^2	788 (35.8)	1811.35
≥90 mL/min/1.73 m^2	105 (4.8)	257.11

Note: One subject had no baseline eGFR value. The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_DNE3001_RMP.

Exposure in CREDENCE Moderate Renal Impairment Subpopulation (CREDENCE Moderate Renal Impairment)

Exposure to canagliflozin in the CREDENCE Moderate Renal Impairment Subpopulation (CREDENCE Moderate Renal Impairment) is summarized in Tables SIII.21 through SIII.24 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.21: Clinical Trial Exposure for Canagliflozin in CREDENCE Moderate Renal Impairment Subpopulation (CREDENCE Moderate Renal Impairment) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	1295 (100)	2837.74
0 - <6 months	84 (6.5)	18.20
6 - <12 months	70 (5.4)	46.14
12 - <18 months	85 (6.6)	94.40
18 - <24 months	122 (9.4)	205.12
24 - <30 months	314 (24.2)	643.68
30 - <36 months	235 (18.1)	598.32
36 - <42 months	222 (17.1)	660.75
42 - <48 months	130 (10.0)	445.05
48 - <54 months	31 (2.4)	117.49
54 - <60 months	2 (0.2)	8.60
60 - <66 months	0	0
66 - <72 months	0	0
≥72 months	0	0

Note: Duration of exposure = last dose date - first dose date + 1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_3001_eGFR30_60_RMP.

Table SIII.22: Clinical Trial Exposure for Canagliflozin in CREDENCE Moderate Renal Impairment Subpopulation (CREDENCE Moderate Renal Impairment) by AGE GROUP AND SEX

	Men		Women	
Age category	**Persons, n (%)**	**Person-years**	**Persons, n (%)**	**Person-years**
INDICATION: T2DM				
Total	849 (100)	1870.96	446 (100)	966.78
18 - <35 years	1 (0.1)	1.83	3 (0.7)	5.02
35 - <65 years	421 (49.6)	916.36	234 (52.5)	494.25
65 - <75 years	323 (38.0)	729.54	156 (35.0)	352.73
≥75 years	104 (12.2)	223.22	53 (11.9)	114.79
≥85 years	1 (0.1)	2.24	2 (0.4)	4.82

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_RN_3001_eGFR30_60_RMP.

Table SIII.23: Clinical Trial Exposure for Canagliflozin in CREDENCE Moderate Renal Impairment Subpopulation (CREDENCE Moderate Renal Impairment) by ETHNIC ORIGIN

Ethnic origin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	1295 (100)	2837.74
White	857 (66.2)	1901.62
Black or African American	69 (5.3)	148.13
Asian	264 (20.4)	576.87
American Indian or Alaska Native	20 (1.5)	36.83
Native Hawaiian or other Pacific Islander	4 (0.3)	8.96
Multiple	18 (1.4)	36.04
Other	57 (4.4)	121.38
Unknown[a]	1 (0.1)	1.60
Not reported[b]	5 (0.4)	6.32

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
[b] The subject did not provide any information regarding ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_RN_3001_eGFR30_60_RMP.

Table SIII.24: Clinical Trial Exposure for Canagliflozin in CREDENCE Moderate Renal Impairment Subpopulation (CREDENCE Moderate Renal Impairment) by BASELINE RENAL STATUS

Baseline eGFR group	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	1294 (100)	2835.54
<60 mL/min/1.73 m^2	1167 (90.2)	2532.15
≥ 60 - <90 mL/min/1.73 m^2	118 (9.1)	280.87
≥ 90 mL/min/1.73 m^2	9 (0.7)	22.51

Note: One subject had no baseline eGFR value. The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_RN_3001_eGFR30_60_RMP.

Exposure in Pooled Phase 3/4 Studies Dataset (DS8)

Exposure to canagliflozin in the Pooled Phase 3/4 Studies Dataset (DS8) is summarized in Tables SIII.25 through SIII.28 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.25: Clinical Trial Exposure for Canagliflozin in Pooled Phase 3/4 Studies Dataset (DS8) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	13278 (100)	27874.09
0 - <6 months	1627 (12.3)	384.99
6 - <12 months	1657 (12.5)	943.78
12 - <18 months	2192 (16.5)	2249.66
18 - <24 months	1279 (9.6)	2145.23
24 - <30 months	2760 (20.8)	5629.57
30 - <36 months	1019 (7.7)	2549.06
36 - <42 months	485 (3.7)	1440.99
42 - <48 months	298 (2.2)	1018.65
48 - <54 months	112 (0.8)	432.05
54 - <60 months	60 (0.5)	263.03
60 - <66 months	64 (0.5)	310.23
66 - <72 months	72 (0.5)	382.71
≥72 months	1653 (12.4)	10124.13

Note: Duration of exposure = last dose date - first dose date + 1 (in days). One month = 28 days; One year = 365.25 days.

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_D8_RMP.

Table SIII.26: Clinical Trial Exposure for Canagliflozin in Pooled Phase 3/4 Studies Dataset (DS8) by AGE GROUP AND SEX

	Men		Women	
Age category	**Persons, n (%)**	**Person-years**	**Persons, n (%)**	**Person-years**
INDICATION: T2DM				
Total	7888 (100)	17670.02	5390 (100)	10204.08
18 - <35 years	44 (0.6)	39.32	49 (0.9)	46.62
35 - <65 years	4937 (62.6)	10733.15	3587 (66.5)	6363.07
65 - <75 years	2359 (29.9)	5735.23	1448 (26.9)	3149.47
≥75 years	548 (6.9)	1162.32	306 (5.7)	644.93
≥85 years	15 (0.2)	23.93	12 (0.2)	21.45

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_D8_RMP.

Table SIII.27: Clinical Trial Exposure for Canagliflozin in Pooled Phase 3/4 Studies Dataset (DS8) by ETHNIC ORIGIN

Ethnic origin	**Persons, n (%)**	**Person-years**
INDICATION: T2DM		
Total	13278 (100)	27874.09
White	9541 (71.9)	20740.88
Black or African American	563 (4.2)	857.84
Asian	2215 (16.7)	4527.27
American Indian or Alaska Native	83 (0.6)	133.07
Native Hawaiian or other Pacific Islander	29 (0.2)	61.49
Multiple	101 (0.8)	210.28
Other	728 (5.5)	1314.67
Unknown[a]	7 (0.1)	16.83
Not reported[b]	11 (0.1)	11.77

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
[b] The subject did not provide any information regarding ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_D8_RMP.

Table SIII.28: Clinical Trial Exposure for Canagliflozin in Pooled Phase 3/4 Studies Dataset (DS8) by BASELINE RENAL STATUS

Baseline eGFR group	**Persons, n (%)**	**Person-years**
INDICATION: T2DM		
Total	13276 (100)	27870.44
<60 mL/min/1.73 m^2	2797 (21.1)	6143.03
≥ 60 - <90 mL/min/1.73 m^2	6707 (50.5)	14907.58
≥ 90 mL/min/1.73 m^2	3772 (28.4)	6819.83

Note: Two subjects had no baseline eGFR value. The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_D8_RMP.

SIII.2.2 Clinical Trial Exposure: Canagliflozin/Metformin HCl FDC

To bridge the results from the canagliflozin Phase 3 program (that examined once-daily dosing of 100 and 300 mg) to support the canagliflozin/metformin HCl FDC tablet (that is to be administered

bid, at the total daily doses of 100 mg and 300 mg canagliflozin) for the requested indication, the following additional trials were conducted: (1) Phase 1 trials showing the bioequivalence of the canagliflozin/metformin HCl FDC tablet to the individual components (DIA1038, DIA1039, DIA1051, and DIA1052); (2) trial DIA1037 evaluating the to-be-marketed canagliflozin/metformin HCl FDC that showed that food did not affect canagliflozin bioavailability following single-dose administration of the 150/1,000 mg canagliflozin/metformin HCl FDC tablet; (3) a Phase 1 trial (DIA1032) that demonstrated that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 or 300 mg) regardless of once- or twice-daily administration; (4) a relative bioavailability trial (DIA1036) that served as a pilot for the 4 Phase 1 bioequivalence trials; (5) a drug-drug interaction trial (DIA1028) with canagliflozin and metformin, and (6) a Phase 2 18-week trial in subjects with T2DM (DIA2003) showing comparable efficacy and safety/tolerability with bid administered canagliflozin (at total daily doses of 100 and 300 mg) in add-on use to metformin, as had been previously observed in the Phase 3 trials evaluating canagliflozin as add-on therapy to metformin.

The Pooled Non-CANVAS/Non-CREDENCE Dataset (DS12) and CANVAS Integrated Dataset (CANVAS/CANVAS-R) were used to generate a dataset of the subset of subjects who were on a background of metformin. This dataset was referred to as the Pooled Phase 3/4 Studies Dataset-Metformin (DS6M). The purpose of this dataset was the assessment of adverse events of lactic acidosis, a labeled adverse drug reaction (ADR) for metformin.

The occurrence of lactic acidosis was also assessed in the CREDENCE Dataset. Events of lactic acidosis were not assessed in a pooled dataset since patients with DKD are at increased risk for acidosis, and a pooled assessment could dilute a potential increase in risk in the CREDENCE population. Because of this increased risk for acidosis, all subjects in the CREDENCE dataset, not just those receiving metformin, were included in this assessment.

Pooled Phase 3 and Phase 4 Trials in Subjects on Metformin Background (with CANVAS and CANVAS-R)
(Short Name: **Pooled Phase 3/4 Studies Dataset-Metformin [DS6M]**)

This dataset included the subset of subjects who were on a background of metformin from 12 Phase 3/4 Non-CANVAS/Non-CREDENCE trials (DIA3002, DIA3004, DIA3005, DIA3010, DIA3012, DIA3014, DIA4002 DIA4004, DIA3009, DIA3011, DIA3015, and DIA3006) and 2 Phase 3/4 trials in the CANVAS Integrated Dataset (CANVAS/CANVAS-R). The majority of subjects from trials DIA3004 and DIA3005, which disallowed background metformin therapy were excluded from this dataset, with the exception of 4 subjects (3 in the canagliflozin group and 1 in the non-canagliflozin group) who took metformin in DIA3004. Five of the trials included in this dataset (DIA3002, DIA3006, DIA3009, DIA3012, and DIA3015) were limited to enrolling patients on maximally effective dose of metformin (on a dose of ≥2,000 mg/day, or ≥1,500 mg/day, if unable to tolerate a higher dose), DIA3014 required metformin doses of ≥1,500 mg/ day, DIA3011 added metformin and uptitrated to the maximally effective dose (up to 2,000 mg/day) during the trial, and 5 other trials (DIA3008, DIA3010, DIA4002, DIA4003, and DIA4004) were open to any background AHA medication. Overall, this dataset comprised of 76%

of subjects included in the 14 Phase 3/4 trials, and had similar baseline demographic and disease characteristics compared to subjects who were not on a background of metformin. This dataset was used to provide further information on adverse event experience with canagliflozin on a background of metformin with longer-term exposure and in support of analyses of specific adverse events (namely, lactic acidosis) where a longer duration of exposure is particularly important.

Exposure in Pooled Phase 3/4 Studies Dataset-Metformin (DS6M)

Exposure to canagliflozin in the Pooled Phase 3/4 Studies Dataset-Metformin (DS6M) is summarized in Tables SIII.29 through SIII.32 for all subjects by duration, by age and sex, by race, and by baseline renal status.

Table SIII.29: Clinical Trial Exposure for Canagliflozin in Background of Metformin in Pooled Phase 3/4 Studies Dataset-Metformin (DS6M) by DURATION

Duration of exposure - canagliflozin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	8152 (100)	17708.30
0 - <6 months	1232 (15.1)	300.71
6 - <12 months	559 (6.9)	359.95
12 - <18 months	1531 (18.8)	1565.27
18 - <24 months	866 (10.6)	1457.11
24 - <30 months	1938 (23.8)	3942.10
30 - <36 months	483 (5.9)	1195.28
36 - <42 months	54 (0.7)	160.73
42 - <48 months	47 (0.6)	161.84
48 - <54 months	47 (0.6)	184.33
54 - <60 months	31 (0.4)	135.47
60 - <66 months	41 (0.5)	200.04
66 - <72 months	56 (0.7)	297.59
≥72 months	1267 (15.5)	7747.88

Note: Duration of exposure = last dose date - first dose date + 1 (in days). One month = 28 days; One year = 365.25 days.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP01_D6M (EU-RMP 7.3).

Table SIII.30: Clinical Trial Exposure for Canagliflozin in Background of Metformin in Pooled Phase 3/4 Studies Dataset-Metformin (DS6M) by AGE GROUP AND SEX

	Men		Women	
Age category	Persons, n (%)	Person-years	Persons, n (%)	Person-years
INDICATION: T2DM				
Total	4817 (100	11190.58	3335 (100)	6517.72
18 - <35 years	23 (0.5)	24.93	24 (0.7)	28.59
35 - <65 years	3162 (65.6)	7166.24	2350 (70.5)	4359.17
65 - <75 years	1378 (28.6)	3471.36	822 (24.6)	1840.05
≥75 years	254 (5.3)	528.06	139 (4.2)	289.91
≥85 years	5 (0.1)	8.59	3 (0.1)	5.21

Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP02_D6M (EU-RMP 7.3).

Table SIII.31: Clinical Trial Exposure for Canagliflozin in Background of Metformin in Pooled Phase 3/4 Studies Dataset-Metformin (DS6M) by ETHNIC ORIGIN

Ethnic origin	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	8152 (100)	17708.30
White	5774 (70.8)	13278.32
Black or African American	321 (3.9)	436.75
Asian	1529 (18.8)	2925.60
American Indian or Alaska Native	31 (0.4)	41.67
Native Hawaiian or other Pacific Islander	17 (0.2)	35.40
Multiple	56 (0.7)	116.42
Other	416 (5.1)	860.24
Unknown[a]	3 (0.0)	8.95
Not reported[b]	5 (0.1)	4.95

[a] The subject was unable to categorize themselves in any of the above categories of ethnic origin.
[b] The subject did not provide any information regarding ethnic origin.
Key: T2DM = type 2 diabetes mellitus.
Source: TSIEXP03_D6M (EU-RMP 7.3).

Table SIII.32: Clinical Trial Exposure for Canagliflozin in Background of Metformin in Pooled Phase 3/4 Studies Dataset-Metformin (DS6M) by BASELINE RENAL STATUS

Baseline eGFR group	Persons, n (%)	Person-years
INDICATION: T2DM		
Total	8152 (100)	17708.30
<60 mL/min/1.73 m^2	735 (9.0)	1592.92
≥60 - <90 mL/min/1.73 m^2	4518 (55.4)	10510.82
≥90 mL/min/1.73 m^2	2899 (35.6)	5604.56

Note: The % in each subcategory may not add up to 100% due to rounding.
Key: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.
Source: TSIEXP04_D6M (EU-RMP 7.3).

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

The majority of exclusion criteria were established in order to not confound the assessment of safety and efficacy or to prevent enrollment of subjects with conditions for whom participation in a clinical trial would not be in their best interest. Important exclusion criteria in the clinical development program are discussed below. Criteria #1 to #5 are not listed as contraindications in the SmPC but are subpopulations in which canagliflozin is not recommended for use, as documented in Posology and Method of administration (Section 4.2), Special warnings and precautions for use (Section 4.4) or Fertility, pregnancy and lactation (Section 4.6).

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Type 1 diabetes mellitus**
Reason for being an exclusion criterion	The safety and efficacy of canagliflozin in patients with T1DM have not been established. Limited data from clinical trials suggest that DKA occurs more frequently in patients with T1DM as compared to T2DM when treated with canagliflozin.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	Type 1 diabetes mellitus is not relevant for the approved indication. INVOKANA and VOKANAMET are indicated in adults with T2DM. Although not listed as a contraindication in the SmPC, T1DM is among the subpopulations in which canagliflozin and canagliflozin/metformin is not recommended for use, as stated in Special warnings and precautions for use (Section 4.4). Canagliflozin should not be used for treatment of patients with T1DM.
Criterion 2	**Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, end-stage kidney disease, and patients on dialysis**
Reason for being an exclusion criterion	The glycemic efficacy of canagliflozin is dependent upon renal function and its efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Yes/No	
Rationale (if not included as missing information)	The use of INVOKANA and VOKANAMET for glycemic control in the population of patients eGFR <30 mL/min/1.73 m^2, end-stage kidney disease, or patients on dialysis is not in alignment with dosing recommendations for these products. The Periodic Safety Update Report (PSUR) evaluation has not identified new safety issues in these patient populations and there is no reasonable expectation that future pharmacovigilance activities could further characterize the safety profile of the product with respect to these areas of missing information.
Criterion 3	**Patients <18 years of age**
Reason for being an exclusion criterion	There are currently no safety or efficacy data to support the use of canagliflozin in the pediatric population. The safety and efficacy of canagliflozin/metformin HCl FDC in children under 18 years of age have not been established.
Considered to be included as missing information	No
Yes/No	
Rationale (if not included as missing information)	Currently canagliflozin is only indicated in adults.
Criterion 4	**Pregnancy/Nursing mothers**
Reason for being an exclusion criterion	There are currently no safety or efficacy data to support the use of canagliflozin during pregnancy/breast-feeding. Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued. Canagliflozin should not be used during breast-feeding. There are no data to support the use of canagliflozin/metformin HCl FDC during pregnancy/breast-feeding. Canagliflozin/metformin HCl FDC should not be used during pregnancy/breast-feeding.
Considered to be included as missing information	Yes (Use in pregnancy, Use in nursing mothers)
Yes/No	
Rationale (if not included as missing	Not applicable

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

information)	
Criterion 5	**Severe hepatic impairment**
Reason for being an exclusion criterion	There are currently no safety or efficacy data to support the use of canagliflozin in patients with severe hepatic impairment. Canagliflozin is not recommended for use in these patients. Canagliflozin/metformin HCl FDC is not recommended in patients with hepatic impairment due to the active substance metformin. There is no clinical experience with canagliflozin/metformin HCl FDC in patients with hepatic impairment. Canagliflozin/metformin HCl FDC is contraindicated in patients with hepatic impairment.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	The PSUR evaluation has not identified new safety issues in this patient population and there is no reasonable expectation that future pharmacovigilance activities could further characterize the safety profile of the product with respect to this area of missing information. Section 4.2 of the SmPC states that canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.
Criterion 6	**Alanine aminotransferase level >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at screening (or clinically active liver disease)**
Reason for being an exclusion criterion	These values are suggestive of ongoing liver disease, warranting further investigation and/or treatment
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	Currently available data support the assessment that there is no evidence of direct or dose-related hepatotoxicity associated with canagliflozin. No dose adjustment is required for patients with mild or moderate hepatic impairment.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 7	**Congestive heart failure New York Heart Association (NYHA) class IV**
Reason for being an exclusion criterion	Patients with advanced disease (other than studied indication) are excluded from clinical trials due to their potential vulnerability to an agent whose safety had not yet been fully characterized. Subjects with congestive heart failure NYHA class I, II, and III were enrolled within the Phase 3 development program. Events of congestive heart failure leading to hospitalization were adjudicated and the incidence of these events was numerically lower in canagliflozin-treated subjects compared with non-canagliflozin-treated subjects.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	The PSUR evaluation has not identified new safety issues in this patient population and there is no reasonable expectation that future pharmacovigilance activities could further characterize the safety profile of the product with respect to this area of missing information.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The canagliflozin clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

Clinical data are available in subjects with long-term exposure to canagliflozin (mean of 110 weeks [DS8]). Long-term cardiovascular safety was prospectively evaluated in two long-term safety trials (CANVAS/CANVAS-R (mean exposure of 149 weeks, 162 weeks for canagliflozin, and 132 weeks for placebo) where major adverse cardiovascular events (MACE) endpoints were independently adjudicated in a blinded fashion. In addition, a total of 2,200 patients with diabetic nephropathy were exposed to canagliflozin (mean of 117 weeks) in the CREDENCE study to evaluate renal and cardiovascular outcomes. Therefore, the clinical development program is likely to be able to detect adverse reactions following prolonged or cumulative exposure, and adverse reactions with a long latency. Evaluation of the safety profile of canagliflozin following longer exposure did not reveal any adverse reactions in addition to those previously identified.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women Breast-feeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Canagliflozin has not been studied in patients with severe hepatic impairment. There is no clinical experience with canagliflozin/metformin HCl FDC in patients with hepatic impairment, as the combination product is not recommended in these patients due to the active substance metformin.
• Patients with renal impairment	In the CREDENCE dataset, canagliflozin was studied in T2DM patients with renal impairment (eGFR ≥30- <90 mL/min/1.73 m^2) and albuminuria. Of 2,201 subjects who were randomized to canagliflozin and had a baseline eGFR in the CREDENCE trial, 1,308 subjects had an eGFR <60 mL/min/1.73 m^2 at baseline. Of these, 84 subjects had an eGFR <30 mL/min/1.73 m^2 at baseline, including 1 subject with a baseline eGFR <15 mL/min/1.73 m^2. Post baseline, a total of 929 subjects (417 in the canagliflozin treatment group and 512 in the placebo treatment group) randomized in the CREDENCE study continued with canagliflozin treatment per protocol and had a final on-treatment eGFR <30 mL/min/1.73 m^2. While this was not a randomized cohort, subject demographic and baseline characteristics were well balanced between treatment groups. No additional safety concerns were observed in these subjects and the findings were consistent with those seen in the overall study population. Of 5,794 subjects in the CANVAS Integrated dataset who were randomized to canagliflozin and had a baseline eGFR, 1,110 subjects had an eGFR <60 mL/min/1.73 m^2 at baseline. In the CANVAS Integrated dataset, a total of 331 subjects had an eGFR <30 mL/min/1.73 m^2 at baseline and/or at any post-baseline assessment. At baseline, there were 11 of 5,794 subjects in the canagliflozin group and 17 of 4,346 subjects in the placebo group with severe renal impairment. Post baseline, an eGFR <30 mL/min/1.73 m^2 occurred in 188 subjects (incidence rate: 10.24 events per 1,000 subject-years) and 116 subjects (incidence rate: 10.30 events per 1,000 subject-years) in the canagliflozin and placebo groups, respectively. Patients with eGFR <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based upon restriction of metformin use in the metformin local label) were excluded from the other trials supportive of canagliflozin/metformin HCl FDC.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
• Patients with cardiovascular impairment	There is no experience in clinical trials with canagliflozin in patients with NYHA class IV. Canagliflozin/metformin HCl FDC is contraindicated in patients with acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, or shock.
• Patients with a history of being HIV antibody positive.	Not included in the clinical development program
• Patients with current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent.	
• Patients with a disease severity different from inclusion criteria in clinical trials	The effect of canagliflozin was not studied in patients with HbA1c >12%. Safety of canagliflozin was studied in 91 patients with high baseline HbA1c >10% and ≤ 12% randomized to canagliflozin 100 mg or 300 mg (Mod5.3.5.1\DIA3005). Subjects experienced clinically meaningful reductions in HbA1c from baseline to Week 26 with mean changes of 2.2% and 2.6%, respectively, for the canagliflozin 100 mg and 300 mg dose groups. The overall incidence of adverse events and serious adverse events were similar in both canagliflozin groups, and were similar to those observed in canagliflozin-treated subjects in the Main Study part of trial DIA3005.
Population with relevant different ethnic origin	Of the 13,278 canagliflozin-treated subjects in the Pooled Phase 3/4 Studies Dataset (DS8), 9,541 (71.9%) were white, 563 (4.2%) were black, 2,215 (16.7%) were Asian, and 941 (7.1%) subjects were of other or mixed racial background or ethnicity; for 18 (0.1%) subjects, race/ethnicity was unknown or not reported. There is no evidence to indicate that efficacy or safety of canagliflozin or canagliflozin/metformin HCl FDC may be affected by race or ethnicity.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	The enzymes responsible for canagliflozin metabolism are UGT1A9 and UGT2B4, which are known to show genetic polymorphism. Given the minimal impact of UGT2B4 or UGT1A9 polymorphisms other than the UGT1A9*3 allele on canagliflozin exposures based on an initial analysis, only the wildtype and UGT1A9*3 alleles were examined in a pharmacogenomics exposure analysis using data from 2 Phase 3 trials (DIA3005 and DIA3009). A 26-54% increase in canagliflozin plasma AUC was shown in the UGT1A9*3 carriers compared with subjects carrying the wildtype. As increases in canagliflozin steady-state AUC24h by up to 118% compared with that for a 300-mg qd canagliflozin dose was considered to be safe and well tolerated (based on the population pharmacokinetic predictions and the safety data from 12-week Phase 2 trial (DIA2001), the above AUC increases observed in UGT1A9*3 carriers are not considered to be clinically relevant. UGT1A9 genotyping was performed in 2 Phase 3 trials (DIA3005 [placebo-controlled monotherapy trial] and DIA3009 [active-controlled {glimepiride}, add-on to metformin trial]) in a subgroup of subjects who consented to genotyping. Given the low incidence of UGT1A9*3 carriers (44 subjects across the 2 trials), safety data from the 2 trials were pooled. Hence, given the relatively small number of UGT1A9*3 carrier comparison to the overall population should be viewed with caution. In UGT1A9*3 carriers, no notable increase in the overall incidences of adverse events or in adverse events related to study drug in subjects treated with canagliflozin, relative to placebo or glimepiride. A very low incidence of serious adverse events or adverse events leading to discontinuation, similar to that of non UGT1A9*3 carriers, were reported in UGT1A9*3 carriers. There are no polymorphisms of SGLT2 that are known to affect its function.
Children and adolescents ≥10-<18 years of age	The safety of canagliflozin and canagliflozin/metformin HCl FDC in pediatric patients (ie, in children <18 years of age) has not been established. A waiver has been granted for canagliflozin in patients <10 years of age as the disease/condition does not occur in this population subset. A waiver across the entire pediatric population has been granted for canagliflozin/metformin HCl FDC on the grounds that canagliflozin/metformin HCl FDC product would not provide significant therapeutic benefit over existing therapies in this pediatric population due to the anticipated availability of the individual components. A pediatric Phase 1 trial examined the pharmacokinetics and pharmacodynamics of canagliflozin in 17 children and adolescents ≥10- <18 years of age with T2DM. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Elderly	A limited number of very elderly patients (ie, ≥85 years of age) were enrolled in the canagliflozin and canagliflozin/metformin HCl FDC clinical development programs. Data regarding the risks associated with use of canagliflozin in very elderly patients (≥85 years) are therefore limited. Canagliflozin: Of the 13,278 canagliflozin-treated subjects in the Pooled Phase 3/4 Studies Dataset, 4,661 (35.1%) were ≥65 years, 854 (6.4%) were ≥75 years, and 27 (0.2%) were ≥85 years. Canagliflozin/Metformin HCl FDC: Of the 9,427 subjects who received both canagliflozin and metformin in the Pooled Phase 3/4 Studies Dataset-Metformin, 3,164 (33.6%) were ≥65 years, 508 (5.4%) were ≥75 years, and 13 (0.1%) were ≥85 years.

Key: AUC = area under plasma concentration-time curve; eGFR = estimated glomerular filtration rate; FDC = fixed-dose combination; HbA1c = glycosylated hemoglobin (hemoglobin A1c); HCl = hydrochloride; HIV = human immunodeficiency virus; NYHA = New York Heart Association; SGLT = sodium glucose co-transporter; T2DM = type 2 diabetes mellitus; UGT = uridine 5' diphospho-glucuronosyltransferase

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy Use in nursing mothers

PART II: SAFETY SPECIFICATION

Module SV: Post-authorization Experience

SV.1. Post-authorization Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and, therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by the patient.

SV.1.1. Method Used to Calculate Exposure (Canagliflozin Single-agent)

Patient cumulative exposure from 02 April 2013 (ie, launch) to 31 March 2023 for the canagliflozin single-agent has been estimated by calculation from company distribution data. Estimates of exposure are based upon finished product.

The recommended dose of canagliflozin is 100 or 300 mg once daily. Therefore, for the single-agent product, at the minimum dose, one 100-mg tablet equals 1 person-day of exposure. At the maximum dose, one 300-mg tablet equals 1 person-day of exposure.

The International Birth Date for canagliflozin is 29 March 2013 and the first launch of the product was on 02 April 2013. Exposure for canagliflozin was calculated starting with worldwide launch through 31 March 2023.

Additional stratifications are provided using IQVIA (formerly IMS MIDAS^{TM}) data where possible and appropriate. Exposures by age and sex are presented as percentages of prescription sales. Regional prescription data by age group and sex were only available for the last 3 years ending December 2018 (Table SV.2) or December 2022 (Table SV.3 and Table SV.4). Further splits such as sex within age group are not provided since it is not appropriate to stratify to this level of detail based on prescription information available from IQVIA for these subcategories. Prescription units are reported as absolute values.

Market research sources for post-authorization exposure data for canagliflozin are unavailable for breakdowns such as: usage in pregnant or breast-feeding women, usage in hepatic impairment population, or usage in renal impairment population.

SV.1.2. Exposure (Canagliflozin Single-agent)

Cumulative Exposure Estimates Worldwide

Based on the 1,789,828,457 canagliflozin 100-mg tablets and 1,165,912,365 canagliflozin 300-mg tablets distributed worldwide from launch to 31 March 2023, the estimated cumulative exposure to canagliflozin is 2,955,740,822 person-days or 8,097,920 person-years. The cumulative exposure for canagliflozin from launch to 31 March 2023 is summarized in the table below.

Table SV.1: Exposure Table by Indication (Canagliflozin Single-agent, Launch to 31 March 2023)

Region	Person-days (100 mg Tablets, Minimum Dose)	Person-days (300 mg Tablets, Maximum Dose)	Total Person-days	Total Person-years[a,b]
T2DM				
Worldwide[c]	**1,789,828,457**	**1,165,912,365**	**2,955,740,822**	**8,097,920**

[a] Assuming 365 person-days = 1 person-year. 1 person-day = 1 tablet.
[b] The distribution was first observed in April 2013.
[c] Regional stratification is not possible due to various sources/algorithm refinements throughout the product's lifecycle.
Key: T2DM = type 2 diabetes mellitus.

Exposure Estimates by Sex and Age Group

Prescription sales for canagliflozin stratified by age and sex available from IQVIA are presented as percentages of total prescriptions for the last 3 years ending December 2018 (Table SV.2) or December 2022 (Table SV.3 and Table SV.4).

Table SV.2: Post-marketing (Non-study) Canagliflozin Exposure by Age Group in Europe (01 January 2016 to 31 December 2018)

Age Groups (Years)[a]	EU (783,627 Rx[b])
18-35	1.1%
36-64	48.7%
65 and over	50.2%

[a] Regional Rx data by age were only available for the last 3 years ending December 2018. Data stratified by age were only available in Spain.
[b] Included retail channels.
Key: EU = European Union; Rx = prescription(s).

Table SV.3: Post-marketing (Non-study) Canagliflozin Exposure by Age Group Outside Europe (01 January 2020 to 31 December 2022)

Age Groups (Years)[a]	Non-EU (87,104 Rx[b])
0-17	0.1%
18-35	1.9%
36-65	57.1%
66 and over	40.9%

[a] Regional Rx data by age were only available for the last 3 years ending in December 2022. Data were only available for the United States.
[b] Included retail channels.
Key: EU = European Union; Rx = prescription(s).

Table SV.4: Post-marketing (Non-study) Canagliflozin Exposure by Sex (01 January 2020 to 31 December 2022)

Country	Females[a]	Males[a]
United States (87,104 Rx[b])	44%	56%

[a] Regional Rx data by sex were only available for the last 3 years ending December 2022. Data were only available for the United States.
[b] Included retail channels.
Key: Rx = prescription(s).

SV.1.3. Method Used to Calculate Exposure (Canagliflozin/Metformin HCl FDC)

Patient cumulative exposure from launch (12 August 2014 or 20 September 2016 depending on formulation; see below) to 31 March 2023 for canagliflozin/metformin HCl FDC has been estimated by calculation from company distribution data. Estimates of exposure are based upon finished product.

For the combination product, exposure is based on two 50 or 150 mg combination tablets equaling one person-day. The dose of metformin may vary but the number of tablets per day is always recommended to be two.

Exposure for the immediate release (IR) formulation of canagliflozin/metformin HCl FDC was calculated starting with 12 August 2014 (first launch of the product) through 31 March 2023. Exposure for the extended release (ER) formulation of canagliflozin/metformin HCl FDC was calculated starting from 20 September 2016 (first launch of the product) through 31 March 2023.

Additional stratifications are provided using IQVIA data where possible and appropriate. Exposure by age and sex presented as percentages of prescription sales. Regional prescription data by age group and sex were only available for the last 3 years ending December 2018 (Table SV.7) or December 2022 (Table SV.8 and Table SV.9). Further splits such as sex within age group are not provided since it is not appropriate to stratify to this level of detail based on prescription information available from IQVIA for these subcategories. Prescription units are reported as absolute values.

Market research sources for post-authorization exposure data for canagliflozin/metformin HCl FDC (both formulations) are unavailable for breakdowns such as: usage in pregnant or breast-feeding women, usage in hepatic impairment population, or usage in renal impairment population.

SV.1.4. Exposure (Canagliflozin/Metformin HCl FDC)

Cumulative Exposure Estimates Worldwide

Based on the 480,589,210 canagliflozin/metformin HCl FDC tablets (IR formulation) distributed worldwide from 12 August 2014 (ie, launch) to 31 March 2023, the estimated exposure to the IR formulation of canagliflozin/metformin HCl FDC is 240,294,605 person-days or 658,342 person-years.

Based on the 70,521,600 tablets distributed worldwide from 20 September 2016 (ie, launch) to 31 March 2023, the estimated exposure to the ER formulation of canagliflozin/metformin HCl FDC is 35,260,800 person-days or 96,605 person-years.

The cumulative exposure for IR formulation of canagliflozin/metformin HCl FDC from launch to 31 March 2023 is summarized in the table below.

Table SV.5: Exposure Table by Indication (Canagliflozin/Metformin [IR formulation], Launch to 31 March 2023)

Region Formulation	Total Tablets	Total Person-days	Total Person-years[a,b]
T2DM			
Worldwide[c]			
50/500 mg tablets	23,999,460	11,999,730	32,876
50/850 mg tablets	51,586,100	25,793,050	70,666
50/1000 mg tablets	152,001,140	76,000,570	208,221
150/500 mg tablets	26,557,560	13,278,780	36,380
150/850 mg tablets	35,191,580	17,595,790	48,208
150/1000 mg tablets	191,253,370	95,626,685	261,991
Total	**480,589,210**	**240,294,605**	**658,342**

[a] Assuming 365 person-days = 1 person-year. 1 person-day = 2 tablets
[b] The distribution was first observed in August 2014.
[c] Regional stratification is not possible due to various sources/algorithm refinements throughout the product's lifecycle.
Key: IR=immediate release; T2DM = type 2 diabetes mellitus.

The cumulative exposure for the ER formulation of canagliflozin/metformin HCl FDC from launch to 31 March 2023 is summarized in the table below.

Table SV.6: Exposure Table by Indication (Canagliflozin/Metformin [ER formulation], Launch to 31 March 2023)

Region Formulation	Total Tablets	Total Person-days	Total Person-years[a,b]
T2DM			
Worldwide[c]			
50/500 mg tablets	5,902,020	2,951,010	8,085
50/1000 mg tablets	13,734,360	6,867,180	18,814
150/500 mg tablets	8,293,680	4,146,840	11,361
150/1000 mg tablets	42,591,540	21,295,770	58,345
Total	**70,521,600**	**35,260,800**	**96,605**

[a] Assuming 365 person-days = 1 person-year. 1 person-day = 2 tablets
[b] The distribution was first observed in September 2016.
[c] Regional stratification is not possible due to various sources/algorithm refinements throughout the product's lifecycle.
Key: ER = extended release; T2DM = type 2 diabetes mellitus.

Exposure Estimates by Sex and Age Group

Prescription sales for canagliflozin/metformin HCl FDC stratified by age and sex available from IQVIA are presented as percentages of total prescriptions for the last 3 years ending December 2018 (Table SV.7) or December 2022 (Table SV.8 and Table SV.9).

Table SV.7: Post-marketing (Non-study) Canagliflozin/Metformin Exposure by Age Group in Europe (01 January 2016 to 31 December 2018)

Age Groups (Years)[a]	EU (391,573 Rx[b])
18-35	1.9%
36-64	58.6%
65 and over	39.6%

[a] Regional Rx data by age were only available for the last 3 years ending December 2018. Data stratified by age were only available in Spain.
[b] Included retail channels.
Key: EU = European Union; Rx = prescription(s).

Table SV.8: Post-marketing (Non-study) Canagliflozin/Metformin Exposure by Age Group Outside Europe (01 January 2020 to 31 December 2022)

Age Groups (Years)[a]	Non-EU (11,072 Rx[b])
0-17	0.1%
18-35	2.2%
36-65	66.9%
66 and over	30.8%

[a] Regional Rx data by age were only available for the last 3 years ending December 2022. Data were only available for the United States.
[b] Included retail channels.
Key: EU = European Union; Rx = prescription(s).

Table SV.9: Post-marketing (Non-study) Canagliflozin/Metformin Exposure by Sex (01 January 2020 to 31 December 2022)

Country	Females[a]	Males[a]
United States (2,689,724 Rx[b])	41.9%	58.1%

[a] Regional Rx data by sex were only available for the last 3 years ending December 2022. Data were available only for the United States.
[b] Included retail channels.
Key: Rx = prescription(s)

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

No potential for drug dependence or drug abuse has been noted for canagliflozin. Therefore, the concern for potential illegal use is unlikely.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Medical Dictionary for Regulatory Activities (MedDRA) versions 19.1 and 21.0 were used to classify the clinical trials adverse event information that is summarized in this Module. MedDRA version 19.1 was used for DS2, DS6M, DS12, and CANVAS datasets; MedDRA version 21.0 was used for DS8 and CREDENCE datasets.

In general, adverse event summaries for each identified risk corresponded to an on-treatment analysis, which included adverse events for treated subjects up to 30 days after the last dose date. However, summaries of adverse events for DKA, fracture, and amputation were performed through the date of last trial contact (bounded by the Global Trial End Date), given the low frequency associated with these particular events and possible delays between study drug exposure and the occurrence of the event.

CANAGLIFLOZIN

The dataset used to summarize the important identified risk of Diabetic ketoacidosis with atypical presentation is summarized below.

- *Diabetic ketoacidosis with atypical presentation*: The primary analysis of these events was based upon datasets DS12, CANVAS/CANVAS-R, and CREDENCE. The CREDENCE dataset reflected a representative population of subjects with T2DM with more advanced renal disease. Due to differences in the occurrence of events across populations, DKA is not assessed in a large, pooled analysis. All DKA adverse events were adjudicated by an independent, blinded committee to determine whether or not the events met criteria for a clinical diagnosis of DKA.

CANAGLIFLOZIN/METFORMIN HCL FDC

The dataset used to summarize the important identified risk of Lactic acidosis is summarized below.

Lactic acidosis: The primary analysis of these events was based upon dataset DS6M, as this reflected a representative population of subjects with T2DM and was composed from similarly designed trials, providing a comparison to placebo. DS6M provided rare risk data from subjects in studies with traditional (non-streamlined) data collection. Lactic acidosis adverse events were also analyzed from the CREDENCE dataset, which also had traditional (non-streamlined) data collection. Cases from the CREDENCE dataset included subjects with and without background metformin use because of the additional risk for lactic acidosis in patients with impaired renal function.

CANAGLIFLOZIN

Important Identified Risk - Diabetic Ketoacidosis With Atypical Presentation

Potential Mechanisms:

Increased plasma ketone body concentrations leading to ketoacidosis may arise from both increases in ketone production and decreases in ketone clearance. Other than a single study performed in dogs using phlorizin (which suggested SGLT inhibition may increase renal ketone reabsorption [Cohen et al, 1956]), no work has been done to characterize the effects of selective SGLT2 inhibitor drugs on renal and whole-body clearance of ketone bodies. In an initial pilot study in Sprague-Dawley rats to test whether a single dose of canagliflozin would alter whole-body clearance of beta-hydroxybutyrate, no differences between vehicle and canagliflozin were observed.

Evidence Source(s) and Strength of Evidence:

Diabetic ketoacidosis has been reported during postmarketing experience with canagliflozin in patients with T2DM, including cases with fatal outcomes. An atypical presentation (blood glucose values less than 13.9 mmol/L [250 mg/dL]) has been observed during postmarketing surveillance

in cases of DKA for canagliflozin and across the class of SGLT2 inhibitors. Cases of ketoacidosis have occurred during off-label use of SGLT2 inhibitors in patients with T1DM and in T1DM clinical trials (EMA, 2017). In an 18-week Phase 2 trial in subjects with T1DM randomized to either canagliflozin or placebo (DIA2004), the frequency of DKA was higher than that observed in T2DM clinical trials.

Characterization of the Risk - Data:

Table SVII.1: Important Identified Risk –Diabetic Ketoacidosis With Atypical Presentation*

	CREDENCE (N=4397)		CANVAS/CANVAS-R (N=10134)		Pooled Non-CANVAS/ Non-CREDENCE Dataset DS12 (N=8114)	
	CANA (N=2200)	Placebo (N=2197)	CANA (N=5790)	Placebo (N=4344)	CANA (N=5288)	Non-CANA (N=2826)
n (%) with at least 1 adverse event[a]	12 (0.5)	2 (0.1)	14 (0.2)	4 (0.1)	3 (0.1)	0
Incidence rate per 1,000 subject-year exposure[b]	2.08	0.35	0.62	0.29	0.51	0.00
Odds ratio (95% CI)[c]	6.02 (1.34, 55.42)		2.63 (0.83, 10.98)		- (-,-)	
Preferred term, n (%)[a,d]						
Acidosis	0	0	1 (<0.1)	0	0	0
Blood ketone body increased	1 (<0.1)	0	0	0	0	0
Diabetic ketoacidosis	11 (0.5)	0	12 (0.2)	4 (0.1)	2 (<0.1)	0
Hyperglycaemia	0	1 (<0.1)	0	0	0	0
Ketoacidosis	0	0	1 (<0.1)	0	1 (<0.1)	0
Metabolic acidosis	0	1 (<0.1)	1 (<0.1)	0	0	0
Seriousness, n (%)[a]						
Serious	9 (0.4)	2 (0.1)	13 (0.2)	3 (0.1)	2 (<0.1)	0
Severity, n (%)[a]						
Severe	6 (0.3)	1 (0.0)	12 (0.2)	3 (0.1)	1 (<0.1)	0
Mild/Moderate	6 (0.3)	1 (<0.1)	2 (<0.1)	1 (<0.1)	2 (<0.1)	0
Total number of events			16	4	3	0
Outcome of events, n (%)[e]						
Recovered/resolved	20 (100)	1 (50.0)	16 (100)	3 (75.0)	2 (66.7)	0
Recovering/resolving	0	0	0	0	0	0
Not recovered/not resolved	0	1 (50.0)	0	1 (25.0)	0	0
Recovered/resolved with sequelae	0	0	0	0	1 (33.3)	0
Fatal	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Not reported	0	0	0	0	0	0

* Based on adjudicated results.

[a] Denominators are the total number of subjects in each group; the subject is counted only once regardless of the number of events or the number of occurrences.

[b] Exposure adjusted incidence rates are per 1,000 person-years and calculated as 1,000*(the total number of subjects with at least one specified event divided by the total person-year exposure for all safety subjects in each treatment group).

[c] Based on Fisher's exact test.

[d] MedDRA versions 19.1 and 21.0 were used to identify potential adverse events of diabetic ketoacidosis for adjudication, MedDRA version 19.1 was used for DS12 and CANVAS datasets; MedDRA version 21.0 was used for CREDENCE dataset. See Annex 7.3 for MedDRA terms used to select events for adjudication.

[e] Denominators are the total number of events in each group.

Key: CI = confidence interval.

Source: TSFAE08A_DKA_PB_ADJ_DCV, TSFAE08B_DKA_PB_ADJ_DCV, TSFAE08A_DKA_PB_ADJ_D12, TSFAE08B_DKA_PB_ADJ_D12 (EU-RMP 7.3); TSFAE08A_DKA_PB_ADJ_DNE3001_RMP,

Table SVII.1: Important Identified Risk –Diabetic Ketoacidosis With Atypical Presentation*

	CREDENCE (N=4397)		CANVAS/CANVAS-R (N=10134)		Pooled Non-CANVAS/ Non-CREDENCE Dataset DS12 (N=8114)	
	CANA (N=2200)	Placebo (N=2197)	CANA (N=5790)	Placebo (N=4344)	CANA (N=5288)	Non-CANA (N=2826)

TSFAE08B_DKA_PB_ADJ_DNE3001_RMP, TSFAE08A_DKA_PB_ADJ_D8_RMP, TSFAE08B_DKA_PB_ADJ_D8_RMP.

Characterization of the Risk - Discussion:

Diabetic ketoacidosis is a serious complication of diabetes caused by a relative reduction in a patient's ratio of insulin:glucagon levels, acceleration of hepatic ketogenesis, and associated intercurrent illness and/or insulin pump malfunction (Kitabchi et al, 2009). Rare cases of DKA, including life-threatening ones, have occurred in patients taking SGLT2 inhibitors for T2DM. Some of these cases have been atypical, with patients not having blood sugar levels as high as expected (EMA, 2017). The atypical presentation of DKA cases in SGLT2-inhibitor treated patients with diabetes, combined with the otherwise non-specific symptoms presented by patients with DKA may delay the diagnosis and therefore lead to the development of more serious or life-threatening conditions.

In the CREDENCE Dataset, there were 14 subjects with adjudicated DKA events (canagliflozin group: 12 subjects; placebo group: 2 subjects). The odds ratio was 6.02 with a 95% CI that included 1. Most of these subjects reported a serious adverse event, and half were considered severe. None of the events were fatal, and all but 1 subject, who received placebo, were considered recovered.

More than one-half of the subjects with adjudicated adverse events of DKA on study had a screening eGFR of ≥30 to <45 mL/min/1.73 m^2 (7 of 12 subjects in canagliflozin group, 1 subject in placebo group) [CREDENCE CSR Section 6.1.5.6]. Further, compared with those in the Intent-to-Treat analysis set, subjects who experienced an adjudicated adverse event of DKA had a longer duration of T2DM (mean, 23.6 vs 15.8 years), higher baseline HbA1c (mean, 8.9% vs 8.3%), and lower baseline eGFR (mean, 52.9 vs 56.2 mL/min/1.73 m^2) [CREDENCE CSR Table 82]. All adjudicated DKA events on study in the canagliflozin group occurred while on background insulin treatment, and 3 of the 12 subjects showed evidence of autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or tested positive for GAD65 antibodies) [CREDENCE CSR Section 6.1.5.6].

In the CANVAS Integrated Dataset (CANVAS/CANVAS-R), there were 18 subjects with adjudicated DKA events (combined canagliflozin group: 14 subjects; placebo group: 4 subjects). The odds ratio was 2.63 with a 95% CI that included 1. In the DS12 dataset, there were 3 events in the canagliflozin group and no events in the non-canagliflozin group (odds ratio could not be calculated) [Table SVII.1].

In all but 1 subject (placebo group), no history of DKA prior to study entry was reported. All subjects were receiving insulin at the time of the event. Five of the 14 subjects in the canagliflozin group had evidence of autoimmune diabetes, based on a reported history of T1DM (1 subject) or the presence of glutamic acid decarboxylase or insulin antibodies detected after the DKA event (4 subjects), compared to no subjects with these findings in the placebo group. Precipitating factors (mainly recent or concurrent illness, or recent reduction in insulin dose) were identified in 100% of adjudicated cases in the placebo group, and 75% of cases in the canagliflozin group [CANVAS ISS Table 51]. In all cases, concomitant blood glucose levels were >13.9 mmol/L (>250 mg/dL) [CANVAS ISS Section 2.1.4.1.7].

For further information on the characterization of the risk, see table above for data from clinical trials.

Diabetic ketoacidosis has been reported during postmarketing surveillance and has occurred in patients with blood glucose values ≤ 13.9 mmol/L. In postmarketing reports of DKA, precipitating factors for development of DKA included infection, dehydration, surgery, renal and respiratory failure, weight loss before the event, reduced carbohydrate intake, alcohol use, and, reduction in insulin administration.

Risk Factors and Risk Groups:

The available clinical trial data suggest that patients diagnosed as having T2DM or misdiagnosed as T2DM (eg, T1DM, LADA), and who have a low beta-cell reserve, are unable to produce sufficient insulin to suppress hepatic ketogenesis and peripheral lipolysis. In the setting of known DKA precipitating factors, such as an acute illness (and associated increase in insulin resistance), these patients can develop DKA. The increased rate of DKA in the CREDENCE trial was observed predominantly in subjects in the lowest eGFR stratum; which included subjects with a longer duration of diabetes, higher proportion of insulin use, and higher baseline HbA1c than the overall population.

Preventability:

Before initiating treatment with SGLT2 inhibitors, factors that may predispose patients to ketoacidosis should be considered. These include history of diabetes (to assess whether the subject might be misdiagnosed with T1DM or LADA), and additional risk factors for developing DKA during treatment with canagliflozin such as low beta-cell function reserve. In addition, patients should be counselled to prevent or recognize situations that may increase the risk of DKA such as restricted food intake, severe dehydration, increased alcohol consumption, sudden reduction in insulin, acute serious medical illness, and major surgery. Canagliflozin should be used with caution in these patients and patients should be informed of the signs and symptoms of DKA.

A substantial proportion of the cases where DKA has been observed have concerned the off-label usage in patients with T1DM; canagliflozin should not be used in this population.

Section 4.4 of the SmPC provides prescribers with information regarding the factors that could indicate an increased risk of DKA in particular patients or clinical situations, and reminds prescribers that canagliflozin should not be used in patients with T1DM. Section 4.4 of the SmPC also provides prescribers with instructions on treatment interruption in patients hospitalized for acute serious medical illnesses. In addition, this section also recommends that prescribers withhold treatment, 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. Section 2 of the package leaflet (PL) advises patients to ask their doctor if they need to stop taking canagliflozin if they are going to have major surgery or a procedure that requires prolonged fasting. Section 4.4 of the SmPC also advises prescribers that monitoring for serum ketones is recommended. Alternative anti-hyperglycemic therapy, including insulin, should be considered during interruptions in canagliflozin treatment.

Guidance is included within the EU Product Information (both the SmPC and PL) to advise prescribers and patients of the signs and symptoms of DKA to assist with the identification of potential DKA with both typical and atypical presentation.

Impact on the Risk-Benefit Balance of the Product:

In patients with T2DM presenting with metabolic acidosis, a diagnosis of DKA should be considered even if blood glucose levels are ≤ 13.9 mmol/L.

Patients on canagliflozin should be tested for ketones when they present with early signs and symptoms of ketoacidosis, such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, or unusual fatigue or sleepiness, in order to prevent delayed diagnosis and to facilitate appropriate patient management.

In patients where DKA is suspected or diagnosed, treatment with canagliflozin should be discontinued immediately. Treatment with canagliflozin should be interrupted in patients with T2DM who are hospitalized for acute serious medical illnesses. Section 4.4 of the SmPC recommends that prescribers withhold treatment with canagliflozin, 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. Alternative anti-hyperglycemic therapy, including insulin, should be considered during interruptions in canagliflozin treatment. Measurement of blood ketone levels is preferred to urine. Treatment with canagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilized.

Public Health Impact:

As the occurrence of DKA in subjects with T2DM is rare, this risk is not likely to have a significant impact on public health.

Annex 1 MedDRA Term:

Preferred term of Diabetic ketoacidosis.

CANAGLIFLOZIN/METFORMIN HCL FDC

Important Identified Risk – Lactic Acidosis

Potential Mechanisms:

The pathogenesis of metformin-associated lactic acidosis is not completely understood. Biguanides, a class of drugs that include metformin, are believed to decrease gluconeogenesis from alanine, pyruvate and lactate, and levels of lactic acid could accumulate under certain circumstances (Salpeter et al, 2010). However, research has also shown that metformin enhanced glucose oxidation without significantly affecting fasting lactate production in peripheral tissues (Cusi et al, 1996). On the other hand, metformin has affinity for the mitochondrion membrane, and may affect the electron transport and inhibit oxidative metabolism. Especially when metformin levels are high, oxidative phosphorylation is reduced and aerobic metabolism switches to anaerobic metabolism (Bruijstens et al, 2008). Metformin may be either a cause of lactic acidosis or merely a coincidental factor (Lalau, 2010), because most of the reported cases have occurred in patients with severe acute conditions, such as renal failure, that could in themselves have caused the lactic acidosis. True metformin-induced lactic acidosis may result from a combination of anaerobic stimulation of lactate production by intestinal cells with defective lactate elimination by the liver, via metformin accumulation due to kidney failure, liver failure, or overdosing (Lalau, 2010).

Evidence Source(s) and Strength of Evidence:

Evidence for lactic acidosis from metformin is based on the literature, including case reports, review of clinical trials and observational studies, as well as metformin drug labels. Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure (Metformin SmPC, 2015). Lactic acidosis has been reported in Phase 3/4 clinical trials when canagliflozin was given to subjects who were on a background of metformin, but at a lower incidence than observed in the comparator group.

Characterization of the Risk - Data:

Table SVII.2: Important Identified Risk – Lactic Acidosis

	CREDENCE Metformin (N=2543)		CREDENCE Non-Metformin (N=1854)		Pooled Phase 3/4 Studies Dataset-Metformin (DS6M) (N=13791)	
	CANA (N=1275)	Placebo (N=1268)	CANA (N=925)	Placebo (N=929)	CANA (N=8152)	Non-CANA (N=5639)
n (%) with at least 1 adverse event[a]	3 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	3 (<0.1)	3 (0.1)
Incidence rate per 1,000 subject-year exposure[b]	1.00	0.34	0.48	1.00	0.16	0.27
Odds ratio (95% CI)[c]	2.99 (0.24, 156.99)		0.50 (0.01, 9.65)		0.69 (0.09, 5.17)	
Preferred term, n (%)[a]						
Blood lactic acid increased	0	0	0	0	1 (<0.1)	0
Lactic acidosis	3 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	2 (<0.1)	3 (0.1)
Seriousness, n (%)[a]						
Serious	0	0	1 (0.1)	0	2 (<0.1)	1 (<0.1)
Severity, n (%)[a]						
Severe	0	0	1 (0.1)	0	2 (<0.1)	3 (0.1)
Mild/Moderate	3 (0.2)	1 (0.1)	0	2 (0.2)	1 (<0.1)	0
Total number of events	3	1	1	2	3	3
Outcome of events, n (%)[e]						
Recovered/resolved	2 (66.7)	1 (100)	1 (100)	2 (100)	1 (33.3)	2 (66.7)
Recovering/resolving	0	0	0	0	1 (33.3)	0
Not recovered/not resolved	1 (33.3)	0	0	0	0	0
Recovered/resolved with sequelae	0	0	0	0	0	0
Fatal	0	0	0	0	1 (33.3)	1 (33.3)
Unknown	0	0	0	0	0	0
Not reported	0	0	0	0	0	0

[a] Denominators are the total number of subjects in each group; the subject is counted only once regardless of the number of events or the number of occurrences.
[b] Exposure adjusted incidence rates are per 1,000 person-years and calculated as 1,000*(the total number of subjects with at least one specified event divided by the total person-year exposure for all safety subjects in each treatment group).
[c] Based on Fisher's exact test.
[d] MedDRA versions 19.1 and 21.0 were used to classify the clinical trials adverse event information summarized in this table, MedDRA version 19.1 was used for DS6M dataset; MedDRA version 21.0 was used for CREDENCE dataset.
[e] Denominators are the total number of events in each group.
Key: CI = confidence interval.
Source: TSFAE13A_LA_D6M, TSFAE13A_LA_D6M (EU-RMP 7.3); TSFAE13A_LA_NMET_3001_RMP., TSFAE13B_LA_3001_MET_RMP.

Characterization of the Risk - Discussion:

The US Food and Drug Administration has estimated the rate of fatal or nonfatal lactic acidosis to be 5 cases per 100,000 persons treated over the course of one year (Misbin et al, 1998). Population-based studies have estimated a rate of 2 to 9 cases of lactic acidosis in metformin users per 100,000 person-years (Bodmer et al, 2008; Campbell, 1985; Stang et al, 1999; Wiholm & Myrhed, 1993).

In the Pooled Phase 3/4 Dataset where canagliflozin was given to subjects who were on a background of metformin (DS6M), there were 6 events of lactic acidosis (canagliflozin: 3 subjects; placebo: 3 subjects). The incidence rates were low and the 95% CI for the odds ratio included 1. Half of the subjects reported serious events and most events were severe. There were 2 fatal events (canagliflozin: 1 subject; placebo: 1 subject) and all other events resolved or were resolving. [Table SVII.2].

Due to the increased risk for acidosis in patients with DKD, lactic acidosis was assessed in the CREDENCE population separately from DS6M, and also regardless of baseline metformin use. In the Intent-to-Treat population of CREDENCE, 57.9% subjects in the canagliflozin group and 57.7% subjects in the placebo group were using metformin at baseline. The incidence of lactic acidosis in the CREDENCE dataset overall was low, with 7 subjects experiencing events of lactic acidosis (canagliflozin: 4 subjects; placebo: 3 subjects). In the CREDENCE Metformin dataset, lactic acidosis events occurred in 3 subjects in the canagliflozin group and 1 subject in the placebo group. The odds ratio was >1, but the 95% CI included 1 and was very wide. In the CREDENCE Non-metformin dataset lactic acidosis events occurred in 1 subject in the canagliflozin group and 2 subjects in the placebo group. The odds ratio was <1, and the 95% CI included 1 and was wide [Table SVII.2].

For further information on the characterization of the risk, see table above for data from clinical trials.

Review of postmarketing data for this Important Identified Risk of lactic acidosis was consistent with findings in the clinical trials database. No new safety information pertaining to this risk emerged from postmarketing experience.

Risk Factors and Risk Groups:

Risk factors include conditions that may be associated with or promote hypoxia, including heart failure, tissue hypoxia, respiratory failure, defective lactate clearance (alcohol abuse, and liver failure), renal impairment, renal or hepatic insufficiency. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age.

Preventability:

The risk of lactic acidosis may be significantly decreased by regular monitoring of renal function in patients taking metformin, and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of CrCl demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic,

when taking metformin. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

Impact on the Risk-Benefit Balance of the Product:

Lactic acidosis is a medical emergency that must be treated in a hospital setting. Case reports have documented that patients went through renal function replacement therapies (ie, hemodialysis and continuous hemofiltration) to restore blood volume, enhance renal blood flow, correct metabolic acidosis (as a very low pH may compromise myocardial function) and remove lactate and metformin (Bruijstens et al, 2008). However, reports of long-term impact on patients' quality of life has not been found.

Public Health Impact:

Lactic acidosis is a rare, potentially fatal metabolic condition that can occur whenever substantial tissue hypoperfusion and hypoxia exist (Salpeter et al, 2010). The mortality in reported cases have ranged from 8% to 50% (Salpeter et al, 2010). However, prognosis is excellent in isolated metformin-induced lactic acidosis in the absence of other patient risk factors and concomitant medications (Lalau, 2010), in which case metformin can be withdrawn.

Annex 1 MedDRA Term:

Preferred term of Lactic acidosis.

SVII.3.2. Presentation of the Missing Information

Missing information: **Use in pregnancy**

Evidence source:

Canagliflozin: Studies in animals have shown reproductive toxicity. Data from nonclinical studies are provided in Part II Module SII. Pregnancy has been an exclusion criterion for all clinical trials conducted to date. Women of childbearing potential included in trials have been required to use 2 effective birth control methods. Pregnancy, once detected, has been a condition for required withdrawal of the subject from the trial. A total of 11 cases of pregnancy were reported during the entire canagliflozin programme (Phase 1-3 trials), of which, 7 were in women enrolled in the trial (6 canagliflozin-treated subjects and 1 placebo-treated subject) and 4 in partners of subjects (3 canagliflozin-treated subjects and 1 placebo-treated subject). There are no data to support the use of canagliflozin in pregnant women. Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued.

Canagliflozin/Metformin HCl FDC: Studies in animals with canagliflozin have shown reproductive toxicity. Data from nonclinical studies are provided in Part II Module SII. A large amount of data from the use of metformin in pregnant women (more than 1,000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) do not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition, or postnatal development. There are no data to support the use of canagliflozin/metformin HCl FDC in pregnant women. Canagliflozin/metformin HCl FDC should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin/metformin HCl FDC should be discontinued.

Anticipated risk/consequence of the missing information:

There are no data from the use of canagliflozin in pregnant women. Studies in animals with canagliflozin have shown reproductive toxicity. Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued.

Missing information: **Use in nursing mothers**

Evidence source:

Canagliflozin: 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. A risk to newborns/infants cannot be excluded. Canagliflozin should not be used during breast-feeding.

Canagliflozin/Metformin HCl FDC: No studies in lactating animals have been conducted with the combined active substances of canagliflozin/metformin HCl FDC. 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. Metformin is excreted into human breast milk in small amounts. A risk to newborns/infants cannot be excluded. Canagliflozin/metformin HCl FDC should not be used during breast-feeding.

Anticipated risk/consequence of the missing information:

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. A risk to newborns/infants cannot be excluded. Canagliflozin should not be

used during breast-feeding.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns (Canagliflozin)

Important identified risks	Diabetic ketoacidosis with atypical presentation
Important potential risks	None
Missing information	Use in pregnancy
	Use in nursing mothers

Table SVIII.2: Summary of Safety Concerns (Canagliflozin/Metformin HCl FDC)

Important identified risks	Diabetic ketoacidosis with atypical presentation
	Lactic acidosis
Important potential risks	None
Missing information	Use in pregnancy
	Use in nursing mothers

PART III: PHARMACOVIGILANCE PLAN (Including Post-authorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	**Purpose/Description**
Diabetic ketoacidosis with atypical presentation	Targeted follow-up of DKA adverse events through guided questionnaire.
Lactic acidosis (canagliflozin/metformin HCl FDC)	Targeted follow-up of lactic acidosis adverse events reported for canagliflozin/metformin HCl FDC through guided questionnaire.

Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
Adjudication of DKA events from ongoing clinical trials by an independent blinded committee.	• Further characterize the impact of this safety concern on the safety profile of canagliflozin, to improve patient management.	The DKA adjudication process will be applied to the canagliflozin development program.

III.2. Additional Pharmacovigilance Activities

Not applicable.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Post-authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern (Canagliflozin)

Safety Concern	Routine Risk Minimization Activities
Diabetic ketoacidosis with atypical presentation	Routine risk communication: • SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations regarding appropriate dosing and patient management (including advice on interruption, discontinuation, and restart of canagliflozin and consideration of alternative anti-hyperglycemic therapy, including insulin, during interruptions in canagliflozin treatment) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2; • Advice that DKA may be prolonged in some patients and insulin deficiency may play a role and should be corrected is given in SmPC Section 4.4; • Advice to patients to speak to their doctor if they need to stop taking canagliflozin and when to restart if they are going to have major surgery or a procedure that requires prolonged fasting is provided in PL Section 2.
Use in pregnancy	Routine risk communication: • SmPC Section 4.6 and PL Section 2. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation regarding use of canagliflozin during pregnancy is provided in SmPC Section 4.6 and PL Section 2
Use in nursing mothers	Routine risk communication: • SmPC Section 4.6 and PL Section 2. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation regarding use of canagliflozin during breast-feeding is provided in SmPC Section 4.6 and PL Section 2.

Key: DKA = diabetic ketoacidosis; PL = Package Leaflet; SmPC = Summary of Product Characteristics; T1DM = type 1 diabetes mellitus.

Table Part V.2: Description of Routine Risk Minimization Measures by Safety Concern (Canagliflozin/Metformin HCl FDC)

Safety Concern	Routine Risk Minimization Activities
Diabetic ketoacidosis with atypical presentation	Routine risk communication: • SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations regarding appropriate dosing and patient management (including advice on interruption, discontinuation, and restart of canagliflozin and consideration of alternative anti-hyperglycemic therapy, including insulin, during interruptions in canagliflozin treatment) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin/metformin HCl FDC should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin/metformin HCl FDC in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2; • Advice that DKA may be prolonged in some patients and insulin deficiency may play a role and should be corrected is given in SmPC Section 4.4; • Advice to patients to speak to their doctor if they need to stop taking canagliflozin/metformin HCl FDC and when to restart if they are going to have major surgery or a procedure that requires prolonged fasting is provided in PL Section 2.

Table Part V.2: Description of Routine Risk Minimization Measures by Safety Concern (Canagliflozin/Metformin HCl FDC)

Safety Concern	Routine Risk Minimization Activities
Lactic acidosis	Routine risk communication: • SmPC Section 4.2; • SmPC Section 4.4 and PL Section 2; • SmPC Section 4.8 and PL Section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Contraindication in patients with an increased risk of lactic acidosis is described in SmPC Section 4.3 and PL Section 2, including detailed list of conditions; • Patient management of dehydration is described in SmPC Section 4.4 and PL Section 2; • Recommendations regarding concomitant use with medicinal products that acutely impair renal function or cause lactic acidosis or its use in patients with risk factors for lactic acidosis are provided in SmPC Section 4.4; • Patient management of lactic acidosis, including guidance on diagnosis, discontinuation, and need for medical attention, is described in SmPC Section 4.4 and PL Section 4; • Recommendations for monitoring renal function is provided in SmPC Section 4.4 and PL Section 4; • Advice on concomitant use with alcohol, medicinal products containing alcohol, cationic drugs that are eliminated by renal tubular secretion, iodinated contrast agents, and medicinal products that can adversely affect renal function is provided in SmPC Section 4.5 and PL Section 2; • Advice on patient management of overdose, including how to remove lactate and metformin (hemodialysis), is provided in SmPC Section 4.9.
Use in pregnancy	Routine risk communication: • SmPC Section 4.6 and PL Section 2. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation regarding use of canagliflozin/metformin HCl FDC during pregnancy is provided in SmPC Section 4.6 and PL Section 2.
Use in nursing mothers	Routine risk communication: • SmPC Section 4.6 and PL Section 2. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation regarding use of canagliflozin/metformin HCl FDC during breast-feeding is provided in SmPC Section 4.6 and PL Section 2.

Key: DKA = diabetic ketoacidosis; FDC = fixed-dose combination; HCl = hydrochloride; PL = Package Leaflet; SmPC = Summary of Product Characteristics; T1DM = type 1 diabetes mellitus.

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Canagliflozin)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Diabetic ketoacidosis with atypical presentation	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4; • Recommendations regarding appropriate dosing and patient management (including advice on interruption, discontinuation, and restart of canagliflozin and consideration of alternative anti-hyperglycemic therapy, including insulin, during interruptions in canagliflozin treatment) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2; • Advice that DKA may be prolonged in some patients and insulin deficiency may play a role and should be corrected is given in SmPC Section 4.4; • Advice to patients to speak to their doctor if they need to stop taking canagliflozin and when to restart if they are going to have major surgery or a procedure that requires prolonged fasting is provided in PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire; • Adjudication of DKA events from ongoing clinical trials by an independent blinded committee. Additional pharmacovigilance activities: • None.
Use in pregnancy	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Canagliflozin)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	canagliflozin during pregnancy is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.	• None. Additional pharmacovigilance activities: • None.
Use in nursing mothers	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin during breast-feeding is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

Key: DKA = diabetic ketoacidosis; PL = Package Leaflet; SmPC = Summary of Product Characteristics; T1DM = type 1 diabetes mellitus.

Table Part V.4: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Canagliflozin/Metformin HCl FDC)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Diabetic ketoacidosis with atypical presentation	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4; • Recommendations regarding appropriate dosing and patient management (including advice on interruption, discontinuation, and restart of canagliflozin and consideration of alternative anti-hyperglycemic therapy, including insulin, during interruptions in canagliflozin treatment) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin/metformin HCl FDC should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin/metformin HCl FDC in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2; • Advice that DKA may be prolonged in some patients and insulin deficiency may play a role and should be corrected is given in SmPC Section 4.4; • Advice to patients to speak to their doctor if they need to stop taking canagliflozin/metformin HCl FDC and when to restart if they are going to have major surgery or a procedure that requires prolonged fasting is provided in PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire; • Adjudication of DKA events from ongoing clinical trials by an independent blinded committee. Additional pharmacovigilance activities: • None.
Lactic acidosis	Routine risk communication: • SmPC Section 4.2; • SmPC Section 4.4 and PL Section 2; • SmPC Section 4.8 and PL Section 4; • Contraindication in patients with an increased risk of lactic acidosis is described in SmPC Section 4.3 and PL Section 2, including detailed list of conditions; • Patient management of dehydration is described in SmPC Section 4.4 and PL Section 2; • Recommendations regarding concomitant use with medicinal products that acutely impair renal function or cause lactic acidosis or its use in patients with risk factors for lactic acidosis are provided in SmPC Section 4.4;	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire. Additional pharmacovigilance activities: • None.

Table Part V.4: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern (Canagliflozin/Metformin HCl FDC)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Patient management of lactic acidosis, including guidance on diagnosis, discontinuation, and need for medical attention, is described in SmPC Section 4.4; • Recommendations for monitoring of renal function is provided in SmPC Section 4.4 and PL Section 4; • Advice on concomitant use with alcohol, medicinal products containing alcohol, cationic drugs that are eliminated by renal tubular secretion, iodinated contrast agents, and medicinal products that can adversely affect renal function is provided in SmPC Section 4.5 and PL Section 2; • Advice on patient management of overdose, including how to remove lactate and metformin (hemodialysis), is provided in SmPC Section 4.9. Additional risk minimization measures: • None.	
Use in pregnancy	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin/metformin HCl FDC during pregnancy is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Use in nursing mothers	Routine risk minimization measures: • Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin/metformin HCl FDC during breast-feeding is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

Key: DKA = diabetic ketoacidosis; FDC = fixed-dose combination; HCl = hydrochloride; PL = Package Leaflet; SmPC = Summary of Product Characteristics; T1DM = type 1 diabetes mellitus.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

PART VI: Summary of Risk Management Plan for INVOKANA (Canagliflozin)

This is a summary of the risk management plan (RMP) for INVOKANA. The RMP details important risks of INVOKANA, how these risks can be minimized, and how more information will be obtained about INVOKANA's risks and uncertainties (missing information).

INVOKANA's summary of product characteristics (SmPC) and its package leaflet (PL) provide essential information to healthcare professionals and patients on how INVOKANA should be used.

This summary of the RMP for INVOKANA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of INVOKANA's RMP.

I. The Medicine and What it is Used For

INVOKANA is authorized for treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise (see SmPC for the full indication). It can be used by itself, or in combination with other medicinal products for the treatment of diabetes. This medicine works by increasing the amount of sugar removed from your body in your urine. This reduces the amount of sugar in your blood and can help prevent heart disease in T2DM. It also helps to slow down deterioration of kidney function in T2DM by a mechanism beyond blood glucose lowering.

It contains canagliflozin as the active substance and it is given as an oral tablet (canagliflozin 100 mg, canagliflozin 300 mg). Further information about the evaluation of INVOKANA's benefits can be found in INVOKANA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/invokana

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of INVOKANA, together with measures to minimize such risks and the proposed studies for learning more about INVOKANA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of INVOKANA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INVOKANA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Diabetic ketoacidosis with atypical presentation
Important potential risks	None
Missing information	Use in pregnancy
	Use in nursing mothers

II.B. Summary of Important Risks

Important Identified Risk: Diabetic ketoacidosis with atypical presentation	
Evidence for linking the risk to the medicine	Diabetic ketoacidosis (DKA) has been reported during postmarketing experience with canagliflozin in T2DM patients, including cases with fatal outcomes. An atypical presentation (blood glucose values less than 13.9 mmol/L [250 mg/dL]) has been observed during postmarketing surveillance in cases of DKA for canagliflozin and across the class of sodium-glucose co-transporter-2 (SGLT2) inhibitors. Cases of ketoacidosis have occurred during off-label use of SGLT2 inhibitors in type 1 diabetes mellitus (T1DM) patients and in T1DM clinical trials (EMA, 2017). In an 18-week Phase 2 trial in subjects with T1DM randomized to either canagliflozin or placebo (DIA2004), the frequency of DKA was higher than that observed in T2DM clinical trials.
Risk factors and risk groups	The available clinical trial data suggest that patients diagnosed as having T2DM or misdiagnosed as T2DM (eg, T1DM, latent autoimmune diabetes of adulthood), and who have a low beta-cell reserve, are unable to produce sufficient insulin to suppress hepatic ketogenesis and peripheral lipolysis. In the setting of known DKA precipitating factors, such as an acute illness (and associated increase in insulin resistance), these patients can develop DKA. The increased rate of DKA in the CREDENCE trial was observed predominantly in subjects in the lowest eGFR

Important Identified Risk: Diabetic ketoacidosis with atypical presentation

	stratum; which included subjects with a longer duration of diabetes, higher proportion of insulin use, and higher baseline glycosylated hemoglobin (HbA1c) than the overall population.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4; • Recommendations regarding appropriate dosing and patient management (including advice on interruption, discontinuation, and restart of canagliflozin and consideration of alternative anti-hyperglycemic therapy, including insulin, during interruptions in canagliflozin treatment) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2; • Advice that DKA may be prolonged in some patients and insulin deficiency may play a role and should be corrected is given in SmPC Section 4.4; • Advice to patients to speak to their doctor if they need to stop taking canagliflozin and when to restart if they are going to have major surgery or a procedure that requires prolonged fasting is provided in PL Section 2. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire; • Adjudication of DKA events from ongoing clinical trials by an independent blinded committee. Additional pharmacovigilance activities: • None. See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Use in pregnancy	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin during pregnancy is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

Missing Information: Use in nursing mothers	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin during breast-feeding is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

II.C. Post-authorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of INVOKANA.

II.C.2. Other Studies in Post-authorization Development Plan

There are no studies required for INVOKANA.

Part VI: Summary of Risk Management Plan for VOKANAMET (Canagliflozin/Metformin Hydrochloride Fixed-dose Combination)

This is a summary of the risk management plan (RMP) for VOKANAMET. The RMP details important risks of VOKANAMET, how these risks can be minimized, and how more information will be obtained about VOKANAMET's risks and uncertainties (missing information).

VOKANAMET's summary of product characteristics (SmPC) and its package leaflet (PL) provide essential information to healthcare professionals and patients on how VOKANAMET should be used.

This summary of the RMP for VOKANAMET should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VOKANAMET's RMP.

I. The Medicine and What it is Used For

VOKANAMET is authorized for treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise (see SmPC for the full indication). VOKANAMET is a fixed-dose combination (FDC) containing canagliflozin and metformin as two different active substances. These are two medicines that work together in different ways to lower blood glucose (sugar) levels and can help prevent heart disease in adults with T2DM. It can be used by itself, or in combination with other medicinal products for the treatment of diabetes. It also can be used in patients already being treated with the combination of canagliflozin and metformin as separate tablets. VOKANAMET is given as an oral film-coated tablet (canagliflozin/metformin hydrochloride [HCl] 50 mg/850 mg, 50 mg/1000 mg, 150 mg/850 mg, 150 mg/1000 mg).

Further information about the evaluation of VOKANAMET's benefits can be found in VOKANAMET's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/vokanamet

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of VOKANAMET, together with measures to minimize such risks and the proposed studies for learning more about VOKANAMET's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of VOKANAMET are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VOKANAMET. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Diabetic ketoacidosis with atypical presentation Lactic acidosis
Important potential risks	None
Missing information	Use in pregnancy Use in nursing mothers

II.B. Summary of Important Risks

Important Identified Risk: Diabetic ketoacidosis with atypical presentation	
Evidence for linking the risk to the medicine	Diabetic ketoacidosis (DKA) has been reported during postmarketing experience with canagliflozin in T2DM patients, including cases with fatal outcomes. An atypical presentation (blood glucose values less than 13.9 mmol/L [250 mg/dL]) has been observed during postmarketing surveillance in cases of DKA for canagliflozin and across the class of sodium-glucose co-transporter-2 (SGLT2) inhibitors. Cases of ketoacidosis have occurred during off-label use of SGLT2 inhibitors in type 1 diabetes mellitus (T1DM) patients and in T1DM clinical trials (EMA, 2017). In an 18-week Phase 2 trial in subjects with T1DM randomized to either canagliflozin or placebo (DIA2004), the frequency of DKA was higher than that observed in T2DM clinical trials.

Important Identified Risk: Diabetic ketoacidosis with atypical presentation	
Risk factors and risk groups	The available clinical trial data suggest that patients diagnosed as having T2DM or misdiagnosed as T2DM (eg, T1DM, latent autoimmune diabetes of adulthood), and who have a low beta-cell reserve, are unable to produce sufficient insulin to suppress hepatic ketogenesis and peripheral lipolysis. In the setting of known DKA precipitating factors, such as an acute illness (and associated increase in insulin resistance), these patients can develop DKA. The increased rate of DKA in the CREDENCE trial was observed predominantly in subjects in the lowest eGFR stratum; which included subjects with a longer duration of diabetes, higher proportion of insulin use, and higher baseline glycosylated hemoglobin (HbA1c) than the overall population.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4; • Recommendations regarding appropriate dosing and patient management (including advice on interruption, discontinuation, and restart of canagliflozin and consideration of alternative anti-hyperglycemic therapy, including insulin, during interruptions in canagliflozin treatment) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin/metformin HCl FDC should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin/metformin HCl FDC in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2; • Advice that DKA may be prolonged in some patients and insulin deficiency may play a role and should be corrected is given in SmPC Section 4.4; • Advice to patients to speak to their doctor if they need to stop taking canagliflozin/metformin HCl FDC and when to restart if they are going to have major surgery or a procedure that requires prolonged fasting is provided in PL Section 2. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire; • Adjudication of DKA events from ongoing clinical trials by an independent blinded committee. Additional pharmacovigilance activities: • None. See Section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Lactic acidosis

Evidence for linking the risk to the medicine	Evidence for lactic acidosis from metformin is based on the literature, including case reports, review of clinical trials and observational studies, as well as metformin drug labels. Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure (Metformin SmPC, 2015). Lactic acidosis has been reported in Phase 3/4 clinical trials when canagliflozin was given to subjects who were on a background of metformin, but at a lower incidence than observed in the comparator group.
Risk factors and risk groups	Risk factors include conditions that may be associated with or promote hypoxia, including heart failure, tissue hypoxia, respiratory failure, defective lactate clearance (alcohol abuse, and liver failure), renal impairment, renal or hepatic insufficiency. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age.
Risk minimization measures	Routine risk communication: • SmPC Section 4.2; • SmPC Section 4.4 and PL Section 2; • SmPC Section 4.8 and PL Section 4; • Contraindication in patients with an increased risk of lactic acidosis is described in SmPC Section 4.3 and PL Section 2, including detailed list of conditions; • Patient management of dehydration is described in SmPC Section 4.4 and PL Section 2; • Recommendations regarding concomitant use with medicinal products that acutely impair renal function or cause lactic acidosis or its use in patients with risk factors for lactic acidosis are provided in SmPC Section 4.4; • Patient management of lactic acidosis, including guidance on diagnosis, discontinuation, and need for medical attention, is described in SmPC Section 4.4 and PL Section 4; • Recommendations for monitoring of renal function is provided in SmPC Section 4.4 and PL Section 4; • Advice on concomitant use with alcohol, medicinal products containing alcohol, cationic drugs that are eliminated by renal tubular secretion, iodinated contrast agents, and medicinal products that can adversely affect renal function is provided in SmPC Section 4.5 and PL Section 2; • Advice on patient management of overdose, including how to remove lactate and metformin (hemodialysis), is provided in SmPC Section 4.9. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire.

Missing Information: Use in pregnancy	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin/metformin HCl FDC during pregnancy is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

Missing Information: Use in nursing mothers	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2; • Recommendation regarding use of canagliflozin/metformin HCl FDC during breast-feeding is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

II.C. Post-authorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of VOKANAMET.

II.C.2. Other Studies in Post-authorization Development Plan

There are no studies required for VOKANAMET.

PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

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The following specific adverse drug reaction questionnaire is utilized in conjunction with a complementary form, the Healthcare Professional Adverse Event Follow-up Form, which is used for collecting additional global adverse event information and in accordance with standard case follow-up procedures to obtain complete case information.

Specific Adverse Drug Reaction Follow-up Questionnaire
Canagliflozin (INVOKANA®) or Canagliflozin/Metformin (INVOKAMET®) Targeted Follow-Up Questionnaire (TFUQ) for Diabetic Ketoacidosis or Lactic Acidosis

Follow-up Forms

Canagliflozin (INVOKANA®) or Canagliflozin/Metformin (INVOKAMET®) Targeted Follow-Up Questionnaire (TFUQ) for Diabetic Ketoacidosis or Lactic Acidosis

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

Note: In the event of lactic acidosis, it is important to add information on concomitant METFORMIN-containing medications (other than INVOKAMET®) in the table below.

1. **Co-suspect Medications** *(e.g., Metformin)* Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

2. **Previous Anti-Diabetic Medications: Insulin or Oral Medications** *(e.g., Metformin, Glimepiride, Pioglitazine, Rosiglitazone, Sitagliptin)* Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

3. **Medical History Relevant to Diabetic Ketoacidosis or Lactic Acidosis (Provide onset date and end date [if applicable]. Other details may be placed in the space provided or in the Comments section [#7]).**

Medical condition	Onset date (MM-DD-YYYY)	End date (MM-DD-YYYY)	Other details
Diabetes mellitus type 1			
Diabetes mellitus type 2			
Latent Autoimmune Diabetes of Adult (LADA)			
Ketosis Prone Type II			
Obesity			
Hypertension			
Hyperlipidemia			
Myocardial infarction			
Cerebral Vascular Accident			
Hyperthyroidism			
Autoimmune disorder			
Infection			
Pancreatitis			
Trauma			
Dehydration			
Non-compliance			

MCN:

Medical condition	Onset date (MM-DD-YYYY)	End date (MM-DD-YYYY)	Other details
Alcohol use			

List Relevant Family History:
☐ Diabetes Mellitus
☐ Other (Specify):

4. Adverse Event Description (Place details in the space provided or in the 'Comments' section [#7].)

☐ **Co-Morbid Inciting Events:**

☐ Dehydration
If yes, did dehydration occur before onset of DKA? ☐ No ☐ Yes
☐ Non-Compliance with Medications:
☐ Alcohol Use ☐ Infection/Sepsis
☐ Trauma ☐ Diarrhea
☐ Acute Myocardial Infarction ☐ Vomiting
☐ Acute Heart Failure ☐ Pancreatitis
☐ Cerebrovascular Accident (CVA) ☐ Hyperthyroidism
☐ Renal Disease (Specify diagnosis, onset date, details):
☐ Other (Specify):

Patient's signs and symptoms:

☐ Polyuria ☐ Polydypsia
☐ Polyphagia ☐ Abdominal Pain
☐ Nausea or Vomiting ☐ Dehydration
☐ Weakness ☐ Altered Mental Status or Coma
☐ Kussmaul Respirations ☐ Tachycardia
☐ Hypotension ☐ Weight Loss
☐ Other (Specify):

MCN:

5. Relevant Results of Diagnostic Tests Including Laboratory Tests, Imaging, Biopsies, etc.
(Note positive/negative, and date performed.)

			Before Start of Drug			Normalized After Drug
			Date	Date	Date	Date
Lab Test:	Units	Normal Range	dd/MM/yy	dd/MM/yy	dd/MM/yy	dd/MM/yy
Glucose						
Sodium						
Potassium						
Chloride						
Bicarbonate						
Serum Osmolality						
Anion Gap						
BUN						
Creatinine						
Serum Ketones						
Urine Ketones*						
Lactic Acid						
Hgb						
Hct						
WBC						
Venous pH						
Venous pCO2						
Arterial pH						
Arterial pCO2						
Arterial HCO3						
Arterial pO2						

*Quantitative or Semi Quantitative

☐ Chest Radiograph: Date: [dd-MMM-yyyy], Results:
☐ Magnetic Resonance Imaging (MRI): Date: [dd-MMM-yyyy], Results:
☐ Magnetic Resonance Angiography (MRA Date: [dd-MMM-yyyy], Results:
☐ Computerized Tomography (CT): Date: [dd-MMM-yyyy], Results:
☐ Computerized Tomography Angiography (CTA): Date: [dd-MMM-yyyy], Results:
☐ Other (Specify):

MCN:

6. Treatment and Outcome (Place details in the space provided or in the Comments section [#7].)

Patient was treated for the event? ☐ No ☐ Yes (Details of treatment):

☐ Fluids (Details - type and amount):

☐ Insulin (Details - type and amount):

☐ Electrolytes (Details - type and amount):

☐ Pulmonary Support (Details):

☐ Circulatory Support (Details):

☐ Other (Specify):

Outcome:

7. Comments:

Thank you for completing this form.

Annex 6: Details of Proposed Additional Risk Minimization Activities

Not applicable.